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# Guide to Receptors and Channels (GRAC), 5th edition

## Abstract

The Fifth Edition of the 'Guide to Receptors and Channels' is a compilation of the major pharmacological targets divided into seven sections: G protein-coupled receptors, ligand-gated ion channels, ion channels, catalytic receptors, nuclear receptors, transporters and enzymes. These are presented with nomenclature guidance and summary information on the best available pharmacological tools, alongside suggestions for further reading. Available alongside this publication is a portal at <http://www.GuideToPharmacology.org> which is produced in close association with NC-IUPHAR and allows free online access to the information presented in the Fifth Edition.

## Introduction

The great proliferation of drug targets in recent years has driven the need to provide a logically-organised synopsis of the nomenclature and pharmacology of these targets. This is the underlying reason for this 'Guide to Receptors and Channels', distributed with the *British Journal of Pharmacology*, and produced in association with NC-IUPHAR, the Nomenclature Committees of the International Union of Basic and Clinical Pharmacology. Thanks to a closer collaboration between the British Pharmacological Society and NC-IUPHAR, a free online portal containing the information presented in the Guide to Receptors and Channels has been established at <http://www.GuideToPharmacology.org>. The new portal gathers in one place the previously separate information on drug targets of GRAC and IUPHAR-DB, the database produced by NC-IUPHAR. Over time, these will steadily be integrated and the portal will be developed as a one-stop-shop for information on drug targets and other information of assistance to pharmacology and drug development in both academia and industry. The free online portal has been created by the IUPHAR Database Team (Joanna Sharman, Chido Mpamhanga, Adam Pawson, Helen Benson, Vincent Bombail and Tony Harmar) in the Centre for Cardiovascular Science, University of Edinburgh.

Our intent is to produce an authoritative but user-friendly publication, which allows a rapid overview of the key properties of a wide range of established or potential pharmacological targets. The aim is to provide information succinctly, so that a newcomer to a particular target group can identify the main elements 'at a glance'. It is not our goal to produce all-inclusive reviews of the targets presented; references to these are included in the Further Reading sections of the entries or, for many targets, the website of NC-IUPHAR (<http://www.iuphar-db.org>) provides extensive information. The 'Guide to Receptors and Channels' presents each entry, typically a circumscribed target class family on, wherever possible, a single page, so as to allow easy access and rapid oversight.

Targets have been selected for inclusion where there is sufficient pharmacological information to allow clear definition or where, in our view, there is clear interest in this molecular class from the pharmacological community. Our philosophy has been to present data on human proteins wherever possible, both in terms of structural information and pharmacology. To this end, the Ensembl ID allows rapid access through a free online database (<http://www.ensembl.org>) to genomes from many other species, including mouse and rat. From this database, links are also provided to structural information in a number of formats. Where structural or pharmacological information is not available for human targets, we have used data from other species, as indicated. A priority in constructing these tables was to present agents which represent the most selective and which are available by donation or from commercial sources, now or in the near future.

The Guide is divided into seven sections, which comprise pharmacological targets of similar structure/function. These are G protein-coupled receptors, ligand-gated ion channels, ion channels, catalytic receptors, nuclear receptors, transporters and enzymes. In comparison with the Fourth Edition of the 'Guide to Receptors and Channels' (Alexander *et al.*, 2009), we have added a number of new records, expanding the total to include over 1600 protein targets. The expansion for the Fifth Edition comes primarily from including the full complement of transporters defined in the human genome, as well as increasing the content on enzymes. As in the Fourth Edition, we have also included lists of 'orphan' G protein-coupled and nuclear receptors. The preliminary pairings for orphan GPCR and nuclear receptors provide information on targets, where there is some evidence for an endogenous ligand or a link to a disease or disorder.

The Editors of the Guide have compiled the individual records, taking advice from many Consultants (listed on page S3). With each record, an indication is given of the status of the nomenclature, as proposed by NC-IUPHAR, published in *Pharmacological Reviews*. Where this guidance is lacking, advice from several prominent, independent experts has been obtained to produce an authoritative consensus, which attempts to fit in within the general guidelines from NC-IUPHAR (Vanhoutte *et al.*, 1996). Tabulated data provide ready comparison of selective agents and probes (radioligands and PET ligands, where available) within a family of targets and additional commentary highlights whether species differences or ligand metabolism are potential confounding factors. We recommend that any citations to information in the Guide are presented in the following format:

Alexander SPH, Mathie A, Peters JA (2011). Guide to Receptors and Channels (GRAC), 5<sup>th</sup> edn. *Br J Pharmacol* **164** (Suppl. 1): S1–S324.

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# G PROTEIN-COUPLED RECEPTORS

**Overview:** The completion of the Human Genome Project allowed the identification of a large family of proteins with a common motif of seven groups of 20–24 hydrophobic amino acids arranged as  $\alpha$ -helices. Approximately 800 of these seven transmembrane (7TM) receptors have been identified of which over 300 are non-olfactory receptors (see Fredriksson *et al.*, 2003; Lagerstrom and Schioth, 2008). Subdivision on the basis of sequence homology allows the definition of rhodopsin, secretin, adhesion, glutamate and Frizzled receptor families. NC-IUPHAR recognizes Classes A, B, and C, which equate to the rhodopsin, secretin, and glutamate receptor families.

The nomenclature of 7TM receptors is commonly used interchangeably with G protein-coupled receptors (GPCR), although the former nomenclature recognises signalling of 7TM receptors through pathways not involving G proteins. For example, adiponectin and membrane progesterin receptors have some sequence homology to 7TM receptors but signal independently of G proteins and appear to reside in membranes in an inverted fashion compared to conventional GPCR. Additionally, the NPR-C natriuretic peptide receptor (see Page S195) has a single transmembrane domain structure, but appears to couple to G proteins to generate cellular responses. The 300+ non-olfactory GPCR are the targets for the majority of drugs in clinical usage (Overington *et al.*, 2006), although only a minority of these receptors are exploited therapeutically.

Signalling through GPCR is enacted by the activation of heterotrimeric GTP-binding proteins (G proteins), made up of  $\alpha$ ,  $\beta$  and  $\gamma$  subunits, where the  $\alpha$  and  $\beta\gamma$  subunits are responsible for signalling. The  $\alpha$  subunit (tabulated below) allows definition of one series of signalling cascades and permits grouping of GPCRs to suggest common cellular, tissue and behavioural responses.  $G\beta\gamma$  subunits (tabulated below) also are able to signal, in a manner independent of the  $G\alpha$  subunits. Recently, the concept of agonist bias, or functional selectivity, has arisen (see Kenakin and Miller, 2010), which suggests that particular agonists, or allosteric modulators, may be able to promote post-receptor signalling through one cascade at the expense of an alternative. This has complicated the scenario for classification of GPCR. For the purposes of the Guide to Receptors and Channels, 'Principal transduction' is limited to the predominant established  $G\alpha$  signalling.

**$G\alpha_s$  family:**  $\beta_1$ -adrenoceptors (see Page S26) in the heart couple principally through  $G\alpha_s$  to activate adenylyl cyclase activity (see Page S288) and elevate intracellular cyclic AMP levels. This in turn leads to activation of protein kinase A (see Page S310) and the consequent phosphorylation and enhancement of function of voltage-gated calcium channels ( $Ca_v1.2$ , see Page S142). This, in turn leads to the observed action of noradrenaline (norepinephrine) or adrenaline (epinephrine) in increasing cardiac rate and force of contraction. The identification of other  $G_s$ -coupled GPCR in the heart would allow prediction of a similar effect on heart rate and force through the same mechanisms. In other tissues,  $G_s$ -coupled receptors would be predicted to evoke smooth muscle relaxation (e.g.  $\beta_2$ -adrenoceptors in bronchioles, Page S26), enhance secretion (e.g.  $H_2$  histamine receptors in gastric parietal cells, Page S70), stimulate lipolysis in adipocytes (e.g.  $\beta_3$ -adrenoceptors, Page S26) and inhibit platelet aggregation (e.g. IP prostanoid receptors, Page S97).

| Nomenclature   | HGNC nomenclature | Other names           | Ensembl ID      |
|----------------|-------------------|-----------------------|-----------------|
| $\alpha_s$     | <i>GNAS</i>       | Stimulatory G protein | ENSG00000087460 |
| $\alpha_{olf}$ | <i>GNAL</i>       | Olfactory type        | ENSG00000141404 |

**G $\alpha_i$  family:** M<sub>2</sub> muscarinic acetylcholine receptors (see Page S20) in the heart couple *via* G $\alpha_i$  subunits to inhibit adenylyl cyclase activity (see Page S288). Vagal innervation targets these receptors, primarily in the atria, to counteract the effects of noradrenaline and adrenaline in the cardiac myocyte, leading to a reduction in heart rate and force of contraction. In addition, G $\alpha_i$  subunits and G $\beta\gamma$  subunits (see below) enhance potassium channel opening (K<sub>IR2.x</sub>, see Page S158). The ensuing hyperpolarization of the cardiac myocyte leads to a reduction in voltage-gated L-type calcium channel activity and a consequent inhibition of rate and force of cardiac contraction – the manifestation of vagal nerve stimulation. In other tissues, G<sub>i</sub>-coupled receptors would be predicted to inhibit neurotransmitter release (e.g.  $\mu$  opioid receptors, Page S88, on parasympathetic nerve terminals in the small intestine), inhibit lipolysis in adipocytes (e.g. A<sub>1</sub> adenosine receptors, Page S22) and enhance platelet aggregation (e.g. P2Y<sub>12</sub> receptors, Page S91).

In the retina, transducin ( $\alpha_t$ ) subunits allow coupling to a cyclic GMP-specific phosphodiesterase, PDE6 (see Page S290). This reduces cellular cyclic GMP levels leading to a reduction of currents through cyclic nucleotide-gated channels (CNG, Page S153) and subsequent decrease of the 'dark' current.

| Nomenclature  | HGNC nomenclature | Other names                           | Ensembl ID      |
|---------------|-------------------|---------------------------------------|-----------------|
| $\alpha_{i1}$ | <i>GNAI1</i>      | Inhibitory G protein $\alpha$ subunit | ENSG00000127955 |
| $\alpha_{i2}$ | <i>GNAI2</i>      | Inhibitory G protein $\alpha$ subunit | ENSG00000114353 |
| $\alpha_{i3}$ | <i>GNAI3</i>      | Inhibitory G protein $\alpha$ subunit | ENSG00000065135 |
| $\alpha_{t1}$ | <i>GNAT1</i>      | Transducin 1 $\alpha$ subunit         | ENSG00000114349 |
| $\alpha_{t2}$ | <i>GNAT2</i>      | Transducin 2 $\alpha$ subunit         | ENSG00000134183 |
| $\alpha_{t3}$ | <i>GNAT3</i>      | Gustducin $\alpha$ subunit            | ENSG00000214415 |
| $\alpha_o$    | <i>GNAO1</i>      | $\alpha$ other                        | ENSG00000087258 |
| $\alpha_z$    | <i>GNAZ</i>       | –                                     | ENSG00000128266 |

**G $\alpha_q$  family:** M<sub>3</sub> muscarinic acetylcholine receptors (see Page S20) in bronchial smooth muscle couple *via* G $\alpha_{q/11}$  subunits to stimulate phospholipase C- $\beta$  activity (see Page S302). This leads to an elevation of intracellular calcium ions through inositol 1,4,5-trisphosphate action at IP<sub>3</sub> receptors (see Page S157), activation of protein kinase C (see Page S311) and the consequent smooth muscle contraction and reduced airway conductance. In other tissues, G<sub>q</sub>-coupled receptor activation leads to increased platelet aggregation (e.g. P2Y<sub>1</sub> receptors, Page S91).

Lysophosphatidic acid receptors (see Page S76) and proteinase-activated receptors (see Page S95) are examples of GPCR which couple through multiple G protein families, including G $\alpha_{12/13}$  leading to activation of a guanine nucleotide exchange factor, or GEF, for the Rho family of low molecular GTP-binding proteins (ENSEM00500000269651), the subsequent activation of Rho kinase (see Page S313) and regulation of the cytoskeleton, leading to cellular shape changes and/or migration.

| Nomenclature  | HGNC nomenclature | Ensembl ID      |
|---------------|-------------------|-----------------|
| $\alpha_q$    | <i>GNAQ</i>       | ENSG00000156052 |
| $\alpha_{11}$ | <i>GNA11</i>      | ENSG00000088256 |
| $\alpha_{12}$ | <i>GNA12</i>      | ENSG00000146535 |
| $\alpha_{13}$ | <i>GNA13</i>      | ENSG00000120063 |
| $\alpha_{14}$ | <i>GNA14</i>      | ENSG00000156049 |
| $\alpha_{15}$ | <i>GNA15</i>      | ENSG00000060558 |

GNAQP1 is a pseudogene (ENSG00000214077).

**G $\beta\gamma$  subunits:** although  $\beta$  and  $\gamma$  subunits are synthesised as separate entities, they are considered to generate a complex which is essentially biologically irreversible. Acylation and prenylation ensure an association with the plasma membrane, where G $\beta\gamma$  subunits may regulate ion channel activities, or recruit members of the G protein-coupled receptor kinase family, also known as  $\beta$ -adrenoceptor kinases (see Page S310). Phosphorylation of particular cytoplasmic serine/threonine residues of GPCR allows binding of  $\beta$ -arrestin (ENSEM00250000000572). These proteins act as scaffolding partners facilitating internalization of GPCR as a mechanism of desensitization, or coupling to alternative signalling pathways (e.g. MAP kinases, see Page S312).

| Nomenclature | HGNC nomenclature | Ensembl ID      |
|--------------|-------------------|-----------------|
| $\beta_1$    | <i>GNB1</i>       | ENSG00000078369 |
| $\beta_2$    | <i>GNB2</i>       | ENSG00000172354 |
| $\beta_3$    | <i>GNB3</i>       | ENSG00000111664 |
| $\beta_4$    | <i>GNB4</i>       | ENSG00000114450 |
| $\beta_5$    | <i>GNB5</i>       | ENSG00000069966 |

| Nomenclature | HCNC nomenclature | Ensembl ID      |
|--------------|-------------------|-----------------|
| $\gamma 2$   | <i>GNG2</i>       | ENSG00000186469 |
| $\gamma 3$   | <i>GNG3</i>       | ENSG00000162188 |
| $\gamma 4$   | <i>GNG4</i>       | ENSG00000168243 |
| $\gamma 5$   | <i>GNG5</i>       | ENSG00000174021 |
| $\gamma 7$   | <i>GNG7</i>       | ENSG00000176533 |
| $\gamma 8$   | <i>GNG8</i>       | ENSG00000167414 |
| $\gamma 10$  | <i>GNG10</i>      | ENSG00000242616 |
| $\gamma 11$  | <i>GNG11</i>      | ENSG00000127920 |
| $\gamma 12$  | <i>GNG12</i>      | ENSG00000172380 |
| $\gamma 13$  | <i>GNG13</i>      | ENSG00000127588 |
| $\gamma t1$  | <i>GNGT1</i>      | ENSG00000127928 |
| $\gamma t2$  | <i>GNGT2</i>      | ENSG00000167083 |

GNB1L (ENSG00000185838) and GNB2L1 (ENSG00000204628) are described as G $\beta$ -like proteins on the basis of sequence homology. Four G $\gamma$  pseudogenes are defined in the human genome (GNG5P1, ENSG00000213536; GNG5P2, ENSG00000133136; GNG5P3, ENSG00000254949; GNG5P5, ENSG00000234590).

### Further Reading

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# Orphan G protein-coupled receptors

## Preliminary pairings

While the remainder of this section focuses on those GPCR for which there is substantial pharmacological information, or interest, listed below are a number of putative GPCR identified by IUPHAR (Foord *et al.*, 2005), for which only preliminary evidence for an endogenous ligand has been published, or for which there exists a potential link to a disease, or disorder. The GPCR in the table below are all Class A, rhodopsin-like GPCR.

| IUPHAR name | Ensembl ID      | Other names                                                                                    | Putative endogenous ligand                                                                  | Comment                                                                                                                                                                                                                                                                                                                                                           |
|-------------|-----------------|------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CCRL2       | ENSG00000121797 | Chemokine (C-C motif) receptor-like 2, HCR, CRAM-B, CKRX, CRAM-A, CCR11, Cmkbr112, L-CCR, CRAM | Chemerin (Zabel <i>et al.</i> , 2008)                                                       | –                                                                                                                                                                                                                                                                                                                                                                 |
| GPR1        | ENSG00000183671 | –                                                                                              | Chemerin (Barnea <i>et al.</i> , 2008)                                                      | Reported to act as a co-receptor for HIV (Shimizu <i>et al.</i> , 1999)                                                                                                                                                                                                                                                                                           |
| GPR3        | ENSG00000181773 | ACCA                                                                                           | Fails to respond to a variety of lipid-derived agents (Yin <i>et al.</i> , 2009)            | Reported to activate adenylyl cyclase constitutively through G <sub>s</sub> (Eggerickx <i>et al.</i> , 1995). Gene disruption results in premature ovarian aging (Ledent <i>et al.</i> , 2005), reduced $\beta$ -amyloid deposition (Thathiah <i>et al.</i> , 2009) and heightened pain behaviours (Ruiz-Medina <i>et al.</i> , 2011) in mice                     |
| GPR4        | ENSG00000177464 | –                                                                                              | Protons (Ludwig <i>et al.</i> , 2003; Tobo <i>et al.</i> , 2007; Liu <i>et al.</i> , 2010a) | An initial report suggesting activation by lysophosphatidylcholine, sphingosylphosphorylcholine (Zhu <i>et al.</i> , 2001) has been retracted (Zhu <i>et al.</i> , 2005). Gene disruption is associated with increased perinatal mortality and impaired vascular proliferation (Yang <i>et al.</i> , 2007)                                                        |
| GPR6        | ENSG00000146360 | –                                                                                              | Fails to respond to a variety of lipid-derived agents (Yin <i>et al.</i> , 2009)            | Reported to activate adenylyl cyclase constitutively through G <sub>s</sub> and to be located intracellularly (Padmanabhan <i>et al.</i> , 2009)                                                                                                                                                                                                                  |
| GPR12       | ENSG00000132975 | GPCR21, Gpcr01, Gpcr12, Gpcr20                                                                 | Fails to respond to a variety of lipid-derived agents (Yin <i>et al.</i> , 2009)            | Gene disruption results in dyslipidemia and obesity (Bjursell <i>et al.</i> , 2006)                                                                                                                                                                                                                                                                               |
| GPR15       | ENSG00000154165 | BOB                                                                                            | –                                                                                           | Reported to act as a co-receptor for HIV (Edinger <i>et al.</i> , 1997)                                                                                                                                                                                                                                                                                           |
| GPR17       | ENSG00000144230 | R12                                                                                            | Dual leukotriene and UDP receptor (Ciana <i>et al.</i> , 2006)                              | Reported to antagonize CysLT1 receptor signalling <i>in vivo</i> and <i>in vitro</i> (Maekawa <i>et al.</i> , 2009)                                                                                                                                                                                                                                               |
| GPR20       | ENSG00000204882 | –                                                                                              | –                                                                                           | Reported to inhibit adenylyl cyclase constitutively through G <sub>i/o</sub> (Hase <i>et al.</i> , 2008)                                                                                                                                                                                                                                                          |
| GPR22       | ENSG00000172209 | –                                                                                              | –                                                                                           | Reported to inhibit adenylyl cyclase constitutively through G <sub>i/o</sub> ; gene disruption results in increased severity of functional decompensation following aortic banding (Adams <i>et al.</i> , 2008). Identified as a susceptibility locus for osteoarthritis (Evangelou <i>et al.</i> , 2011, Kerkhof <i>et al.</i> , 2010, Valdes and Spector, 2010) |
| GPR26       | ENSG00000154478 | –                                                                                              | –                                                                                           | Reported to activate adenylyl cyclase constitutively through G <sub>s</sub> (Jones <i>et al.</i> , 2007)                                                                                                                                                                                                                                                          |

| IUPHAR name | Ensembl ID      | Other names                                                                                              | Putative endogenous ligand                                                                                                               | Comment                                                                                                                                                                                                                                                                                                                                                 |
|-------------|-----------------|----------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| GPR31       | ENSG00000120436 | bA517H2.2                                                                                                | 12(S)-Hydroxyeicosatetraenoic acid (Guo <i>et al.</i> , 2011)                                                                            |                                                                                                                                                                                                                                                                                                                                                         |
| GPR34       | ENSG00000171659 | –                                                                                                        | Lysophosphatidylserine (Sugo <i>et al.</i> , 2006), but fails to respond to a variety of lipid-derived agents (Yin <i>et al.</i> , 2009) | Gene disruption results in an enhanced immune response (Liebscher <i>et al.</i> , 2011)                                                                                                                                                                                                                                                                 |
| GPR35       | ENSG00000178623 | –                                                                                                        | Kynurenic acid (Wang <i>et al.</i> , 2006); lysophosphatidic acid (Oka <i>et al.</i> , 2010)                                             | Reported to respond to the phosphodiesterase inhibitor zaprinast (Taniguchi <i>et al.</i> , 2006) the chloride channel blocker 5-nitro-2-(3-phenylpropylamino) benzoic acid (Taniguchi <i>et al.</i> , 2008), the pharmaceutical adjuvant pamoic acid (Zhao <i>et al.</i> , 2010) and tyrosine kinase inhibitor tyrphostins (Deng <i>et al.</i> , 2011) |
| GPR37       | ENSG00000170775 | PAELR, EDNRBL, Endothelin B receptor-like protein 1, Parkin-associated endothelin receptor-like receptor | Head activator peptide (Rezgaoui <i>et al.</i> , 2006)                                                                                   | Reported to associate and regulate the dopamine transporter (Marazziti <i>et al.</i> , 2007) and to be a substrate for parkin (Marazziti <i>et al.</i> , 2009). Gene disruption results in altered striatal signalling (Marazziti <i>et al.</i> , 2011)                                                                                                 |
| GPR39       | ENSG00000183840 |                                                                                                          | Zn <sup>2+</sup> (Holst <i>et al.</i> , 2007)                                                                                            | Obestatin was reported initially as an endogenous ligand (Zhang <i>et al.</i> , 2005), but subsequent studies failed to reproduce these findings. Has been reported to be down-regulated in adipose tissue in obesity-related diabetes (Catalan <i>et al.</i> , 2007). Gene disruption results in obesity (Petersen <i>et al.</i> , 2011)               |
| GPR50       | ENSG00000102195 | Melatonin-related receptor, H9, MTNRL                                                                    | –                                                                                                                                        | A potential orthologue of an avian melatonin receptor (Dufourny <i>et al.</i> , 2008)                                                                                                                                                                                                                                                                   |
| GPR63       | ENSG00000112218 | PSP24B                                                                                                   | Fails to respond to a variety of lipid-derived agents (Yin <i>et al.</i> , 2009)                                                         |                                                                                                                                                                                                                                                                                                                                                         |
| GPR65       | ENSG00000140030 | TDAG8, T-cell death associated gene 8                                                                    | Protons (Wang <i>et al.</i> , 2004; Ihara <i>et al.</i> , 2010)                                                                          | Reported to activate adenylyl cyclase; gene disruption leads to reduced eosinophilia in models of allergic airway disease (Kottyan <i>et al.</i> , 2009)                                                                                                                                                                                                |
| GPR68       | ENSG00000119714 | OGR1                                                                                                     | Protons (Ludwig <i>et al.</i> , 2003; Liu <i>et al.</i> , 2010b)                                                                         | –                                                                                                                                                                                                                                                                                                                                                       |
| GPR75       | ENSG00000119737 | WI-31133                                                                                                 | RANTES (Ignatov <i>et al.</i> , 2006)                                                                                                    | –                                                                                                                                                                                                                                                                                                                                                       |
| GPR84       | ENSG00000139572 | EX33                                                                                                     | Medium chain fatty acids (Wang <i>et al.</i> , 2006)                                                                                     | –                                                                                                                                                                                                                                                                                                                                                       |
| GPR87       | ENSG00000138271 | GPR95                                                                                                    | Lysophosphatidic acid (Tabata <i>et al.</i> , 2007)                                                                                      | –                                                                                                                                                                                                                                                                                                                                                       |
| GPR88       | ENSG00000181656 | STRG                                                                                                     | –                                                                                                                                        | Gene disruption results in altered striatal signalling (Logue <i>et al.</i> , 2009)                                                                                                                                                                                                                                                                     |
| GPR120      | ENSG00000186188 |                                                                                                          | Free fatty acids (Katsuma <i>et al.</i> , 2005; Hirasawa <i>et al.</i> , 2005)                                                           | –                                                                                                                                                                                                                                                                                                                                                       |
| GPR132      | ENSG00000183484 | G2A                                                                                                      | Protons (Murakami <i>et al.</i> , 2004)                                                                                                  | Reported to respond to lysophosphatidylcholine (Kabarowski <i>et al.</i> , 2001), but later retracted (Witte <i>et al.</i> , 2005)                                                                                                                                                                                                                      |
| GPR143      | ENSG00000101850 | OA1                                                                                                      | L-DOPA (Lopez <i>et al.</i> , 2008)                                                                                                      | Loss-of-function mutations underlie ocular albinism type 1 (Bassi <i>et al.</i> , 1995)                                                                                                                                                                                                                                                                 |

| IUPHAR name       | Ensembl ID       | Other names                                                                             | Putative endogenous ligand                                                                         | Comment                                                                                                                                                              |
|-------------------|------------------|-----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| GPR149            | ENSG00000174948  | PGR10, IEDA                                                                             |                                                                                                    | Gene disruption results in enhanced fertility (Edson <i>et al.</i> , 2010)                                                                                           |
| GPR161            | ENSG00000143147  | RE2                                                                                     | –                                                                                                  | Gene disruption is associated with a failure of asymmetric embryonic development in zebrafish (Leung <i>et al.</i> , 2008)                                           |
| GPR183            | ENSG00000169508  | EBI2, Epstein-Barr virus induced gene 2, lymphocyte-specific G protein-coupled receptor | Oxysterols (Hannedouche <i>et al.</i> , 2011; Liu <i>et al.</i> , 2011)                            | –                                                                                                                                                                    |
| GPRC <sub>6</sub> | ENSG00000173612  | GPRC6A                                                                                  | Basic amino acids, such as L-arginine, L-lysine and L-ornithine (Wellendorph <i>et al.</i> , 2005) | –                                                                                                                                                                    |
| LGR4              | ENSG00000205213  | Leucine-rich repeat-containing G-protein coupled receptor 4, GPR48                      | R-spondins (Carmon <i>et al.</i> , 2011; de Lau <i>et al.</i> , 2011)                              | Gene disruption leads to multiple developmental disorders (Luo <i>et al.</i> , 2009; Jin <i>et al.</i> , 2008; Song <i>et al.</i> , 2008; Weng <i>et al.</i> , 2008) |
| LGR5              | ENSG00000139292  | Leucine-rich repeat-containing G-protein coupled receptor 5, GPR49, GPR67, FEX, HG38    | R-spondins (Carmon <i>et al.</i> , 2011; de Lau <i>et al.</i> , 2011)                              | –                                                                                                                                                                    |
| LGR6              | ENSG00000133067; | FLJ14471, VTS20631                                                                      | R-spondins (Carmon <i>et al.</i> , 2011; de Lau <i>et al.</i> , 2011)                              | –                                                                                                                                                                    |
| MAS1              | ENSG00000130368  | Mas                                                                                     | Angiotensin-(1-7) (Santos <i>et al.</i> , 2003)                                                    |                                                                                                                                                                      |
| MRGPRD            | ENSG00000172938  | TGR7, Mas-related GPR member D, MrgD                                                    | β-Alanine (Shinohara <i>et al.</i> , 2004)                                                         | Potentially exists as a heteromer with MRGPRE (Milasta <i>et al.</i> , 2006)                                                                                         |
| MRGPRX1           | ENSG00000170255  | SNSR4, Mas-related GPR member X1, MrgX1                                                 | BAM8-22 (Chen and Ikeda, 2004)                                                                     | Reported to mediate the sensation of itch (Liu <i>et al.</i> , 2009; Sikand <i>et al.</i> , 2011)                                                                    |
| MRGPRX2           | ENSG00000183695  | Mas-related GPR member X2, MrgX2                                                        | PAMP (Kamohara <i>et al.</i> , 2005), cortistatin (Robas <i>et al.</i> , 2003)                     | –                                                                                                                                                                    |
| P2RY10            | ENSG00000078589  | Purinergic receptor, P2Y10, P2Y-like                                                    | Sphingosine 1-phosphate and lysophosphatidic acid (Murakami <i>et al.</i> , 2008)                  | –                                                                                                                                                                    |
| OXGR1             | ENSG00000165621  | GPR80, GPR99, P2Y15                                                                     | 2-Oxoglutarate (He <i>et al.</i> , 2004)                                                           | –                                                                                                                                                                    |
| SUCNR1            | ENSG00000198829  | GPR91                                                                                   | Succinate (He <i>et al.</i> , 2004; Hogberg <i>et al.</i> , 2011)                                  | –                                                                                                                                                                    |

#### Additional 'orphan' GPCRs

In the set of tables below, putative GPCR with as-yet unidentified endogenous ligands are listed.

#### Class A orphan GPCR

| IUPHAR name | Ensembl ID         | Other names                                                                                            |
|-------------|--------------------|--------------------------------------------------------------------------------------------------------|
| GPR19       | ENSG00000183150    | GPR-NGA                                                                                                |
| GPR21       | ENSG00000188394    | –                                                                                                      |
| GPR25       | ENSG00000170128    | –                                                                                                      |
| GPR27       | ENSG00000170837    | SREB1, super-conserved receptor expressed in brain 1                                                   |
| GPR33       | ENSMUSG00000035148 | Pseudogene in man                                                                                      |
| GPR37L1     | ENSG00000170075    | Endothelin B receptor-like protein 2, ETBR-LP-2, G-protein coupled receptor 37-like 1, CAG-18, DOKist8 |
| GPR45       | ENSG00000135973    | PSP24                                                                                                  |

| IUPHAR name | Ensembl ID      | Other names                                                                                                     |
|-------------|-----------------|-----------------------------------------------------------------------------------------------------------------|
| GPR52       | ENSG00000203737 | –                                                                                                               |
| GPR61       | ENSG00000156097 | BALGR, GPCR3                                                                                                    |
| GPR62       | ENSG00000180929 | GPCR8                                                                                                           |
| GPR78       | ENSG00000155269 | –                                                                                                               |
| GPR82       | ENSG00000171657 | –                                                                                                               |
| GPR83       | ENSG00000123901 | GPR72, KIAA1540, glucocorticoid-induced receptor, GIR, RP105, RP39, RP82                                        |
| GPR85       | ENSG00000164604 | SREB2, Super Conserved Receptor Expressed in Brain 2, Srep2, MGC105281                                          |
| GPR101      | ENSG00000165370 | GPCR6, RGD1564196                                                                                               |
| GPR135      | ENSG00000181619 | HUMNPIIY20, PAFR                                                                                                |
| GPR139      | ENSG00000180269 | PGR3, GPRg1                                                                                                     |
| GPR141      | ENSG00000187037 | PGR13                                                                                                           |
| GPR142      | ENSG00000257008 | PGR2, KIF19                                                                                                     |
| GPR146      | ENSG00000164849 | PGR8                                                                                                            |
| GPR148      | ENSG00000173302 | PGR6, brain and testis restricted GPCR                                                                          |
| GPR150      | ENSG00000178015 | PGR11                                                                                                           |
| GPR151      | ENSG00000173250 | PGR7, GALR4, GPCR-2037                                                                                          |
| GPR152      | ENSG00000175514 | PGR5                                                                                                            |
| GPR153      | ENSG00000158292 | PGR1                                                                                                            |
| GPR160      | ENSG00000173890 | GPCR150, GPCR1                                                                                                  |
| GPR162      | ENSG00000110811 | A-2, GRCA                                                                                                       |
| GPR171      | ENSG00000174946 | H963                                                                                                            |
| GPR173      | ENSG00000184194 | Super conserved receptor expressed in brain 3, SREB3                                                            |
| GPR174      | ENSG00000147138 | FKSG79                                                                                                          |
| GPR176      | ENSG00000166073 | Gm1012, HB954                                                                                                   |
| GPR182      | ENSG00000166856 | adrenomedullin receptor, hrhAMR, AM-R, G10-D, Gpcr17, Gpcr22, MB10, NOW, ADMR                                   |
| MAS1L       | ENSG00000204687 | MAS-L, MRG, dj994E9.2, MAS-R, MGC119987, MAS1 oncogene-like                                                     |
| MGRPRX3     | ENSG00000179826 | MAS-related GPR, member X3, Mrga10, SNSR1, SNSR2, MRGX3, sensory neuron-specific G-protein coupled receptor 1/2 |
| MGRPRX4     | ENSG00000179817 | MAS-related GPR, member X4, MRGX4, SNSR5, SNSR6, sensory neuron-specific G-protein coupled receptor 5/6         |
| MRGPRE      | ENSG00000184350 | MAS-related GPR, member E, mrgE, GPR167, MGC138408                                                              |
| MRGPRF      | ENSG00000172935 | GPR168, GPR140, MGC21621, mrgF, MAS-related GPR, member F, RTA                                                  |
| MRGPRG      | ENSG00000182170 | MAS-related GPR, member G, GPR169, mrgG, MRGG, EBRT2                                                            |
| OPN3        | ENSG00000054277 | Opsin-3, Encephalopsin, Panopsin, ECPN, ERO, NMO-1                                                              |
| OPN5        | ENSG00000124818 | GPR136, neuropsin, PGR12, TMEM13                                                                                |
| P2RY8       | ENSG00000182162 | purinergic receptor P2Y, G-protein coupled, 8, P2Y8, MGC50878                                                   |

### Class B Orphan GPCR

| IUPHAR name | Ensembl ID      | Other names |
|-------------|-----------------|-------------|
| GPR157      | ENSG00000180758 | FLJ12132    |

**Adhesion GPCRs:** Adhesion GPCRs are structurally identified on the basis of a large extracellular region, similar to the Class B GPCR, but which is linked to the 7TM region by a 'stalk' motif containing a GPCR proteolytic site. The N-terminus often shares structural homology with proteins such as lectins and immunoglobulins, leading to the term adhesion GPCR (see Fredriksson *et al.*, 2003; Yona *et al.*, 2008).

| IUPHAR name | Ensembl ID      | Other names                                                                                                                                               | Comment                                                                                                                                                      |
|-------------|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| BAI1        | ENSG00000181790 | Brain-specific angiogenesis inhibitor 1                                                                                                                   | Reported to respond to phosphatidylserine (Park <i>et al.</i> , 2007)                                                                                        |
| BAI2        | ENSG00000121753 | Brain-specific angiogenesis inhibitor 2                                                                                                                   | –                                                                                                                                                            |
| BAI3        | ENSG00000135298 | Brain-specific angiogenesis inhibitor 3                                                                                                                   | –                                                                                                                                                            |
| CD97        | ENSG00000123146 | Leukocyte antigen CD97                                                                                                                                    | –                                                                                                                                                            |
| CELSR1      | ENSG00000075275 | Cadherin EGF LAG seven-pass G-type receptor 1, flamingo homolog 2, hFmi2                                                                                  | –                                                                                                                                                            |
| CELSR2      | ENSG00000143126 | Cadherin EGF LAG seven-pass G-type receptor 2, epidermal growth factor-like 2, multiple epidermal growth factor-like domains 3, flamingo 1                | –                                                                                                                                                            |
| CELSR3      | ENSG00000008300 | Cadherin EGF LAG seven-pass G-type receptor 3, flamingo homolog 1, hFmi1, multiple epidermal growth factor-like domains 2, epidermal growth factor-like 1 | –                                                                                                                                                            |
| ELTD1       | ENSG00000162618 | EGF, latrophilin and seven transmembrane domain-containing protein 1, EGF-TM7-latrophilin-related protein, ETL                                            | –                                                                                                                                                            |
| EMR1        | ENSG00000174837 | EGF-like module-containing mucin-like hormone receptor-like 1, cell surface glycoprotein EMR1, EMR1 hormone receptor                                      | –                                                                                                                                                            |
| EMR2        | ENSG00000127507 | EGF-like module-containing mucin-like hormone receptor-like 2, EGF-like module EMR2, CD312 antigen                                                        | –                                                                                                                                                            |
| EMR3        | ENSG00000131355 | EGF-like module-containing mucin-like hormone receptor-like 3, EGF-like module-containing mucin-like receptor EMR3                                        | –                                                                                                                                                            |
| GPR56       | ENSG00000205336 | TM7LN4, TM7XN1                                                                                                                                            | Reported to bind tissue transglutaminase 2 (Xu <i>et al.</i> , 2006) and collagen, which activates the G <sub>12/13</sub> pathway (Luo <i>et al.</i> , 2011) |
| GPR64       | ENSG00000173698 | HE6                                                                                                                                                       | –                                                                                                                                                            |
| GPR97       | ENSG00000182885 | Pb99, PGR26                                                                                                                                               | –                                                                                                                                                            |
| GPR98       | ENSG00000164199 | VLGR1, FEB4, KIAA0686, USH2C, Frings, MASS1, monogenic audiogenic seizure susceptibility 1 homolog                                                        | Loss-of-function mutations are associated with Usher syndrome, a sensory deficit disorder (Jacobson <i>et al.</i> , 2008)                                    |
| GPR110      | ENSG00000153292 | hGPCR36, PGR19                                                                                                                                            | –                                                                                                                                                            |
| GPR111      | ENSG00000164393 | hGPCR35, PGR20                                                                                                                                            | –                                                                                                                                                            |
| GPR112      | ENSG00000156920 | RP1-299I16, PGR17                                                                                                                                         | –                                                                                                                                                            |
| GPR113      | ENSG00000173567 | hGPCR37, PGR23                                                                                                                                            | –                                                                                                                                                            |
| GPR114      | ENSG00000159618 | PGR27                                                                                                                                                     | –                                                                                                                                                            |
| GPR115      | ENSG00000153294 | FLJ38076, PGR18                                                                                                                                           | –                                                                                                                                                            |
| GPR116      | ENSG00000069122 | DKFZp564O1923, KIAA0758                                                                                                                                   | –                                                                                                                                                            |
| GPR123      | ENSG00000197177 | KIAA1828                                                                                                                                                  | –                                                                                                                                                            |
| GPR124      | ENSG00000020181 | Tumour endothelial marker 5                                                                                                                               | –                                                                                                                                                            |
| GPR125      | ENSG00000152990 | PGR21                                                                                                                                                     | –                                                                                                                                                            |
| GPR126      | ENSG00000112414 | FLJ14937                                                                                                                                                  | –                                                                                                                                                            |
| GPR128      | ENSG00000144820 | FLJ14454                                                                                                                                                  | –                                                                                                                                                            |
| GPR133      | ENSG00000111452 | PGR25                                                                                                                                                     | –                                                                                                                                                            |
| GPR144      | ENSG00000180264 | PGR24                                                                                                                                                     | –                                                                                                                                                            |
| LPHN1       | ENSG00000072071 | Lectomedin-2, LEC2, latrophilin-1, calcium-independent $\alpha$ -latrotoxin receptor 1                                                                    | –                                                                                                                                                            |
| LPHN2       | ENSG00000117114 | Lectomedin-1, LEC1, latrophilin-2, calcium-independent $\alpha$ -latrotoxin receptor 2, latrophilin homolog 1                                             | –                                                                                                                                                            |
| LPHN3       | ENSG00000150471 | Lectomedin-3, LEC3, Latrophilin-3, calcium-independent $\alpha$ -latrotoxin receptor 3, l                                                                 | –                                                                                                                                                            |

## Class C Orphan GPCR

| IUPHAR name | Ensembl ID      | Other names                                                                                                                          |
|-------------|-----------------|--------------------------------------------------------------------------------------------------------------------------------------|
| GPR156      | ENSG00000175697 | PGR28, GABABL                                                                                                                        |
| GPR158      | ENSG00000151025 | KIAA1136                                                                                                                             |
| GPR179      | ENSG00000188888 | GPR158L1                                                                                                                             |
| GPRC5A      | ENSG00000013588 | RAIG <sub>1</sub> , Retinoic acid-induced protein 3, retinoic acid-induced gene 1 protein, orphan G-protein-coupling receptor PEIG-1 |
| GPRC5B      | ENSG00000167191 | RAIG <sub>2</sub> , Retinoic acid-induced gene 2 protein, A-69G12.1                                                                  |
| GPRC5C      | ENSG00000170412 | RAIG <sub>3</sub> , Retinoic acid-induced gene 3 protein,                                                                            |
| GPRC5D      | ENSG00000111291 | RAIG <sub>4</sub> , G-protein coupled receptor family C group 5 member D                                                             |

## Taste receptors

Whilst the taste of acid and salty foods appears to be sensed by regulation of ion channel activity, bitter, sweet and umami tastes are sensed by specialised GPCR. Two classes of taste GPCR have been identified, T1R and T2R, which are similar in sequence and structure to Class C and Class A GPCR, respectively. Activation of taste receptors appears to involve gustducin (G $\alpha_{t3}$ , see Page S6) and G $\alpha_{t4}$ -mediated signalling, although the precise mechanisms remain obscure. Gene disruption studies suggest the involvement of PLC $\beta$ 2 (Zhang *et al.*, 2003), TRPM5 (Zhang *et al.*, 2003) and IP<sub>3</sub> (Hisatsune *et al.*, 2007) receptors in post-receptor signalling of taste receptors.

Although predominantly associated with the oral cavity, taste receptors are also located elsewhere, including further down the gastrointestinal system, in the lungs and in the brain.

Sweet/Umami: T1R3 acts as an obligate partner in T1R1/T1R3 and T1R2/T1R3 heterodimers, which sense umami or sweet, respectively. T1R1/T1R3 heterodimers respond to L-glutamate and may be positively allosterically modulated by 5'-nucleoside monophosphates, such as GMP (Li *et al.*, 2002). T1R2/T1R3 heterodimers respond to sugars, such as sucrose, and artificial sweeteners, such as saccharin (Nelson *et al.*, 2001).

| Nomenclature | HGNC nomenclature | Ensembl ID      | Other names |
|--------------|-------------------|-----------------|-------------|
| T1R1         | TAS1R1            | ENSG00000173662 | GPR70, TR1  |
| T1R2         | TAS1R2            | ENSG00000179002 | GPR71, TR2  |
| T1R3         | TAS1R3            | ENSG00000169962 | –           |

Bitter: the composition and stoichiometry of bitter taste receptors is not yet established. Bitter receptors appear to separate into two groups, with very restricted ligand specificity or much broader responsiveness. For example, T2R5 responded to cycloheximide, but not 10 other bitter compounds (Chandrashekar *et al.*, 2000), while T2R14 responded to at least eight different bitter tastants, including (-)- $\alpha$ -thujone and picrotoxinin (Behrens *et al.*, 2004).

| Nomenclature | HGNC nomenclature | Ensembl ID      | Other names             |
|--------------|-------------------|-----------------|-------------------------|
| T2R1         | TAS2R1            | ENSG00000169777 | TRB7                    |
| T2R3         | TAS2R3            | ENSG00000127362 | –                       |
| T2R4         | TAS2R4            | ENSG00000127364 | –                       |
| T2R5         | TAS2R5            | ENSG00000127366 | –                       |
| T2R7         | TAS2R7            | ENSG00000121377 | TRB4                    |
| T2R8         | TAS2R8            | ENSG00000121314 | TRB5                    |
| T2R9         | TAS2R9            | ENSG00000121381 | TRB6                    |
| T2R10        | TAS2R10           | ENSG00000121318 | TRB2                    |
| T2R13        | TAS2R13           | ENSG00000212128 | TRB3                    |
| T2R14        | TAS2R14           | ENSG00000212127 | TRB1                    |
| T2R16        | TAS2R16           | ENSG00000128519 | –                       |
| T2R19        | TAS2R19           | ENSG00000212124 | T2R23, TAS2R23, TAS2R48 |
| T2R20        | TAS2R20           | ENSG00000255837 | T2R56, TAS2R49          |
| T2R24        | TAS2R24           | ENSG00000186136 | hT2R55, T2R55, TAS2R55  |

| Nomenclature | HGNC nomenclature | Ensembl ID      | Other names    |
|--------------|-------------------|-----------------|----------------|
| T2R30        | TAS2R30           | ENSG00000256188 | TAS2R47        |
| T2R31        | TAS2R31           | ENSG00000256436 | T2R53, TAS2R44 |
| T2R39        | TAS2R39           | ENSG00000236398 | –              |
| T2R40        | TAS2R40           | ENSG00000221937 | GPR60          |
| T2R51        | TAS2R50           | ENSG00000212126 | –              |
| T2R52        | TAS2R43           | ENSG00000255374 | –              |
| T2R54        | TAS2R46           | ENSG00000226761 | –              |
| T2R59        | TAS2R41           | ENSG00000221855 | –              |
| T2R60        | TAS2R60           | ENSG00000185899 | –              |
| T2R61        | TAS2R38           | ENSG00000257138 | PTC            |

### Further Reading

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# 5-HT (5-Hydroxytryptamine)

5-HT receptors [nomenclature as agreed by NC-IUPHAR Subcommittee on 5-HT receptors (Hoyer *et al.*, 1994) and subsequently revised (Hartig *et al.*, 1996)] are, with the exception of the ionotropic 5-HT<sub>3</sub> class, GPCR where the endogenous agonist is 5-HT. The diversity of metabotropic 5-HT receptors is increased by alternative splicing that produces isoforms of the 5-HT<sub>2A</sub> (non-functional), 5-HT<sub>2C</sub> (non-functional), 5-HT<sub>4</sub>, 5-HT<sub>6</sub> (non-functional) and 5-HT<sub>7</sub> receptors. Unique amongst the GPCRs, RNA editing produces 5-HT<sub>2C</sub> receptor isoforms that differ in function, such as efficiency and specificity of coupling to G<sub>q/11</sub> and also pharmacology (reviewed by Bockaert *et al.*, 2006; Werry *et al.*, 2008). Most 5-HT receptors (except 5-HT<sub>1e</sub> and 5-HT<sub>5a/Sb</sub>) play specific roles mediating functional responses in different tissues (reviewed by Villalón and Centurión, 2007; Ramage and Villalón, 2008).

| Nomenclature               | 5-HT <sub>1A</sub>                                                                                                                                                                                                                                                                           | 5-HT <sub>1B</sub>                                                                                                                                                                                                                                                                                                                                  | 5-HT <sub>1D</sub>                                                                                                                                                                                         | 5-HT <sub>1e</sub>                          |
|----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| Other names                | –                                                                                                                                                                                                                                                                                            | 5-HT <sub>1DB</sub>                                                                                                                                                                                                                                                                                                                                 | 5-HT <sub>1Dα</sub>                                                                                                                                                                                        | –                                           |
| Ensembl ID                 | ENSG00000178394                                                                                                                                                                                                                                                                              | ENSG00000135312                                                                                                                                                                                                                                                                                                                                     | ENSG00000179546                                                                                                                                                                                            | ENSG00000168830                             |
| Principal transduction     | G <sub>i/o</sub>                                                                                                                                                                                                                                                                             | G <sub>i/o</sub>                                                                                                                                                                                                                                                                                                                                    | G <sub>i/o</sub>                                                                                                                                                                                           | G <sub>i/o</sub>                            |
| Selective agonists (pK)    | 8-OH-DPAT (8.4–9.4), U92016A (9.7)<br>F15599 (8.6, Newman-Tancredi <i>et al.</i> , 2009)                                                                                                                                                                                                     | L694247 (9.2), CP94253 (8.7), sumatriptan (6.5–8.1), eliptriptan (8.0)                                                                                                                                                                                                                                                                              | PNU109291 (9.0 – gorilla, Ennis <i>et al.</i> , 1998)<br>sumatriptan (8.0–8.7), eletriptan (8.9), L694247 (9.0, Wurch <i>et al.</i> , 1998)                                                                | BRL-54443 (8.7, Brown <i>et al.</i> , 1998) |
| Selective antagonists (pK) | (±)WAY100635 (7.9–9.2), (S)-UH301 (7.9–8.6), NAD299 (robalzotan, 9.2)                                                                                                                                                                                                                        | SB236057 (8.2, inverse agonist, Middlemiss <i>et al.</i> , 1999), SB224289 (inverse agonist, 8.2–8.6), GR55562 (pK <sub>B</sub> 7.4, Hoyer <i>et al.</i> , 2002)                                                                                                                                                                                    | SB714786 (9.1) BRL15572 (7.9)                                                                                                                                                                              | –                                           |
| Probes (K <sub>D</sub> )   | [ <sup>3</sup> H]WAY100635 (0.3 nM, Khawaja <i>et al.</i> , 1997), [ <sup>3</sup> H]NAD299 (0.16 nM), [ <sup>3</sup> H]8-OH-DPAT (0.4 nM), [ <sup>3</sup> H]F13640 (1.4 nM, Heusler <i>et al.</i> , 2010)<br>[ <sup>11</sup> C]WAY100635 (PET ligand), p-[ <sup>18</sup> F]MPPF (PET ligand) | [N-methyl- <sup>3</sup> H <sub>3</sub> ]-AZ10419369 (0.37 nM, Maier <i>et al.</i> , 2009)<br>[ <sup>3</sup> H]alniditan (2.0–2.4 nM)<br>[ <sup>3</sup> H]eletriptan (3 nM), [ <sup>3</sup> H]sumatriptan (11 nM)<br>[ <sup>125</sup> I]GTI, [ <sup>3</sup> H]GR125743 (2.6 nM, Xie <i>et al.</i> , 1999), [ <sup>11</sup> C]AZ10419369 (PET ligand) | [ <sup>3</sup> H]alniditan (1.2–1.4 nM)<br>[ <sup>3</sup> H]eletriptan (0.9 nM), [ <sup>3</sup> H]sumatriptan (7 nM), [ <sup>125</sup> I]GTI, [ <sup>3</sup> H]GR125743 (2.8 nM, Xie <i>et al.</i> , 1999) | [ <sup>3</sup> H]5-HT (6 nM)                |

| Nomenclature               | 5-HT <sub>1F</sub>                                                                                                                                                                              | 5-HT <sub>2A</sub>                                                                                                                                                                                                | 5-HT <sub>2B</sub>                                                                                                                              | 5-HT <sub>2C</sub>                                                                                                                 |
|----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| Other names                | 5-HT <sub>1EB</sub> , 5-HT <sub>6</sub>                                                                                                                                                         | D, 5-HT <sub>2</sub>                                                                                                                                                                                              | 5-HT <sub>2F</sub>                                                                                                                              | 5-HT <sub>1C</sub>                                                                                                                 |
| Ensembl ID                 | ENSG00000179097                                                                                                                                                                                 | ENSG00000102468                                                                                                                                                                                                   | ENSG00000135914                                                                                                                                 | ENSG00000147246                                                                                                                    |
| Principal transduction     | G <sub>i/o</sub>                                                                                                                                                                                | G <sub>q/11</sub>                                                                                                                                                                                                 | G <sub>q/11</sub>                                                                                                                               | G <sub>q/11</sub>                                                                                                                  |
| Selective agonists (pK)    | LY344864 (8.2, Phebus <i>et al.</i> , 1997) LY334370 (8.7), LY573144 (8.7, Nelson <i>et al.</i> , 2010), BRL-54443 (8.9, Brown <i>et al.</i> , 1993), eliptriptan (8.0), sumatriptan (7. 2–7.9) | DOI (7.4–9.2)                                                                                                                                                                                                     | DOI (7.6–7.7), Ro600175 (8.3), BW723C86 (7.3–8.6)                                                                                               | DOI (7.2–8.6), Ro600175 (7.7–8.2)<br>WAY163909 (8.0, Dunlop <i>et al.</i> , 2005)<br>Locaserin (7.8, Thomsen <i>et al.</i> , 2008) |
| Selective antagonists (pK) | –                                                                                                                                                                                               | ketanserin (8.1–9.7), MDL100907 (9.4)                                                                                                                                                                             | RS127445 (9.0), EGIS-7625 (9.0)                                                                                                                 | SB242084 (8.2 – 9.0), RS102221 (8.3–8.4)<br>FR260010 (8.9, Harada <i>et al.</i> , 2006)                                            |
| Probes (K <sub>D</sub> )   | [ <sup>3</sup> H]LY334370 (0.5 nM), [ <sup>125</sup> I]LSD                                                                                                                                      | [ <sup>3</sup> H]ketanserin (0.2–1.3 nM), [ <sup>3</sup> H]RP62203 (fananserin, 0.13 nM – rat, Malgouris <i>et al.</i> , 1993), [ <sup>11</sup> C]M100907 (PET ligand), [ <sup>18</sup> F]altanserin (PET ligand) | [ <sup>3</sup> H]5-HT (8 nM – rat)<br>[ <sup>3</sup> H]mesulergine (5–10 nM), [ <sup>3</sup> H]LSD (5–10 nM), [ <sup>125</sup> I]DOI (20–25 nM) | [ <sup>3</sup> H]mesulergine (0.5–2.2 nM), [ <sup>125</sup> I]DOI (6–25 nM), [ <sup>3</sup> H]LSD                                  |

| Nomenclature                             | 5-HT <sub>4</sub>                                                                                                                                                                                                                       | 5-HT <sub>5A</sub>                                              | 5-HT <sub>5B</sub>                            | 5-HT <sub>6</sub>                                                                                                                                                                    |
|------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Other names                              | –                                                                                                                                                                                                                                       | 5-HT <sub>5α</sub>                                              | –                                             | –                                                                                                                                                                                    |
| Ensembl ID                               | ENSG00000164270                                                                                                                                                                                                                         | ENSG00000157219                                                 | ENSMUSG00000050534                            | ENSG00000158748                                                                                                                                                                      |
| Principal transduction                   | G <sub>s</sub>                                                                                                                                                                                                                          | G <sub>i</sub> /G <sub>o</sub> ?                                | None identified                               | G <sub>s</sub>                                                                                                                                                                       |
| Selective agonists (pK <sub>i</sub> )    | BIMU8 (7.3), ML10302 (7.9–9.0), RS67506 (8.8–guinea-pig, Eglen <i>et al.</i> , 1995)                                                                                                                                                    | –                                                               | –                                             | WAY181187 (8.7, Schechter <i>et al.</i> , 2008)<br>E6801 (partial agonist, 8.7, Holenz <i>et al.</i> , 2005)                                                                         |
| Selective antagonists (pK <sub>i</sub> ) | GR113808 (9.3–10.3), SB204070 (9.8 – 10.4), RS100235 (8.7–12.2)                                                                                                                                                                         | SB699551 (8.2)                                                  | –                                             | SB399886 (9.4, Hirst <i>et al.</i> , 2006)<br>SB271046 (8.9), SB357134 (8.5, Bromidge <i>et al.</i> , 2001), Ro630563 (7.9–8.4)                                                      |
| Probes (K <sub>D</sub> )                 | [ <sup>3</sup> H]GR113808 (50 – 200 pM), [ <sup>125</sup> I]SB207710 (86 pM – piglet, Brown <i>et al.</i> , 1993), [ <sup>3</sup> H]RS57639 (0.25 nM–guinea-pig, Bonhaus <i>et al.</i> , 1997) [ <sup>11</sup> C] SB207145 (PET ligand) | [ <sup>3</sup> H]5-CT (2.5 nM), [ <sup>125</sup> I]LSD (0.2 nM) | [ <sup>3</sup> H]5-CT, [ <sup>125</sup> I]LSD | [ <sup>125</sup> I]SB258585 (1.0 nM, Hirst <i>et al.</i> , 2000), [ <sup>3</sup> H]Ro630563 (5 nM, Boess <i>et al.</i> , 1998), [ <sup>3</sup> H]5-CT, [ <sup>125</sup> I]LSD (2 nM) |

|                                          |                                                                                                                                                                                        |
|------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature                             | 5-HT <sub>7</sub>                                                                                                                                                                      |
| Other names                              | 5-HT <sub>1</sub> -like, 5-HT <sub>1V</sub> , orphan                                                                                                                                   |
| Ensembl ID                               | ENSG00000148680                                                                                                                                                                        |
| Principal transduction                   | G <sub>s</sub>                                                                                                                                                                         |
| Selective agonists (pK <sub>i</sub> )    | E55888 (8.6, Brenchat <i>et al.</i> , 2009)                                                                                                                                            |
| Selective antagonists (pK <sub>i</sub> ) | SB656104 (8.7, Forbes <i>et al.</i> , 2002), SB269970 (8.6–8.9 Thomas <i>et al.</i> , 2000), SB258719 (7.5)                                                                            |
| Radioligands (K <sub>D</sub> )           | [ <sup>3</sup> H]SB269970 (1.2 nM, Thomas <i>et al.</i> 2000), [ <sup>3</sup> H]5-CT (0.4 nM, Thomas <i>et al.</i> , 2000) [ <sup>3</sup> H]LSD (3 nM), [ <sup>3</sup> H]5-HT (1–8 nM) |

Tabulated pK<sub>i</sub> and K<sub>D</sub> values refer to binding to human 5-HT receptors unless indicated otherwise. Unreferenced values are extracted from the NC-IUPHAR database ([www.iuphar-db.org](http://www.iuphar-db.org)). The nomenclature of 5-HT<sub>1B</sub>/5-HT<sub>1D</sub> receptors has been revised (Hartig *et al.*, 1996). Only the non-rodent form of the receptor was previously called 5-HT<sub>1DB</sub>. The human 5-HT<sub>1B</sub> receptor (tabulated) displays a different pharmacology to the rodent forms of the receptor due to Thr335 of the human sequence being replaced by Asn in rodent receptors. NAS181 is a selective antagonist of the rodent 5-HT<sub>1B</sub> receptor. Fananserin and ketanserin bind with high affinity to dopamine D4 and histamine H<sub>1</sub> receptors respectively, and ketanserin is a potent α1 adrenoceptor antagonist, in addition to blocking 5-HT<sub>2A</sub> receptors. The human 5-HT<sub>5A</sub> receptor has been claimed to couple to several signal transduction pathways when stably expressed in C6 glioma cells (Noda *et al.*, 2003). The human orthologue of the mouse 5-HT<sub>5B</sub> receptor is non-functional due to interruption of the gene by stop codons. The 5-HT<sub>1C</sub> receptor appears not to have been cloned from mouse, or rat, impeding definition of its function. In addition to the receptors listed in the table, an 'orphan' receptor, unofficially termed 5-HT<sub>1P</sub>, has been described (Gershon, 1999).

**Abbreviations:** 5-CT, 5-carboxamidotryptamine; 8-OH-DPAT, 8-hydroxy-2-(di-*n*-propylamino)tetralin; [**N-methyl-<sup>3</sup>H]**AZ10419369**, 5-methyl-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; **BIMU8**, (endo-*N*-8-methyl-8-azabicyclo [3.2.1]oct-3-yl)-2,3-dihydro-3-isopropyl-2-oxo-1*H*-benzimidazol-1-carboxamide hydrochloride; **BRL15572**, 3-[4-(3-chlorophenyl) piperazin-1-yl]-1,1-diphenyl-2-propanol; **BRL54443**, 5-hydroxy-3-(1-methylpiperidin-4-yl)-1*H*-indole; **BW723C86**, 1-[5-(2-thienylmethoxy)-1*H*-3-indolyl]propan-2-amine hydrochloride; **CP94253**, 3-(1,2,5,6-tetrahydro-4-pyridyl)-5-propoxypyrrolo[3, 2-*b*] pyridine; **E6801**, 6-chloro-*N*-(3-(2-dimethylamino)ethyl)-1*H*-indol-5-yl)imidazo[2,1-*b*]thiazole-5-sulfonamide; **E55888**, dimethyl-2-[3-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-phenyl]-ethyl-amine; **EGIS-7625**, 1-benzyl-4-[(2-nitro-4-methyl-5-amino)-phenyl]-piperazine; **F13640**, 3-chloro-4-fluoro-phenyl-[4-fluoro-4-[(5-methyl-piperidin-2-ylmethyl)-amino]-methyl]piperidin-1-yl]-methanone ; **F15599**, 3-chloro-4-fluorophenyl-(4-fluoro-4-[(5-methylpyrimidin-2-ylmethyl)-amino]-methyl)-piperidin-1-yl)-methanone; **FR260010**, (*N*-[3-(4-methyl-1*H*-imidazol-1-yl)phenyl]-5,6-dihydrobenzo[h]quinazolin-4-amine; **GR55562**, 3-[3-(dimethylamino)propyl]-4-hydroxy-*N*-[4-(4-pyridinyl)phenyl]benzamide; **GR113808**, [1-2[(methylsulphonyl)amino]ethyl]-4-piperidinyl)methyl-1-methyl-1*H*-indole-3-carboxylate; **GR125743**, *n*-[4-methoxy-3-(4-methyl-1-piperizinyl)phenyl]-3-methyl-4-(4-pyridinyl)benzamide; **GTI**, 5-hydroxytryptamine-5-*O*-carboxymethylglycyltyrosinamide; **L694247**, 2-[5-[3-(4-methylsulphonylamino)benzyl-1,2,4-oxadiazol-5-yl]-1*H*-indol-3-yl] ethanamine; **LY334370**, 5-(4-fluorobenzoyl)amino-3-(1-methylpiperidin-4-yl)-1*H*-indole fumarate; **LY344864**, *N*-[(6*R*)-6-dimethylamino-6,7,8,9-tetrahydro-5*H*-carbazol-3-yl]-4-fluorobenzamide; **LY573144**, 2,4,6-trifluoro-*N*-[6-[(1-methylpiperidin-4-yl)carbonyl]pyridin-2-yl]benzamide; **MDL100907**, (+/-)-2,3-dimethoxyphenyl-1-[2-(4-piperidine)-methanol]; **NAD299**, (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-[6-3*H*]-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide; **NAS181**, (*R*)-(+)-2-[[[3-(morpholinomethyl)-2*H*-chromen-8-yl]oxy]methyl] morpholine methane sulfonate; **p-[<sup>18</sup>F]MPPF** 4-(2'-methoxyphenyl)-1-[2'-(*N*-2'-pyridinyl)-p-fluorobenzamido]-ethyl piperazine; **PNU109291**, (*S*)-3,4-dihydro-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-methyl-1*H*-2-benzopyran-6-carboximide; **RP62203**, 2-[3-(4-(4-fluorophenyl)-piperazinyl)propyl]naphto[1,8-*cd*]isothiazole-1,1-dioxide; **Ro600175**, (*S*)-2-(6-chloro-5-fluorindol-1-yl)-1-methylethylamine; **Ro630563**, 4-amino-*N*-[2,6-bis(methylamino)pyridin-4-yl]benzenesulphonamide; **RS57639**, 4-amino-5-chloro-2-methoxy benzoic acid 1-(3-[2,3-dihydrobenzo[1,4]dioxin-6-yl]-propyl)-piperidin-4-yl methyl ester; **RS67506**, 1-(4-amino-5-chloro-2-methoxyphenyl)-3-[1-(2-methyl sulphonylamino)ethyl-4-piperidinyl]-1-propanone hydrochloride; **RS100235**, 1-(8-amino-7-chloro-1,4-benzodioxan-5-yl)-5-((3-(3,4-dimethoxyphenyl)prop-1-yl)piperidin-4-yl)propan-1-one; **RS102221**, 8-[5-(5-amino 2,4-dimethoxyphenyl) 5-oxopentyl]-1,3,8-triazaspiro**

[4,5]decane-2,4-dione; **RS127445**, (2-amino-4-(4-fluoronaphthyl-1-yl)-6-isopropylpyrimidine); **SB204070**, 1-butyl-4-piperidinylmethyl-8-amino-7-chloro-1,4-benzodioxan-5-carboxylate; **SB207710**, 1-butyl-4-piperidinylmethyl-8-amino-7-iodo-1,4-benzodioxan-5-carboxylate; **SB224289**, 1'-methyl-5[[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]carbonyl-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine]oxalate; **SB236057**, 1'-ethyl-5-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-f]indol-3,4'-piperidine]; **SB242084**, 6-chloro-5-methyl-1-[2-(2-methylpyridyl-3-oxy)-pyrid-5-yl carbamoyl] indoline; **SB258585**, 4-iodo-N-[4-methoxy-3-(4-methylpiperazin-1-yl)-phenyl]-benzenesulphonamide; **SB258719**, (R)-3,N-dimethyl-N-[1-methyl-3-(4-methylpiperidin-1-yl)propyl]benzene sulphonamide; **SB269970**, (R)-3-(2-(2-(4-methylpiperidin-1-yl)ethyl)pyrrolidine-1-sulphonyl)phenol; **SB271046**, 5-chloro-N-(4-methoxy-3-piperazin-1-yl-phenyl)-3-methyl-2-benzothiophenesulphonamide; **SB357134**, N-(2,5-dibromo-3-fluorophenyl)-4-methoxy-3-piperazin-1-ylbenzenesulphonamide; **SB-399885**, N-[3,5-dichloro-2-(methoxy)phenyl]-4-(methoxy)-3-(1-piperazinyl)benzenesulphonamide; **SB656104**, 6-((R)-2-[2-[4-(4-chloro-phenoxy)-piperidin-1-yl]-ethyl]-pyrrolidine-1-sulphonyl)-1H-indole hydrochloride; **SB699551**, 3-cyclopentyl-N-[2-(dimethylamino)ethyl]-N-[(4'-[(2-phenylethyl)amino]methyl)-4-biphenyl)methyl]propanamide dihydrochloride; **SB714786**, 2-methyl-5-[(2-[4-(8-quinolinylmethyl)-1-piperazinyl]ethyl)oxy]quinoline; **UH301**, 5-fluoro-8-hydroxy-2-(dipropylamino) tetralin; **U92016A**, (+)-R-2-cyano-N,N-dipropyl-8-amino-6,7,8,9-tetrahydro-3H-benz[e]indole; **WAY100635**, N-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-(2-pyridyl)-cyclohexanecarboxamide trichloride, **WAY163909**, (7bR, 10aR)-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta-[b][1,4]diazepino[6,7,1h]indole; **WAY-181187**, 2-[1-(6-chloroimidazo[2,1-b]thiazol-5-ylsulfonyl)-1H-indol-3-yl]ethylamine

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# Acetylcholine (muscarinic)

**Overview:** Muscarinic acetylcholine receptors (nomenclature as agreed by NC-IUPHAR sub-committee on Muscarinic Acetylcholine Receptors, Caulfield and Birdsall, 1998) are GPCR of the Class A, rhodopsin-like family where the endogenous agonist is acetylcholine. In addition to the agents listed in the table, AC-42, its structural analogues AC-260584 and 77-LH-28-1, desmethylozapine, TBPB and LuAE51090 have been described as functionally selective agonists of the M<sub>1</sub> receptor subtype *via* binding in a mode distinct from that utilized by non-selective agonists (Spalding *et al.*, 2002, 2006; Sur *et al.*, 2003; Langmead *et al.*, 2006, 2008; May *et al.*, 2007; Jones *et al.*, 2008; Lebon *et al.*, 2009; Avlani *et al.*, 2010; Sams *et al.*, 2010). There are two pharmacologically characterised allosteric sites on muscarinic receptors, one defined by it binding gallamine, strychnine and brucine, and the other binds KT5720, WIN62,577, WIN51,708 and staurosporine (Lazareno *et al.*, 2000, 2002). There are selective enhancers of acetylcholine binding and action; brucine, BQCA, KT5720, VU0090157, VU0029767 and ML169 (VU0405652) at M<sub>1</sub> receptors, PG135 at M<sub>2</sub> receptors, N-chloromethylbrucine and WIN62,577 at M<sub>3</sub> receptors and thiochrome, LY2033298, VU0152099 and VU0152100 at M<sub>4</sub> receptors, and VU0238429 at M<sub>5</sub> receptors (Birdsall and Lazareno, 2005; Brady *et al.*, 2008; Chan *et al.*, 2008; Shirey *et al.*, 2008; Bridges *et al.*, 2009; Ma *et al.*, 2009; Marlo *et al.*, 2009; Reid *et al.*, 2011). LY2033298 has also been shown to activate the M<sub>4</sub> receptor directly *via* an allosteric site (Nawaratne *et al.*, 2008; 2010; Leach *et al.*, 2010; 2011). The allosteric site for gallamine and strychnine on M<sub>2</sub> receptors can be labelled by [<sup>3</sup>H]dimethyl-W84 (Tränkle *et al.*, 2003). McN-A-343 is a functionally selective partial agonist that appears to interact in a bitopic mode with both the orthosteric and an allosteric site on the M<sub>2</sub> muscarinic receptor (Valant *et al.*, 2008). THR-160209, hybrid 1 and hybrid 2, are multivalent (bitopic) ligands that also achieve selectivity for M<sub>2</sub> receptors by binding both to the orthosteric and a nearby allosteric site (Steinfeld *et al.*, 2007; Antony *et al.*, 2009). VU0255035 is a recently described competitive orthosteric antagonist with selectivity for the M<sub>1</sub> receptor (Sheffler *et al.*, 2009), and LY593093 has recently been described as a selective orthosteric partial agonist of the M<sub>1</sub> receptor (Watt *et al.*, 2011).

| Nomenclature                   | M <sub>1</sub>                                                                                                                                                                                                                                                                             | M <sub>2</sub>                                                                                                                                                                                          | M <sub>3</sub>                                                                                                                                                                                      |
|--------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ensembl ID                     | ENSG00000168539                                                                                                                                                                                                                                                                            | ENSG00000181072                                                                                                                                                                                         | ENSG00000133019                                                                                                                                                                                     |
| Principal transduction         | G <sub>q/11</sub>                                                                                                                                                                                                                                                                          | G <sub>i/o</sub>                                                                                                                                                                                        | G <sub>q/11</sub>                                                                                                                                                                                   |
| Antagonists (pK <sub>i</sub> ) | MT7 (10.9-11.0), 4-DAMP (9.2), triptiramine (8.8), darifenacin (8.3), pirenzepine (6.3-8.3), VU0255035 (7.8), guanylpirenzepine (7.7), AFDX384 (7.3-7.5), MT3 (6.5-7.1), himbacine (6.7-7.1), AFDX116 (6.2)                                                                                | triptiramine (9.6), AFDX384 (8.0-9.0), 4-DAMP (8.3), himbacine (7.9-8.4), darifenacin (7.3-7.6), AFDX116 (6.7-7.3), VU0255035 (6.2), pirenzepine (4.9-6.4), MT3 (<6), guanylpirenzepine (5.6), MT7 (<5) | 4-DAMP (9.3), darifenacin (9.1), AFDX384 (7.2-7.8), triptiramine (7.1-7.4), himbacine (6.9-7.2), pirenzepine (5.6-6.7), guanylpirenzepine (6.5), VU0255035 (6.1), AFDX116 (6.1), MT3 (<6), MT7 (<5) |
| Probes (K <sub>D</sub> )       | [ <sup>3</sup> H]NMS (80-150 pM), [ <sup>3</sup> H]QNB (15-60 pM), [ <sup>3</sup> H]pirenzepine (3-15 nM), ( <i>R,R</i> )-quinuclidinyl-4-[ <sup>18</sup> F]-fluoromethyl-benzilate (PET ligand), [ <sup>11</sup> C]xanomeline (PET ligand), [ <sup>11</sup> C]butylthio-TZTP (PET ligand) | [ <sup>3</sup> H]NMS (200-400 pM), [ <sup>3</sup> H]QNB (20-50 pM), [ <sup>18</sup> F]FP-TZTP (PET ligand),                                                                                             | [ <sup>3</sup> H]NMS (150-250 pM), [ <sup>3</sup> H]QNB (30-90 pM), [ <sup>3</sup> H]darifenacin (300 pM)                                                                                           |

| Nomenclature                   | M <sub>4</sub>                                                                                                                                                                                         | M <sub>5</sub>                                                                                                                                                                                      |
|--------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ensembl ID                     | ENSG00000180720                                                                                                                                                                                        | ENSG00000184984                                                                                                                                                                                     |
| Principal transduction         | G <sub>i/o</sub>                                                                                                                                                                                       | G <sub>q/11</sub>                                                                                                                                                                                   |
| Antagonists (pK <sub>i</sub> ) | 4-DAMP (8.9), MT3 (8.7), AFDX384 (8.0-8.7), AFDX116 (7-8.7), himbacine (7.9-8.2), triptiramine (7.8-8.2), darifenacin (8.1), pirenzepine (5.9-7.6), guanylpirenzepine (6.5), VU0255035 (5.9), MT7 (<5) | 4-DAMP (9.0), darifenacin (8.6), triptiramine (7.3-7.5), guanylpirenzepine (6.8), pirenzepine (6.2-6.9), himbacine (5.4-6.5), AFDX384 (6.3), AFDX116 (5.3-5.6), VU0255035 (5.6), MT3 (<6), MT7 (<5) |
| Probes (K <sub>D</sub> )       | [ <sup>3</sup> H]NMS (50-100 pM), [ <sup>3</sup> H]QNB (20-80 pM)                                                                                                                                      | [ <sup>3</sup> H]NMS (500-700 pM), [ <sup>3</sup> H]QNB (20-60 pM)                                                                                                                                  |

Antagonist data tabulated are pK<sub>i</sub> values determined for human recombinant receptors. MT3 (m4-toxin) and MT7 (m1-toxin1) are toxins contained with the venom of the Eastern green mamba (*Dendroaspis augusticeps*) (see Potter *et al.*, 2004; Servent and Fruchart-Gaillard, 2009).

**Abbreviations:** 77-LH-28-1, 1-[3-(4-butyl-1-piperidinyl)propyl]-3,4-dihydro-2(1H)-quinolinone; AC-42, 4-*n*-butyl-1-[4-(2-methylphenyl)-4-oxo-1-butyl]-piperidine hydrogen chloride; AC-260584, 4-[3-(4-butylpiperidin-1-yl)-propyl]-7-fluoro-4H-benzo[1,4]oxazin-3-one; AFDX116 (otenzepad), 1-[2-[2-(diethylaminomethyl)piperidin-1-yl]acetyl]-5H-pyrido[2,3-*b*][1,4]benzodiazepin-6-one; AFDX384, (±)-5,11-dihydro-11-[(2-[2-(dipropylamino)methyl]-1-piperidinyl)ethyl]amino)carbonyl-6H-pyrido[2,3-*b*](1,4)benzodiazepine-6-one; BQCA, benzyl quinolone carboxylic acid; Butylthio-TZTP, butylthio-thiadiazolyltetrahydro-1-methyl-pyridine; Dimethyl-W84, N,N'-bis[3-(1,3-dihydro-1,3-dioxo-4-methyl-2H-isoindol-2-yl)propyl]-N,N,N',N'-tetramethyl-1,6-hexanediaminium diiodide; FP-TZTP, [3-(3-(3-Fluoropropyl)thio)-1,2,5-thiadiazol-4-yl]-1,2,5,6-tetrahydro-1-methylpyridine; 4-DAMP, 4-diphenylacetoxo-N-methylpiperidine methiodide; Hybrid 1, 2-[3-[1-(6-[1,1-dimethyl-1-[4-(isoxazol-3-yloxy)but-2-ynyl]-ammonium]hexyl)-1,1 dimethylammonio]propyl]isoindoline-1,3-dione dibromide; Hybrid 2, 2-[3-[1-(6-[1,1-dimethyl-1-[4-(isoxazol-3-yloxy)but-2-ynyl]-ammonium]hexyl)-1,1 dimethylammonio]-2,2-dimethylpropyl]-benzo[*de*]isoquinoline-1,3-dione dibromide; KT5720, (9S,10S,12R)-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-9,12-epoxy-1H-diindolo[1,2,3-*fg*:3',2',1'-*kl*]pyrrolo[3,4-*ij*][1,6]benzodiazocine-10-carboxylic acid hexyl ester; LuAE51090, N-[1-[3-(3-oxo-2,3-dihydrobenzo[1,4]oxazin-4-yl)propyl]piperidin-4-yl]-2-phenylacetamide; LY2033298, 3-amino-5-chloro-6-methoxy-4-methyl-thieno(2,3-*b*)pyridine-2-carboxylic acid cyclopropylamide; LY593093, N-[(1R,2R)-6-((1E)-1-[4-(4-fluorobenzyl)(methyl)amino]ethylidene)amino]-2-hydroxy-2,3-dihydro-1H-inden-1-yl]biphenyl-4-carboxamide; McN-A-343, 4-(3-chlorophenyl) carbamoyloxy-2-butynyltrimethyl ammonium chloride; ML169 (or VU0405652), 2-((1-(5-bromo-2-fluorobenzyl)-1H-indol-3-yl)sulfonyl-N-(5-methylisoxazol-3-yl)acetamide; NMS, N-methylscopolamine; PG135, (3aS,12R,12aS,12bR)-2-amino-2,3,3a,4,11,12a,12b-octahydro-10-hydroxyisoquinolo[2,1,8-*lm*]carbazol-5(1H)-one hydrochloride; QNB, 3-quinuclidinylbenzilate; TBPB, 1-(1'-2-methylbenzyl)-1,4'-bipiperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one; THR-160209, 4-[N-[7-(3-(S)-(1-carbamoyl-1,1-diphenylmethyl)

pyrrolidin-1-yl]hept-1-yl]-N-(n-propyl)amino]-1-(2,6-dimethoxy-benzyl)piperidine; **VU0029767**, (E)-2-(4-ethoxyphenylamino)-N'-((2-hydroxynaphthalen-1-yl)methylene)acetohydrazide; **VU0090157**, cyclopentyl 1,6-dimethyl-4-(6-nitrobenzo[d][1,3]-dioxol-5-yl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate; **VU0152099**, 3-amino-N-(benzo[d][1,3]dioxol-5-ylmethyl)-4,6-dimethylthieno[2,3-b]pyridine carboxamide; **VU0152100**, 3-amino-N-(4-methoxybenzyl)-4,6-dimethylthieno[2,3-b]pyridine carboxamide; **VU0238429**, structure not available; **VU0255035**, N-(3-oxo-3-(4-(pyridine-4-yl)piperazin-1-yl)propyl)-benzo[c][1,2,5]thiadiazole-4 sulfonamide; **WIN51,708**, 17- $\beta$ -hydroxy-17- $\alpha$ -ethynyl-5- $\alpha$ -androstano[3,2-b]pyrimido[1,2-a]benzimidazole; **WIN62,577**, 17- $\beta$ -hydroxy-17- $\alpha$ -ethynyl- $\Delta^4$ -androstano[3,2-b]pyrimido[1,2-a]benzimidazole

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# Adenosine

**Overview:** Adenosine receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Adenosine Receptors; Fredholm *et al.*, 2011) are activated by the endogenous ligand adenosine (potentially inosine also at A<sub>3</sub> receptors). NECA is a non-selective agonist, while XAC and CGS15943 display submicromolar affinity for antagonism of all four adenosine receptors (Klotz *et al.*, 1998; Ongini *et al.*, 1999). Crystal structures for the antagonist-bound and agonist-bound A<sub>2A</sub> adenosine receptors have been described (Jaakola *et al.*, 2008; Xu *et al.*, 2011).

| Nomenclature           | A <sub>1</sub>                                                                                    | A <sub>2A</sub>                                                                  | A <sub>2B</sub>                                                                          | A <sub>3</sub>                                                                                        |
|------------------------|---------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Ensembl ID             | ENSG00000163485                                                                                   | ENSG00000128271                                                                  | ENSG00000170425                                                                          | ENSG00000121933                                                                                       |
| Principal transduction | G <sub>i/o</sub>                                                                                  | G <sub>s</sub>                                                                   | G <sub>s</sub>                                                                           | G <sub>i/o</sub>                                                                                      |
| Selective agonists     | CPA, CCPA, S-ENBA, GR79236                                                                        | CGS21680, HENECA, ATL-146e (Peirce <i>et al.</i> , 2001)                         | Bay60-6583 (Eckle <i>et al.</i> , 2007)                                                  | CI-IB-MECA, IB-MECA                                                                                   |
| Selective antagonists  | PSB36 (9.8, Abo-Salem <i>et al.</i> , 2004), DPCPX (8.5), SLV320 (9.0, Kalk <i>et al.</i> , 2007) | SCH442416 (10.3, Todde <i>et al.</i> , 2000), ZM241385 (9.0), SCH58261 (7.9–9.5) | PSB603 (9.3, Borrmann <i>et al.</i> , 2009), MRS1754 (8.7), MRS1706 (8.4), PSB1115 (7.7) | MRS1220 (8.8), VUF5574 (8.4, van Muijlwijk-Koezen <i>et al.</i> , 2000), MRS1523 (7.7), MRS1191 (7.0) |
| Probes                 | [ <sup>3</sup> H]-CCPA, [ <sup>3</sup> H]-DPCPX (0.6–1.2 nM)                                      | [ <sup>3</sup> H]-CGS21680, [ <sup>3</sup> H]-ZM241385 (0.8 nM)                  | [ <sup>3</sup> H]-MRS1754 (1.1 nM)                                                       | [ <sup>125</sup> I]-AB-MECA (0.6 nM)                                                                  |

Adenosine inhibits many intracellular ATP-utilising enzymes, including adenylyl cyclase (P-site). A pseudogene exists for the A<sub>2B</sub> adenosine receptor (ENSG00000182537) with 79% identity to the A<sub>2B</sub> adenosine receptor cDNA coding sequence, but which is unable to encode a functional receptor. DPCPX also exhibits antagonism at A<sub>2B</sub> receptors (pK<sub>i</sub> ca. 7, Alexander *et al.*, 1996; Klotz *et al.*, 1998). HENECA also shows activity at A<sub>3</sub> receptors (Varani *et al.*, 1998). Antagonists at A<sub>3</sub> receptors exhibit marked species differences, such that only MRS1523 and MRS1191 are selective at the rat A<sub>3</sub> receptor. In the absence of other adenosine receptors, [<sup>3</sup>H]-DPCPX and [<sup>3</sup>H]-ZM241385 can also be used to label A<sub>2B</sub> receptors (K<sub>D</sub> ca. 30 and 60 nM, respectively). [<sup>125</sup>I]-AB-MECA also binds to A<sub>1</sub> receptors (Klotz *et al.*, 1998). [<sup>3</sup>H]-CGS21680 is relatively selective for A<sub>2A</sub> receptors, but may also bind to other sites in cerebral cortex (Johansson and Fredholm, 1995; Cunha *et al.*, 1996). [<sup>3</sup>H]-NECA binds to other non-receptor elements, which also recognise adenosine (e.g. Lorenzen *et al.*, 1996). XAC-BY630 has been described as a fluorescent antagonist for labelling A<sub>1</sub> adenosine receptors in living cells, although activity at other adenosine receptors was not examined (Briddon *et al.*, 2004).

**Abbreviations:** AB-MECA, N<sup>6</sup>-(4-aminobenzyl)-adenosine-5'-N-methyluronamide; ATL-146e, 4-[3-[6-amino-9-(5-ethylcarbamoyl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-9H-purin-2-yl]-prop-2-ynyl]-cyclohexanecarboxylic acid methyl ester; Bay 60-6583, 2-(6-amino-3,5-dicyano-4-(4-cyclopropylmethoxy)phenyl) pyridin-2-ylthioacetamide; CCPA, 2-chloro-N<sup>6</sup>-cyclopentyladenosine; CGS15943, 5-amino-9-chloro-2-(2-furyl)1,2,4-triazolo[1,5-c]quinazoline; CGS21680, 2-(4-[2-carboxyethyl]-phenethylamino)adenosine-5'-N-ethyluronamide; CI-IB-MECA, 2-chloro-N<sup>6</sup>-(3-iodobenzyl)adenosine-5'-N-methyluronamide; CPA, N<sup>6</sup>-cyclopentyladenosine; DPCPX, 8-cyclopentyl-1,3-dipropylxanthine; GR79236, N-[(1s,2s)-2-hydroxycyclopentyl adenosine; HENECA, 2-(1-(E)-hexenyl)adenosine-5'-N-ethyluronamide; MRS1191, 1,4-dihydro-2-methyl-6-phenyl-4-(phenylethynyl)-3,5-pyridinedicarboxylic acid, 3-ethyl 5-(phenylmethyl) ester; MRS1220, 9-chloro-2-(2-furyl)5-phenylacetamino[1,2,4]triazolo[1,5c]quinazoline; MRS1523, 2,3-ethyl-4,5-dipropyl-6-phenylpyridine-3-thiocarboxylate-5-carboxylate; MRS1706, N-(4-acetylphenyl)-2-(4-[2,3,6,7-tetrahydro-2,6-dioxo-1,3-dipropyl-1H-purin-8-yl]phenoxy)acetamide; MRS1754, 8-(4-[[4-cyanophenyl]carbamoylmethyl]oxy]phenyl)-1,3-di(n-propyl)xanthine; NECA, adenosine-5'-N-ethyluronamide; PSB1115, 4-[2,3,6,7-tetrahydro-2,6-dioxo-1-propyl-1H-purin-8-yl]benzenesulphonic acid; PSB36, 1-butyl-8-(3-noradamantanyl)-3-(3-hydroxypropyl)xanthine; PSB603, 8-[4-[4-(4-chlorophenyl)piperazine-1-sulfonyl]phenyl]-1-propylxanthine; S-ENBA, (2S)-N<sup>6</sup>-(2-endonorbanyl)adenosine; SCH442416, 2-(2-furanyl)-7-[3-(4-methoxyphenyl)propyl]-7H-pyrazolo [4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-5-amine; SCH58261, 5-amino-2-(2-furyl)-7-phenylethyl-pyrazolo[4,3-e]-1,2,4-triazolo[1,5c]pyrimidine; SLV320, trans-4-[(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]cyclohexanol; VUF5574, N-(2-methoxyphenyl)-N-(2-[3-pyridyl]quinazolin-4-yl)urea; XAC, 8-(4-[[[2-aminoethyl]amino]carbonyl]methyl]oxy]phenyl)-1,3-dipropylxanthine; also known as xanthine amine congener; XAC-BY630, N-(2-aminoethyl)-2-[4-(2,6-dioxo-1,3-dipropyl-7H-purin-8-yl)phenoxy]acetamide; ZM241385, 4-(2-[7-amino-2-(2-furyl)]{1,2,4}triazolo[2,3-a]{1,3,5}triazin-5-yl amino)ethyl)phenol

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# Adrenoceptors, $\alpha_1$

**Overview:**  $\alpha_1$ -Adrenoceptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Adrenoceptors, Bylund *et al.*, 1994) are GPCR activated by the endogenous agonists adrenaline and noradrenaline with equal potency. Phenylephrine, methoxamine and cirazoline are agonists selective for  $\alpha_1$ -adrenoceptors relative to  $\alpha_2$ -adrenoceptors, while prazosin (8.5–10.5) and corynanthine (6.5–7.5) are antagonists considered selective for  $\alpha_1$ -adrenoceptors relative to  $\alpha_2$ -adrenoceptors. [ $^3$ H]-Prazosin (0.25 nM) and [ $^{125}$ I]-HEAT (0.1 nM; also known as BE2254) are relatively selective radioligands. Numerous splice variants of the  $\alpha_1$ -adrenoceptors exist, some of which may display a different spectrum of signalling properties. One polymorphism of the  $\alpha_{1A}$ -adrenoceptor has been described but is not associated with disease.

| Nomenclature           | $\alpha_{1A}$                                                              | $\alpha_{1B}$     | $\alpha_{1D}$                     |
|------------------------|----------------------------------------------------------------------------|-------------------|-----------------------------------|
| Other names            | $\alpha_{1a}$ , $\alpha_{1c}$                                              | $\alpha_{1b}$     | $\alpha_{1A/D}$ , $\alpha_{1a/d}$ |
| Ensembl ID             | ENSG00000120907                                                            | ENSG00000170214   | ENSG00000171873                   |
| Principal transduction | G <sub>q/11</sub>                                                          | G <sub>q/11</sub> | G <sub>q/11</sub>                 |
| Selective agonists     | A61603, dabuzalgron (Blue <i>et al.</i> , 2004)                            | –                 | –                                 |
| Selective antagonists  | Tamsulosin (10.5), silodosin (10.4), (+)niguldipine (10.0), SNAP5089 (9.7) | –                 | BMY7378 (8.4)                     |

The clone originally called the  $\alpha_{1C}$ -adrenoceptor corresponds to the pharmacologically defined  $\alpha_{1A}$ -adrenoceptor (see Hieble *et al.*, 1995). Some tissues possess  $\alpha_{1A}$ -adrenoceptors that display relatively low affinity in functional and binding assays for prazosin ( $pK_i < 9$ ) that might represent different receptor states (termed  $\alpha_{1L}$ -adrenoceptors, Ford *et al.*, 1997; Morishima *et al.*, 2007).  $\alpha_{1A}$ -Adrenoceptor C-terminal splice variants form homo and heterodimers, but fail to generate a functional  $\alpha_{1L}$ -adrenoceptor (Ramsay *et al.*, 2004). Recent studies suggest that the  $\alpha_{1L}$ -adrenoceptor phenotype may result from the interaction of  $\alpha_{1A}$ -adrenoceptors with cysteine-rich epidermal growth factor-like domain 1 $\alpha$  (CRELD1 $\alpha$ ) (Nishimune *et al.*, 2010).  $\alpha_{1D}$ -Adrenoceptors form heterodimers with  $\alpha_{1B}$ - or  $\beta_2$ -adrenoceptors that show increased cell-surface expression (Uberti *et al.*, 2005). Heterodimers formed between  $\alpha_{1D}$ - and  $\alpha_{1B}$ -adrenoceptors have distinct functional properties (Hague *et al.*, 2004).  $\alpha_{1D}$ -Adrenoceptors are mainly located intracellularly. (+)Niguldipine also has high affinity for L-type Ca<sup>2+</sup> channels.

Signalling is predominantly via G<sub>q/11</sub> but  $\alpha_1$ -adrenoceptors also couple to G<sub>i/o</sub>, G<sub>s</sub>, and G<sub>12/13</sub>. Several ligands activating  $\alpha_{1A}$ -adrenoceptors display ligand directed signalling bias. For example, oxymetazoline is a full agonist for extracellular acidification rate (ECAR) and a partial agonist for Ca<sup>2+</sup> release but does not stimulate cAMP production. Phenylephrine is biased toward ECAR versus Ca<sup>2+</sup> release or cAMP accumulation but not between Ca<sup>2+</sup> release and cAMP accumulation (Evans *et al.*, 2011). There are also differences between subtypes in coupling efficiency to different pathways – e.g. coupling efficiency to Ca<sup>2+</sup> signalling is  $\alpha_{1A} > \alpha_{1B} > \alpha_{1D}$  but for MAP kinase signalling is  $\alpha_{1D} > \alpha_{1A} > \alpha_{1B}$ . The subtypes also seem to show differences in regulation.

**Abbreviations:** A61603, N-(5-[4,5-dihydro-1H-imidazol-2-yl]-2-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)methanesulfonamide hydrobromide; BMY7378, 8-(2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl)-8-azaspiro[4,5]decane-7,9-dione dihydrochloride; HEAT, 2- $\beta$ -4-hydroxy-3-iodophenylethylaminomethyltetralone; RS17053, N-[2-(2-cyclopropylmethoxyphenoxy)ethyl]-5-chloro- $\alpha,\alpha$ -dimethyl-1H-indole-3-ethanamide; silodosin, (-)-(R)-1-(3-hydroxypropyl)-5-(2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethylamino)propyl)indoline-7-carboxamide, also known as KMD3213; SNAP5089, 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate-N-[3-(4,4-diphenylpiperidin-1-yl)propyl]amide methyl ester

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# Adrenoceptors, $\alpha_2$

**Overview:**  $\alpha_2$ -Adrenoceptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Adrenoceptors; Bylund *et al.*, 1994) are GPCR activated by endogenous agonists with a relative potency of adrenaline>noradrenaline. UK14304 (brimonidine) and BHT920 are agonists selective for  $\alpha_2$ -adrenoceptors relative to  $\alpha_1$ -adrenoceptors. Rauwolscine (9.0) and yohimbine (9.0) are antagonists selective for  $\alpha_2$ -adrenoceptors relative to  $\alpha_1$ -adrenoceptors. [ $^3$ H]-rauwolscine (1 nM), [ $^3$ H]-UK14304 (5 nM) and [ $^3$ H]-RX821002 (0.5 nM and 0.1 nM at  $\alpha_{2C}$ ) are relatively selective radioligands. There is species variation in the pharmacology of the  $\alpha_{2A}$ -adrenoceptor; for example, yohimbine, rauwolscine and oxymetazoline have an ~20-fold lower affinity for rat, mouse and bovine  $\alpha_{2A}$ -adrenoceptors compared to the human receptor. These  $\alpha_{2A}$  orthologues are sometimes referred to as  $\alpha_{2D}$ -adrenoceptors. Multiple mutations of  $\alpha_2$ -adrenoceptors have been described, some of which are associated with alterations in function. The effects of classical (not subtype selective)  $\alpha_2$ -adrenoceptor agonists such as clonidine, guanabenz and UK14304 (brimonidine) on central baroreflex control (hypotension and bradycardia), hypnotic, analgesic, seizure modulation and platelet aggregation are mediated by  $\alpha_{2A}$ -adrenoceptors. The roles of  $\alpha_{2B}$  and  $\alpha_{2C}$ -adrenoceptors are less clear but the  $\alpha_{2B}$  subtype appears to be involved in neurotransmission in the spinal cord and  $\alpha_{2C}$  in regulating catecholamine release from adrenal chromaffin cells.

| Nomenclature           | $\alpha_{2A}$                              | $\alpha_{2B}$                               | $\alpha_{2C}$                               |
|------------------------|--------------------------------------------|---------------------------------------------|---------------------------------------------|
| Other names            | $\alpha_{2D}$                              | –                                           | –                                           |
| Ensembl ID             | ENSG00000150594                            | ENSG00000222040                             | ENSG00000184160                             |
| Principal transduction | G <sub>i/o</sub>                           | G <sub>i/o</sub>                            | G <sub>i/o</sub>                            |
| Selective agonists     | Oxymetazoline                              | –                                           | –                                           |
| Selective antagonists  | BRL44408 (8.0, Young <i>et al.</i> , 1989) | Imiloxan (7.3, Michel <i>et al.</i> , 1990) | JP1302 (7.8, Sallinen <i>et al.</i> , 2007) |

Oxymetazoline is a reduced efficacy agonist. ARC239 (pK<sub>i</sub> 8.0) and prazosin (pK<sub>i</sub> 7.5) show selectivity for  $\alpha_{2B}$ - and  $\alpha_{2C}$ -adrenoceptors over  $\alpha_{2A}$ -adrenoceptors. Binding sites for imidazolines, distinct from  $\alpha_2$ -adrenoceptors, have been identified and classified as I<sub>1</sub>, I<sub>2</sub> and I<sub>3</sub> sites and catecholamines have a low affinity for these sites. I<sub>1</sub>-imidazoline receptors are involved in central inhibition of sympathetic tone, I<sub>2</sub>-imidazoline receptors are an allosteric binding site on monoamine oxidase B, and I<sub>3</sub>-imidazoline receptors regulate insulin secretion from pancreatic  $\beta$ -cells.

**Abbreviations:** ARC239, 2-(2,4-[O-methoxyphenyl]-piperazin)-1-yl; BHT920, 6-allyl-2-amino-5,6,7,8-tetrahydro-4H-thiazolo-[4,5-d]-azepine; BRL44408, 2-(4,5-dihydro-1H-imidazol-2-ylmethyl)-1-methyl-1,3-dihydroisindole; JP1302, N-(4-[4-methyl-1-piperazinyl]phenyl)-9-acridinamine dihydrochloride; MK912, (2S,12bS)1',3'-dimethylspiro(1,3,4,5',6,6',7,12b-octahydro-2H-benzo[b]furo[2,3-a]quinolizine)-2,4'-pyrimidin-2'-one; RX821002, 2-(2-methoxy-1,4-benzodioxan-2-yl)-2-imidazoline; UK14304, 5-bromo-6-[2-imidazolin-2-ylamino]quinoxaline, also known as brimonidine

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# Adrenoceptors, $\beta$

**Overview:**  $\beta$ -Adrenoceptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Adrenoceptors, see Bylund *et al.*, 1994) are GPCR activated by the endogenous agonists adrenaline and noradrenaline. Isoprenaline is a synthetic agonist selective for  $\beta$ -adrenoceptors relative to  $\alpha_1$ - and  $\alpha_2$ -adrenoceptors, while propranolol ( $pK_i$  8.2–9.2) and cyanopindolol ( $pK_i$  10.0–11.0) are relatively selective antagonists.  $\beta_3$ -Adrenoceptors are relatively resistant to blockade by propranolol ( $pK_i$  5.8–7.0), but can be blocked by high concentrations of bupranolol ( $pK_i$  8.65, Sato *et al.*, 2008). Numerous polymorphisms exist for the  $\beta_1$ - and  $\beta_2$ -adrenoceptors and some of these are associated with alterations in signalling in response to agonists. These polymorphisms are likely to be associated with disease susceptibility and altered responses to drugs. The X-ray crystal structures have recently been described of the agonist bound (Warne *et al.*, 2011) and antagonist bound forms of the  $\beta_1$ - (Warne *et al.*, 2008), agonist-bound (Cherezov *et al.*, 2007) and antagonist-bound forms of the  $\beta_2$ -adrenoceptor (Rosenbaum *et al.*, 2011; Rasmussen *et al.*, 2011a), as well as agonist-bound,  $G_s$  protein-coupled  $\beta_2$ -adrenoceptor (Rasmussen *et al.*, 2011b).

| Nomenclature           | $\beta_1$                                            | $\beta_2$                                                                                      | $\beta_3$                                                            |
|------------------------|------------------------------------------------------|------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| Other names            | –                                                    | –                                                                                              | atypical $\beta$                                                     |
| Ensembl ID             | ENSG00000043591                                      | ENSG00000169252                                                                                | ENSG00000188778                                                      |
| Principal transduction | $G_s$                                                | $G_s$                                                                                          | $G_s$                                                                |
| Rank order of potency  | Noradrenaline>adrenaline                             | Adrenaline> noradrenaline                                                                      | Noradrenaline =adrenaline                                            |
| Selective agonists     | Noradrenaline, xamoterol, RO363, denopamine          | Procaterol, salbutamol, zinterol, salmeterol, formoterol, terbutaline, fenoterol (Baker, 2010) | BRL37344, CL316243, CGP12177A, carazolol, L742791, L755507, SB251023 |
| Selective antagonists  | CGP20712A (8.5–9.3), betaxolol (8.5), atenolol (7.6) | ICI118551 (8.3–9.2)                                                                            | SR59230A (8.8), L748337 (8.4)                                        |
| Probes                 | [ <sup>125</sup> I]-ICYP (20–50 pM)+70 nM ICI118551  | [ <sup>125</sup> I]-ICYP (20–50 pM)+100 nM CGP20712A                                           | [ <sup>125</sup> I]-ICYP (0.5 nM)                                    |

Noradrenaline, xamoterol and RO363 are agonists that show selectivity for  $\beta_1$ - relative to  $\beta_2$ -adrenoceptors. Pharmacological differences exist between human and mouse  $\beta_3$ -adrenoceptors, and the 'rodent selective' agonists BRL37344 and CL316243 have low efficacy at the human  $\beta_3$ -adrenoceptor whereas CGP12177A and L755507 activate human  $\beta_3$ -adrenoceptors (Sato *et al.*, 2008). All  $\beta$ -adrenoceptors couple to  $G_s$  (activating adenylyl cyclase and elevating cyclic AMP levels), but it is also clear that they activate other G proteins such as  $G_i$  and many other signalling pathways, particularly mitogen-activated protein kinases. Many antagonists at  $\beta_1$ - and  $\beta_2$ -adrenoceptors are agonists at  $\beta_3$ -adrenoceptors (CL316243, CGP12177A and carazolol). Many 'antagonists' appear to be able to selectively activate mitogen-activated protein kinase pathways (Baker *et al.*, 2003a; Galandrin and Bouvier, 2006; Galandrin *et al.*, 2008; Sato *et al.*, 2007; Sato *et al.*, 2008; Evans *et al.*, 2010) and display ligand-directed signalling bias. Bupranolol appears to act as a neutral antagonist in most systems so far examined. SR59230A has reasonably high affinity at  $\beta_3$ -adrenoceptors (Manara *et al.*, 1996), but does not discriminate well between the three  $\beta$ -adrenoceptor subtypes (Candelore *et al.*, 1999) and has been reported to have lower affinity for the  $\beta_3$ -adrenoceptor in some circumstances (Kaumann and Molenaar, 1996).

The  $\beta_3$ -adrenoceptor has introns, but splice variants have only been described for the mouse (Evans *et al.*, 1999), where the isoforms display different signalling characteristics (Hutchinson *et al.*, 2002). There are 3  $\beta$ -adrenoceptors in turkey (termed the  $t\beta$ ,  $t\beta 3c$  and  $t\beta 4c$ ) that have a pharmacology that differs from the human  $\beta$ -adrenoceptors (Baker, 2011). The 'putative  $\beta_4$ -adrenoceptor' is not a novel receptor but is likely to represent an alternative site of interaction of CGP12177A and other nonconventional partial agonists at  $\beta_1$ -adrenoceptors, since 'putative  $\beta_4$ -adrenoceptor'-mediated agonist effects of CGP12177A are absent in mice lacking  $\beta_1$ -adrenoceptors (Konkar *et al.*, 2000; Kaumann *et al.*, 2001).

Radioligand binding with [<sup>125</sup>I]-ICYP can be used to define  $\beta_1$ - or  $\beta_2$ -adrenoceptors when conducted in the presence of a 'saturating' concentration of either a  $\beta_1$ - or  $\beta_2$ -adrenoceptor-selective antagonist. [<sup>3</sup>H]-CGP12177 or [<sup>3</sup>H]-dihydroalprenolol can be used in place of [<sup>125</sup>I]-ICYP. Binding of a fluorescent analogue of CGP12177 to  $\beta_2$ -adrenoceptors in living cells has been described (Baker *et al.*, 2003b). [<sup>125</sup>I]-ICYP at higher (nM) concentrations can be used to label  $\beta_3$ -adrenoceptors in systems where there are few if any other  $\beta$ -adrenoceptor subtypes.

**Abbreviations:** BRL37344, sodium 4-(2-[2-hydroxy-3-chlorophenyl]ethylamino)propyl)phenoxyacetate; CGP12177A, (-)-4-(3-tert-butylamino-2-hydroxypropoxy)-benzimidazol-2-one; CGP20712A, 2-hydroxy-5-(2-[[2-(3-chlorophenyl)-2-hydroxyethyl]-amino]propyl)-1,3-benzodioxole-2,2-dicarboxylate; ICYP, iodocyanopindolol; L742791, (S)-N-(4-[2-((3-[4-hydroxyphenoxy]-2-hydroxypropyl)amino)ethyl]phenyl)-4-iodobenzenesulfonamide; L748337, N-[[3-[(2S)-2-hydroxy-3-[[2-[4-[(phenylsulfonyl)amino]phenyl]ethyl]amino]propoxy]phenyl]methyl]-acetamide; RO363, (-)-1-(3,4-dimethoxyphenethylamino)-3-(3,4-dihydroxyphenoxy)-2-propanol)oxalate; SB251023, (4-[1-(2-(S)-hydroxy-3-(4-hydroxyphenoxy)-propylamino]cyclopentylmethyl]phenoxy)methyl]phenylphosphonic acid lithium salt; SR59230A, 3-(2-ethylphenoxy)-1-[(1S)-1,2,3,4-tetrahydronaphth-1-ylamino]-2S-propanol oxalate

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# Anaphylatoxin

**Overview:** anaphylatoxin receptors (provisional nomenclature) are activated by the endogenous ~75 amino-acid anaphylatoxin polypeptides C3a (ENSG00000125730) and C5a (ENSG00000106804), generated upon stimulation of the complement cascade.

|                        |                                                                                         |                                                                                                                                                                                                               |
|------------------------|-----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature           | C3a                                                                                     | C5a                                                                                                                                                                                                           |
| Other names            | AZ3B, HNFAG09                                                                           | CD88                                                                                                                                                                                                          |
| Ensembl ID             | ENSG00000171860                                                                         | ENSG00000134830                                                                                                                                                                                               |
| Principal transduction | G <sub>i/o</sub> , G <sub>z</sub>                                                       | G <sub>i/o</sub> , G <sub>z</sub> , G <sub>16</sub> (Buhl <i>et al.</i> , 1993)                                                                                                                               |
| Rank order of potency  | C3a>C5a (Ames <i>et al.</i> , 1996)                                                     | C5a, C5a des Arg>C3a (Ames <i>et al.</i> , 1996)                                                                                                                                                              |
| Selective agonists     | Trp-Trp-Gly-Lys-Lys-Tyr-Arg-Ala-Ser-Lys-Leu-Gly-Leu-Ala-Arg (Ames <i>et al.</i> , 1997) | Phe-Lys-Pro-Cha-Cha-Phe-Lys-D-Cha-Cha-D-Arg (Kontekatis <i>et al.</i> , 1994), S19 (Yamamoto, 2000)                                                                                                           |
| Selective antagonists  | SB290157 (pIC <sub>50</sub> 7.5, Ames <i>et al.</i> , 2001)                             | NMe-Phe-Lys-Pro-D-Cha-Trp-D-Arg (Kontekatis <i>et al.</i> , 1994), AcPhe-Orn-Pro-D-Cha-Trp-Arg (Wong <i>et al.</i> , 1998), W54011 (8.7, Sumichika <i>et al.</i> , 2002), CHIPS (Postma <i>et al.</i> , 2004) |
| Probes                 | [ <sup>125</sup> I]-C3a                                                                 | [ <sup>125</sup> I]-C5a                                                                                                                                                                                       |

SB290157 has also been reported to have agonist properties (Mathieu *et al.*, 2005). A putative chemoattractant receptor termed C5L2 (also known as GPR77, ENSG00000134830) binds [<sup>125</sup>I]-C5a, with no clear signalling function, but a putative role opposing inflammatory responses (Cain and Monk, 2002; Gao *et al.*, 2005; Gavriluk *et al.*, 2005). Binding to this site may be displaced with the rank order C5a des Arg>C5a (Cain and Monk, 2002; Okinaga *et al.*, 2003), while there is controversy over the ability of C3a and C3a des Arg to compete (Kalant *et al.*, 2003; Okinaga *et al.*, 2003; Honczarenko *et al.*, 2005; Kalant *et al.*, 2005). C5L2 appears to lack G protein signalling and has been termed a decoy receptor (Scola *et al.*, 2009).

**Abbreviations:** BOC-PLPLP, Boc-Phe-Leu-Phe-Leu-Phe; **CHIPS**, chemotaxis inhibitory protein of *Staphylococcus aureus*; **SB290157**, N<sup>2</sup>-([2,2-diphenylethoxy]acetyl)-L-arg; **W54011**, N-([4-dimethylaminophenyl]methyl)-N-(4-isopropylphenyl)-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-carboxamide hydrochloride

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# Angiotensin

**Overview:** The actions of angiotensin II (Ang II) are mediated by AT<sub>1</sub> and AT<sub>2</sub> receptors (nomenclature agreed by the NC-IUPHAR Subcommittee on Angiotensin Receptors; see de Gasparo *et al.*, 2000), which have around 30% sequence similarity. AT<sub>1</sub> receptors are predominantly coupled to G<sub>q/11</sub>, however they are also linked to arrestin recruitment and stimulate G protein independent arrestin signalling (Luttrell and Gesty-Palmer 2010). Most species express a single AT<sub>1</sub> gene, but two related AT<sub>1A</sub> and AT<sub>1B</sub> receptor genes are expressed in rodents. The AT<sub>2</sub> receptor counteracts several of the growth responses initiated by the AT<sub>1</sub> receptors. The AT<sub>2</sub> receptor is much less abundant than the AT<sub>1</sub> receptor in adult tissues and is upregulated in pathological conditions. Endogenous ligands are Ang II and angiotensin III (Ang III), while angiotensin I is weakly active in some systems.

| Nomenclature           | AT <sub>1</sub>                                                                                                                           | AT <sub>2</sub>                                              |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|
| Ensembl ID             | ENSG00000144891                                                                                                                           | ENSG00000180772                                              |
| Principal transduction | G <sub>q/11</sub>                                                                                                                         | G <sub>i</sub> / G <sub>o</sub> , Tyr & Ser/Thr phosphatases |
| Selective agonists     | L162313                                                                                                                                   | [p-NH <sub>2</sub> -Phe <sup>6</sup> ]-Ang II, CGP42112      |
| Selective antagonists  | EXP3174, eprosartan, valsartan, irbesartan, losartan, candesartan                                                                         | PD123319, PD123177                                           |
| Probes                 | [ <sup>3</sup> H]-A81988, [ <sup>3</sup> H]-L158809, [ <sup>3</sup> H]-eprosartan, [ <sup>3</sup> H]-losartan, [ <sup>125</sup> I]-EXP985 | [ <sup>125</sup> I]-CGP42112                                 |

There is also evidence for an AT<sub>4</sub> receptor that specifically binds angiotensin IV and is located in the brain and kidney. An additional putative endogenous ligand for the AT<sub>4</sub> receptor has been described (LVV-hemorphin, a globin decapeptide) (Moeller *et al.*, 1997). The AT<sub>1</sub> and bradykinin B2 receptors have been proposed to form a heterodimeric complex (Abdalla *et al.*, 2000). The antagonist activity of CGP42112 has also been reported (Lokuta *et al.*, 1995). Novel AT<sub>1</sub> receptor antagonists bearing substituted 4-phenylquinoline moieties have recently been designed and synthesized. The best of these compounds bind to AT<sub>1</sub> receptors with nanomolar affinity and are slightly more potent than losartan in functional studies (Cappelli *et al.*, 2004).

**Abbreviations:** **A81988**, 2(*N*-propyl-*N*-[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methylamino)pyridine-3-carboxylate; **candesartan**, 2-ethoxy-3-[[4-[2-(2*H*-tetrazol-5-yl)phenyl]phenyl]methyl]benzimidazole-4-carboxylic acid; **CGP42112A**, nicotinic acid-Tyr-(*N*-benzoylcarbonyl-Arg)-Lys-His-Pro-Ile-OH; **eprosartan**, (E)-α-([2-butyl-1-[(4-carboxyphenyl)methyl]-1*H*-imidazol-5-yl]methylene)-2-thiophenepropanoate; **EXP3174**, *n*-butyl-4-chloro-1-([2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl)imidazole-5-carboxylate; **EXP985**, *N*-(2-[4-hydroxy-3-iodophenyl]ethyl)-4-chloro-2-propyl-1-([2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl)imidazole-5-carboxamide; **irbesartan**, 2-butyl-3-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,3-diazaspiro[4.4]non-1-en-4-one; **L158809**, 5,7-dimethyl-2-ethyl-3-(2-[1*H*-tetrazol-5-yl]biphenyl-4-yl)imidazo[4,5-*b*]pyridine; **L162313**, 5,7-dimethyl-2-ethyl-3-[[4-[2(*n*-butyloxycarbonylsulfonamido)-5-isobutyl-3-thienyl]phenyl]methyl]imidazo[4,5,6]pyridine; **losartan**, 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-([2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl)imidazole, also known as Dup 753; **PD123177**, 1-(4-amino-3-methylphenyl)methyl-3-(diphenylacetyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylate; **PD123319**, (S)-1-(4-[dimethylamino]-3-methylphenyl)methyl-5-(diphenylacetyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylate; **valsartan**, *N*-(1-oxopentyl)-*N*-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-L-valine

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# Apelin

**Overview:** The apelin receptor (APJ, nomenclature as agreed by NC-IUPHAR on apelin receptors, Pitkin *et al.*, 2010) responds to apelin, a 36 amino-acid peptide derived initially from bovine stomach. Apelin-36, apelin-13 and (Pyr<sup>1</sup>)apelin-13 are the predominant endogenous ligands which are cleaved from a 77 amino-acid precursor peptide (ENSG00000171388) by a so far unidentified enzymatic pathway (Tatemoto *et al.*, 1998).

|                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature           | APJ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Other names            | Apelin receptor, angiotensin receptor-like 1                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Ensembl ID             | ENSG00000134817                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Principal transduction | G <sub>i/o</sub>                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Rank order of potency  | [Pyr <sup>1</sup> ]apelin-13 ≥ apelin-13 > apelin-36 (Tatemoto <i>et al.</i> , 1998; Fan <i>et al.</i> , 2003)                                                                                                                                                                                                                                                                                                                                                                           |
| Selective agonists     | [Pyr <sup>1</sup> ]apelin-13, apelin-13, apelin-17, apelin-36                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Probes                 | [ <sup>125</sup> I]-[Pyr <sup>1</sup> ]Apelin-13 (0.3 nM, Katugampola <i>et al.</i> , 2001), [ <sup>125</sup> I]-apelin-13 (Fan <i>et al.</i> , 2003), [ <sup>3</sup> H]-[Pyr <sup>1</sup> ][Met(O) <sup>11</sup> ]apelin-13 (Medhurst <i>et al.</i> , 2003), [ <sup>125</sup> I]-[Nle <sup>75</sup> ,Tyr <sup>77</sup> ]apelin-36 (Kawamata <i>et al.</i> , 2001), [ <sup>125</sup> I]-[Glp <sup>65</sup> Nle <sup>75</sup> ,Tyr <sup>77</sup> ]apelin-13 (Hosoya <i>et al.</i> , 2000) |

Potency order determined for heterologously expressed human APJ receptor (pD<sub>2</sub> values range from 9.5 to 8.6). APJ may also act as a co-receptor with CD4 for isolates of human immunodeficiency virus, with apelin blocking this function (Cayabyab *et al.*, 2000). A modified apelin-13 peptide, apelin-13(F13A) was reported to block the hypotensive response to apelin in rat *in vivo* (Lee *et al.*, 2005), however this peptide exhibits agonist activity in HEK293 cells stably expressing the recombinant APJ receptor (Fan *et al.*, 2003).

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# Bile acid

**Overview:** The bile acid receptor (GPBA, provisional nomenclature) responds to bile acids produced during the liver metabolism of cholesterol.

|                        |                                                                                                                                         |
|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature           | GPBA                                                                                                                                    |
| Other names            | GPBAR1, BG37, GPCR19, GPR131, M-BAR, MGC40597, TGR5                                                                                     |
| Ensembl ID             | ENSG00000179921                                                                                                                         |
| Principal transduction | G <sub>s</sub> (Maruyama <i>et al.</i> , 2002)                                                                                          |
| Rank order of potency  | Lithocholic acid > deoxycholic acid > chenodeoxycholic acid, cholic acid (Maruyama <i>et al.</i> , 2002; Kawamata <i>et al.</i> , 2003) |
| Selective agonists     | Oleanolic acid (Sato <i>et al.</i> , 2007), betulinic acid (Genet <i>et al.</i> , 2010)                                                 |

The triterpenoid natural product betulinic acid has also been reported to inhibit inflammatory signalling through the NFκB pathway (Takada and Aggarwal, 2003). Disruption of GPBA expression is reported to protect from cholesterol gallstone formation (Vassileva *et al.*, 2006).

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# Bombesin

**Overview:** Bombesin receptors (nomenclature recommended by the NC-IUPHAR Subcommittee on bombesin receptors, Jensen *et al.*, 2008) are activated by the endogenous ligands gastrin-releasing peptide (GRP), neuromedin B (NMB) and GRP-18-27 (previously named neuromedin C). Bombesin is a tetradecapeptide, originally derived from amphibians. These receptors couple primarily to the G<sub>q/11</sub> family of G proteins (but see also Jian *et al.*, 1999). Activation of BB<sub>1</sub> and BB<sub>2</sub> receptors causes a wide range of physiological actions, including the stimulation of tissue growth, smooth-muscle contraction, secretion and many central nervous system effects (Tokita *et al.*, 2002). A physiological role for the BB<sub>3</sub> receptor has yet to be fully defined although receptor knockout experiments suggest a role in energy balance and the control of body weight (see Jensen *et al.*, 2008).

| Nomenclature           | BB <sub>1</sub>                                                                                                                      | BB <sub>2</sub>                                                                                                                                    | BB <sub>3</sub>                                                                                                 |
|------------------------|--------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Other names            | NMB-R, BB1                                                                                                                           | GRP-R, BB2                                                                                                                                         | BRS-3, bb3                                                                                                      |
| Ensembl ID             | ENSG00000135577                                                                                                                      | ENSG00000126010                                                                                                                                    | ENSG00000102239                                                                                                 |
| Principal transduction | G <sub>q/11</sub>                                                                                                                    | G <sub>q/11</sub>                                                                                                                                  | G <sub>q/11</sub>                                                                                               |
| Selective agonists     | NMB                                                                                                                                  | GRP                                                                                                                                                | [D-Tyr <sup>6</sup> ,Apa-4Cl <sup>11</sup> ,Phe <sup>13</sup> ,Nle <sup>14</sup> ] bombesin <sub>6-14</sub> ,   |
| Selective antagonists  | PD165929,<br>dNal-cyc(Cys-Tyr-dTrp-Orn-Val)-Nal-NH <sub>2</sub> ,<br>dNal-Cys-Tyr-dTrp-Lys-Val-Cys-Nal-NH <sub>2</sub> ,<br>PD168368 | [D-Phe <sup>6</sup> ,Cpa <sup>14</sup> ,ψ13-14]Bn <sub>6-14</sub> ,<br>JMV594,<br>Ac-GRP <sub>20-26</sub> methylester                              | –                                                                                                               |
| Probes                 | [ <sup>125</sup> I]-BH-NMB,<br>[ <sup>125</sup> I]-[Tyr <sup>4</sup> ]bombesin                                                       | [ <sup>125</sup> I]-[D-Tyr <sup>6</sup> ]bombesin-6-13-methylester,<br>[ <sup>125</sup> I]-GRP,<br>[ <sup>125</sup> I]-[Tyr <sup>4</sup> ]bombesin | [ <sup>125</sup> I]-[Tyr <sup>6</sup> ,βAla <sup>11</sup> ,Phe <sup>13</sup> ,Nle <sup>14</sup> ] bombesin-6-14 |

All three subtypes may be activated by [dPhe<sup>6</sup>,βAla<sup>11</sup>,Phe<sup>13</sup>,Nle<sup>14</sup>]bombesin-6-14 (Mantey *et al.*, 1997). [D-Tyr<sup>6</sup>, Apa-4Cl, Phe<sup>13</sup>, Nle<sup>14</sup>] bombesin-6-14, has more than 200-fold selectivity for BB<sub>3</sub> receptors over BB<sub>1</sub> and BB<sub>2</sub> (Mantey *et al.*, 2004).

**Abbreviations:** PD165929, 2-[3-(2,6-diisopropylphenyl)-ureido]3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionate, PD168368, 3-(1H-indol-3-yl)-2-methyl-2-[3(4-nitro-phenyl)-ureido]N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide, JMV594 H-D-Phe,Gln,Trp,Ala,Val,Gly,His-NH-CH[CH<sub>2</sub>-CH(CH<sub>3</sub>)<sub>2</sub>]-CHOH-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>3</sub>.

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# Bradykinin

**Overview:** Bradykinin (or kinin) receptors (nomenclature recommended by the NC-IUPHAR subcommittee on bradykinin (kinin) receptors, Leeb-Lundberg *et al.*, 2005) are activated by the endogenous peptides bradykinin (BK), [des-Arg<sup>9</sup>]BK, Lys-BK (kallidin), Lys-[des-Arg<sup>9</sup>]BK, T-kinin (Ile-Ser-BK), [Hyp<sup>3</sup>]BK and Lys-[Hyp<sup>3</sup>]BK. The variation in affinity or inactivity of B<sub>2</sub> receptor antagonists could reflect the existence of species homologues of B<sub>2</sub> receptors.

| Nomenclature           | B <sub>1</sub>                                                                                                                                                                                  | B <sub>2</sub>                                                                                                                     |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| Ensembl ID             | ENSG00000100739                                                                                                                                                                                 | ENSG00000168398                                                                                                                    |
| Principal transduction | G <sub>q/11</sub>                                                                                                                                                                               | G <sub>q/11</sub>                                                                                                                  |
| Rank order of potency  | Lys-[des-Arg <sup>9</sup> ]BK > [des-Arg <sup>9</sup> ]BK = Lys-BK > BK                                                                                                                         | Lys-BK ≥ BK > [des-Arg <sup>9</sup> ]BK, Lys-[des-Arg <sup>9</sup> ]BK                                                             |
| Selective agonists     | Lys-[des-Arg <sup>9</sup> ]BK, Sar[D <sup>1</sup> Phe <sup>8</sup> ][des-Arg <sup>9</sup> ]BK                                                                                                   | [Phe <sup>8</sup> , ψ(CH <sub>2</sub> -NH)Arg <sup>9</sup> ]BK, [Hyp <sup>3</sup> , Tyr(Me) <sup>8</sup> ]BK                       |
| Selective antagonists  | B9958 (9.2, Regoli <i>et al.</i> , 1998), R914 (8.6, Gobeil <i>et al.</i> , 1999), R715 (8.5, Gobeil <i>et al.</i> , 1996a), Lys-[Leu <sup>8</sup> ][des-Arg <sup>9</sup> ]BK (8.0)             | Icatibant (8.4, Gobeil <i>et al.</i> , 1996b), FR173657 (8.2, Rizzi <i>et al.</i> , 1997), LF160687 (Pruneau <i>et al.</i> , 1999) |
| Probes                 | [ <sup>3</sup> H]-Lys-[des-Arg <sup>9</sup> ]BK (0.4 nM),<br>[ <sup>3</sup> H]-Lys-[Leu <sup>8</sup> ][des-Arg <sup>9</sup> ]BK,<br>[ <sup>125</sup> I]-Hpp-desArg <sup>9</sup> HOE140 (0.1 nM) | [ <sup>3</sup> H]-BK (0.2 nM), [ <sup>3</sup> H]-NPC17731 (50–900 pM),<br>[ <sup>125</sup> I]-[Tyr <sup>8</sup> ]BK                |

**Abbreviations:** B9958, Lys-Lys[Hyp<sup>3</sup>, Cpg<sup>5</sup>, dTic<sup>7</sup>, Cpg<sup>8</sup>][des-Arg<sup>9</sup>]BK; FR173657, (E)-3-(6-acetamido-3-pyridyl)-N-(N-[2,4-dichloro-3-((2-methyl-8-quinolinyl)oxymethyl) phenyl]-N-methylaminocarbonyl-methyl)acrylamide; Icatibant, DArg[Hyp<sup>3</sup>, Thi<sup>5</sup>, DTic<sup>7</sup>, Oic<sup>8</sup>]BK, also known as HOE140; LF160687, 1-([2,4-dichloro-3-((2,4-dimethylquinolin-8-yl)oxy)methyl]phenyl)sulfonyl)-N-(3-[[4-(aminoimethyl)phenyl]carbonylamino]propyl)-2(S)-pyrrolidinecarboxamide; NPC17731, DArg[Hyp<sup>3</sup>, DHypE(transpropyl)<sup>7</sup>, Oic<sup>8</sup>]BK; R715, AcLys[D Nal<sup>7</sup>, Ile<sup>8</sup>][des-Arg<sup>9</sup>]BK; R914, AcLys-Lys-([αMe]Phe<sup>5</sup>δ-βNal<sup>7</sup>, Ile<sup>8</sup>)desArg<sup>9</sup>BK

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# Calcitonin, amylin, CGRP and adrenomedullin

**Overview:** Calcitonin (CT), amylin (AMY), calcitonin gene-related peptide (CGRP) and adrenomedullin (AM) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on CGRP, AM, AMY, and CT receptors, see Poyner *et al.*, 2002; Hay *et al.*, 2008) are generated by the genes *CALCR* (which codes for the CT receptor (CTR), ENSG00000064989) and *CALCRL* (which codes for the calcitonin receptor-like receptor, CLR, previously known as CRLR, ENSG0000004948). Their function and pharmacology are altered in the presence of RAMPs (receptor activity-modifying protein), which are single TM domain proteins of *ca.* 130 amino acids, identified as a family of three members; RAMP1 (ENSG00000132329), RAMP2 (ENSG00000131477) and RAMP3 (ENSG00000122679). There are splice variants of CTR; these in turn produce variants of the AMY receptor (see Poyner *et al.*, 2002). The endogenous agonists are the peptides CT,  $\alpha$ CGRP (formerly known as CGRP-I),  $\beta$ CGRP (formerly known as CGRP-II), AMY (occasionally called islet-amyloid polypeptide, diabetes-associated polypeptide), AM and AM2/Intermedin (AM2/IMD). There are species differences in peptide sequences, particularly for the CTs. CTR-stimulating peptide (CRSP) is another member of the family with selectivity for the CTR but it is not expressed in humans (Katafuchi *et al.*, 2003). BIBN4096BS (also known as olcegepant,  $pK_i$  ~10.5) and MK0974 (also known as telcagepant,  $pK_i$  ~9) are the most selective antagonists available, having a high selectivity for CGRP receptors, with a particular preference for those of primate origin.

CLR by itself binds no known endogenous ligand, but in the presence of RAMPs it gives receptors for CGRP, AM and AM2/IMD

| Nomenclature           | CGRP                                                                                                                      | AM <sub>1</sub>                          | AM <sub>2</sub>                            |
|------------------------|---------------------------------------------------------------------------------------------------------------------------|------------------------------------------|--------------------------------------------|
| Composition            | <i>CALCRL+RAMP1</i>                                                                                                       | <i>CALCRL+RAMP2</i>                      | <i>CALCRL+RAMP3</i>                        |
| Principal transduction | G <sub>s</sub>                                                                                                            | G <sub>s</sub>                           | G <sub>s</sub>                             |
| Rank order of potency  | CGRP > AM $\geq$ AM2/IMD > AMY $\geq$ salmon CT                                                                           | AM > CGRP, AM2/IMD > AMY > salmon CT     | AM = AM2/IMD $\geq$ CGRP > AMY > salmon CT |
| Selective agonists     | $\alpha$ CGRP                                                                                                             | AM                                       | AM                                         |
| Selective antagonists  | BIBN4096BS (10.5, Doods <i>et al.</i> , 2000; Hay <i>et al.</i> , 2003, 2006); MK0974 (9, Salvatore <i>et al.</i> , 2008) | AM-(22–52) (7, Hay <i>et al.</i> , 2003) | –                                          |
| Probes                 | [ <sup>125</sup> I]- $\alpha$ CGRP (0.1 nM)                                                                               | [ <sup>125</sup> I]-AM (rat, 0.1–1.0 nM) | [ <sup>125</sup> I]-AM (rat, 0.1–1.0 nM)   |

Transfection of human CTR with any RAMP can generate receptors with a high affinity for both salmon CT and AMY and varying affinity for different antagonists (Christopoulos *et al.*, 1999; Hay *et al.*, 2005, 2006). The insert negative (and major) human CTR splice variant (hCT<sub>(a)</sub>) with RAMP1 (i.e. the AMY<sub>1(a)</sub> receptor) has a high affinity for CGRP, unlike hCT<sub>(a)</sub>–RAMP3 (i.e. AMY<sub>3(a)</sub> receptor) (Christopoulos *et al.*, 1999; Hay *et al.*, 2005). However, the AMY receptor phenotype is RAMP-type, splice variant and cell-line-dependent (Tilakaratne *et al.*, 2000).

| Nomenclature           | Calcitonin (CT)                                                                     | AMY <sub>1</sub>                                                                 | AMY <sub>2</sub>                             | AMY <sub>3</sub>                                                            |
|------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------|-----------------------------------------------------------------------------|
| Composition            | <i>CALCR</i>                                                                        | <i>CALCR+RAMP1</i>                                                               | <i>CALCR+RAMP2</i>                           | <i>CALCR+RAMP3</i>                                                          |
| Principal transduction | G <sub>s</sub>                                                                      | G <sub>s</sub>                                                                   | G <sub>s</sub>                               | G <sub>s</sub>                                                              |
| Rank order of potency  | Salmon CT $\geq$ human CT $\geq$ AMY, CGRP > AM, AM2/IMD                            | AMY <sub>1(a)</sub> : Salmon CT $\geq$ AMY $\geq$ CGRP > AM2/IMD > human CT > AM | Poorly defined                               | AMY <sub>3(a)</sub> : Salmon CT $\geq$ AMY > CGRP > AM2/IMD > human CT > AM |
| Selective agonists     | Human CT                                                                            | AMY                                                                              | AMY                                          | AMY                                                                         |
| Probes                 | [ <sup>125</sup> I]-CT (salmon, 0.1 nM), [ <sup>125</sup> I]-CT (human, 0.1–1.0 nM) | [ <sup>125</sup> I]-BH-AMY (rat, 0.1–1.0 nM)                                     | [ <sup>125</sup> I]-BH-AMY (rat, 0.1–1.0 nM) | [ <sup>125</sup> I]-BH-AMY (rat, 0.1–1.0 nM)                                |

The ligands described represent the best available but their selectivity is limited, apart from BIBN4096BS and MK0974. For example, AM has appreciable affinity for CGRP receptors. CGRP can show significant cross-reactivity at AMY receptors and AM<sub>2</sub> receptors. AM2/IMD also has high affinity for the AM<sub>2</sub> receptor (Hong *et al.*, 2011). CGRP-(8–37) acts as an antagonist of CGRP ( $pK_i$  ~8) and inhibits some AM and AMY responses ( $pK_i$  ~6–7). It is inactive at CT receptors. Salmon CT-(8–32) is an antagonist at both AMY and CT receptors. AC187, a salmon CT analogue, is also an antagonist at AMY and CT receptors. Human AM-(22–52) has some selectivity towards AM receptors, but with modest potency ( $pK_i$  ~7), limiting its use (Hay *et al.*, 2003). AM-(22–52) is slightly more effective at AM<sub>1</sub> than AM<sub>2</sub> receptors but this difference is not sufficient for this peptide to be a useful discriminator of the AM receptor subtypes.

Ligand responsiveness at CTR and AMY receptors can be affected by receptor splice variation and can depend on the pathway being measured. Particularly for AMY receptors, relative potency can vary with the type and level of RAMP present and can be influenced by other factors such as G proteins (Tilakaratne *et al.*, 2000; Morfis *et al.*, 2008).

G<sub>s</sub> is a prominent route for effector coupling for CLR and CTR but other pathways (e.g. Ca<sup>2+</sup>, ERK, Akt) and G proteins can be activated (Walker *et al.*, 2010). There is evidence that CGRP-RCP (a 148 amino-acid hydrophilic protein, ENSG00000126522) is important for the coupling of CLR to adenylyl cyclase (Evans *et al.*, 2000).

[<sup>125</sup>I]-Salmon CT is the most common radioligand for CT receptors but it has high affinity for AMY receptors and is also poorly reversible. [<sup>125</sup>I]-Tyr<sup>0</sup>-CGRP is widely used as a radioligand for CGRP receptors.

Some early literature distinguished between  $CGRP_1$  and  $CGRP_2$  receptors. It is now clear that *CALCRL/RAMP1* represents the  $CGRP_1$  subtype and is now known simply as the CGRP receptor (Hay *et al.*, 2008). The  $CGRP_2$  receptor is considered to have arisen from the actions of CGRP at  $AM_2$  and AMY receptors. This term should not be used (Hay *et al.*, 2008).

**Abbreviations:** AC187, acetyl-[Asn<sup>30</sup>,Tyr<sup>32</sup>]salmon CT; BIBN4096BS, 1-piperidinecarboxamide, *N*-(2-[[5-amino-1-([4-{4-pyridinyl}-1-piperazinyl]carbonyl)pentyl]amino]-1-[[3,5-dibromo-4-hydroxyphenyl]methyl]-2-oxoethyl)-4-(1,4-dihydro-2-oxo-3[2*H*]-quinazolinyl); MK0974, *N*-[(3*R*,6*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide

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# Calcium-sensing

**Overview:** The calcium-sensing receptor (CaS, provisional nomenclature) responds to extracellular calcium and magnesium in the millimolar range and to gadolinium and some polycations in the micromolar range (Brown *et al.*, 1993). The sensitivity of CaS to primary agonists can be increased by aromatic L-amino acids (Conigrave *et al.*, 2000) and also by elevated extracellular pH (Quinn *et al.*, 2004) or decreased extracellular ionic strength (Quinn *et al.*, 1998).

|                                  |                                                                                                                                                                      |
|----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature                     | CaS                                                                                                                                                                  |
| Other names                      | CaSR, CaR                                                                                                                                                            |
| Ensembl ID                       | ENSG00000036828                                                                                                                                                      |
| Principal transduction           | G <sub>q/11</sub> , G <sub>i/o</sub> , G <sub>12/13</sub> (Ward, 2004)                                                                                               |
| Cation rank order of potency     | Gd <sup>3+</sup> > Ca <sup>2+</sup> > Mg <sup>2+</sup> (Brown <i>et al.</i> , 1993)                                                                                  |
| Polyamine rank order of potency  | Spermine>spermidine>putrescine (Quinn <i>et al.</i> , 1997)                                                                                                          |
| Amino-acid rank order of potency | L-Phe, L-Trp, L-His>L-Ala>L-Ser, L-Pro, L-Glu>L-Asp but not L-Lys, L-Arg, L-Leu, and L-Ile (Conigrave <i>et al.</i> , 2000)                                          |
| Positive allosteric modulators   | NPS R568 (Nemeth <i>et al.</i> , 1998), calindol (Petrel <i>et al.</i> , 2004), cinacalcet (Nemeth <i>et al.</i> , 2004), AC265347 (Ma <i>et al.</i> , 2011)         |
| Negative allosteric modulators   | NPS 2143, NPS 89636 (Nemeth <i>et al.</i> , 2001), Calhex-231 (Petrel <i>et al.</i> , 2004), 2-benzylpyrrolidine derivatives of NPS 2143 (Yang <i>et al.</i> , 2005) |

Positive allosteric modulators are termed Type II calcimimetics and can suppress parathyroid hormone (PTH) secretion (Nemeth *et al.*, 1998). Negative allosteric modulators are called calcilytics and can act to increase PTH secretion (Nemeth *et al.*, 2001).

The central role of CaS in the maintenance of extracellular calcium homeostasis is seen most clearly in patients with loss-of-function CaS mutations who develop familial hypocalcaemic hypercalcaemia (heterozygous mutation) or neonatal severe hyperparathyroidism (homozygous mutation) and in CaS null mice (Ho *et al.*, 1995; Chang *et al.*, 2008), which exhibit similar increases in PTH secretion and blood Ca<sup>2+</sup> levels. A gain-of-function mutation in the CaS gene is associated with autosomal dominant hypocalcaemia.

GPRC<sub>6</sub> (ENSG00000173612, also known as GPRC6A) is a related G<sub>q</sub>-coupled receptor which responds to basic amino acids (Wellendorph *et al.*, 2005).

**Abbreviations:** AC265347, 1-benzothiazol-2-yl-1-(2,4-dimethyl-phenyl)-ethanol; Calhex-231, (1S,2S,1'R)-N<sup>1</sup>-(4-chlorobenzoyl)-N<sup>2</sup>-[1-(1-naphthyl)ethyl]-1,2-diaminocyclohexane; calindol, (R)-2-[1-(1-naphthyl) ethylaminomethyl]-1H-indole; NPS R568, (R)-N-(3-methoxy- $\alpha$ -phenylethyl)-3-(2-chlorophenyl)-1-propylamine hydrochloride; NPS 2143, N-[(R)-2-hydroxy-3-(2-cyano-3-chlorophenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine;

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# Cannabinoid

**Overview:** Cannabinoid receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Cannabinoid Receptors; see Pertwee *et al.*, 2010) are activated by endogenous ligands that include *N*-arachidonylethanolamine (anandamide), *N*-homo- $\gamma$ -linolenylethanolamine, *N*-docosatetra-7,10,13,16-enylethanolamine and 2-arachidonoylglycerol. Potency determinations of endogenous agonists at these receptors are complicated by the possibility of differential susceptibility to enzymatic conversion (see Alexander and Kendall, 2007).

| Nomenclature           | CB <sub>1</sub>                                                                                                                                                               | CB <sub>2</sub>                                                                                                                                                                                           |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ensembl ID             | ENSG00000118432                                                                                                                                                               | ENSG00000188822                                                                                                                                                                                           |
| Principal transduction | G <sub>i/o</sub>                                                                                                                                                              | G <sub>i/o</sub>                                                                                                                                                                                          |
| Selective agonists     | ACEA (Hillard <i>et al.</i> , 1999), ACPA (Hillard <i>et al.</i> , 1999), methanandamide (Khanolkar <i>et al.</i> , 1996), O-1812 (Di Marzo <i>et al.</i> , 2001)             | HU308 (Hanus <i>et al.</i> , 1999), JWH133 (Huffman <i>et al.</i> , 1999; Pertwee, 2000), L759633 (Ross <i>et al.</i> , 1999), L759656 (Ross <i>et al.</i> , 1999), AM1241 (Ibrahim <i>et al.</i> , 2003) |
| Selective antagonists  | AM251 (8.1, Lan <i>et al.</i> , 1999a), AM281 (7.9, Lan <i>et al.</i> , 1999b), rimonabant (7.9, Showalter <i>et al.</i> , 1996), LY320135 (6.9, Felder <i>et al.</i> , 1998) | SR144528 (9.2, Rinaldi-Carmona <i>et al.</i> , 1998), AM630 (7.5, Ross <i>et al.</i> , 1999)                                                                                                              |
| Probes                 | [ <sup>3</sup> H]-rimonabant (0.6 nM, Rinaldi-Carmona <i>et al.</i> , 1996)                                                                                                   | –                                                                                                                                                                                                         |

Both CB<sub>1</sub> and CB<sub>2</sub> receptors may be labelled with [<sup>3</sup>H]-CP55940 (0.6 nM; Showalter *et al.*, 1996) and [<sup>3</sup>H]-WIN55212-2 (2–12 nM; Slipetz *et al.*, 1995; Song and Bonner, 1996). Anandamide is also an agonist at vanilloid receptors (TRPV1, see Page S166) and PPARs (see Page S181 and O'Sullivan, 2007; Zygmunt *et al.*, 1999). There is evidence for an allosteric site on the CB<sub>1</sub> receptor (Price *et al.*, 2005). All of the compounds listed as antagonists behave as inverse agonists in some bioassay systems (see Pertwee *et al.*, 2010). For some cannabinoid receptor ligands, additional pharmacological targets that include GPR55 and GPR119 have been identified (see Pertwee *et al.*, 2010). Moreover, GPR18, GPR55 and GPR119 (see Page S69), although showing little structural similarity to CB<sub>1</sub> and CB<sub>2</sub> receptors, respond to endogenous agents that are structurally similar to the endogenous cannabinoid ligands (see Pertwee *et al.*, 2010).

**Abbreviations:** ACEA, arachidonoyl-2-chloroethylamide; ACPA, arachidonoylcyclopropylamide; **AM1241**, (2-iodo-5-nitro-phenyl)-[1-(1-methyl-piperidin-2-ylmethyl)-1*H*-indol-3-yl]-methanone; **AM251**, *N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide; **AM281**, 1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-*N*-4-morpholinyl-1*H*-pyrazole-3-carboxamide; **AM630**, 6-iodopravadoline; **CP55940**, (1*R*,3*R*,4*R*)-3-[2-hydroxy-4-(1,1-dimethylheptyl) phenyl]-4-(3-hydroxypropyl)cyclohexan-1-ol; **HU308**, [4-[4-(1,1-dimethylheptyl)-2,6-dimethoxy-phenyl]-6,6-dimethyl-bicyclo[3.1.1]hept-2-en-2-yl]-methanol; **JWH133**, (3-(1,1-dimethylbutyl)-6,6,9-trimethyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromene; **L759633**, (6*a*,10*a*)-3-(1,1-dimethylheptyl)-1-methoxy-6,6,9-trimethyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromene; **L759656**, (6*a*,10*a*)-3-(1,1-dimethylheptyl)-1-methoxy-6,6-dimethyl-9-methylene-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromene; **LY320135**, (6-methoxy-2-[4-methoxyphenyl]benzo[*b*]thien-3-yl)(4-cyanophenyl)methanone; **methanandamide**, (*R*)-(+)-arachidonoyl-1'-hydroxy-2'-propylamide; **O-1812**, (*R*)-(20-cyano-16,16-dimethyldocosa-*cis*-5,8,11,14-tetraenyl)-1'-hydroxy-2'-propylamine; **rimonabant**, *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride, also known as SR141716A; **SR144528**, *N*-([1*S*]-endo-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-carboxamide; **WIN55212-2**, (*R*)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo-[1,2,3-*de*]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone mesylate

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# Chemokine

**Overview:** Chemokine receptors (nomenclature agreed by NC-IUPHAR Subcommittee on Chemokine Receptors, Murphy *et al.*, 2000; Murphy, 2002) comprise a large subfamily of GPCR activated by one or more of the chemokines, a large family of small cytokines typically possessing chemotactic activity for leukocytes.

Chemokines can be divided by structure into four subclasses by the number and arrangement of conserved cysteines. CC (also known as  $\beta$ -chemokines;  $n = 28$ ), CXC (also known as  $\alpha$ -chemokines;  $n = 16$ ) and CX<sub>3</sub>C ( $n = 1$ ) chemokines all have four conserved cysteines, with zero, one and three amino acids separating the first two cysteines, respectively. C chemokines ( $n = 2$ ) have only the second and fourth cysteines found in other chemokines. Chemokines can also be classified by function into homeostatic and inflammatory subgroups. Most chemokine receptors are able to bind multiple high affinity chemokine ligands, but the ligands for a given receptor are almost always restricted to the same structural subclass. Most chemokines bind to more than one receptor subtype. Receptors for inflammatory chemokines are typically highly promiscuous with regard to ligand specificity, and may lack a selective endogenous ligand. Listed are those human agonists with EC<sub>50</sub> values <50 nM in either Ca<sup>2+</sup> flux or chemotaxis assays at human recombinant receptors expressed in mammalian cell lines. There can be substantial cross-species differences in the sequences of both chemokines and chemokine receptors, and in the pharmacology and biology of chemokine receptors. Endogenous and HIV-encoded non-chemokine ligands have also been identified for chemokine receptors. Many chemokine receptors function as HIV co-receptors, and at least two, CCR5 and CXCR4, play prominent roles in pathogenesis. The tables include both standard chemokine names (Zlotnik and Yoshie, 2000) and the most commonly used synonyms. Numerical data quoted are typically pKi or pIC<sub>50</sub> values from radioligand binding to heterologously expressed receptors.

| Nomenclature           | CCR1                                                                                                                            | CCR2                                                                   | CCR3                                                                                                                                        | CCR4                                                      | CCR5                                                                                                                                       |
|------------------------|---------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| Other names            | CKR1, CC CK <sub>1</sub> , CC CKR1, MIP-1 $\alpha$ R, MIP-1 $\alpha$ /RANTES                                                    | CKR2, CC CK <sub>2</sub> , CC CKR2, MCP-1                              | CKR3, CC CK <sub>3</sub> , CC CKR3                                                                                                          | CKR4, CC CK <sub>4</sub> , CC CKR4                        | CKR5, CC CK <sub>5</sub> , CC CKR <sub>5</sub> , CHEMR13                                                                                   |
| Ensembl ID             | ENSG00000163823                                                                                                                 | ENSG00000121807                                                        | ENSG00000183625                                                                                                                             | ENSG00000183813                                           | ENSG00000160791                                                                                                                            |
| Principal transduction | G <sub>i/o</sub>                                                                                                                | G <sub>i/o</sub>                                                       | G <sub>i/o</sub>                                                                                                                            | G <sub>i/o</sub>                                          | G <sub>i/o</sub>                                                                                                                           |
| Agonists               | CCL3 (MIP-1 $\alpha$ ), CCL5 (RANTES), CCL7 (MCP-3), CCL8 (MCP-2), CCL13 (MCP-4), CCL14a (HCC-1), CCL15 (HCC-2), CCL23 (MPIF-1) | CCL2 (MCP-1), CCL7 (MCP-3), CCL8 (MCP-2), CCL13 (MCP-4), CCL16 (HCC-4) | CCL11 (eotaxin), CCL5 (RANTES), CCL7 (MCP-3), CCL8 (MCP-2), CCL13 (MCP-4), CCL15 (HCC-2), CCL24 (eotaxin-2), CCL26 (eotaxin-3), CCL28 (MEC) | CCL22 (MDC), CCL17 (TARC), vMIP-III                       | CCL3 (MIP-1 $\alpha$ ), CCL4 (MIP-1 $\beta$ ), CCL5 (RANTES), CCL8 (MCP-2), CCL11 (eotaxin), CCL14a (HCC-1), CCL16 (HCC-4), R5 HIV-1 gp120 |
| Selective agonists     | CCL15 (HCC-2), CCL23 (MPIF-1)                                                                                                   | CCL2 (MCP-1)                                                           | CCL11 (Eotaxin), CCL24 (eotaxin-2), CCL26 (eotaxin-3),                                                                                      | CCL22 (MDC), CCL17 (TARC)                                 | MIP-1 $\beta$ , R5-HIV gp120                                                                                                               |
| Selective antagonists  | BX471 (8.3-9), 2b-1 (8.7), UCB35625 (8.0), CP481715 (8.0), CCL4 (MIP-1 $\beta$ )                                                | CCL11 (eotaxin), CCL26 (eotaxin-3), GSK Compound 34 (7.6)              | Banyu Compound 1b (8.6), SB328437 (8.4), BMS Compound 87b (8.1), CXCL10 (IP10), CXCL9 (Mig), CXCL11 (I-TAC)                                 | –                                                         | TAK779 (9.0), CCL7 (MCP-3), SCH C, SCH D, MRK-1, E913 (8.7), maraviroc, aplaviroc                                                          |
| Probes                 | [ <sup>125</sup> I]-MIP-1 $\alpha$ , [ <sup>125</sup> I]-RANTES, [ <sup>125</sup> I]-MCP-3                                      | [ <sup>125</sup> I]-MCP-1, [ <sup>125</sup> I]-MCP-3                   | [ <sup>125</sup> I]-RANTES, [ <sup>125</sup> I]-eotaxin, [ <sup>125</sup> I]-MCP-3                                                          | [ <sup>125</sup> I]-TARC, [ <sup>125</sup> I]-CTACK/CCL27 | [ <sup>125</sup> I]-RANTES, [ <sup>125</sup> I]-MCP-2, [ <sup>125</sup> I]-MIP-1 $\alpha$ , [ <sup>125</sup> I]-MIP-1 $\beta$              |

| Nomenclature           | CCR6                                               | CCR7                                             | CCR8                                                                          | CCR9                     | CCR10                                   |
|------------------------|----------------------------------------------------|--------------------------------------------------|-------------------------------------------------------------------------------|--------------------------|-----------------------------------------|
| Other names            | GPR-CY4, CKR-L3, STRL-22, DRY-6, DCR2, BN-1, GPR29 | EBI-1, BLR-2                                     | TER1, CKR-L1, GPR-CY6, ChemR1                                                 | GPR 9-6                  | GPR-2                                   |
| Ensembl ID             | ENSG00000112486                                    | ENSG00000126353                                  | ENSG00000179934                                                               | ENSG00000173585          | ENSG00000184451                         |
| Principal transduction | G <sub>i/o</sub>                                   | G <sub>i/o</sub>                                 | G <sub>i/o</sub>                                                              | G <sub>i/o</sub>         | G <sub>i/o</sub>                        |
| Agonists               | CCL20 (LARC), HBD2                                 | CCL19 (ELC, MIP-3 $\beta$ ), CCL21 (SLC)         | CCL1 (I-309), CCL4 (MIP-1 $\beta$ ), CCL16 (HCC-4), CCL17 (TARC), HHV8 vMIP-I | CCL25 (TECK)             | CCL27 (Eskine, ALP, CTACK), CCL28 (MEC) |
| Selective agonists     | LARC, HBD2                                         | ELC, SLC                                         | I-309                                                                         | TECK                     | Eskine, MEC                             |
| Selective antagonists  | –                                                  | –                                                | MCV MC148R (vMCC-I)                                                           | –                        | –                                       |
| Probes                 | [ <sup>125</sup> I]-LARC                           | [ <sup>125</sup> I]-ELC, [ <sup>125</sup> I]-SLC | [ <sup>125</sup> I]-I309                                                      | [ <sup>125</sup> I]-TECK | –                                       |

| Nomenclature           | CXCR1                                                            | CXCR2                                                                                                                                                | CXCR3                                                      | CXCR4                                                              | CXCR5               | CXCR6                      |
|------------------------|------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|--------------------------------------------------------------------|---------------------|----------------------------|
| Other names            | IL8R <sub>A</sub> , IL-8 receptor type I, IL-8 receptor $\alpha$ | IL8R <sub>B</sub> , IL-8 receptor type II, IL-8 receptor $\beta$                                                                                     | IP10/Mig R, GPR9                                           | HUMSTSR, LESTR, fusin, HM89, LCR1                                  | BLR-1, MDR15        | STRL-33, BONZO, TYMSTR     |
| Ensembl ID             | ENSG00000163464                                                  | ENSG00000180871                                                                                                                                      | ENSG00000186810                                            | ENSG00000121966                                                    | ENSG00000160683     | ENSG00000172215            |
| Principal transduction | G <sub>i/o</sub>                                                 | G <sub>i/o</sub>                                                                                                                                     | G <sub>i/o</sub>                                           | G <sub>i/o</sub>                                                   | G <sub>i/o</sub>    | G <sub>i/o</sub>           |
| Agonists               | CXCL6 (GCP-2), CXCL8 (IL-8),                                     | CXCL1 (GRO $\alpha$ ), CXCL2 (GRO $\beta$ ), CXCL3 (GRO $\gamma$ ), CXCL5 (ENA-78), CXCL6 (GCP-2), CXCL7 (NAP-2), CXCL8 (IL-8), HCMV UL146 (vCXCL-1) | CXCL9 (Mig), CXCL10 (IP10), CXCL11 (I-TAC)                 | CXCL12 $\alpha$ (SDF-1 $\alpha$ ), CXCL12 $\beta$ (SDF-1 $\beta$ ) | CXCL13 (BLC, BCA-1) | CXCL16 (SR-PSOX)           |
| Selective agonists     | –                                                                | GRO $\alpha$ , GRO $\gamma$ , GRO $\beta$ , NAP-2, ENA78                                                                                             | IP10, MIG, I-TAC                                           | SDF-1 $\alpha$ , SDF-1 $\beta$ , X4-HIV gp120                      | BLC                 | CXCL16                     |
| Selective antagonists  | –                                                                | SB225002 (7.7)                                                                                                                                       | eotaxin, MCP-3                                             | AMD3100, HIV-1 Tat, T134, ALX40-4C                                 | –                   | –                          |
| Probes                 | [ <sup>125</sup> I]-IL8                                          | [ <sup>125</sup> I]-IL8, [ <sup>125</sup> I]-GRO $\alpha$ , [ <sup>125</sup> I]-NAP-2, [ <sup>125</sup> I]-ENA78                                     | [ <sup>125</sup> I]-IP10, [ <sup>125</sup> I]-I-TAC/CXCL11 | [ <sup>125</sup> I]-SDF-1                                          | –                   | [ <sup>125</sup> I]-CXCL16 |

CXCR1 and CXCR2 also couple to phospholipase C when co-transfected with members of the G<sub>q/11</sub> family of G proteins. Mouse CXCR2 binds iodinated mouse KC and mouse MIP-2 with high affinity (mouse KC and MIP-2 are homologues of human GRO chemokines), but shows low affinity for human IL-8.

| Nomenclature           | CX <sub>3</sub> CR1             | XCRI                                                           |
|------------------------|---------------------------------|----------------------------------------------------------------|
| Other names            | CMKBRL1, V28                    | GPR5                                                           |
| Ensembl ID             | ENSG00000168329                 | ENSG00000173578                                                |
| Principal transduction | G <sub>i/o</sub>                | G <sub>i/o</sub>                                               |
| Agonists               | CX3CL1 (Fractalkine)            | XC11 $\alpha$ and $\beta$ (Lymphotactin $\alpha$ and $\beta$ ) |
| Selective agonists     | Fractalkine                     | Lymphotactin                                                   |
| Probes                 | [ <sup>125</sup> I]-Fractalkine | SEAP-XCL1                                                      |

Three human 7TM chemokine binding proteins have been identified that lack a known signalling function: 1) D6 (ENSG00000144648), which binds multiple CC chemokines and is expressed on lymphatic endothelial cells and placental trophoblasts; 2) a molecule previously inappropriately named CCR11 and now known as CCX CKR or the human homologue of the bovine gustatory receptor PPAR1 (ENSG00000118519, ENSG00000129048), which binds ELC, SLC and TECK; and 3) Duffy, a highly promiscuous CC and CXC chemokine binding protein expressed mainly on erythrocytes, endothelial cells and Purkinje cells. CXCR7 (former aliases: RDC1, CMKOR1 and GPR159, ENSG00000144476) binds CXCL11 and CXCL12 with high affinity, and is expressed in all four cardiac valves and by marginal zone B cells in mammals. Mice lacking this receptor undergo perinatal mortality because of valvular stenosis. Work in zebrafish has identified a role for a highly conserved CXCR7 homologue in shaping CXCL12 gradients, which guide primordial germ cell migration. Whether this is how it works in mammals, or whether there is, in addition, a signal transduction function for CXCR7 has not yet been fully resolved. Thus, the name CXCR7, though widely used in the field, has not yet been endorsed officially by IUPHAR. Specific chemokine receptors facilitate cell entry by microbes, such as *Plasmodium vivax*, HIV-1 and the poxvirus myxoma virus. Virally encoded chemokine receptors are known (e.g. US28, a homologue of CCR1 from human cytomegalovirus and ECRF3, a homologue of CXCR2 from *Herpesvirus saimiri*), but their role in viral life cycles is not established. Viruses can exploit or subvert the chemokine system by producing chemokine antagonists and scavengers.

The CC chemokine family (CCL1–28) includes I309 (CCL1), MCP-1 (CCL2), MIP-1 $\alpha$  (CCL3), MIP-1 $\beta$  (CCL4), RANTES (CCL5), MCP-3 (CCL7), MCP-2 (CCL8), eotaxin (CCL11), MCP-4 (CCL13), HCC-1 (CCL14), Lkn-1/HCC-2 (CCL15), TARC (CCL17), ELC (CCL19), LARC (CCL20), SLC (CCL21), MDC (CCL22), MPIF-1 (CCL23), eotaxin-2 (CCL24), TECK (CCL25), eotaxin (CCL26), eskine/CTACK (CCL27) and MEC (CCL28). The CXC chemokine family (CXCL1–16) includes GRO $\alpha$  (CXCL1), GRO $\beta$  (CXCL2), GRO $\gamma$  (CXCL3), platelet factor 4 (CXCL4), ENA78 (CXCL5), GCP-2 (CXCL6), NAP-2 (CXCL7), IL-8 (CXCL8), MIG (CXCL9), IP10 (CXCL10), I-TAC (CXCL11), SDF-1 (CXCL12), BLC (CXCL13), BRAK (CXCL14), mouse lungkine (CXCL15) and SR-PSOX (CXCL16). The CX<sub>3</sub>C chemokine (CX3CL1) is also known as fractalkine (neurotactin in the mouse). Like CXCL16, and unlike other chemokines, CX3CL1 is multimodular containing a chemokine domain, an elongated mucin-like stalk, a transmembrane domain and a cytoplasmic tail. Both plasma membrane-associated and shed forms have been identified. The C chemokine (XCL1) is also known as lymphotactin. The non-chemokine family includes the cytokine domain of tyrosyl-tRNA synthetase, HBD2, HIV gp120 and HIV Tat. Two chemokine receptor antagonists have now been approved by the FDA: the CCR5 antagonist maraviroc (Pfizer) for treatment of HIV/AIDS in patients with CCR5-using strains; and the CXCR4 antagonist AMD3100 (Plerixifor, Mozibil from Genzyme) for hematopoietic

stem cell mobilization with G-CSF in patients undergoing transplantation in the context of chemotherapy for lymphoma and multiple myeloma.

**Abbreviations:** BLC, B-lymphocyte chemokine; ELC, Epstein–Barr virus-induced receptor ligand chemokine; ENA-78, epithelial cell-derived neutrophil-activating factor-78 amino acids; GCP-2, granulocyte chemoattractant protein 2; HBD2, human  $\beta$  defensin 2; HCC, hemofiltrate CC chemokine; IL-8, interleukin 8; IP-10,  $\gamma$ -interferon-inducible protein 10; I-TAC, interferon-inducible T-cell  $\alpha$  chemoattractant; LARC, liver and activation-related chemokine (CCL20); MCP, monocyte chemoattractant protein; MDC, macrophage-derived chemokine; MEC, mucosa expressed chemokine; MIG, monokine-induced by  $\gamma$ -interferon; MIP, macrophage inflammatory protein; MPIF-1, myeloid progenitor inhibitory factor 1; NAP-2, neutrophil-activating peptide 2; RANTES, regulated on activation normal T cell expressed and secreted; SDF, stromal cell-derived factor; SLC, secondary lymphoid tissue chemokine; SEAP, secreted alkaline phosphatase; TARC, T-cell and activation-related chemokine; TECK, thymus-expressed chemokine

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# Cholecystokinin

**Overview:** Cholecystokinin receptors (nomenclature recommended by the NC-IUPHAR Subcommittee on CCK receptors, Noble *et al.*, 1999) are activated by the endogenous peptides cholecystokinin (CCK)-4, CCK-8, CCK-33 and gastrin. There is evidence for species homologues of CCK<sub>2</sub> receptors distinguished by the relative affinities of the two stereoisomers of devazepide, *R*-L365260 and *S*-L365260, or by the differences in affinity of the agonist BC264 (Durieux *et al.*, 1992).

|                        |                                                                                                    |                                                                                                                                                                                                                      |
|------------------------|----------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature           | CCK <sub>1</sub>                                                                                   | CCK <sub>2</sub>                                                                                                                                                                                                     |
| Other names            | CCK <sub>A</sub>                                                                                   | CCK <sub>B</sub> , CCK <sub>8</sub> /gastrin                                                                                                                                                                         |
| Ensembl ID             | ENSG00000163394                                                                                    | ENSG00000110148                                                                                                                                                                                                      |
| Principal transduction | G <sub>q/11</sub> /G <sub>s</sub>                                                                  | G <sub>s</sub>                                                                                                                                                                                                       |
| Rank order of potency  | CCK-8 >>gastrin, des-CCK-8 >CCK-4                                                                  | CCK-8 ≥gastrin, des-CCK-8, CCK-4                                                                                                                                                                                     |
| Selective agonists     | A71623, JMV180, GW5823                                                                             | Desulfated CCK-8, gastrin, CCK-4, PBC264, RB400                                                                                                                                                                      |
| Selective antagonists  | Devazepide (9.8), T0632 (9.6), SR27897 (9.2), IQM95333 (9.2), PD140548 (7.9–8.6), lorglumide (7.2) | YM022 (10.2), L740093 (10.0), GV150013 (9.3), RP73870 (9.3), L365260 (7.5–8.7), LY262691 (7.5)                                                                                                                       |
| Probes                 | [ <sup>3</sup> H]-Devazepide (0.2 nM)                                                              | [ <sup>3</sup> H]-Propionyl-BC264 (0.15 nM), [ <sup>3</sup> H]-PD140376 (0.2 nM), [ <sup>3</sup> H]-L365260 (2 nM), [ <sup>3</sup> H]- or [ <sup>125</sup> I]-gastrin (1 nM), [ <sup>125</sup> I]-PD142308 (0.25 nM) |

A mitogenic gastrin receptor, which can be radiolabelled with [<sup>125</sup>I]-gastrin-(1–17) and which appears to couple to the G<sub>s</sub> family of G proteins, has been described in human colon cancer cells (Bold *et al.*, 1994) and other cell lines (e.g. pancreatic AR42J and Swiss 3T3 fibroblasts, Seva *et al.*, 1994; Singh *et al.*, 1995).

**Abbreviations:** A71623, Boc-Trp-Lys(O-toluylaminocarbonyl)-Asp-(NMe)Phe-NH<sub>2</sub>; BC264, Tyr(SO<sub>3</sub>H)-gNle-mGly-Trp-(NMe)Nle-Asp-Phe-NH<sub>2</sub>; GV150013, (+)-*N*-(1-[1-adamantane-1-methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl)-*N'*-phenylurea; GW5823, 2-[3-(1*H*-indazol-3-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-(methoxyphenyl)acetamide; IQM95333, (4*α*S,5*R*)-2-benzyl-5-[*N*-(*tert*-butoxycarbonyl)-L-Trp]amino-1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine; JMV180, Boc-Tyr(SO<sub>3</sub>H)Ahx-Gly-Trp-Ahx-Asp<sup>2</sup>phenylethyl ester; L365260, 3*R*(+)-*N*-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-Napos;-(3-methylphenyl)urea; L740093, *N*-([3*R*]-5-[3-azabicyclo[3.2.2]nonan-3-yl]-2,3-dihydro-1-methyl-2-oxo-1*H*-1,4-benzodiazepin-3-yl)-*N'*-(3-methylphenyl)urea; LY262691, *trans*-*N*-(4-bromophenyl)-3-oxo-4,5-diphenyl-1-pyrazolidinecarboxamide(3.3.1.1<sup>3,7</sup>); PD140376, L-3-([4-aminophenyl]methyl)-*N*-(*α*-methyl-*N*-[[tricyclo(3.3.1.1*D*-Trp)-*β*-Ala]; PD140548, *N*-(*α*-methyl-*N*-[[tricyclo(3.3.1.1*L*-Trp)-D-3-(phenylmethyl)-*β*-Ala]; PD142308, iodinated PD140548; RB400, HOOC-CH<sub>2</sub>-CO-Trp-NMe(Nle)-Asp-Phe-NH<sub>2</sub>; RP73870, (([*R*]); SR27897, 1-([2-(4-(2-chlorophenyl)thiazole-2-yl)aminocarbonyl]indolyl)acetic acid; T0632, sodium (S)-3-(1-[2-fluorophenyl]-2,3-dihydro-3-[[3-isoquinolyl]-carbonyl]amino-6-methoxy-2-oxo-1*H*-indole)propanoate; YM022, (*R*)-1-(2,3-dihydro-1-[2'-methylphenacyl]-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-3-(3-methylphenyl)urea

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# Corticotropin-releasing factor

**Overview:** Corticotropin-releasing factor (CRF, nomenclature as recommended by the NC-IUPHAR on Corticotropin-releasing Factor Receptors, see Hauger *et al.*, 2003) receptors are activated by the endogenous peptides CRF (also known as corticotropin-releasing hormone [CRH], a 41 amino-acid peptide, ENSG00000147571), urocortin 1 (a 40 amino-acid peptide, ENSG00000163794), urocortin 2 (a 38 amino-acid peptide, ENSG00000145040) and urocortin 3 (a 38 amino-acid peptide, ENSG00000178473). CRF<sub>1</sub> and CRF<sub>2</sub> receptors are activated non-selectively by CRF and urocortin 1. Binding to CRF receptors can be conducted using [<sup>125</sup>I]-Tyr<sup>0</sup>-CRF or [<sup>125</sup>I]-Tyr<sup>0</sup>-sauvagine with K<sub>d</sub> values of 0.1–0.4 nM. CRF<sub>1</sub> and CRF<sub>2</sub> receptors are non-selectively antagonized by  $\alpha$ -helical CRF-(9-41), D-Phe-CRF-(12-41) and astressin.

|                        |                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                              |
|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature           | CRF <sub>1</sub>                                                                                                                                                                                                                                                                                                                                                                           | CRF <sub>2</sub>                                                                                                                             |
| Other names            | CRF-RA, PC-CRF                                                                                                                                                                                                                                                                                                                                                                             | CRF-RB, HM-CRF                                                                                                                               |
| Ensembl ID             | ENSG00000120088                                                                                                                                                                                                                                                                                                                                                                            | ENSG00000106113                                                                                                                              |
| Principal transduction | G <sub>s</sub>                                                                                                                                                                                                                                                                                                                                                                             | G <sub>s</sub>                                                                                                                               |
| Selective agonists     | –                                                                                                                                                                                                                                                                                                                                                                                          | Urocortin 2 (Reyes <i>et al.</i> , 2001), urocortin 3 (Lewis <i>et al.</i> , 2001)                                                           |
| Selective antagonists  | CP154526 (8.3–9.0, Lundkvist <i>et al.</i> , 1996), NBI27914 (8.3–9.0, Chen <i>et al.</i> , 1996), antalarmin (8.3–9.0, Webster <i>et al.</i> , 1996), CRA1000 (8.3–9.0, Chaki <i>et al.</i> , 1999), DMP696 (8.3–9.0, He <i>et al.</i> , 2000), R121919 (8.3–9.0, Zobel <i>et al.</i> , 2000), SRA125543A (8.7–9.0, Gully <i>et al.</i> , 2002) CP376395 (7.8, Chen <i>et al.</i> , 2008) | K41498 (9.2, Lawrence <i>et al.</i> , 2002), K31440 (8.7–8.8, Ruhmann <i>et al.</i> , 2002), antisauvagine-30 (Ruhmann <i>et al.</i> , 1998) |

A CRF binding protein has been identified (CRF-BP, ENSG00000145708) to which both CRF and urocortin 1 bind with high affinities, which has been suggested to bind and inactivate circulating CRF (Perkins *et al.*, 1995).

**Abbreviations:** antalarmin, N-butyl-N-ethyl-(2,5,6-trimethyl)-7-[2,4,6-trimethylphenyl]-7H-pyrrolo[2,3-*d*]pyrimidin-4-yl-amine; astressin, cyc<sup>30–33</sup>[D-Phe<sup>12</sup>,Nle<sup>21,38</sup>,Glu<sup>30</sup>,Lys<sup>33</sup>]CRF-(12-41); CP154526, butyl-ethyl-(2,5-dimethyl-7-[2,4,6-trimethylphenyl]-7H-pyrrolo[2,3-*d*]pyrimidin-4-yl)amine; CRA1000, 2-(N-[2-methylthio-4-isopropylphenyl]-N-ethyl-amino-4-[4-{3-fluorophenyl}-1,2,3,6-tetrahydropyridin-1-yl]-6-methylpyrimidine); DMP696, 4-(1,3-dimethoxyprop-2-ylamino)-2,7-dimethyl-8-(2,4-dichlorophenyl)pyrazolo[1,5-*a*]-1,3,5-triazine; D-Phe-CRF-(12-41), D-Phe<sup>12</sup>,Nle<sup>21,38</sup>, $\alpha$ MeLeu<sup>37</sup>-CRF; K31440, Ac-(D-Tyr<sup>11</sup>,His<sup>12</sup>,Nle<sup>17</sup>)sauvagine-(11-40); K41498, [D-Phe<sup>11</sup>,His<sup>12</sup>,Nle<sup>17</sup>]sauvagine-(11-40); NBI27914, 2-methyl-4-(N-propyl-N-cyclopropanemethylamino)-5-chloro-6-(2,4,6-trichloroanilino)pyrimidine; R121919, 3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-N,N-dipropylpyrazolo[1,5-*a*]pyrimidin-7-amine; SRA125543A, 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]5-methyl-N-(2-propynyl)-1,3-thiazol-2-amine hydrochloride

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# Dopamine

**Overview:** Dopamine receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Dopamine Receptors, see Schwartz *et al.*, 1998) are commonly divided into D<sub>1</sub>-like (D<sub>1</sub> and D<sub>5</sub>) and D<sub>2</sub>-like (D<sub>2</sub>, D<sub>3</sub> and D<sub>4</sub>) families, where the endogenous agonist is dopamine. Quinpirole is an agonist with selectivity for D<sub>2</sub>-like receptors.

| Nomenclature           | D <sub>1</sub>                                                                      | D <sub>2</sub>                                               | D <sub>3</sub>                                                                                                                                                              | D <sub>4</sub>                                                                                                                                                        | D <sub>5</sub>                                                                     |
|------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| Other names            | D <sub>1A</sub>                                                                     | –                                                            | –                                                                                                                                                                           | –                                                                                                                                                                     | D <sub>1B</sub>                                                                    |
| Ensembl ID             | ENSG00000184845                                                                     | ENSG00000149295                                              | ENSG00000151577                                                                                                                                                             | ENSG00000069696                                                                                                                                                       | ENSG00000169676                                                                    |
| Principal transduction | G <sub>s</sub> , G <sub>olf</sub>                                                   | G <sub>i/o</sub>                                             | G <sub>i/o</sub>                                                                                                                                                            | G <sub>i/o</sub>                                                                                                                                                      | G <sub>s</sub>                                                                     |
| Selective agonists     | R(+)-SKF81297,<br>R(+)-SKF38393                                                     | Sumanitrole (McCall<br><i>et al.</i> , 2005)                 | PD128907                                                                                                                                                                    | PD168077, A412997<br>(Moreland <i>et al.</i> ,<br>2005)                                                                                                               | –                                                                                  |
| Selective antagonists  | SCH23390,<br>SKF83566,<br>SCH39166                                                  | Raclopride,<br>domperidone                                   | S33084 (9.6, Millan<br><i>et al.</i> , 2000),<br>nafadotride (9.5),<br>(+)-S14297 (7.9,<br>Millan <i>et al.</i> , 1994),<br>SB277011 (8.0,<br>Reavill <i>et al.</i> , 2000) | L745870 (9.3),<br>U101958 (8.9,<br>Schlachter <i>et al.</i> ,<br>1997), L741742<br>(8.5)                                                                              | –                                                                                  |
| Probes                 | [ <sup>3</sup> H]-SCH23390<br>(0.2 nM),<br>[ <sup>125</sup> I]-SCH23982<br>(0.7 nM) | [ <sup>3</sup> H]-Raclopride,<br>[ <sup>3</sup> H]-spiperone | [ <sup>3</sup> H]-7-OH-DPAT,<br>[ <sup>3</sup> H]-PD128907,<br>[ <sup>3</sup> H]-spiperone                                                                                  | [ <sup>3</sup> H]-NGD941 (5 nM,<br>Primus <i>et al.</i> , 1997),<br>[ <sup>125</sup> I]-L750667 (1 nM,<br>Patel <i>et al.</i> , 1996),<br>[ <sup>3</sup> H]-spiperone | [ <sup>125</sup> I]-SCH23982<br>(0.8 nM)<br>[ <sup>3</sup> H]-SCH23390<br>(0.5 nM) |

The selectivity of many of these agents is less than two orders of magnitude. [<sup>3</sup>H]-Raclopride exhibits similar high affinity for D<sub>2</sub> and D<sub>3</sub> receptors (low affinity for D<sub>4</sub>), but has been used to label D<sub>2</sub> receptors in the presence of a D<sub>3</sub>-selective antagonist. [<sup>3</sup>H]-7-OH-DPAT has similar affinity for D<sub>2</sub> and D<sub>3</sub> receptors, but labels only D<sub>3</sub> receptors in the absence of divalent cations. The pharmacological profile of the D<sub>5</sub> receptor is similar to, yet distinct from, that of the D<sub>1</sub> receptor. The splice variants of the D<sub>2</sub> receptor are commonly termed D<sub>2S</sub> and D<sub>2L</sub> (short and long). The *DRD4* gene encoding the D<sub>4</sub> receptor is highly polymorphic in humans, with allelic variations of the protein from amino acid 387 to 515.

**Abbreviations:** L741742, 5-(4-chlorophenyl)-4-methyl-3-(1-[2-phenethyl]piperidin-4-yl)isoxazole; L745870, 3-[[4-(4-chlorophenyl)piperazin-1-yl]methyl]-1H-pyrrolo[2,3-*b*]pyridine; L750667, iodinated L745870; NGD941, 2-phenyl-4(S)-(4-[2-pyrimidinyl]-[piperazin-1-yl]-methyl)-imidazole dimaleate; (+)-7-OH-DPAT, (+)-7-hydroxy-2-aminopropylaminotetralin; PD128907, *R*-(+)-*trans*-3,4,4a,10b-tetrahydro-4-propyl-2H,5H-[1]benzopyrano[4,3-*b*]-1,4-oxazine-9-ol; PD168077, *N*-methyl-4-(2-cyanophenyl)piperazinyl-3-methylbenzamide; (+)-S14297, (+)-7-(*N,N*-dipropylamino)-5,6,7,8-tetrahydronaphtho(2,3*b*)dihydro-2,3-furane; S33084, (3*aR*,9*bS*)-*N*[4-(8-cyano-1,3*a*,4,9*b*-tetrahydro-3*H*-benzopyrano[3,4-*c*]pyrrole-2-yl)-butyl] (4-phenyl)benzamide; SB277011, *trans*-*N*-(4-[2-[6-cyano-1,2,3,4-tetrahydroisoquinolin-2-yl]ethyl]cyclohexyl)-4-quinolininecarboxamide; SCH23390, 7-chloro-8-hydroxy-3-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine; SCH23982, 8-iodo-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepine; SCH39166, (-)-*trans*-6,7,7*a*,8,9,13*b*-hexahydro-3-chloro-2-hydroxy-*N*-ethyl-5*H*-benzo[*d*]naphtho(2,3*b*)azepine; R(+)-SKF38393, *R*-(+)-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine; R(+)-SKF81297, *R*-(+)-6-chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-benzazepine; SKF83566, (-)-7-bromo-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-3-benzazepine; U101958, 3-isopropoxy-*N*-methyl-*N*-(1-[phenylmethyl]-4-piperidinyl)-2-pyridinylamine

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# Endothelin

**Overview:** Endothelin receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on endothelin receptors, Davenport, 2002) are activated by the endogenous 21 amino-acid peptides endothelin-1 (ET-1, ENSG00000078401), ET-2 (ENSG00000127129) and ET-3 (ENSG00000124205). Non-selective peptide (e.g. TAK044, pA<sub>2</sub> 8.4) and non-peptide (e.g. bosentan, pA<sub>2</sub> 6.0–7.2; SB209670, pA<sub>2</sub> 9.4) antagonists can block both ET<sub>A</sub> and ET<sub>B</sub> receptors. Splice variants of the ET<sub>A</sub> receptor have been identified in rat pituitary cells; one of these, ET<sub>A</sub>R-C13, appeared to show loss of function with comparable plasma membrane expression (Hatae *et al.*, 2007).

| Nomenclature           | ET <sub>A</sub>                                                                                                                                                                                                                                                                                                                                                                                                                                               | ET <sub>B</sub>                                                                                                                                                                                                                     |
|------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ensembl ID             | ENSG00000151617                                                                                                                                                                                                                                                                                                                                                                                                                                               | ENSG00000136160                                                                                                                                                                                                                     |
| Principal transduction | G <sub>q/11</sub> , G <sub>s</sub>                                                                                                                                                                                                                                                                                                                                                                                                                            | G <sub>q/11</sub> , G <sub>i/o</sub>                                                                                                                                                                                                |
| Potency order          | ET-1, ET-2 > ET-3 (Maguire and Davenport, 1995)                                                                                                                                                                                                                                                                                                                                                                                                               | ET-1, ET-2, ET-3                                                                                                                                                                                                                    |
| Selective agonists     | –                                                                                                                                                                                                                                                                                                                                                                                                                                                             | [Ala <sup>1,3,11,15</sup> ]ET-1 (Molenaar <i>et al.</i> , 1992), sarafotoxin S6c (Russell and Davenport, 1996), IRL1620 (Watakabe <i>et al.</i> , 1992), BQ3020 (Russell and Davenport, 1996)                                       |
| Selective antagonists  | A127722 (9.2–10.5, Opgenorth <i>et al.</i> , 1996), LU135252 (8.9, Riechers <i>et al.</i> , 1996), SB234551 (8.7–9.0, Ohlstein <i>et al.</i> , 1998), PD156707 (8.2–8.5, Maguire <i>et al.</i> , 1997), FR139317 (7.3–7.9, Maguire and Davenport, 1995), BQ123 (6.9–7.4, Maguire and Davenport, 1995), ZD4054 (pIC <sub>50</sub> 8.3, Morris <i>et al.</i> , 2005), sitaxsentan (8.0, Wu <i>et al.</i> , 1997), ambrisentan (7.1, Bolli <i>et al.</i> , 2004) | BQ788 (8.4, Russell and Davenport, 1996), A192621 (8.1, von Geldern <i>et al.</i> , 1999), IRL2500 (7.2, Russell and Davenport, 1996), Ro468443 (7.1, Breu <i>et al.</i> , 1996)                                                    |
| Probes                 | [ <sup>3</sup> H]-S0139 (0.6 nM), [ <sup>3</sup> H]-BQ123 (3.2 nM, Ihara <i>et al.</i> , 1995), [ <sup>125</sup> I]-PD164333 (0.2 nM, Davenport <i>et al.</i> , 1998), [ <sup>125</sup> I]-PD151242 (0.5 nM, Davenport <i>et al.</i> , 1994)                                                                                                                                                                                                                  | [ <sup>125</sup> I]-IRL1620 (20 pM, Watakabe <i>et al.</i> , 1992), [ <sup>125</sup> I]-BQ3020 (0.1 nM, Molenaar <i>et al.</i> , 1992), [ <sup>125</sup> I]-[Ala <sup>1,3,11,15</sup> ]ET-1 (0.2 nM, Molenaar <i>et al.</i> , 1992) |

Subtypes of the ET<sub>B</sub> receptor have been proposed, although gene disruption studies in mice suggest that the heterogeneity results from a single gene product (Mizuguchi *et al.*, 1997).

**Abbreviations:** A127722, *trans-trans*-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-([N,N-dibutylamino]carbonylmethyl)pyrrolidine-3-carboxylate; A192621, (2*R*,3*R*,4*S*)-2-(4-propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-[2,6-diethylphenyl]acetamido)pyrrolidine-3-carboxylic acid; **ambrisentan**, 2-(4,6-dimethylpyrimidin-2-yl)oxy-3-methoxy-3,3-diphenylpropanoic acid; **BQ123**, *cyc*(DTrp-DAsp-Pro-D-Val-Leu); **BQ3020**, N-acetyl-Leu-Met-Asp-Lys-Glu-Ala-Val-Tyr-Phe-Ala-His-Leu-Asp-Ile-Ile-Trp; **BQ788**, N-*cis*-2,6-dimethylpiperidinocarbonyl-L-γ-methylleucyl-D-1-methoxycarbonyl-D-norleucine; **FR139317**, (R)-2-([R-2-((S)-2-([1-[hexahydro-1*H*-azepinyl]carbonyl]amino)methyl]pentanoyl]amino-3-(3-[methyl-1*H*-indodolyl]propionylamino-3-(2-pyridyl))propionate; **IRL1620**, Suc[Glu<sup>9</sup>,Ala<sup>11,15</sup>]ET-1<sub>10–21</sub>; **IRL2500**, N-(3,5-dimethylbenzoyl)-N-methyl-D-(4-phenylphenyl)-Ala-Trp; **LU135252**, (+)-(S)-2-(4,6-dimethoxypyrimidin-2-yl)oxy-3-methoxy-3,3-propionic acid; **PD151242**, (N-[hexahydro-1-azepinyl]carbonyl)Leu(1-Me)-DTrp-DTyr; **PD156707**, 2-benzo[1,3]dioxol-5-yl-4-(4-methoxyphenyl)-4-oxo-3-(3,4,5-trimethoxybenzyl)-but-2-enoate; **PD164333**, 2-benzo[1,3]dioxol-5-yl-4-(3-[2-(4-hydroxyphenyl)-ethylcarbamoyl]-propoxy)-4,5-dimethoxy-phenyl-3-(4-methoxy-benzoyl)-but-2-enoate; **RES7011**, *cyc*(Gly-Asn-Trp-His-Gly-Thr-Ala-Pro-Asp)-Trp-Phe-Phe-Asn-Tyr-Tyr-Trp; **Ro468443**, (R)-4-*tert*-butyl-N-(6-[2,3-dihydroxypropoxy]-5-[2-methoxyphenoxy]-2-[4-methoxyphenyl]-pyrimidin-4-yl)-benzenesulfonamide; **S0139**, 27-O-3-(2-[3-carboxyacryloylamino]-5-hydroxyphenyl)-acryloyloxymyricone, sodium salt; **SB209670**, (+)-1*S*,2*R*,5-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxypheyl)-5-prop-1-yloxyindane-2-carboxylate; **SB234551**, (E)-α-([1-butyl-5-[2-([2-carboxyphenyl]methoxy)-4-methoxyphenyl]-1*H*-pyrazol-4-yl]methylene)-6-methoxy-1,3-benzodioxole-5-propanoic acid; **sitaxsentan**, N-(4-chloro-3-methyl-1,2-oxazol-5-yl)-2-[2-(6-methyl-1,3-benzodioxol-5-yl)acetyl]thiophene-3-sulfonamide; **TAK044**, *cyc*(D-Asp-Asp(Php)-Asp-D-Thg-Leu-D-Trp)-4-oxobut-2-enoate; **ZD4054**, N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulfonamide

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# Formylpeptide

**Overview:** The formylpeptide receptors (ENSM00510000502765, nomenclature agreed by NC-IUPHAR Subcommittee on the formyl peptide receptor family, see Ye *et al.*, 2009) respond to exogenous ligands such as the bacterial product formyl-Met-Leu-Phe (fMLP) and endogenous ligands such as annexin I (ENSG00000135046), cathepsin G (ENSG00000100448) and spinorphin, derived from  $\beta$ -haemoglobin (ENSG00000244734).

| Nomenclature           | FPR1                                                                                                                                                         | FPR2/ALX                                                                                                                                                                                                                                              | FPR3                                |
|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|
| Other names            | Formyl peptide, fMLP, FPR                                                                                                                                    | FPRL1, FPR2, FPRH2, RFP, ALX                                                                                                                                                                                                                          | FPRH1, FMLPY, RMLP-R-I, FPRL2       |
| Ensembl ID             | ENSG00000171051                                                                                                                                              | ENSG00000171049                                                                                                                                                                                                                                       | ENSG00000187474                     |
| Principal transduction | G <sub>i/o</sub> , G <sub>z</sub>                                                                                                                            | G <sub>i</sub> (Maddox <i>et al.</i> , 1997)                                                                                                                                                                                                          | –                                   |
| Rank order of potency  | fMLP > Cathepsin G > Annexin I (Le <i>et al.</i> , 2002; Sun <i>et al.</i> , 2004)                                                                           | LXA <sub>4</sub> = ATL = ATLa2 > LTC <sub>4</sub> = LTD <sub>4</sub> >> 15-deoxy-LXA <sub>4</sub> >> fMLP (Clish <i>et al.</i> , 1999; Fiore <i>et al.</i> , 1994; Fiore and Serhan, 1995; Gronert <i>et al.</i> , 2001; Takano <i>et al.</i> , 1997) | –                                   |
| Selective agonists     | fMLP (Le <i>et al.</i> , 1999)                                                                                                                               | LXA <sub>4</sub> , ATL, ATLa2 (Guilford <i>et al.</i> , 2004), RvD1 (Krishnamoorthy <i>et al.</i> , 2010)                                                                                                                                             | F2L (Migeotte <i>et al.</i> , 2005) |
| Selective antagonists  | Cyclosporin H (6.3–7.0, Wenzel-Seifert and Seifert, 1993), BOC-PLPLP (6.0–6.5, Wenzel-Seifert and Seifert, 1993), spinorphin (4, Liang <i>et al.</i> , 2001) | –                                                                                                                                                                                                                                                     | –                                   |
| Probes                 | [ <sup>3</sup> H]-fMLP                                                                                                                                       | [ <sup>3</sup> H]-LXA <sub>4</sub> (0.2–1.7 nM; Fiore <i>et al.</i> , 1994; Takano <i>et al.</i> , 1997)                                                                                                                                              | –                                   |

Note that the data for FPR2/ALX are also reproduced on the Leukotriene, lipoxin, oxoeicosanoid and resolvin receptor pages (see Page S74).

**Abbreviations:** BOC-PLPLP, Boc-Phe-Leu-Phe-Leu-Phe; ATL, aspirin-triggered lipoxin A<sub>4</sub> [15-*epi*-LXA<sub>4</sub>, 5S,6R,15R-trihydroxyl-7E,9E,13E,11Z-eicosatetraenoic acid]; ATLa2, ATL analog [15-*epi*-16-(para-fluoro)-phenoxy-LXA<sub>4</sub>]; F2L, an acetylated 21-aa cleavage protein of haem-binding protein (ENSG00000013583); LTC<sub>4</sub>, leukotriene C<sub>4</sub>; LTD<sub>4</sub>, leukotriene D<sub>4</sub>; LXA<sub>4</sub>, lipoxin A<sub>4</sub> [5S,6R,15S-trihydroxyl-7E,9E,13E-11Z-eicosatetraenoic acid]; RvD1, resolvin D1

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# Free fatty acid

**Overview:** Free fatty acid receptors (FFA, nomenclature as agreed by NC-IUPHAR Subcommittee on free fatty acid receptors, Stoddart *et al.*, 2008) are activated by free fatty acids. Long chain saturated and unsaturated fatty acids (C16:0, C18:0, C18:1, C18:2, C18:3,n-6, C20:4, C20:5,n-3, C22:6,n-3, Briscoe *et al.*, 2003; Itoh *et al.*, 2003; Kotarsky *et al.*, 2003) activate FFA<sub>1</sub> receptors, while short chain fatty acids (C2, C3, C4 and C5) activate FFA<sub>2</sub> (Brown *et al.*, 2003; Le Poul *et al.*, 2003; Nilsson *et al.*, 2003) and FFA<sub>3</sub> (Brown *et al.*, 2003; Le Poul *et al.*, 2003) receptors. In addition, thiazolidinedione PPAR $\gamma$  agonists such as rosiglitazone activate FFA<sub>1</sub> (pEC<sub>50</sub> 5.2; Kotarsky *et al.*, 2003; Stoddart *et al.*, 2007; Smith *et al.*, 2009) and small molecule allosteric modulators, such as 4-CMTB, have recently been characterised for FFA<sub>2</sub> (Lee *et al.*, 2008; Smith *et al.*, 2011).

| Nomenclature           | FFA <sub>1</sub>                                                                                                                                                                                                                                                                            | FFA <sub>2</sub>                                                                                                              | FFA <sub>3</sub>                                                                                           |
|------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|
| Other names            | GPR40 (Sawzdargo <i>et al.</i> , 1997)                                                                                                                                                                                                                                                      | GPR43 (Sawzdargo <i>et al.</i> , 1997)                                                                                        | GPR41 (Sawzdargo <i>et al.</i> , 1997).<br>LSSIG (Senga <i>et al.</i> , 2003)                              |
| Ensembl ID             | ENSG00000126266                                                                                                                                                                                                                                                                             | ENSG00000126262                                                                                                               | ENSG00000185897                                                                                            |
| Principal transduction | G <sub>q/11</sub> (Briscoe <i>et al.</i> , 2003; Itoh <i>et al.</i> , 2003; Stoddart <i>et al.</i> , 2007)                                                                                                                                                                                  | G <sub>q/11</sub> , G <sub>i/o</sub> (Brown <i>et al.</i> , 2003; Le Poul <i>et al.</i> , 2003; Nilsson <i>et al.</i> , 2003) | G <sub>i/o</sub> (Brown <i>et al.</i> , 2003; Le Poul <i>et al.</i> , 2003; Stoddart <i>et al.</i> , 2007) |
| Selective agonists     | Linoleic acid (Briscoe <i>et al.</i> , 2003; Itoh <i>et al.</i> , 2003), TUG424 (pEC <sub>50</sub> 7.5, Christiansen <i>et al.</i> , 2008), GW9508 (pEC <sub>50</sub> 7.3; Briscoe <i>et al.</i> , 2006; Sum <i>et al.</i> , 2007), Cpd B (pEC <sub>50</sub> 6.1; Tan <i>et al.</i> , 2008) | (S)-2-(4-chlorophenyl)-N-(5-fluorothiazol-2-yl)-3-methylbutanamide (pEC <sub>50</sub> 6.4 Lee <i>et al.</i> , 2008)           | –                                                                                                          |
| Selective antagonists  | GW1100 (Briscoe <i>et al.</i> , 2006; Stoddart <i>et al.</i> , 2007)                                                                                                                                                                                                                        | –                                                                                                                             | –                                                                                                          |

GW1100 is also an oxytocin receptor antagonist (Briscoe *et al.*, 2006).

GPR42 (ENSG00000126251) was originally described as a pseudogene within the family (ENSM00250000002583), but the discovery of several polymorphisms suggests that some versions of GPR42 may be functional (Liaw and Connolly, 2009). GPR120 (ENSG00000186188) and GPR84 (ENSG00000139572) are structurally-unrelated G protein-coupled receptors. GPR120 is activated by unsaturated long chain free fatty acids (Gotoh *et al.*, 2007; Hirasawa *et al.*, 2005; Katsuma *et al.*, 2005) and GW9508 (pEC<sub>50</sub> 5.7; Briscoe *et al.*, 2006), while GPR84 was found to respond to medium chain fatty acids (Wang *et al.*, 2006).

**Abbreviations:** C16:0, palmitic acid; C18:0, stearic acid; C18:1, oleic acid; C18:2, linoleic acid; C18:3,n-6,  $\gamma$ -linolenic acid; C2, acetic acid; C20:4, arachidonic acid; C20:5,n-3, 5z,8z,11z,14z,17z-eicosapentaenoic acid, EPA; C22:6,n-3, 4z,7z,10z,13z,16z,19z-docosahexaenoic acid, DHA; C3, propionic acid; C4, butyric acid; C5, valeric acid; 4-CMTB, 4-chloro- $\alpha$ -(1-methylethyl)-N-2-thiazolylbenzeneacetamide; Cpd B, 3-chloro-5-trifluoromethyl-pyridin-2-yl-methoxy(4-(3-methylphenyl)methyl-1,3-thiazolidinedione-2,4-dione); GW1100, ethyl 4-(5-[[2-(ethyloxy)-5-pyrimidinyl]methyl]-2-[[4-(4-fluorophenyl)methyl]thio]-4-oxo-1[4H]-pyrimidinyl]benzoate; GW9508, 3-(4-[[3-(phenyloxy)phenyl]methyl]amino]phenyl)propanoic acid; TUG424, 4-[2-(2-methylphenyl)ethynyl]-benzenepropanoic acid

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# Frizzled

**Overview:** Receptors of the Class Frizzled (FZD, nomenclature as agreed by the NC-IUPHAR committee on Frizzled receptors, Schulte, 2010), which also includes Smoothened (Smo, ENSG00000128602, not considered here), are GPCR originally identified in *Drosophila* (Chan *et al.*, 1992), which are highly conserved across species. FZD are activated by WNTs, which are lipidated, cysteine-rich glycoprotein hormones with fundamental functions in ontogeny and tissue homeostasis. FZD signalling was initially divided into two pathways, being either dependent on the accumulation of the transcription factor  $\beta$ -catenin (ENSG00000168036) or being  $\beta$ -catenin-independent (often referred to as canonical vs non-canonical WNT/FZD signaling, respectively). WNT stimulation of FZDs can, in cooperation with the low density lipoprotein receptors (LRP 5, ENSG00000162337 and LRP6, ENSG00000070018), lead to the inhibition of a constitutively active destruction complex, which results in the accumulation of  $\beta$ -catenin.  $\beta$ -Catenin, in turn, modifies gene transcription in concert with TCF/LEF transcription factors.  $\beta$ -Catenin-independent FZD signaling is far more complex with regard to the diversity of the activated pathways. WNT/FZD signalling can lead to the activation of pertussis toxin-sensitive heterotrimeric G proteins (Kilander *et al.* 2011), the elevation of intracellular calcium (Slusarski *et al.*, 1997), activation of cGMP-specific PDE6 (Ahumada *et al.*, 2002) and elevation of cAMP (Hansen *et al.*, 2009). FZD signalling can also occur through Dishevelled phosphoproteins (ENSF00000001536) to RAC-1 and JNK, as well as Rho and ROCK kinases. As with other GPCRs, members of the Frizzled family are functionally dependent on the  $\beta$ -arrestin scaffolding protein for internalization (Chen *et al.*, 2003),  $\beta$ -catenin-dependent (Bryja *et al.*, 2007) and -independent (Bryja *et al.*, 2008; Kim and Han, 2007) signalling. The pattern of cell signalling is complicated by the presence of additional ligands which can enhance (Norrin or R-spondin) or inhibit FZD function (secreted Frizzled-related proteins [sFRP], Wnt inhibitory factor [WIF], SOST or Dickkopf), as well as modulatory proteins with positive (Ryk, ENSG00000163785; ROR1, ENSG00000185483 and ROR2, ENSG00000169071, see Page S183) and negative (Kremen) regulatory features, which may also function as independent signalling proteins.

| Nomenclature      | Other names        | Ensembl ID      |
|-------------------|--------------------|-----------------|
| FZD <sub>1</sub>  | Frizzled-1         | ENSG00000157240 |
| FZD <sub>2</sub>  | Frizzled-2         | ENSG00000180340 |
| FZD <sub>3</sub>  | Frizzled-3         | ENSG00000104290 |
| FZD <sub>4</sub>  | Frizzled-4, CD344  | ENSG00000174804 |
| FZD <sub>5</sub>  | Frizzled-5         | ENSG00000163251 |
| FZD <sub>6</sub>  | Frizzled-6         | ENSG00000164930 |
| FZD <sub>7</sub>  | Frizzled-7         | ENSG00000155760 |
| FZD <sub>8</sub>  | Frizzled-8         | ENSG00000177283 |
| FZD <sub>9</sub>  | Frizzled-9, CD349  | ENSG00000188763 |
| FZD <sub>10</sub> | Frizzled-10, CD350 | ENSG00000111432 |

There is limited knowledge about WNT/FZD specificity and which molecular entities determine the signalling outcome of a specific WNT/FZD pair. There is also a scarcity of information on basic pharmacological characteristics of FZDs, such as binding constants, ligand specificity or concentration-response relationships (see Kikuchi *et al.*, 2009).

## Ligands associated with FZD signalling

WNTs: WNT1 (ENSG00000125084), WNT2 (ENSG00000105989, also known as Int-1-related protein), WNT2B (ENSG00000134245, also known as WNT-13), WNT3 (ENSG00000108379), WNT3A (ENSG00000154342), WNT4 (ENSG00000162552), WNT5A (ENSG00000114251), WNT5B (ENSG00000111186), WNT6 (ENSG00000115596), WNT7A (ENSG00000154764), WNT7B (ENSG00000188064), WNT8A (ENSG00000061492), WNT8B (ENSG00000075290), WNT9A (ENSG00000143816, also known as WNT-14), WNT9B (ENSG00000158955, also known as WNT-15 or WNT-14b), WNT10A (ENSG00000135925), WNT10B (ENSG00000169884, also known as WNT-12), WNT11 (ENSG00000085741) and WNT16 (ENSG000000002745).

*Extracellular proteins that interact with FZDs:* Norrin (ENSG00000124479), R-spondin 1 (ENSG00000169218), R-spondin 2 (ENSG00000147655), R-spondin 3 (ENSG00000146374), R-spondin 4 (ENSG00000101282), sFRP 1 (ENSG00000104332), sFRP 2 (ENSG00000145423), sFRP 3 (ENSG00000162998), sFRP 4 (ENSG00000106483), sFRP 5 (ENSG00000120057),

*Extracellular proteins that interact with WNTs or LRPs:* Dickkopf 1 (ENSG00000104901), WIF 1 (ENSG00000156076), SOST (ENSG00000167941), Kremen 1 (ENSG00000183762) and Kremen 2 (ENSG00000131650)

**Abbreviations:** FZD, Frizzled; TCF/LEF, T cell factor/lymphoid enhancer binding factor

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# GABA<sub>B</sub>

**Overview:** Functional GABA<sub>B</sub> receptors (nomenclature agreed by NC-IUPHAR Subcommittee on GABA<sub>B</sub> receptors, Bowery *et al.*, 2002; see also Pin *et al.*, 2007) are formed from the heterodimerization of two similar 7TM subunits termed GABA<sub>B1</sub> and GABA<sub>B2</sub> (Bowery *et al.*, 2002; Pin *et al.*, 2004; Emson, 2007; Pin *et al.*, 2007; Ulrich and Bettler, 2007). GABA<sub>B</sub> receptors are widespread in the CNS and regulate both pre- and post-synaptic activity. The GABA<sub>B1</sub> subunit, when expressed alone, binds both antagonists and agonists, but the affinity of the latter is generally 10-100-fold less than for the native receptor. The GABA<sub>B1</sub> subunit when expressed alone is not transported to the cell membrane and is non-functional. Co-expression of GABA<sub>B1</sub> and GABA<sub>B2</sub> subunits allows transport of GABA<sub>B1</sub> to the cell surface and generates a functional receptor that can couple to signal transduction pathways such as high-voltage-activated Ca<sup>2+</sup> channels (Ca<sub>v</sub>2.1, Ca<sub>v</sub>2.2), or inwardly rectifying potassium channels (Kir3) (Bowery and Enna, 2000; Bowery *et al.*, 2002; Bettler *et al.*, 2004). The GABA<sub>B2</sub> subunit also determines the rate of internalisation of the dimeric GABA<sub>B</sub> receptor (Hannan *et al.*, 2011). The GABA<sub>B1</sub> subunit harbours the GABA (orthosteric)-binding site within an extracellular domain (ECD) venus flytrap module (VTM), whereas the GABA<sub>B2</sub> subunit mediates G-protein coupled signalling (Bowery *et al.*, 2002, Pin *et al.*, 2004). The two subunits interact by direct allosteric coupling (Monnier *et al.*, 2011) such that GABA<sub>B2</sub> increases the affinity of GABA<sub>B1</sub> for agonists and reciprocally GABA<sub>B1</sub> facilitates the coupling of GABA<sub>B2</sub> to G proteins (Pin *et al.*, 2004; Kubo and Tateyama, 2005). GABA<sub>B1</sub> and GABA<sub>B2</sub> subunits assemble in a 1:1 stoichiometry by means of a coiled-coil interaction between  $\alpha$ -helices within their carboxy-termini that masks an endoplasmic reticulum retention motif (RXRR) within the GABA<sub>B1</sub> subunit but other domains of the proteins also contribute to their heteromerization (Bettler *et al.*, 2004; Pin *et al.*, 2004). Recent evidence indicates that higher order assemblies of GABA<sub>B</sub> receptor comprising dimers of heterodimers occur in recombinant expression systems and *in vivo* and that such complexes exhibit negative functional cooperativity between heterodimers (Pin *et al.*, 2009; Comps-Agrar *et al.*, 2011). Adding further complexity, KCTD (potassium channel tetramerization proteins) 8, 12, 12b and 16 associate as tetramers with the carboxy terminus of the GABA<sub>B2</sub> subunit to impart altered signalling kinetics and agonist potency to the receptor complex (Bartoi *et al.*, 2010; Schwenk *et al.*, 2010 and reviewed by Pinard *et al.*, 2010). Four isoforms of the human GABA<sub>B1</sub> subunit have been cloned. The predominant GABA<sub>B1(a)</sub> and GABA<sub>B1(b)</sub> isoforms, which are most prevalent in neonatal and adult brain tissue respectively, differ in their ECD sequences as a result of the use of alternative transcription initiation sites. GABA<sub>B1(a)</sub>-containing heterodimers localise to distal axons and mediate inhibition of glutamate release in the CA3-CA1 terminals, and GABA release onto the layer 5 pyramidal neurons, whereas GABA<sub>B1(b)</sub>-containing receptors occur within dendritic spines and mediate slow postsynaptic inhibition (Vigot *et al.*, 2006; Pérez-García *et al.*, 2006). Isoforms generated by alternative splicing are GABA<sub>B1(c)</sub> that differs in the ECD, and GABA<sub>B1(e)</sub>, which is a truncated protein that can heterodimerize with the GABA<sub>B2</sub> subunit but does not constitute a functional receptor. Only the 1a and 1b variants are identified as components of native receptors (Bowery *et al.*, 2002). Additional GABA<sub>B1</sub> subunit isoforms have been described in rodents and humans (Lee *et al.*, 2010 and reviewed by Bettler *et al.*, 2004).

|                          |                                                                                                                                                                                                                                                                                                                          |
|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature             | GABA <sub>B</sub>                                                                                                                                                                                                                                                                                                        |
| Ensembl ID               | GABA <sub>B1</sub> ENSG00000237051; GABA <sub>B2</sub> ENSG00000136928                                                                                                                                                                                                                                                   |
| Principal transduction   | G <sub>i/o</sub>                                                                                                                                                                                                                                                                                                         |
| Selective agonists       | 3-APPA (CGP27492, 5 nM), 3-APMPA (CGP35024, 16 nM), (R)-(-)-baclofen (32 nM), CGP44532 (45 nM)                                                                                                                                                                                                                           |
| Selective antagonists    | CGP62349 (2.0 nM), CGP55845A (6 nM), SCH50911 (3 $\mu$ M), 2-hydroxy-s-(-)-saclofen (11 $\mu$ M), CGP35348 (27 $\mu$ M)                                                                                                                                                                                                  |
| Probes (K <sub>D</sub> ) | [ <sup>3</sup> H](R)-(-)-baclofen, [ <sup>3</sup> H]CGP54626 (1.5 nM; Bittiger <i>et al.</i> , 1992), [ <sup>3</sup> H]CGP62349 (0.9 nM, Keir <i>et al.</i> , 1999), [ <sup>125</sup> I]CGP64213 (1 nM, Galvez <i>et al.</i> , 2000), [ <sup>125</sup> I]CGP71872 (K <sub>i</sub> = 0.5 nM, Belley <i>et al.</i> , 1999) |

Potencies of agonists and antagonists listed in the table, quantified as IC<sub>50</sub> values for the inhibition of [<sup>3</sup>H]CGP27492 binding to rat cerebral cortex membranes, are from Froestl and Mickel (1997), Bowery *et al.* (2002) and Froestl (2011). Radioligand K<sub>D</sub> values relate to binding to rat brain membranes. CGP71872 is a photoaffinity ligand for the GABA<sub>B1</sub> subunit (Belley *et al.*, 1999). CGP27492, CGP35024 and CGP44532 act as antagonists at human GABA<sub>A</sub>  $\rho$ 1 receptors, with potencies in the low micromolar range (Froestl, 2011). In addition to the ligands listed in the table, Ca<sup>2+</sup> binds to the VTM of the GABA<sub>B1</sub> subunit to act as a positive allosteric modulator of GABA (Galvez *et al.*, 2000). In cerebellar Purkinje neurones, the interaction of Ca<sup>2+</sup> with the GABA<sub>B</sub> receptor enhances the activity of mGlu<sub>1</sub> through functional cross-talk involving G-protein G $\beta\gamma$  subunits (Tabata *et al.*, 2004; Rives *et al.*, 2009). Synthetic positive allosteric modulators with low, or no, intrinsic activity include CGP7930, GS39783, BHF177 and (+)-BHFF (Bettler *et al.*, 2004; Binet *et al.*, 2004; Adams and Lawrence, 2007; Froestl, 2011). The site of action of CGP7930 and GS39783 appears to be on the heptahelical domain of the GABA<sub>B2</sub> subunit (Pin *et al.*, 2004; Dupuis *et al.*, 2006). In the presence of CGP7930, or GS39783, CGP35348 and 2-hydroxy-saclofen behave as partial agonists (Froestl, 2011). Knock-out of the GABA<sub>B1</sub> subunit in C57B mice causes the development of severe tonic-clonic convulsions that prove fatal within a month of birth, whereas GABA<sub>B1</sub><sup>-/-</sup> BALB/c mice, although also displaying spontaneous epileptiform activity, are viable. The phenotype of the latter animals additionally includes hyperalgesia, hyperlocomotion (in a novel, but not familiar, environment), hyperdopaminergia, memory impairment and behaviours indicative of anxiety (Enna and Bowery, 2004; Vacher *et al.*, 2006). A similar phenotype has been found for GABA<sub>B2</sub><sup>-/-</sup> BALB/c mice (Gassmann *et al.*, 2004).

**Abbreviations:** 3-APMPA (CGP35024), 3-amino-propyl-(P-methyl)-phosphinic acid; 3-APPA (CGP27492), 3-amino-propyl-phosphinic acid; (+)-BHFF, (-)-5,7-di-tert-butyl-3-hydroxy-3-trifluoromethyl-3H-benzofuran-2-one; BHF177, (1R,2R,4S)-bicyclo[2.2.1]hept-2-yl]-2-methyl-5-[4-(trifluoromethyl)phenyl]-4-pyrimidinamine; CGP7930, 2,6-Di-tert-butyl-4-(3-hydroxy-2,2-dimethyl-propyl)-phenol; CGP35348, p-(3-aminopropyl)-P-diethoxymethylphosphinic acid; CGP44532, 3-amino-2-hydroxypropylmethylphosphinic acid; CGP54626, [S-(R,R)]-[3-[[1-(3,4-dichlorophenyl)ethyl]amino]-2-hydroxypropyl](cyclohexylmethyl)phosphinic acid; CGP55845A, 3-[-1-(S)-(3,4-dichlorophenyl)-ethyl]amino-2(S)-hydroxypropyl-(P-benzyl)-phosphinic acid; CGP62349, [3-[1-R-[[3-(methoxyphenylmethyl)hydroxyphosphinyl]-2(S)-hydroxypropyl]amino]ethyl]-benzoic acid; CGP64213, [3-[-(R)-[[3-5N-[1-[2-[[3-iodo-4-hydroxyphenyl]ethyl]carboxamido]pentyl]hydroxyphosphinyl]-2(S)-hydroxy-propyl]amino]ethyl]-benzoic acid; CGP71872, 3-(1-(R)-3-((5-(4-azido-2-hydroxy-5-iodobenzoylamino)pentyl)hydroxyphosphoryl)-2-(S)-hydroxypropylamino)ethyl)benzoic acid; GS39783, N,N'-dicyclopentyl-2-methylsulfanyl-5-nitro-pyrimidine-4,6-diamine; SCH50911, (+)-(2S)-5,5-dimethyl-2-morpholineacetic acid; VTM, Venus flytrap module

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# Galanin

**Overview:** Galanin receptors (provisional nomenclature, see Foord *et al.*, 2005) are activated by the endogenous peptides galanin (ENSG0000069482) and galanin-like peptide (GALP, ENSG00000197487). Human galanin is a 30 amino-acid non-amidated peptide (Evans and Shine, 1991); in other species, it is 29 amino acids long and C-terminally amidated. Amino acids 1–14 of galanin are highly conserved in mammals, birds, reptiles, amphibia and fish. Shorter peptide species (e.g. human galanin-1–19, (Bersani *et al.*, 1991a) and porcine galanin-5–29 (Sillard *et al.*, 1992)) and N-terminally extended forms (e.g. N-terminally seven and nine residue elongated forms of porcine galanin (Bersani *et al.*, 1991b; Sillard *et al.*, 1992)) have been reported.

| Nomenclature           | GAL <sub>1</sub>                                                               | GAL <sub>2</sub>                                                                                                                           | GAL <sub>3</sub>                         |
|------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| Other names            | Galanin-1 receptor, GALR1                                                      | Galanin-2 receptor, GALR2                                                                                                                  | Galanin-3 receptor, GALR3                |
| Ensembl ID             | ENSG00000166573                                                                | ENSG00000182687                                                                                                                            | ENSG00000128310                          |
| Principal transduction | G <sub>i/o</sub>                                                               | G <sub>i/o</sub> , G <sub>q/11</sub>                                                                                                       | G <sub>i/o</sub>                         |
| Rank order of potency  | Galanin>GALP (Ohtaki <i>et al.</i> , 1999)                                     | GALP≥galanin (Ohtaki <i>et al.</i> , 1999)                                                                                                 | GALP>galanin (Lang <i>et al.</i> , 2005) |
| Selective agonists     | –                                                                              | Galanin-(2–29) (Fathi <i>et al.</i> , 1997; Wang <i>et al.</i> , 1997),<br>D-Trp <sup>2</sup> -galanin-(1–29) (Smith <i>et al.</i> , 1997) | –                                        |
| Selective antagonists  | 2,3-Dihydro-dithiin-1,4-dithiin-1,1,4,4-tetroxide (Scott <i>et al.</i> , 2000) | M871 (7.9, Sollenberg <i>et al.</i> , 2006)                                                                                                | –                                        |

Galanin-(1–11) is a high-affinity agonist at GAL<sub>1</sub>/GAL<sub>2</sub> (pK<sub>i</sub> 9) and galanin-(2–11) is selective for GAL<sub>2</sub> and GAL<sub>3</sub> compared to GAL<sub>1</sub> (Lu *et al.*, 2005). [<sup>125</sup>I]-[Tyr<sup>26</sup>]galanin binds to all three subtypes with K<sub>d</sub> values ranging from 0.05 to 1 nM (Skofitsch *et al.*, 1986; Smith *et al.*, 1997;1998; Wang *et al.*, 1997; Fitzgerald *et al.*, 1998). Porcine galanin-(3–29) does not bind to cloned GAL<sub>1</sub>, GAL<sub>2</sub> or GAL<sub>3</sub> receptors, but a receptor that is functionally activated by porcine galanin-(3–29) has been reported in pituitary and gastric smooth muscle cells (Wynick *et al.*, 1993; Gu *et al.*, 1995). Additional galanin receptor subtypes are also suggested from studies with chimeric peptides (e.g. M15, M35 and M40), which act as antagonists in functional assays in the cardiovascular system (Ulman *et al.*, 1993), spinal cord (Wiesenfeld-Hallin *et al.*, 1992), locus coeruleus, hippocampus (Bartfai *et al.*, 1991) and hypothalamus (Leibowitz and Kim, 1992; Bartfai *et al.*, 1993), but exhibit agonist activity at some peripheral sites (Bartfai *et al.*, 1993; Gu *et al.*, 1995). The chimeric peptides M15, M32, M35, M40 and C7 are agonists at GAL<sub>1</sub> receptors expressed endogenously in Bowes human melanoma cells (Ohtaki *et al.*, 1999), and at heterologously expressed recombinant GAL<sub>1</sub>, GAL<sub>2</sub> and GAL<sub>3</sub> receptors (Smith *et al.*, 1997; Fitzgerald *et al.*, 1998; Smith *et al.*, 1998).

**Abbreviations:** C7, galanin-(1–13)-spantide; M15, galanin-(1–13)-substance P-5–11 amide, also known as galantide; M32, galanin-(1–13)-neuropeptide Y amide-(25–36) amide; M35, galanin-(1–13)-bradykinin-(2–9) amide; M40, galanin-(1–13)-Pro-Pro-Ala-Leu-Ala-Leu-Ala-Leu-Ala amide; M871, galanin-(2–13)-Glu-His-(Pro)<sub>3</sub>-(Ala-Leu)<sub>2</sub>-Ala-amide

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# Ghrelin

**Overview:** Ghrelin receptors (see Davenport *et al.*, 2005) are activated by a 28 amino-acid peptide originally isolated from rat stomach, where it is cleaved from a 117 amino-acid precursor (ENSG00000157017). The human gene encoding the precursor peptide has 83% sequence homology to rat prepro-ghrelin, although the mature peptides from rat and human differ by only two amino acids (Matsumoto *et al.*, 2001). Alternative splicing results in the formation of a second peptide, des-Gln<sup>14</sup>-ghrelin with equipotent biological activity (Hosoda *et al.*, 2000). A unique post-translational modification (octanoylation of Ser<sup>3</sup>, catalysed by ghrelin O-acyltransferase [MBOAT4, ENSG00000177669], Yang *et al.*, 2008) occurs in both peptides, essential for full activity in binding to the ghrelin receptors in the hypothalamus and pituitary; and the release of growth hormone from the pituitary (Kojima *et al.*, 1999). Structure activity studies showed the first five N-terminal amino acids to be the minimum required for binding (Bednarek *et al.*, 2000) and receptor mutagenesis has indicated overlap of the ghrelin binding site with those for small molecule agonists and allosteric modulators of ghrelin function (Holst *et al.*, 2009). In cell systems, the ghrelin receptor is constitutively active (Holst and Schwartz, 2004), but this is abolished by a naturally occurring mutation (A204E) that results in decreased cell surface receptor expression and is associated with familial short stature (Pantel *et al.*, 2006).

|                        |                                                                                                                                                                                                                                                                           |
|------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature           | Ghrelin                                                                                                                                                                                                                                                                   |
| Other names            | GHS-R1a (Growth hormone secretagogue receptor type 1), growth hormone-releasing peptide receptor                                                                                                                                                                          |
| Ensembl ID             | ENSG00000121853                                                                                                                                                                                                                                                           |
| Principal transduction | G <sub>q/11</sub>                                                                                                                                                                                                                                                         |
| Rank order of potency  | Ghrelin=des-Gln-ghrelin (Matsumoto <i>et al.</i> , 2001; Bedendi <i>et al.</i> , 2003)                                                                                                                                                                                    |
| Selective antagonists  | YIL781 (K <sub>B</sub> 11 nM) (Esler <i>et al.</i> , 2007)                                                                                                                                                                                                                |
| Probes                 | [ <sup>125</sup> I-His <sup>9</sup> ]-ghrelin (0.4 nM, Katugampola <i>et al.</i> , 2001), [ <sup>125</sup> I-Tyr <sup>4</sup> ]-ghrelin (0.5 nM, Bedendi <i>et al.</i> , 2003), [ <sup>125</sup> I]-Tyr <sup>4</sup> -des-octanoyl (0.7 nM, Bedendi <i>et al.</i> , 2003) |

Des-octanoyl ghrelin has been shown to bind (as [<sup>125</sup>I]-Tyr<sup>4</sup>-des-octanoyl ghrelin) and have effects in the cardiovascular system (Bedendi *et al.*, 2003), which raises the possible existence of different receptor subtypes in peripheral tissues and the central nervous system. A potent inverse agonist has been identified ([D-Arg<sup>1</sup>, D-Phe<sup>5</sup>, D-Trp<sup>7,9</sup>, Leu<sup>11</sup>]-substance P, pD<sub>2</sub> 8.3; Holst *et al.*, 2003). TZP101, described as a ghrelin receptor agonist (pK<sub>i</sub> 7.8 and pD<sub>2</sub> 7.5 at human recombinant ghrelin receptors), has been shown to stimulate ghrelin receptor mediated food intake and gastric emptying but not elicit release of growth hormone, or modify ghrelin stimulated growth hormone release, thus pharmacologically discriminating the orexigenic and gastrointestinal actions of ghrelin from the release of growth hormone (Fraser *et al.*, 2008).

**Abbreviations:** TZP101, (4R,7S,10R,13R)-7-cyclopropyl-13-(4-fluorobenzyl)-3-oxa-6,9,12,15-tetraaza-4,9,10-trimethyl-4,5,6,7,10,12,13,15,16,17,18-undecahydro-1,2-benzocyclooctadecene-8,11,14-trione; YIL781, 6-(4-fluorophenoxy)-3-([(3S)-1-isopropylpiperidin-3-yl]methyl)-2-methylquinazolin-4(3H)-one

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# Glucagon, glucagon-like peptide and secretin

**Overview:** The glucagon family of receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on the Glucagon receptor family, see Mayo *et al.*, 2003) are activated by the endogenous peptide (27–44 aa) hormones glucagon, glucagon-like peptide 1 (GLP-1), glucagon-like peptide 2 (GLP-2), glucose-dependent insulintropic polypeptide (also known as gastric inhibitory polypeptide or GIP, ENSG00000159224), growth hormone-releasing hormone (GHRH, ENSG00000118702) and secretin (ENSG00000070031). One common precursor (ENSG00000115263) generates glucagon, GLP-1 and GLP-2 peptides (Irwin, 2001).

| Nomenclature           | Glucagon                                                                                                                                                                                                                      | GLP-1                                                                                                                                                                                     | GLP-2           |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| Ensembl ID             | ENSG00000215644                                                                                                                                                                                                               | ENSG00000112164                                                                                                                                                                           | ENSG00000065325 |
| Principal transduction | G <sub>s</sub>                                                                                                                                                                                                                | G <sub>s</sub>                                                                                                                                                                            | G <sub>s</sub>  |
| Selective agonists     | Glucagon                                                                                                                                                                                                                      | GLP-1-(7-37) (Dillon <i>et al.</i> , 1993);<br>GLP-1-(7-36)amide (Thorens <i>et al.</i> , 1993),<br>exendin-3 (Raufman <i>et al.</i> , 1991),<br>exendin-4 (Thorens <i>et al.</i> , 1993) | GLP-2           |
| Selective antagonists  | L168049 (Cascieri <i>et al.</i> , 1999),<br>des-His <sup>1</sup> -[Glu <sup>9</sup> ]glucagon amide (Post <i>et al.</i> ,<br>1993), BAY27-9955 (Petersen and Sullivan,<br>2001), xNNC92-1687 (Madsen <i>et al.</i> ,<br>1998) | Exendin-(9-39) (Thorens <i>et al.</i> , 1993);<br>T0632 (Tibaduiza <i>et al.</i> , 2001)                                                                                                  | –               |
| Probes                 | [ <sup>125</sup> I]-glucagon                                                                                                                                                                                                  | [ <sup>125</sup> I]-GLP-1-(7-36) amide, [ <sup>125</sup> I]-exendin,<br>[ <sup>125</sup> I]-exendin-(9-39), [ <sup>125</sup> I]-GLP-1-(7-37)                                              | –               |

| Nomenclature           | GIP                     | GHRH                                                                    | Secretin                                                                  |
|------------------------|-------------------------|-------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Ensembl ID             | ENSG00000010310         | ENSG00000106128                                                         | ENSG00000080293                                                           |
| Principal transduction | G <sub>s</sub>          | G <sub>s</sub>                                                          | G <sub>s</sub>                                                            |
| Selective agonists     | GIP                     | BIM28011 (Coy <i>et al.</i> , 1996)                                     | Secretin                                                                  |
| Selective antagonists  | [Pro <sup>3</sup> ]GIP  | JV-1-36 (Schally and Varga, 1999), JV-1-38<br>(Schally and Varga, 1999) | [(CH <sub>2</sub> NH) <sup>4,5</sup> ]secretin (Kim <i>et al.</i> , 1993) |
| Probes                 | [ <sup>125</sup> I]-GIP | [ <sup>125</sup> I]-GHRH                                                | [ <sup>125</sup> I]-(Tyr <sup>10</sup> )secretin                          |

The glucagon receptor has been reported to interact with receptor activity modifying proteins (RAMPs), specifically RAMP2, in heterologous expression systems (Christopoulos *et al.*, 2003), although the physiological significance of this has yet to be established.

**Abbreviations:** BAY27-9955, (+)-3,5-diisopropyl-2-(1-hydroxyethyl)-6-propyl-4'-fluoro-1,1'-biphenyl; BIM28011, [D-Ala<sup>2</sup>,Ala<sup>8,9,15,27</sup>,D-Arg<sup>29</sup>]hGHRH-(1–29)NH<sub>2</sub>; JV-1-36, [PhAc-Tyr<sup>1</sup>,D-Arg<sup>2</sup>,Phe(4-Cl)<sup>6</sup>,Arg<sup>9</sup>,Abu<sup>15</sup>,Nle<sup>27</sup>,D-Arg<sup>28</sup>,Har<sup>29</sup>]hGHRH(1–29)NH<sub>2</sub>; JV-1-38, [PhAc-Tyr<sup>1</sup>,D-Arg<sup>2</sup>,Phe(4-Cl)<sup>6</sup>,Har<sup>9</sup>,Tyr(Me)<sup>10</sup>,Abu<sup>15</sup>,Nle<sup>27</sup>,D-Arg<sup>28</sup>,Har<sup>29</sup>]hGHRH(1–29)NH<sub>2</sub>; L168049, 2-(4-pyridyl)-5-(4-chlorophenyl)-3-(5-bromo-2-propyloxyphenyl)pyrrole; NNC92-1687, 2-(benzimidazol-2-ylthio)-1-(3,4-dihydroxyphenyl)-1-ethanone; T0632, sodium (S)-3-(1-[2-fluorophenyl]-2,3-dihydro-3-[[3-isoquinoliny]-carbonyl]amino-6-methoxy-2-oxo-1H-indole)propanoate

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# Glutamate, metabotropic

**Overview:** Metabotropic glutamate (mGlu) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Metabotropic Glutamate Receptors, Schoepp *et al.*, 2000) are activated by the endogenous ligands L-glutamate, L-aspartate, L-serine-O-phosphate (LSOP), N-acetylaspartylglutamate (NAAG) and L-cysteine sulphinic acid. Examples of agonists selective for mGlu receptors compared with ionotropic glutamate receptors are 1S,3R-ACPD and L-CCG-I, which show limited selectivity for Group II receptors. An example of an antagonist selective for mGlu receptors is LY341495, which blocks mGlu<sub>2</sub> and mGlu<sub>3</sub> at low nanomolar concentrations, mGlu<sub>8</sub> at high nanomolar concentrations, and mGlu<sub>1</sub>, mGlu<sub>4</sub>, mGlu<sub>5</sub> and mGlu<sub>7</sub> in the micromolar range (Kingston *et al.*, 1998). Three groups of native receptors are distinguishable on the bases of similarities of agonist pharmacology, primary sequence and G-protein effector coupling: Group I (mGlu<sub>1</sub> and mGlu<sub>5</sub>); Group II (mGlu<sub>2</sub> and mGlu<sub>3</sub>) and Group III (mGlu<sub>4</sub>, mGlu<sub>6</sub>, mGlu<sub>7</sub> and mGlu<sub>8</sub>) (see Further Reading). Group I mGlu receptors may be activated by DHPG and 3HPG (Brabet *et al.*, 1995), and antagonized by (S)-hexylhomobiphenic acid (Madsen *et al.*, 2005). Group II mGlu receptors may be activated by LY389795 (Monn *et al.*, 1999), LY379268 (Monn *et al.*, 1999), LY354740 (Schoepp *et al.*, 1997; Wu *et al.*, 1998), DCG-IV and 2R,4R-APDC (Schoepp *et al.*, 1996), and antagonised by EGLU (4.3, Jane *et al.*, 1996) and LY307452 (Escibano *et al.*, 1998; Wermuth *et al.*, 1996). Group III mGlu receptors may be activated by (RS)PPG (Gasparini *et al.*, 1999a).

In addition to orthosteric ligands that interact with the glutamate recognition site directly, allosteric modulators have been described. Negative allosteric modulators are listed separately. The positive allosteric modulators most often act as 'potentiators' of an orthosteric agonist response, without significantly activating the receptor in the absence of agonist.

| Nomenclature                             | mGlu <sub>1</sub>                                                                                                                                                                                                                                                                                  | mGlu <sub>2</sub>                                                                                                      | mGlu <sub>3</sub>                      | mGlu <sub>4</sub>                                                                                                                                                         |
|------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Other names                              | mGluR <sub>1</sub>                                                                                                                                                                                                                                                                                 | mGluR <sub>2</sub>                                                                                                     | mGluR <sub>3</sub>                     | mGluR <sub>4</sub>                                                                                                                                                        |
| Ensembl ID                               | ENSG00000152822                                                                                                                                                                                                                                                                                    | ENSG00000164082                                                                                                        | ENSG00000198822                        | ENSG00000124493                                                                                                                                                           |
| Principal transduction                   | G <sub>q/11</sub>                                                                                                                                                                                                                                                                                  | G <sub>i/o</sub>                                                                                                       | G <sub>i/o</sub>                       | G <sub>i/o</sub>                                                                                                                                                          |
| Selective agonists                       | –                                                                                                                                                                                                                                                                                                  | –                                                                                                                      | NAAG (Wroblewska <i>et al.</i> , 1997) | L-AP4, LSOP (Wu <i>et al.</i> , 1998)                                                                                                                                     |
| Selective positive allosteric modulators | Ro01-6128, Ro67-4853, Ro67-7476 (Knoflach <i>et al.</i> , 2001)                                                                                                                                                                                                                                    | LY487379 (Johnson <i>et al.</i> , 2003), CBiPES (Johnson <i>et al.</i> , 2005), BINA (Bonnefous <i>et al.</i> , 2005b) | –                                      | (-)-PHCCC (Maj <i>et al.</i> , 2003), SIB1893, MPEP (Mathiesen <i>et al.</i> , 2003), VU0155041 (Niswender <i>et al.</i> , 2008), VU0361737 (Engers <i>et al.</i> , 2009) |
| Selective competitive antagonists        | 3-MATIDA (Moroni <i>et al.</i> , 2002), AIDA (Moroni <i>et al.</i> , 1997), (S)-(+)-CBPG (Mannaioni <i>et al.</i> , 1999), LY367385 (Clark <i>et al.</i> , 1997), (S)-TBPG (Costantino <i>et al.</i> , 2001)                                                                                       | PCCG-4 (Pellicciari <i>et al.</i> , 1996)                                                                              | –                                      | MAP4                                                                                                                                                                      |
| Selective negative allosteric modulators | CPCCOEt (Litschig <i>et al.</i> , 1999), BAY36-7620 (Carroll <i>et al.</i> , 2001), LY456236 (Li <i>et al.</i> , 2002), 3,5-DMPPP (Micheli <i>et al.</i> , 2003), EM-TBPC (Malherbe <i>et al.</i> , 2003), JNJ16259685 (Lavreysen <i>et al.</i> , 2004), A841720 (8.0, Zheng <i>et al.</i> , 2005) | Ro64-5229 (Kolczewski <i>et al.</i> , 1999)                                                                            | –                                      | –                                                                                                                                                                         |

The activity of NAAG as an agonist at mGlu<sub>3</sub> receptors was questioned on the basis of contamination with glutamate (Chopra *et al.*, 2009; Fricker *et al.*, 2009), but this has been refuted (Neale, 2011).

| Nomenclature           | mGlu <sub>5</sub>                                                                  | mGlu <sub>6</sub>                                                                                 | mGlu <sub>7</sub>                     | mGlu <sub>8</sub>                                                                 |
|------------------------|------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|---------------------------------------|-----------------------------------------------------------------------------------|
| Other names            | mGluR <sub>5</sub>                                                                 | mGluR <sub>6</sub>                                                                                | mGluR <sub>7</sub>                    | mGluR <sub>8</sub>                                                                |
| Ensembl ID             | ENSG00000168959                                                                    | ENSG00000113262                                                                                   | ENSG00000196277                       | ENSG00000179603                                                                   |
| Principal transduction | G <sub>q/11</sub>                                                                  | G <sub>i/o</sub>                                                                                  | G <sub>i/o</sub>                      | G <sub>i/o</sub>                                                                  |
| Selective agonists     | CHPG (Doherty <i>et al.</i> , 1997), (S)-(+)-CBPG (Mannaioni <i>et al.</i> , 1999) | Homo-AMPA (Bräuner-Osborne <i>et al.</i> , 1996), 1-benzyl-APDC (Tuckmantel <i>et al.</i> , 1997) | LSOP (Wu <i>et al.</i> , 1998), L-AP4 | LSOP (Wu <i>et al.</i> , 1998), L-AP4, (S)-3,4-DCPG (Thomas <i>et al.</i> , 2001) |

| Nomenclature                             | mGlu <sub>5</sub>                                                                                                                                                                                                                         | mGlu <sub>6</sub>                          | mGlu <sub>7</sub>                       | mGlu <sub>8</sub>              |
|------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|-----------------------------------------|--------------------------------|
| Selective positive allosteric modulators | DFB (O'Brien <i>et al.</i> , 2003), CPPHA (O'Brien <i>et al.</i> , 2004), CDPBP (Kinney <i>et al.</i> , 2005), VU1545 (de Paulis <i>et al.</i> , 2006)                                                                                    | –                                          | AMN082 (Mitsukawa <i>et al.</i> , 2005) | –                              |
| Selective competitive antagonists        | ACDPP (6.5, Bonnefous <i>et al.</i> , 2005a)                                                                                                                                                                                              | MAP4, THPG (Thoreson <i>et al.</i> , 1997) | –                                       | MPPG (Wu <i>et al.</i> , 1998) |
| Selective negative allosteric modulators | SIB1757 (Varney <i>et al.</i> , 1999), SIB1893 (Varney <i>et al.</i> , 1999), MPEP (Gasparini <i>et al.</i> , 1999b), MTEP (Brodskin <i>et al.</i> , 2002), fenobam (Porter <i>et al.</i> , 2005), YM298198 (Kohara <i>et al.</i> , 2005) | –                                          | MMPIP (Suzuki <i>et al.</i> , 2007)     | –                              |

Radioligand binding using a variety of radioligands has been conducted on recombinant receptors (for example, [<sup>3</sup>H]-R214127 (Lavreysen *et al.*, 2003) and [<sup>3</sup>H]-YM298198 (Kohara *et al.*, 2005) at mGlu<sub>1</sub> receptors and [<sup>3</sup>H]-methoxyMPEP (Gasparini *et al.*, 2002) and [<sup>3</sup>H]-methoxymethyl-MTEP (Anderson *et al.*, 2002) at mGlu<sub>5</sub> receptors. Although a number of radioligands have been used to examine binding using native tissues, correlation with individual subtypes is limited. Many pharmacological agents have not been fully tested across all known subtypes of mGlu receptors. Potential differences linked to the species (e.g. human *versus* rat or mouse) of the receptors and the receptor splice variants are generally not known. The influence of receptor expression level on pharmacology and selectivity has not been controlled for in most studies, particularly those involving functional assays of receptor coupling.

(S)-(+)-CBPG is an antagonist at mGlu<sub>1</sub>, but is an agonist (albeit of reduced efficacy) at mGlu<sub>5</sub> receptors. DCG-IV also exhibits agonist activity at NMDA glutamate receptors (Uyama *et al.*, 1997). A potential novel metabotropic glutamate receptor coupled to phosphoinositide turnover has been observed in rat brain; it is activated by 4-methylhomobutyric acid (ineffective as an agonist at recombinant Group I metabotropic glutamate receptors), but resistant to LY341495 (Chung *et al.*, 1997). There are also reports of a distinct metabotropic glutamate receptor coupled to phospholipase D in rat brain, which does not readily fit into the current classification (Klein *et al.*, 1997; Pellegrini-Giampietro *et al.*, 1996).

**Abbreviations:** A841720, 3-(azepan-1-yl)-9-(dimethylamino)-[1]benzothio[3,2-d]pyrimidin-4-one; ACDPP, 3-amino-6-chloro-5-dimethylamino-N-2-pyridinylpyrazinecarboxamide hydrochloride; 1S,3R-ACPD, 1-aminocyclopentane-1S,3R-dicarboxylate; AIDA, 1-aminoindan-1,5(RS)-dicarboxylic acid; also known as UPF523; AMN082, N,N'-bis(diphenylmethyl)-1,2-ethanediamine dihydrochloride; L-AP4, S-2-amino-4-phosphonobutyrate; 2R,4R-APDC, aminopyrrolidine-2R,4R-dicarboxylate; also known as LY314593; BAY 36-7620, (3aS,6aS)-6a-naphthalen-2-ylmethyl-5-methyliden-hexahydro-1,3-dihydro-2H-pyrido[4,3-b]pyrimidin-5-ylmethyl-4-carboxylic acid, also known as biphenyl indanone A; CBiPES, N-[4'-cyano-biphenyl-3-yl]-N-(3-pyridinylmethyl)-ethanesulphonamide hydrochloride; (S)-(+)-CBPG, (S)-1-(2-(39-carboxybicyclo[1.1.1]pentyl)glycine; L-CCG-I, (2S,3S,4S)-α-(carboxycyclopropyl)glycine; CDPBP, 3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide; CHPG, 2-chloro-5-hydroxyphenylglycine; CPCCOEt, cyclopropan[b]chromen-1a-carboxylate; 4CPG, 4-carboxyphenylglycine; CPPHA, N-[4-chloro-2-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]phenyl]-2-hydroxybenzamide; DCG-IV, (2S,1'R,2'R,3'R)-2-(2,3-dicarboxycyclopropyl)glycine; (S)-3,4-DCPG, (S)-3,4-dicarboxyphenylglycine; DFB, 3,3'-difluorobenzaldazine; DHPG, S-3,5-dihydroxyphenylglycine; DMPPP, 3,5-dimethyl pyrrole-2,4-dicarboxylic acid 2-propyl ester 4-(1,2,2-trimethyl-propyl) ester; EGLU, (S)-α-ethylglutamate; EM-TBPC, (1-ethyl-2-methyl-6-oxo-4-(1,2,4,5-tetrahydrobenzo[d]azepin-3-yl)-1,6-dihydropyrimidine-5-carbonitrile; fenobam, N-(3-chlorophenyl)-N'-(4,5-dihydro-1-methyl-4-oxo-1H-imidazole-2-yl)-urea; 3HPG, 3-hydroxyphenylglycine; [<sup>11</sup>C]-JNJ-16567083, (3-ethyl-2-[<sup>11</sup>C]methyl-6-quinolinyl)(cis-4-methoxycyclohexyl) methanone; JNJ16259685, (3,4-dihydro-2H-pyrano[2,3-b]quinolinyl-7-yl)(cis-4-methoxycyclohexyl)methanone; LY307452, 2S,4S-2-amino-4-(4,4-diphenylbut-1-yl)pentan-1,5-diols; LY341495, 2S-2-amino-2-(1S,2S-2-carboxycyclopropan-1-yl)-3-(xanth-9-yl)propanoic acid; LY354740, (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylate; LY367385, (+)-2-methyl-4-carboxyphenylglycine; LY379268, (-)-2-oxa-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylic acid; LY389795, (-)-2-thia-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylic acid; LY393675, α-substituted-cyclobutylglycine; LY456066, (2-[4-(indan-2-ylamino)-5,6,7,8-tetrahydro-quinazolin-2-ylsulfanyl]-ethanol,hydrochloride; LY456236, [(4-methoxy-phenyl)-(6-methoxy-quinazolin-4-yl)-amine hydrochloride; LY487379, 2,2,2-trifluoro-N-[4-(2-methoxyphenoxy)phenyl]-N-(3-pyridinylmethyl)-ethanesulphonamide; 3-MATIDA, α-amino-5-carboxy-3-methyl-2-thiopheneacetic acid; MAP4, (S)-2-methyl-2-amino-4-phosphonobutanoate; methoxy-MPEP, 2-methyl-6-((3-methoxyphenyl)ethynyl)-pyridine; methoxy-PEPy, 3-methoxy-5-(pyridin-2-yl-ethynyl)-pyridine; MMPIP, 6-(4-methoxyphenyl)-5-methyl-3-(4-pyridinyl)-isoxazolo[4,5-c]pyridin-4(5H)-one hydrochloride; MPEP, 2-methyl-6-(phenylethynyl)-pyridine; MPPG, (RS)-α-methyl-4-phosphonophenylglycine; MTEP, 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine; methoxymethyl-MTEP, 3-(methoxymethyl)-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine; NAAG, N-acetylaspartylglutamate, also known as spaglumic acid; PCCG-4, (2S,1'S,2'S,3'R)-2-(2'-carboxy-3'-phenylcyclopropyl)glycine; PHCCC, N-phenyl-7-(hydroxylimino)cyclopropa[b]chromen-1a-carboxamide; (RS)PPG, (R,S)-4-phosphonophenylglycine; R214127, 1-(3,4-dihydro-2H-pyrano[2,3-b]quinolin-7-yl)-2-phenyl-1-ethanone; Ro01-6128, diphenylacetyl-carbamic acid ethyl ester; Ro62-5229, (Z)-1-[2-cycloheptyloxy-2-(2,6-dichlorophenyl)ethynyl]-1H-1,2,4-triazole; Ro67-4853, (9H-xanthene-9-carbonyl)-carbamic acid butyl ester; Ro67-7476, (S)-2-(4-fluorophenyl)-1-(toluene-4-sulfonyl)-pyrrolidine; SIB1757, 6-methyl-2-(phenylazo)-3-pyridinol; SIB1893, [(phenylazo)-3-pyridinol]-2-methyl-6-(2-phenylethenyl)pyridine; S-TBPG, 2-(3'-(1H-tetrazol-5-yl)bicyclo[1.1.1]pent-1-yl)glycine; THPG, (RS)-3,4,5-trihydroxyphenylglycine; VU1545, N-[1-(2-fluorophenyl)-3-phenyl-1H-pyrazol-5-yl]-4-nitrobenzamide; VU0155041, cis-2-[(3,5-dichlorophenyl)amino]carbonylcyclohexanecarboxylic acid; VU0361737, N-(4-chloro-3-methoxyphenyl)-2-pyridinecarboxamide; YM298198, (6-[[[(2-methoxyethyl)amino]methyl]-N-methyl-N-neopentylthio]ol[3,2-a]benzimidazole-2-carboxamide

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# Glycoprotein hormone

**Overview:** Glycoprotein hormone receptors (provisional nomenclature) are activated by a heterodimeric glycoprotein made up of a common  $\alpha$  chain (116 amino-acid ENSG00000135346), with a unique  $\beta$  chain that confers the biological specificity to FSH (follicle-stimulating hormone, follitropin, 129 amino-acid, ENSG00000131808), LH (luteinizing hormone, lutropin, 141 amino-acid ENSG00000104826), CG (choriogonadotropin, chorionic gonadotropin, 165 amino-acid, ENSG00000104818/ENSG00000104827) or TSH (thyrotropin, thyroid-stimulating hormone, 138 amino-acid ENSG00000134200). There is binding cross-reactivity across the endogenous agonists for each of the glycoprotein hormone receptors. The deglycosylated hormones appear to exhibit reduced efficacy at these receptors (Sairam, 1989).

| Nomenclature           | FSH                     | LH                                                    | TSH                                                               |
|------------------------|-------------------------|-------------------------------------------------------|-------------------------------------------------------------------|
| Ensembl ID             | ENSG00000170820         | ENSG00000168546                                       | ENSG00000146013                                                   |
| Principal transduction | G <sub>s</sub>          | G <sub>s</sub> , G <sub>q/11</sub> and G <sub>i</sub> | All four families of G proteins can be activated by this receptor |
| Selective agonists     | FSH                     | LH, CG                                                | TSH                                                               |
| Probes                 | [ <sup>125</sup> I]-FSH | [ <sup>125</sup> I]-LH, [ <sup>125</sup> I]-CG        | [ <sup>125</sup> I]-TSH                                           |

Animal follitropins are less potent than the human hormone as agonists at the human FSH receptor. Autoimmune antibodies that act as agonists of the TSH receptor are found in patients with Grave's disease (e.g. Rapoport *et al.*, 1998). Gain- and loss-of-function mutations of the FSH receptor are associated with human reproductive disorders (Aittomaki *et al.*, 1995; Beau *et al.*, 1998; Gromoll *et al.*, 1996; Touraine *et al.*, 1999). Loss-of-function mutations of the LH receptor are associated with Leydig cell hypoplasia and gain-of-function mutations are associated with male-limited gonadotropin-independent precocious puberty (e.g. Latronico and Segaloff, 1999; Shenker, 2002) and Leydig cell tumours (Liu *et al.*, 1999). Mutations of the TSH receptor exhibiting constitutive activity underlie hyperfunctioning thyroid adenomas (Parma *et al.*, 1993) and congenital hyperthyroidism (Kopp *et al.*, 1995). TSH receptor loss-of-function mutations are associated with thyrotropin resistance (Sunthornthepvarakul *et al.*, 1995). The rat FSH receptor also stimulates phosphoinositide turnover through an unidentified G protein (Quintana *et al.*, 1994).

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# Gonadotropin-releasing hormone (GnRH)

**Overview:** GnRH<sub>1</sub> and GnRH<sub>2</sub> receptors (provisional nomenclature, also called Type I and Type II, respectively) have been cloned from numerous species (most of which express two or three types of GnRH receptor) and grouped phylogenetically (Silver *et al.*, 2005). Gonadotropin-releasing hormone (GnRH) is a hypothalamic decapeptide (pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pr-Gly-NH<sub>2</sub>, also known as luteinising hormone-releasing hormone, gonadoliberin, luliberin, gonadorelin, ENSG00000147437) designated GnRH I, to distinguish it from related peptides, such as GnRH II (pGlu-His-Trp-Ser-His-Gly-Trp-Tyr-Pro-Gly-NH<sub>2</sub>, also known as chicken GnRH-II, ENSG00000180290). Receptors for all three ligands exist in amphibians but only GnRH I and GnRH II (and their cognate receptors) have been found in mammals (Sealfon *et al.*, 1997; Millar, 2005). GnRH<sub>1</sub> receptors are expressed primarily by pituitary gonadotrophs in mammals and mediate central control of reproduction. They are selectively activated by GnRH I and all lack the C-terminal tails found in other GPCR. GnRH<sub>2</sub> receptors all possess C-terminal tails and (where tested) are selective for GnRH II (over GnRH I). An alternative phylogenetic classification (see Millar *et al.*, 2004) divided these receptors into three classes and includes both GnRH I-selective mammalian and GnRH II-selective non-mammalian receptors as GnRH<sub>1</sub> receptors. Although thousands of peptide analogues of GnRH I have been synthesised and several (agonists and antagonists) are used therapeutically (Kiesel *et al.*, 2002), the potency of most of these peptides at GnRH<sub>2</sub> receptors is unknown.

| Nomenclature           | GnRH <sub>1</sub>                                                             | GnRH <sub>2</sub>                         |
|------------------------|-------------------------------------------------------------------------------|-------------------------------------------|
| Other names            | Type I GnRHR, LHRH receptor, GnRH I receptor                                  | Type II GnRHR                             |
| Ensembl ID             | ENSG00000109163                                                               | ENSG00000211451                           |
| Principal transduction | G <sub>q/11</sub>                                                             | G <sub>q/11</sub>                         |
| Rank order of potency  | GnRH I > GnRH II                                                              | GnRH II > GnRH I                          |
| Selective agonists     | Triptorelin, buserelin, leuprorelin, nafarelin, histrelin, goserelin          | –                                         |
| Selective antagonists  | Antide (9.0, Neill, 2002), cetrorelix (8.8, Neill, 2002), ganirelix, abarelix | Trptorelix-1 (Maiti <i>et al.</i> , 2003) |
| Probes                 | [ <sup>125</sup> I]-GnRH I, [ <sup>125</sup> I]-buserelin                     | [ <sup>125</sup> I]-GnRH II               |

GnRH<sub>1</sub> and GnRH<sub>2</sub> receptors couple primarily to G<sub>q/11</sub> (Grosse *et al.*, 2000) but coupling to G<sub>s</sub> and G<sub>i</sub> is evident in some systems (Krsmanovic *et al.*, 2003). GnRH<sub>2</sub> receptors may also mediate (heterotrimeric) G protein-independent signalling to protein kinases (see Caunt *et al.*, 2004). There is increasing evidence for expression of GnRH receptors on hormone-dependent cancer cells where they can exert antiproliferative and/or proapoptotic effects and mediate effects of cytotoxins conjugated to GnRH analogues (Limonta *et al.*, 2003; Harrison *et al.*, 2004; Schally and Nagy, 2004; Cheng and Leung, 2005). In some human cancer cell models GnRH II is more potent than GnRH I, implying mediation by GnRH<sub>2</sub> receptors (Grundker *et al.*, 2002). However, GnRH<sub>2</sub> receptors that are expressed by some primates are probably not expressed in humans because the human *GNRHR2* gene contains a frame shift and internal stop codon (Morgan *et al.*, 2003). The possibility remains that this gene generates GnRH<sub>2</sub> receptor-related proteins (other than the full-length receptor) that mediate responses to GnRH II (see Neill *et al.*, 2004). Alternatively, there is evidence for multiple active GnRH receptor conformations (Caunt *et al.*, 2004; Maudsley *et al.*, 2004; Millar *et al.*, 2004) raising the possibility that GnRH<sub>1</sub> receptor-mediated proliferation inhibition in hormone-dependent cancer cells is dependent upon different conformations (with different ligand specificity) than effects on G<sub>q/11</sub> in pituitary cells (Maudsley *et al.*, 2004). Loss-of-function mutations in the GnRH<sub>1</sub> receptor and deficiency of GnRH I are associated with hypogonadotropic hypogonadism although some 'loss of function' mutations may actually prevent trafficking of 'functional' GnRH<sub>1</sub> receptors to the cell surface, as evidenced by recovery of function by nonpeptide antagonists (Leanos-Miranda *et al.*, 2003). GnRH receptor signalling may be dependent upon receptor oligomerisation (Conn *et al.*, 1982; Kroeger *et al.*, 2001).

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# G protein-coupled estrogen (GPER)

**Overview:** The G protein-coupled estrogen receptor (GPER, provisional nomenclature) was identified following observations of oestrogen-evoked cyclic AMP signalling in breast cancer cells (Aronica *et al.*, 1994), dependent on the expression of an orphan GPCR GPR30 (Owman *et al.*, 1996; Carmeci *et al.*, 1997). There are observations of both cell-surface and intracellular localization of GPER (Revankar *et al.*, 2005; Thomas *et al.*, 2005).

|                        |                                                                                                 |
|------------------------|-------------------------------------------------------------------------------------------------|
| Nomenclature           | GPER                                                                                            |
| Other names            | GPR30, IL8-related receptor DRY12, flow-induced endothelial G-protein coupled receptor, GPCR-BR |
| Ensembl ID             | ENSG00000164850                                                                                 |
| Principal transduction | G <sub>s</sub> (Filardo <i>et al.</i> , 2000), G <sub>i/o</sub> (Revankar <i>et al.</i> , 2005) |
| Selective agonists     | G1 (Bologa <i>et al.</i> , 2006)                                                                |
| Selective antagonists  | G15 (Dennis <i>et al.</i> , 2009)                                                               |
| Probes                 | [ <sup>3</sup> H]-Oestrogen (Revankar <i>et al.</i> , 2005; Thomas <i>et al.</i> , 2005)        |

Antagonists at the nuclear oestrogen receptor, such as ICI182780 and tamoxifen (Filardo *et al.*, 2000), as well as the flavonoid 'phytoestrogens' genistein and quercetin (Maggiolini *et al.*, 2004), are agonists at GPER receptors.

**Abbreviations:** **G1**, 1-(4-[6-bromo-benzo[1,3]dioxol-5-yl]-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl)ethanone; **G15**, 4-(6-bromo-benzo[1,3]dioxol-5-yl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline; **ICI182780**, 7 $\alpha$ -(9-[[4,4,5,5,5-pentafluoropentyl]sulphonyl]nonyl)estra-1,3,5(10)-triene-3,17 $\beta$ -diol

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# GPR18, GPR55 and GPR119

**Overview:** GPR18, GPR55 and GPR119 (provisional nomenclature), although showing little structural similarity to CB<sub>1</sub> and CB<sub>2</sub> receptors, respond to endogenous agents analogous to the endogenous cannabinoid ligands, as well as some natural/synthetic cannabinoid receptor ligands (see Pertwee *et al.*, 2010).

| Nomenclature                 | GPR18                                                      | GPR55                                                                                                                    | GPR119                                                                                                                                                            |
|------------------------------|------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Other names                  | –                                                          | –                                                                                                                        | SNORF25                                                                                                                                                           |
| Ensembl ID                   | ENSG00000125245                                            | ENSG00000135898                                                                                                          | ENSG00000147262                                                                                                                                                   |
| Principal transduction       | G <sub>i/o</sub> (Kohno <i>et al.</i> , 2006)              | G <sub>12/13</sub> (Ryberg <i>et al.</i> , 2007)                                                                         | G <sub>s</sub> (Ning <i>et al.</i> , 2008; Overton <i>et al.</i> , 2006)                                                                                          |
| Putative endogenous agonists | <i>N</i> -Arachidonoylglycine (Kohno <i>et al.</i> , 2006) | Lysophosphatidylinositol (Oka <i>et al.</i> , 2007),<br>2-arachidonoylglycerolphosphoinositol (Oka <i>et al.</i> , 2009) | <i>N</i> -Oleylethanolamine ><br><i>N</i> -palmitoylethanolamine ><br><i>N</i> -stearoylethanolamine<br>(anandamide is ineffective, Overton <i>et al.</i> , 2006) |
| Synthetic agonists           | –                                                          | AM251 (Henstridge <i>et al.</i> , 2009;<br>Kapur <i>et al.</i> , 2009)                                                   | PSN375963, PSN632408 (Overton <i>et al.</i> , 2006), AS1269574 (Yoshida <i>et al.</i> , 2010)                                                                     |

GPR18 failed to respond to a variety of lipid-derived agents in an *in vitro* screen (Yin *et al.*, 2009), but has recently been reported to be activated by Δ<sup>9</sup>-tetrahydrocannabinol (McHugh *et al.*, 2011). GPR55 responds to AM251 and rimonabant at micromolar concentrations, compared to their nanomolar affinity as CB<sub>1</sub> receptor antagonists/inverse agonists (see Pertwee *et al.*, 2010). Lysophosphatidylinositol has been reported to act at other sites (Bondarenko *et al.*, 2011). Oleoyl-lysophosphatidylcholine has also been suggested to act, at least in part, through GPR119 (Ning *et al.*, 2008). Although PSN375963 and PSN632408 produce GPR119-dependent responses in heterologous expression systems, comparison with OEA-mediated responses suggests additional mechanisms of action (Ning *et al.*, 2008).

**Abbreviations:** AM251, *N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide; AS1269574, 2-([2-{4-bromophenyl}-6-methyl-4-pyrimidinyl]amino)ethanol; PSN375963, 4-(5-[4-butylcyclohexyl]-1,2,4-oxadiazol-3-yl)pyridine; PSN632408, 4-([3-{4-pyridinyl}-1,2,4-oxadiazol-5-yl]methoxy)-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester; **rimonabant**, *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride, also known as SR141716A

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# Histamine

**Overview:** Histamine receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Histamine Receptors, see Hill *et al.*, 1997) are activated by the endogenous ligand histamine. Marked species differences exist between histamine receptor orthologues (see Hill *et al.*, 1997).

| Nomenclature           | H <sub>1</sub>                                                                                       | H <sub>2</sub>                                                                               | H <sub>3</sub>                                                                                                                                                                                                      | H <sub>4</sub>                                                            |
|------------------------|------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Ensembl ID             | ENSG00000196639                                                                                      | ENSG00000168546                                                                              | ENSG00000146013                                                                                                                                                                                                     | ENSG00000134489                                                           |
| Principal transduction | G <sub>q/11</sub>                                                                                    | G <sub>s</sub>                                                                               | G <sub>i/o</sub>                                                                                                                                                                                                    | G <sub>i/o</sub>                                                          |
| Selective agonists     | Histaprodifen,<br>N <sup>ε</sup> -methylhistaprodifen                                                | Amthamine                                                                                    | Methimepip (Kitbunnadaj<br><i>et al.</i> , 2005), immethridine<br>(Kitbunnadaj <i>et al.</i> , 2004)                                                                                                                | Clobenpropit,<br>4-methylhistamine,<br>VUF8430 (Lim <i>et al.</i> , 2006) |
| Selective antagonists  | Triprolidine (9.9),<br>mepyramine (9.1)                                                              | Tiotidine (7.8), ranitidine<br>(7.1)                                                         | Clobenpropit (9.9),<br>iodophenpropit (9.6),<br>A331440 (8.5, Hancock<br><i>et al.</i> , 2004), thioperamide<br>(8.4)                                                                                               | JNJ7777120 (8.1)                                                          |
| Probes                 | [ <sup>3</sup> H]-Mepyramine (1 nM),<br>[ <sup>11</sup> C]-Mepyramine,<br>[ <sup>11</sup> C]-doxepin | [ <sup>3</sup> H]-Tiotidine (15 nM),<br>[ <sup>125</sup> I]-iodoaminopotentidine<br>(0.3 nM) | [ <sup>3</sup> H]-R-α-Methylhistamine<br>(0.5 nM),<br>[ <sup>3</sup> H]-N <sup>ε</sup> -methylhistamine<br>(2 nM),<br>[ <sup>125</sup> I]-iodophenpropit<br>(0.6 nM), [ <sup>125</sup> I]-iodoproxyfan<br>(0.06 nM) | [ <sup>3</sup> H]-JNJ7777120 (3.6 nM)                                     |

Histaprodifen and N<sup>ε</sup>-methylhistaprodifen are reduced efficacy agonists. The H<sub>4</sub> receptor appears to exhibit broadly similar pharmacology to the H<sub>3</sub> receptor for imidazole-containing ligands, although R-α-methylhistamine and N-α-methylhistamine are less potent, while clobenpropit acts as a reduced efficacy agonist (Nakamura *et al.*, 2000; Oda *et al.*, 2000; Liu *et al.*, 2001; Nguyen *et al.*, 2001; Zhu *et al.*, 2001). Moreover, 4-methylhistamine is identified as a high affinity, full agonist for the human H<sub>4</sub> receptor (Lim *et al.*, 2005). [<sup>3</sup>H]-Histamine has been used to label the H<sub>4</sub> receptor in heterologous expression systems.

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# Hydroxycarboxylic acid family

**Overview:** The hydroxycarboxylic acid family of receptors (ENSM00500000271913, nomenclature as agreed by NC-IUPHAR Subcommittee on Hydroxycarboxylic acid receptors, see Offermanns *et al.*, 2011) respond to organic acids, including the endogenous short chain fatty acids, butyrate and lactate, as well as the lipid lowering agents nicotinic acid (niacin), acipimox and acifran (Soga *et al.*, 2003; Tunaru *et al.*, 2003; Wise *et al.*, 2003). These receptors were provisionally described as nicotinic acid receptors, although nicotinic acid shows submicromolar potency at HCA<sub>2</sub> receptors only (Tunaru *et al.*, 2003; Wise *et al.*, 2003).

| Nomenclature           | HCA <sub>1</sub>                                             | HCA <sub>2</sub>                                                                                                                                                                           | HCA <sub>3</sub>                                                                          |
|------------------------|--------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Other names            | GPR81, GPR104                                                | GPR109A, Niacin receptor 1, HM74A, Nic1, Puma-G,                                                                                                                                           | GPR109B, Low affinity nicotinic acid receptor, HM74, Nic2                                 |
| Ensembl ID             | ENSG00000196917                                              | ENSG00000182782                                                                                                                                                                            | ENSG00000255398                                                                           |
| Principal transduction | G <sub>i/o</sub> (Ge <i>et al.</i> , 2008)                   | G <sub>i/o</sub> (Soga <i>et al.</i> , 2003; Wise <i>et al.</i> , 2003; Tunaru <i>et al.</i> , 2003)                                                                                       | G <sub>i/o</sub> (Soga <i>et al.</i> , 2003; Wise <i>et al.</i> , 2003)                   |
| Selective agonists     | Lactate (Cai <i>et al.</i> , 2008; Liu <i>et al.</i> , 2009) | Nicotinic acid (Soga <i>et al.</i> , 2003; Wise <i>et al.</i> , 2003; Tunaru <i>et al.</i> , 2003), acipimox (Wise <i>et al.</i> , 2003), 3-hydroxybutyrate (Taggart <i>et al.</i> , 2005) | 3-Hydroxyoctanoic acid (Ahmed <i>et al.</i> , 2009), IBC293 (Semple <i>et al.</i> , 2006) |
| Probes                 | –                                                            | [ <sup>3</sup> H]-Nicotinic acid (Soga <i>et al.</i> , 2003)                                                                                                                               | –                                                                                         |

Further closely-related GPCR include the 5-oxoeicosanoid receptor (ENSG00000162881, see Page S74) and GPR31 (ENSG00000120436).

**Abbreviations:** IBC293, 1-(1-methylethyl)-1H-benzotriazole-5-carboxylic acid

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# KISS1, neuropeptide FF, prolactin-releasing peptide and QRFP

**Overview:** KISS1 (nomenclature agreed by NC-IUPHAR committee on kisspeptin receptors (Kirby *et al.*, 2010), neuropeptide FF (NPFF), prolactin-releasing peptide (PrP) and QRFP receptors (provisional nomenclature) respond to endogenous peptides with an arginine-phenylalanine-amide (RFamide) motif. Kisspeptin-54 (KP54, originally named metastin), KP13 and KP10 are biologically-active peptides cleaved from the KISS1 gene product (ENSG00000170498), while a single propeptide precursor (ENSG00000139574) generates the octapeptides NPFF (FLFQPQRF-NH<sub>2</sub>, neuropeptide FF or F-8-F-amide) and NPSF (SLAAPQRF-NH<sub>2</sub>, neuropeptide SF) and the octadecapeptide NPAF (AGEGLSSPFWSLAAPQRF-NH<sub>2</sub>, neuropeptide AF or A-18-F-amide). NPFF and NPAF were originally isolated from bovine brain (Yang *et al.*, 1985). The precursor (ENSG00000071677) for PrRP generates 31 and 20-amino-acid versions. QRFP (named after a pyroglutamylated arginine-phenylalanine-amide peptide) is a 43 amino acid peptide derived from ENSG00000188710, and is also known as P518 or 26RFa. RFRP is an RF amide-related peptide (Hinuma *et al.*, 2000) derived from a FMRFamide-related peptide precursor (ENSG00000105954), which is cleaved to generate neuropeptide NPSF (Neuropeptide RFRP-1), neuropeptide RFRP-2 and neuropeptide NPVF (neuropeptide RFRP-3).

| Nomenclature           | KISS1                                                                                                                                                                                                   | NPFF1                                                                                                                                      | NPFF2                                                                                                                                     | PrRP                                                                                                                   | QRFP                                                                            |
|------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| Other names            | hOT7T175 (Ohtaki <i>et al.</i> , 2001), GPR54, metastin, hypogonadotropin                                                                                                                               | Neuropeptide FF 1, GPR147 (Bonini <i>et al.</i> , 2000), OT7T022                                                                           | Neuropeptide FF 2, GPR74 (Bonini <i>et al.</i> , 2000), HLWAR77                                                                           | Prolactin-releasing peptide, GPR10 (Hinuma <i>et al.</i> , 1998), hGR3, UHR-1                                          | SP9155 (Jiang <i>et al.</i> , 2003), AQ27 (Fukusumi <i>et al.</i> , 2003), P518 |
| Ensembl ID             | ENSG00000116014                                                                                                                                                                                         | ENSG00000148734                                                                                                                            | ENSG00000056291                                                                                                                           | ENSG00000119973                                                                                                        | ENSG00000186867                                                                 |
| Principal transduction | G <sub>q/11</sub> (Kotani <i>et al.</i> , 2001; Muir <i>et al.</i> , 2001)                                                                                                                              | G <sub>q/11</sub>                                                                                                                          | G <sub>i/o</sub> (Mollereau <i>et al.</i> , 2005)                                                                                         | G <sub>q/11</sub> (Langmead <i>et al.</i> , 2000)                                                                      | G <sub>q/11</sub> , G <sub>i/o</sub> (Fukusumi <i>et al.</i> , 2003)            |
| Potency order          | –                                                                                                                                                                                                       | FMRF, NPFF > NPAF > NPSF, QRFP, PrP31 (Gouardères <i>et al.</i> , 2007)                                                                    | NPAF, NPFF > PrP31 > FMRF, QRFP > NPSF (Gouardères <i>et al.</i> , 2007)                                                                  | PrRP20, PrRP31 (Langmead <i>et al.</i> , 2000)                                                                         | –                                                                               |
| Selective agonists     | KP54, KP13, KP10 (Kotani <i>et al.</i> , 2001; Ohtaki <i>et al.</i> , 2001), 4-fluorobenzoyl-FGLRW-NH <sub>2</sub> (Tomita <i>et al.</i> , 2008), [dY] <sup>1</sup> KP-10 (Curtis <i>et al.</i> , 2010) | NPFF, NPVF                                                                                                                                 | NPFF, dNPA (Roussin <i>et al.</i> , 2005), AC263093 (Lameh <i>et al.</i> , 2010)                                                          | PrRP                                                                                                                   | QRFP                                                                            |
| Selective antagonists  | Peptide 234 (Roseweir <i>et al.</i> , 2009)                                                                                                                                                             | AC262620, AC262970 (Lameh <i>et al.</i> , 2010)                                                                                            | –                                                                                                                                         | Neuropeptide Y (Lagerstrom <i>et al.</i> , 2005)                                                                       | –                                                                               |
| Probes                 | [ <sup>125</sup> I]-KP10 (Kotani <i>et al.</i> , 2001), [ <sup>125</sup> I]KP14 (Mead <i>et al.</i> , 2007), [ <sup>125</sup> I]-Tyr <sup>45</sup> ]-KP15 (Ohtaki <i>et al.</i> , 2001)                 | [ <sup>125</sup> I]-NPFF, [ <sup>125</sup> I]-YVP (Gouardères <i>et al.</i> , 2002), [ <sup>3</sup> H]-NPVF (Talmont <i>et al.</i> , 2009) | [ <sup>125</sup> I]-NPFF, [ <sup>125</sup> I]-EYF (Gouardères <i>et al.</i> , 2002), [ <sup>3</sup> H]-EYF (Talmont <i>et al.</i> , 2009) | [ <sup>125</sup> I]-PrRP20 (Langmead <i>et al.</i> , 2000), [ <sup>125</sup> I]-PrRP31 (Ellacott <i>et al.</i> , 2005) | [ <sup>125</sup> I]-QRFP (Takayasu <i>et al.</i> , 2006)                        |

An orphan receptor GPR83 (ENSG00000123901) shows sequence similarities with NPFF1, NPFF2, PrRP and QRFP receptors. The antagonist RF9 is selective for NPFF receptors, but does not distinguish between the NPFF1 and NPFF2 subtypes (*pK<sub>i</sub>* 7.1 and 7.2, respectively, Simonin *et al.*, 2006).

**Abbreviations:** dNPA, D-Asn-Pro-(N-Me)Ala-Phe-Leu-Phe-Gln-Pro-Gln-Arg-Phe-NH<sub>2</sub>; NPVF, Val-Pro-Asn-Leu-Pro-Gln-Arg-Phe-NH<sub>2</sub>; Peptide 234, ac[(D)-A]NWNGFG[9D]-W]RF; RF9, adamantylcarbonyl-arginyl-phenylalaninamide; AC262620, AC262970, AC263093

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# Leukotriene, lipoxin, oxoeicosanoid and resolvin

**Overview:** Leukotriene receptors (nomenclature agreed by NC-IUPHAR on Leukotriene and Lipoxin Receptors, Brink *et al.*, 2003) are activated by the endogenous ligands leukotriene (LT) B<sub>4</sub>, LTC<sub>4</sub>, LTD<sub>4</sub>, LTE<sub>4</sub>, 12R-HETE and 12S-HETE. CysLT<sub>1</sub> and CysLT<sub>2</sub> are co-expressed by most myeloid cells. However, the function of CysLT<sub>2</sub> remains unclear. CysLT<sub>2</sub> has been demonstrated to exert a suppressive influence on CysLT<sub>1</sub> expression, suggesting an autoregulatory function which is indicated by a reported up-regulation of CysLT-mediated responses in mice lacking CysLT<sub>2</sub> receptors (Jiang *et al.*, 2007).

Leukotrienes bind extensively to enzymes in their metabolic pathways (glutathione-S-transferase/LTC<sub>4</sub> synthase,  $\gamma$ -glutamyltranspeptidase and several aminopeptidases) and can also bind to peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ , Lin *et al.*, 1999) and the FPR2/ALX lipoxin receptor (Fiore *et al.*, 1994), complicating the interpretation of radioligand binding and functional studies (e.g. LTC<sub>4</sub> is rapidly converted in many systems to LTD<sub>4</sub>). Metabolic inhibitors (e.g. serine–borate complex) reduce this problem but can also have non-specific effects.

| Nomenclature           | BLT <sub>1</sub>                                                                           | BLT <sub>2</sub>                                                                                                                      | CysLT <sub>1</sub>                                                                   | CysLT <sub>2</sub>                                                                       |
|------------------------|--------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| Other names            | LTB <sub>4</sub>                                                                           | –                                                                                                                                     | HG55, HMTMF81, LTD <sub>4</sub>                                                      | HPN321, LTC <sub>4</sub>                                                                 |
| Ensembl ID             | ENSG00000116329                                                                            | ENSG00000082556                                                                                                                       | ENSG00000173198                                                                      | ENSG00000152207                                                                          |
| Principal transduction | G <sub>q/11</sub> , G <sub>i/o</sub>                                                       | G <sub>q/11</sub> , G <sub>i/o</sub>                                                                                                  | G <sub>q/11</sub>                                                                    | G <sub>q/11</sub>                                                                        |
| Rank order of potency  | LTB <sub>4</sub> > 20-hydroxy-LTB <sub>4</sub> >> 12R-HETE (Yokomizo <i>et al.</i> , 2001) | LTB <sub>4</sub> > 12S-HETE = 12S-HPETE > 15S-HETE > 12R-HETE = 5S-HETE > 20-hydroxy-LTB <sub>4</sub> (Yokomizo <i>et al.</i> , 2001) | LTD <sub>4</sub> > LTC <sub>4</sub> > LTE <sub>4</sub> (Sarau <i>et al.</i> , 1999)  | LTC <sub>4</sub> = LTD <sub>4</sub> >> LTE <sub>4</sub> (Nothacker <i>et al.</i> , 2000) |
| Selective agonists     | –                                                                                          | 12S-HETE                                                                                                                              | –                                                                                    | BAYu9773                                                                                 |
| Selective antagonists  | CP105696 (pIC <sub>50</sub> 7.2), U75302 (pIC <sub>50</sub> 6.9)                           | LY255283 (pIC <sub>50</sub> 6.0)                                                                                                      | Zafirlukast (9.5), montelukast (9.3), SR2640 (8.7), pobilukast (8.6), sulukast (8.3) | –                                                                                        |
| Probes                 | [ <sup>3</sup> H]-LTB <sub>4</sub> (0.2–0.7 nM), [ <sup>3</sup> H]-CGS23131 (13 nM)        | [ <sup>3</sup> H]-LTB <sub>4</sub> (0.2–23 nM)                                                                                        | [ <sup>3</sup> H]-LTD <sub>4</sub> , [ <sup>3</sup> H]-ICI198615                     | [ <sup>3</sup> H]-LTD <sub>4</sub>                                                       |

BAYu9773 is an antagonist at CysLT<sub>1</sub> (6.8–7.7) and a reduced efficacy agonist at CysLT<sub>2</sub> receptors. The CysLT<sub>1</sub> and CysLT<sub>2</sub> receptors also respond to uracil nucleotides (Mellor *et al.*, 2001; 2003). GPR17 has been described as a ‘dualistic’ receptor responding to both uracil nucleotides and cysteinyl leukotrienes, responses which may be inhibited by antagonists of either P2 or CysLT receptors (Ciana *et al.*, 2006).

Lipoxin A<sub>4</sub> receptors (FPR2/ALX, nomenclature agreed by NC-IUPHAR on Leukotriene and Lipoxin Receptors; Ye *et al.*, 2009) are activated by the endogenous lipid-derived, anti-inflammatory ligands lipoxin A<sub>4</sub> (LXA<sub>4</sub>) and 15-epi-LXA<sub>4</sub> (aspirin-triggered lipoxin A<sub>4</sub>, ATL). The FPR2/ALX receptor also interacts with endogenous peptide and protein ligands, such as MHC binding peptide (Chiang *et al.*, 2000) as well as annexin 1 (ANXA1) and its N-terminal peptides (Perretti *et al.*, 2002). In addition, a soluble hydrolytic product of protease action on the urokinase-type plasminogen activator receptor has been reported to activate the FPR2/ALX receptor (Resnati *et al.*, 2002). Furthermore, FPR2/ALX has been suggested to act as a receptor mediating proinflammatory actions of the acute-phase reactant, serum amyloid A (Su *et al.*, 1999; Sodin-Semrl *et al.*, 2004).

Oxoeicosanoid receptors (OXE, nomenclature agreed by NC-IUPHAR on Oxoeicosanoid Receptors; Brink *et al.*, 2004) are activated by endogenous chemotactic eicosanoid ligands oxidised at the C-5 position, with 5-oxo-EETE the most potent agonist identified for this receptor.

| Nomenclature           | FPR2/ALX                                                                                                                                                                                                                                              | OXE                                                                                                                                    |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Other names            | FPRL1, FPR2, FPRH2, RFP, ALX                                                                                                                                                                                                                          | TG1019 (Hosoi <i>et al.</i> , 2002), R527 (Jones <i>et al.</i> , 2003), hGPCR48 (Koike <i>et al.</i> , 2006)                           |
| Ensembl ID             | ENSG00000171049                                                                                                                                                                                                                                       | ENSG00000162881                                                                                                                        |
| Principal transduction | G <sub>i</sub> (Maddox <i>et al.</i> , 1997)                                                                                                                                                                                                          | G <sub>i/o</sub> (O’Flaherty <i>et al.</i> , 2000; Hosoi <i>et al.</i> , 2002; Jones <i>et al.</i> , 2003; Hosoi <i>et al.</i> , 2005) |
| Rank order of potency  | LXA <sub>4</sub> = ATL = ATLa2 > LTC <sub>4</sub> = LTD <sub>4</sub> >> 15-deoxy-LXA <sub>4</sub> >> fMLP (Clish <i>et al.</i> , 1999; Fiore <i>et al.</i> , 1994; Fiore and Serhan, 1995; Gronert <i>et al.</i> , 2001; Takano <i>et al.</i> , 1997) | 5-Oxo-EETE, 5-oxo-C20:3 >> 5S-HpETE > 5S-HETE (Hosoi <i>et al.</i> , 2002; Jones <i>et al.</i> , 2003; Patel <i>et al.</i> , 2008)     |
| Selective agonists     | LXA <sub>4</sub> , ATL, ATLa2 (Guilford <i>et al.</i> , 2004), RvD1 (Krishnamoorthy <i>et al.</i> , 2010)                                                                                                                                             | 5-Oxo-EETE                                                                                                                             |
| Probes                 | [ <sup>3</sup> H]-LXA <sub>4</sub> (0.2–1.7 nM; Fiore <i>et al.</i> , 1994; Takano <i>et al.</i> , 1997)                                                                                                                                              | [ <sup>3</sup> H]-5-oxo-EETE (3.8 nM, O’Flaherty <i>et al.</i> , 1998)                                                                 |

Note that the data for FPR2/ALX are also reproduced on the Formylpeptide receptor pages (see Page S48). A receptor selective for LXB<sub>4</sub> has been suggested from functional studies (Maddox and Serhan, 1996; Romano *et al.*, 1996; Ariel *et al.*, 2003). Initial characterization of the heterologously expressed OXE receptor suggested that polyunsaturated fatty acids, such as DHA and EPA, acted as receptor antagonists (Hosoi *et al.*, 2002).

Resolvin receptors (provisional nomenclature) are activated by the lipid-derived, anti-inflammatory ligand resolvin E1 (RvE1), which is the result of sequential metabolism of EPA by aspirin-modified cyclooxygenase and lipoxygenase (Arita *et al.*, 2005a,b). In addition, 2 GPCRs for resolvin D1 (RvD1) have been identified, FPR2/ALX, the lipoxin A<sub>4</sub> receptor, and GPR32, an orphan receptor (Krishnamoorthy *et al.*, 2010).

|                        |                                                                                        |                                                                      |
|------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| Nomenclature           | RvE1                                                                                   | RvD1                                                                 |
| Other names            | ChemR23, chemokine receptor-like 1, DEZ                                                | GPR32                                                                |
| Ensembl ID             | ENSG00000174600                                                                        | ENSG00000142511                                                      |
| Principal transduction | Not yet established                                                                    | Not yet established                                                  |
| Rank order of potency  | RvE1 > chemerin C-terminal peptide > 18R-HEPE > EPA<br>(Arita <i>et al.</i> , 2005a,b) | RvD1 > LXA <sub>4</sub>                                              |
| Selective agonists     | RvE1                                                                                   | RvD1, LXA <sub>4</sub>                                               |
| Probes                 | [ <sup>3</sup> H]-RvE1 (11 nM, Arita <i>et al.</i> , 2005a)                            | [ <sup>3</sup> H]-RvD1 (0.2 nM, Krishnamoorthy <i>et al.</i> , 2010) |

**Abbreviations:** 12R-HETE, 12R-hydroxyeicosa-5Z,8Z,10E,14Z-tetraenoic acid; 18R-HEPE, 18R-hydroxyeicosapentaenoic acid; 5s-HETE, 5s-hydroxy-6E,8Z,11Z,14Z-eicosatetraenoic acid; 5s-HpETE, 5s-hydroperoxy-6E,8Z,11Z,14Z-eicosatetraenoic acid; 5-oxo-C20:3, 5-oxo-6E,8Z,11Z-eicosatrienoic acid; 5-oxo-EETE, 5-oxo-6E,8Z,11Z,14Z-eicosatetraenoic acid; ANXA1, annexin 1; ATL, aspirin-triggered lipoxin A<sub>4</sub> [15-*epi*-LXA<sub>4</sub>, 5s,6R,15R-trihydroxyl-7E,9E,13E,11Z-eicosatetraenoic acid]; ATLa2, ATL analog [15-*epi*-16-(para-fluoro)-phenoxy-LXA<sub>4</sub>]; BAYu9773, 6(R)-(4'-carboxyphenyl-thio)-5(S)-hydroxy-7E,11Z,14Z-eicosatetraenoic acid; CGS23131, (E)-5-(3-carboxybenzoyl)-2-[(6-{4-methoxyphenyl}-5-hexenyl)oxy]benzene propanoic acid; also known as LY223982; CP105696, (+)-1-(3S,4R)-[3-(4-phenylbenzyl)-4-hydroxy-chroman-7-yl]cyclopentane carboxylic acid; DHA, 4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoic acid; EPA, 5Z,8Z,11Z,14Z,17Z-eicosapentaenoic acid; ICI198615, (1-[2-methoxy-4-[(phenylsulfonfylamino)carbonyl]phenyl]methyl)-1H-indazol-6-yl)carbamic acid cyclopentyl ester; LTC<sub>4</sub>, leukotriene C<sub>4</sub>; LTD<sub>4</sub>, leukotriene D<sub>4</sub>; LXA<sub>4</sub>, lipoxin A<sub>4</sub> [5S,6R,15S-trihydroxyl-7E,9E,13E-11Z-eicosatetraenoic acid]; LY255283, 1-(5-ethyl-2-hydroxy-4-[[6-methyl-6-(1H-tetrazol-5-yl)-heptyl]-oxy]-phenyl)-ethanone; OXE, oxoeicosanoid; RvE1, resolvin E1 or 5s,12R,18R-trihydroxy-6Z,8E,10E,14Z,16E-EPA; SR2640, 2-(3-[2-quinolylmethoxy]phenylamino)benzoic acid; U75302, 6-(6-(3-hydroxy-1E,5Z-undecadien-1-yl)-2-pyridinyl)-1,5-hexanediol

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# Lysophosphatidic acid

**Overview:** Lysophosphatidic acid (LPA) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Lysophospholipid Receptors; Chun *et al.*, 2010) are activated by the endogenous lipid derivative LPA. Originally identified as members of the endothelial differentiation gene (*edg*) family along with sphingosine 1-phosphate receptors, the gene names have been updated to *LPAR1*, etc. to reflect the receptor function of these proteins. The identified receptors can account for most, although not all, LPA-induced phenomena in the literature, indicating that a majority of LPA-dependent phenomena are receptor-mediated. Radioligand binding has been conducted in heterologous expression systems using [<sup>3</sup>H]-LPA (e.g. Fukushima *et al.*, 1998). In native systems, analysis of binding data is complicated by metabolism and high levels of nonspecific binding, and therefore the relationship between recombinant and endogenously expressed receptors is unclear. Targeted deletion of LPA receptors has clarified signalling pathways and identified physiological and pathophysiological roles. LPA has also been described to be an agonist at PPAR $\gamma$  receptors (McIntyre *et al.*, 2003), although the physiological significance of this observation remains unclear (Simon *et al.*, 2005).

| Nomenclature           | LPA <sub>1</sub>                                                         | LPA <sub>2</sub>                                          | LPA <sub>3</sub>                                      | LPA <sub>4</sub>                                                                                      | LPA <sub>5</sub>                                                                              | LPA <sub>6</sub>                                                                |
|------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------|-------------------------------------------------------|-------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| Other names            | VZG-1, Edg2, <i>lp</i> <sub>A1</sub>                                     | Edg4, <i>lp</i> <sub>A2</sub>                             | Edg7, <i>lp</i> <sub>A3</sub>                         | p2y9, gpr23                                                                                           | GPR92                                                                                         | P2y5, P2RY5                                                                     |
| Ensembl ID             | ENSG00000198121                                                          | ENSG00000064547                                           | ENSG00000171517                                       | ENSG00000147145                                                                                       | ENSG00000184574                                                                               | ENSG00000139679                                                                 |
| Principal transduction | G <sub>i/o</sub> , G <sub>q/11</sub> , G <sub>12/13</sub>                | G <sub>i/o</sub> , G <sub>q/11</sub> , G <sub>12/13</sub> | G <sub>i/o</sub> , G <sub>q/11</sub> , G <sub>s</sub> | G <sub>i/o</sub> , G <sub>q/11</sub> , G <sub>s</sub> , G <sub>12/13</sub> (Lee <i>et al.</i> , 2007) | G <sub>q</sub> , G <sub>12/13</sub> (Kotarsky <i>et al.</i> , 2006; Lee <i>et al.</i> , 2006) | G <sub>12/13</sub> (Yanagida <i>et al.</i> , 2009; Kimura <i>et al.</i> , 2011) |
| Selective agonists     | –                                                                        | FAP10, FAP12 (Virag <i>et al.</i> , 2003)                 | OMPT (Hasegawa <i>et al.</i> , 2003)                  | –                                                                                                     | –                                                                                             | –                                                                               |
| Selective antagonists  | Ki16425 (Ohta <i>et al.</i> , 2003), AM966 (Swaney <i>et al.</i> , 2010) | –                                                         | DGPP 8:0 (Ohta <i>et al.</i> , 2003)                  | –                                                                                                     | –                                                                                             | –                                                                               |

FAP12, VPC12249 and VPC32179 have antagonist activity at LPA<sub>1</sub> and LPA<sub>3</sub> receptors (Bagga *et al.*, 2004; Okusa *et al.*, 2003; Virag *et al.*, 2003). The selectivity of these antagonists is less than two orders of magnitude. None of the currently available chemical tools have validated specificity *in vivo*.

**Abbreviations:** AM966, (4'-[4-[(R)-1-(2-chloro-phenyl)-ethoxycarbonylamino]-3-methyl-isoxazol-5-yl]-biphenyl-4-yl)-acetic acid; DGPP 8:0, dioctanoylglycerol pyrophosphate; FAP10, decanol phosphate; FAP12, dodecanol phosphate; Ki16425, 3-(4-[4-[(1-[2-chlorophenyl]ethoxy)carbonylamino]-3-methyl-5-isoxazolyl]benzylsulfanyl)propanoic acid; OMPT, 1-oleoyl-2-O-methyl-rac-glycerophosphothionate; VPC12249, (s)-phosphoric acid mono-[3-(4-benzyloxy-phenyl)-2-octadec-9-enoylamino-propyl] ester; VPC32179, (R)-phosphoric acid mono-[2-octadec-9-enoylamino-3-[4-(pyridin-2-ylmethoxy)-phenyl]-propyl] ester

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# Melanin-concentrating hormone

**Overview:** Melanin-concentrating hormone (MCH) receptors (provisional nomenclature, see Foord *et al.*, 2005) are activated by an endogenous nonadecameric cyclic peptide identical in humans and rats (DFDMLRCMLGRVYRPCWQV) generated from a precursor (ENSG00000183395), which also produces neuropeptides EI and GE.

|                        |                                                                                                                                                                                                                          |                                                                                                          |
|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Nomenclature           | MCH <sub>1</sub>                                                                                                                                                                                                         | MCH <sub>2</sub>                                                                                         |
| Other names            | SLC-1, GPR24                                                                                                                                                                                                             | SLT, GPRv17                                                                                              |
| Ensembl ID             | ENSG00000128285                                                                                                                                                                                                          | ENSG00000152034                                                                                          |
| Principal transduction | G <sub>q/11</sub> , G <sub>i/o</sub>                                                                                                                                                                                     | G <sub>q/11</sub> (Hill <i>et al.</i> , 2001; Mori <i>et al.</i> , 2001; Rodriguez <i>et al.</i> , 2001) |
| Rank order of potency  | Human MCH > salmon MCH                                                                                                                                                                                                   | Human MCH = salmon MCH (Hill <i>et al.</i> , 2001)                                                       |
| Selective antagonists  | SNAP7941 (9.2, Borowsky <i>et al.</i> , 2002), GW803430 (9, Gehlert <i>et al.</i> , 2009), ATC0175 (pIC <sub>50</sub> 7.9–8.2, Chaki <i>et al.</i> , 2005), T226296 (7.5, Takekawa <i>et al.</i> , 2002)                 | –                                                                                                        |
| Probes                 | [ <sup>3</sup> H]-MCH (Burgaud <i>et al.</i> , 1997), [Phe <sup>13</sup> , [ <sup>125</sup> I]-Tyr <sup>19</sup> ]MCH (Burgaud <i>et al.</i> , 1997), [ <sup>125</sup> I]-S36057 (0.04 nM, Audinot <i>et al.</i> , 2001) | –                                                                                                        |

The MCH<sub>2</sub> receptor appears to be a non-functional pseudogene in rodents (Tan *et al.*, 2002).

**Abbreviations:** ATC0175, N-(cis-4-[[4-(dimethylamino)quinazolin-2-yl]amino]cyclohexyl)-3,4-difluorobenzamide hydrochloride; GW803430, 6-(4-chlorophenyl)-3-[3-methoxy-4-(2-pyrrolidin-1-ylethoxy)phenyl]thieno[3,2-d]pyrimidin-4-one; S36057, 3-iodo-tyr-(8-amino-3,6-dioxo-octanoyl)MCH-(6-17); SNAP7941, (+)-methyl(4S)-3-([3-(4-[3-(acetylamino)phenyl]-1-piperidinyl)propyl]amino)carbonyl)-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate hydrochloride; T226296, (-)-N-[6-(dimethylamino)-methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4'-fluoro[1,1'-biphenyl]-4-carboxamide

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# Melanocortin

**Overview:** Melanocortin receptors (provisional nomenclature, see Foord *et al.*, 2005) are activated by members of the melanocortin family (MSH –  $\alpha$ ,  $\beta$ , and  $\gamma$  forms –  $\delta$  form is not found in mammals) and adrenocorticotrophin (ACTH). Endogenous antagonists include agouti and agouti-related protein (AGRP).

| Nomenclature           | MC <sub>1</sub>                                         | MC <sub>2</sub>                 | MC <sub>3</sub>                                                  | MC <sub>4</sub>                                                                  | MC <sub>5</sub>                                               |
|------------------------|---------------------------------------------------------|---------------------------------|------------------------------------------------------------------|----------------------------------------------------------------------------------|---------------------------------------------------------------|
| Other names            | –                                                       | ACTH                            | –                                                                | –                                                                                | –                                                             |
| Ensembl ID             | ENSG00000258839                                         | ENSG00000185231                 | ENSG00000124089                                                  | ENSG00000166603                                                                  | ENSG00000176136                                               |
| Principal transduction | G <sub>s</sub>                                          | G <sub>s</sub>                  | G <sub>s</sub>                                                   | G <sub>s</sub>                                                                   | G <sub>s</sub>                                                |
| Rank order of potency  | $\alpha$ -MSH > $\beta$ -MSH $\geq$ ACTH, $\gamma$ -MSH | ACTH                            | $\gamma$ -MSH, $\beta$ -MSH $\geq$ ACTH, $\alpha$ -MSH           | $\beta$ -MSH $\geq$ $\alpha$ -MSH, ACTH > $\gamma$ -MSH                          | $\alpha$ -MSH $\geq$ $\beta$ -MSH $\geq$ ACTH > $\gamma$ -MSH |
| Selective agonists     | –                                                       | –                               | D-Trp <sup>8</sup> - $\gamma$ -MSH (Grieco <i>et al.</i> , 2000) | THIQ (Van der Ploeg <i>et al.</i> , 2002), MK0493 (Krishna <i>et al.</i> , 2009) | –                                                             |
| Selective antagonists  | –                                                       | –                               | –                                                                | HS014 (8.5, Schiöth <i>et al.</i> , 1998), MBP10 (Bednarek <i>et al.</i> , 2001) | –                                                             |
| Probes                 | [ <sup>125</sup> I]-NDP-MSH                             | [ <sup>125</sup> I]-ACTH-(1–24) | [ <sup>125</sup> I]-NDP-MSH, [ <sup>125</sup> I]-SHU9119         | [ <sup>125</sup> I]-NDP-MSH, [ <sup>125</sup> I]-SHU9119                         | [ <sup>125</sup> I]-NDP-MSH                                   |

Polymorphisms of the MC<sub>1</sub> receptor have been linked to variations in skin pigmentation. Defects of the MC<sub>2</sub> receptor underlie familial glucocorticoid deficiency. Polymorphisms of the MC<sub>4</sub> receptor have been linked to obesity (Chagnon *et al.*, 1997; Farooqi and O'Rahilly, 2008).

**Abbreviations:** **HS014**, *cyc*(S-S)-(Ac-Cys<sup>11</sup>,D-Nal<sup>14</sup>,Cys<sup>18</sup>,Asp-NH<sub>2</sub>) $\beta$ -MSH-(11-22); **MBP10**, cyclo(6 $\beta$ →10 $\epsilon$ )(succinyl(6)-D-(2')Nal<sup>7</sup>-Arg<sup>8</sup>-Trp<sup>9</sup>-Lys<sup>10</sup>)-NH<sub>2</sub>; **MK0493**, N-1-(2-[1-(tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl)-5-chlorophenyl]ethyl)acetamide; **NDP-MSH**, [Nle<sup>4</sup>,d-Phe<sup>7</sup>] $\alpha$ -MSH; **SHU9119**, Ac-Nle-Asp-His-d-Nal<sup>2</sup>-Arg-Trp-Lys-NH<sub>2</sub>; **THIQ**, N-([3R]-1,2,3,4-tetrahydroisoquinolinium-3-ylcarbonyl)-(1R)-1-(4-chlorobenzyl)-2-(4-cyclohexyl-4-[1H-1,2,4-triazol-1-ylmethyl]piperidin-1-yl)-2-oxoethylamine

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# Melatonin

**Overview:** Melatonin receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on melatonin receptors, Dubocovich *et al.*, 2010) are activated by the endogenous ligands melatonin and *N*-acetylserotonin.

|                        |                                                                                                                                     |                                                                                                                                     |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature           | MT <sub>1</sub>                                                                                                                     | MT <sub>2</sub>                                                                                                                     |
| Other names            | MEL <sub>1A</sub> , ML <sub>1A</sub> , Mel <sub>1a</sub>                                                                            | MEL <sub>1B</sub> , ML <sub>1B</sub> , Mel <sub>1b</sub>                                                                            |
| Ensembl ID             | ENSG00000168412                                                                                                                     | ENSG00000134640                                                                                                                     |
| Principal transduction | G <sub>i/o</sub>                                                                                                                    | G <sub>i/o</sub>                                                                                                                    |
| Selective agonists     | –                                                                                                                                   | IIK7 (Sugden <i>et al.</i> , 1999), 5-methoxyluzindole (Dubocovich <i>et al.</i> , 1997)                                            |
| Selective antagonists  | –                                                                                                                                   | K185 (9.3, Sugden <i>et al.</i> , 1999), 4P-PDOT (8.8, Dubocovich <i>et al.</i> , 1997), DH97 (8.0, Teh and Sugden, 1998)           |
| Probes                 | 2-Iodo-[ <sup>125</sup> I]-melatonin (Dubocovich <i>et al.</i> , 1997), [ <sup>3</sup> H]-melatonin (Browning <i>et al.</i> , 2000) | 2-Iodo-[ <sup>125</sup> I]-melatonin (Dubocovich <i>et al.</i> , 1997), [ <sup>3</sup> H]-melatonin (Browning <i>et al.</i> , 2000) |

Melatonin, 2-iodo-melatonin, S20098, GR196429, LY156735 and TAK375 (Kato *et al.*, 2005) are nonselective agonists for MT<sub>1</sub> and MT<sub>2</sub> receptors. (–)-AMMTC displays an ~400-fold greater agonist potency than (+)-AMMTC at rat MT<sub>1</sub> receptors (Ting *et al.*, 1999). Luzindole is an MT<sub>1</sub>/MT<sub>2</sub> melatonin receptor-selective competitive antagonist with some selectivity for the MT<sub>2</sub> receptor (Dubocovich *et al.*, 1998). MT<sub>1</sub>/MT<sub>2</sub> heterodimers present different pharmacological profiles from MT<sub>1</sub> and MT<sub>2</sub> receptors (Ayoub *et al.*, 2004).

The MT<sub>3</sub> binding site of hamster brain and peripheral tissues such as kidney and testis, also termed the ML<sub>2</sub> receptor, binds selectively 2-iodo-[<sup>125</sup>I]-5MCA-NAT (Molinari *et al.*, 1996). Pharmacological investigations of MT<sub>3</sub> binding sites have primarily been conducted in hamster tissues. At this site, *N*-acetylserotonin (Eison and Mullins, 1993; Popova and Dubocovich, 1995; Molinari *et al.*, 1996; Lucchelli *et al.*, 1997) and 5MCA-NAT (Popova and Dubocovich, 1995) appear to function as agonists, while prazosin (Lucchelli *et al.*, 1997) functions as an antagonist. A suggested physiological function of the MT<sub>3</sub> receptor is in the control of intraocular pressure in rabbits (Pintor *et al.*, 2003). The MT<sub>3</sub> binding site of hamster kidney was also identified as the hamster homologue of human quinone reductase 2 (ENSG00000124588, Nosjean *et al.*, 2000; 2001). *Xenopus* melanophores and chick brain express a distinct receptor (x420, P49219; c346, P49288, initially termed Mel<sub>1c</sub>) coupled to the G<sub>i/o</sub> family of G proteins, for which GPR50 has recently been suggested to be a mammalian counterpart (see Dufourny *et al.*, 2008) although melatonin does not bind to GPR50 receptors.

**Abbreviations:** 4P-PDOT, 4-phenyl-2-propionamidotetraline; AMMTC, *N*-acetyl-4-aminomethyl-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole; DH97, 2-benzyl-*N*-pentanoyltryptamine; GR196429, *N*-(2-[2,3,7,8-tetrahydro-1*H*-furo(2,3-*g*)indol-1-yl]ethyl)acetamide; IIK7, *N*-butanoyl-2-(2-methoxy-6*H*-isoindolo [2,1-*a*]indol-11-yl)ethanamine; K185, *N*-butanoyl-2-(5,6,7-trihydro-11-methoxybenzo[3,4]cyclohept[2,1-*a*]indol-13-yl)ethanamine; LY156735, β-methyl-6-chloromelatonin; 5MCA-NAT, 5-methoxy-carbonylamino-*N*-acetyltryptamine; S20098, *N*-(2-[7-methoxy-1-naphthalenyl]ethyl)acetamide; TAK375, (S)-*N*-[2(1,6,7,8-tetrahydro-2*H*-indeno[5,4-*b*]furan-8-yl)ethyl]propionamide

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# Motilin

**Overview:** Motilin receptors (provisional nomenclature, see Foord *et al.*, 2005) are activated by a 22 amino-acid peptide derived from a precursor (ENSG0000096395), which also generates motilin-associated peptide. These receptors are suggested to be responsible for the gastrointestinal prokinetic effects of motilides (particular macrolide antibiotics) as well as small molecule receptor agonists.

|                        |                                                                                                                                                                      |
|------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature           | Motilin                                                                                                                                                              |
| Other names            | MTLR1 (Feighner <i>et al.</i> , 1999), GPR38 (Mckee <i>et al.</i> , 1997)                                                                                            |
| Ensembl ID             | ENSG00000102539                                                                                                                                                      |
| Principal transduction | G <sub>q/11</sub> (Depoortere and Peeters, 1995; Feighner <i>et al.</i> , 1999)                                                                                      |
| Rank order of potency  | Motilin > ABT229, mitemcinal > erythromycin (Clark <i>et al.</i> , 1999) = GSK962040 (Sanger <i>et al.</i> , 2009)                                                   |
| Selective agonists     | ABT229 (Lartey <i>et al.</i> , 1995), mitemcinal (Koga <i>et al.</i> , 1994; Takanashi <i>et al.</i> , 2007), GSK962040 (Sanger <i>et al.</i> , 2009)                |
| Selective antagonists  | MA2029 ( <i>p</i> A <sub>2</sub> 9.2, Sudo <i>et al.</i> , 2008), GM109 (Takanashi <i>et al.</i> , 1995; <i>p</i> A <sub>2</sub> 7.2-7.5 Clark <i>et al.</i> , 1999) |
| Probes                 | [ <sup>125</sup> I]-Motilin (0.1 nM, Feighner <i>et al.</i> , 1999)                                                                                                  |

In rodents, the gene encoding the motilin precursor appears to be absent, while the receptor appears to be a pseudogene. Functions of motilin are not usually detected in rodents, although brain and other responses to motilin have been reported; the mechanism of action is obscure (see Sanger *et al.*, 2011).

**Abbreviations:** **ABT229**, 8,9-anhydro-4"-deoxy-3'-N-desmethyl-3'-N-ethylerythromycin B 6,9-hemiacetal; **GM109**, phe-cyclo[Lys-Tyr(3-tBu)-β-Ala].trifluoroacetate; **GSK962040**, N-(3-fluorophenyl)-1-[(4-[(3S)-3-methyl-1-piperazinyl]methyl)phenyl]acetyl]-4-piperidinamine; **MA2029**, (S)-N-[(S)-2-(3-tert-butyl-4-hydroxy-phenyl)-1-ethylcarbamoyl-ethyl]-3-methyl-2-[methyl-(S)-2-methylamino-3-phenyl-propionyl]-amino]-butyramide hydrochloride; **mitemcinal**, de(N-methyl)-11-deoxy-N-isopropyl-12-O-methyl-11-oxo-8,9-anhydroerythromycin A 6,9-hemiacetal fumaric acid, also known as GM611

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# Neuromedin U

**Overview:** Neuromedin U receptors (provisional nomenclature) are activated by the endogenous 25 amino acid peptide neuromedin U (NMU), a peptide originally isolated from pig spinal cord (Minamino *et al.*, 1985). In humans, NMU appears to be the sole product of a precursor (ENSG00000109255) showing a broad tissue distribution, but which is expressed at highest levels in the upper gastrointestinal tract, CNS, bone marrow and fetal liver. Much shorter versions of NMU are found in some species, but not human, and are derived at least in some instances from the proteolytic cleavage of the longer NMU. Despite species differences in NMU structure, the C-terminal region (particularly the C-terminal pentapeptide) is highly conserved and contains biological activity. Neuromedin S (NMS) has also been identified as an endogenous agonist (Mori *et al.*, 2005). NMS is a 36 amino-acid product of a precursor protein derived from a single gene (ENSG00000204640) and contains an amidated C-terminal heptapeptide identical to NMU. NMS appears to activate NMU receptors with equivalent potency to NMU.

| Nomenclature           | NMU1                                                                                                                                                                                                                               | NMU2                                                                                                                                   |
|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Other names            | GPR66, FM3, SNORF62 (Fujii <i>et al.</i> , 2000; Hedrick <i>et al.</i> , 2000; Hosoya <i>et al.</i> , 2000; Howard <i>et al.</i> , 2000; Kojima <i>et al.</i> , 2000; Raddatz <i>et al.</i> , 2000; Szekeres <i>et al.</i> , 2000) | FM4, TGR1, SNORF72 (Hosoya <i>et al.</i> , 2000; Howard <i>et al.</i> , 2000; Raddatz <i>et al.</i> , 2000; Shan <i>et al.</i> , 2000) |
| Ensembl ID             | ENSG00000171596                                                                                                                                                                                                                    | ENSG00000132911                                                                                                                        |
| Principal transduction | G <sub>q/11</sub> (Hedrick <i>et al.</i> , 2000; Brighton <i>et al.</i> , 2004a)                                                                                                                                                   | G <sub>q/11</sub> (Hosoya <i>et al.</i> , 2000; Brighton <i>et al.</i> , 2004a)                                                        |
| Antagonists            | –                                                                                                                                                                                                                                  | R-PSOP (Liu <i>et al.</i> , 2009)                                                                                                      |

NMU1 and NMU2 couple predominantly to G<sub>q/11</sub> although there is evidence of good coupling to G<sub>i/o</sub> (see Hosoya *et al.*, 2000; Brighton *et al.*, 2004a; Hsu and Luo, 2007). NMU1 and NMU2 can be labelled with [<sup>125</sup>I]-NMU and [<sup>125</sup>I]-NMS (of various species, e.g. Meng *et al.*, 2008); BODIPY® TMR-NMU or Cy3B-NMU-8 (Brighton *et al.*, 2004a). A range of radiolabelled (<sup>125</sup>I-), fluorescently labelled (e.g. Cy3, Cy5, rhodamine and FAM) and biotin labelled versions of NMU and NMS are now commercially available.

**Abbreviations:** NMS, neuromedin S; NMU, neuromedin U; R-PSOP, (R)-5'-(phenylaminocarbonylamino)spiro[1-azabicyclo[2.2.2.]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

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# Neuropeptide S

**Overview:** The neuropeptide S receptor (NPS, provisional nomenclature, see Foord *et al.*, 2005) responds to the 20 amino-acid peptide neuropeptide S derived from a precursor (ENSG00000214285).

|                        |                                                                                                |
|------------------------|------------------------------------------------------------------------------------------------|
| Nomenclature           | NPS                                                                                            |
| Other names            | GPRA, GPR154, vasopressin receptor-related receptor 1, PGR14                                   |
| Ensembl ID             | ENSG00000187258                                                                                |
| Principal transduction | G <sub>s</sub> , G <sub>q/11</sub> (Gupte <i>et al.</i> , 2004; Vendelin <i>et al.</i> , 2005) |
| Selective agonists     | NPS                                                                                            |
| Probes                 | [ <sup>125</sup> I-Tyr <sup>10</sup> ]-NPS                                                     |

Polymorphisms in the NPS receptor have been suggested to be associated with asthma (Vendelin *et al.*, 2005) and irritable bowel syndrome (D'Amato *et al.*, 2007).

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# Neuropeptide Y

**Overview:** Neuropeptide Y (NPY) receptors (nomenclature agreed by NC-IUPHAR on Neuropeptide Y Receptors, see Michel *et al.*, 1998) are activated by the endogenous peptides NPY, NPY-(3-36), peptide YY (PYY), PYY-(3-36) and pancreatic polypeptide (PP). The receptor originally identified as the Y3 receptor has been identified as the CXCR4 chemokine receptor (originally named LESTR, Loetscher *et al.*, 1994). The y6 receptor is a functional gene product in mouse, absent in rat, but contains a frame-shift mutation in primates producing a truncated non-functional gene (Gregor *et al.*, 1996). Many of the agonists exhibit differing degrees of selectivity dependent on the species examined. For example, the relative potency of PP is greater at the rat Y<sub>4</sub> receptor than at the human receptor (Eriksson *et al.*, 1998). In addition, many agonists lack selectivity for individual subtypes, but can exhibit comparable potency against pairs of NPY receptor subtypes, or have not been examined for activity at all subtypes. [<sup>125</sup>I]-PYY or [<sup>125</sup>I]-NPY can be used to label Y<sub>1</sub>, Y<sub>2</sub>, Y<sub>5</sub> and y<sub>6</sub> subtypes non-selectively, while [<sup>125</sup>I]-[cPP(1-7),NPY(19-23),Ala<sup>31</sup>,Aib<sup>32</sup>,Gln<sup>34</sup>]hPP may be used to label Y<sub>5</sub> receptors preferentially.

| Nomenclature           | Y <sub>1</sub>                                                                                                                           | Y <sub>2</sub>                                                                            | Y <sub>4</sub>         | Y <sub>5</sub>                                                                                                                      | y <sub>6</sub>                                     |
|------------------------|------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|------------------------|-------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|
| Other names            | –                                                                                                                                        | –                                                                                         | PP <sub>1</sub>        | –                                                                                                                                   | Y <sub>5</sub> , PP <sub>2</sub> , Y <sub>28</sub> |
| Ensembl ID             | ENSG00000164128                                                                                                                          | ENSG00000185149                                                                           | ENSG00000204174        | ENSG00000164129                                                                                                                     | ENSG00000226306                                    |
| Principal transduction | G <sub>i/o</sub>                                                                                                                         | G <sub>i/o</sub>                                                                          | G <sub>i/o</sub>       | G <sub>i/o</sub>                                                                                                                    | G <sub>i/o</sub>                                   |
| Rank order of potency  | NPY ≥ PYY >> PP                                                                                                                          | NPY ≥ PYY >> PP                                                                           | PP > NPY = PYY         | NPY ≥ PYY ≥ PP                                                                                                                      | NPY = PYY > PP                                     |
| Selective agonists     | [Leu <sup>31</sup> ,Pro <sup>34</sup> ]NPY, [Pro <sup>34</sup> ]NPY, [Leu <sup>31</sup> ,Pro <sup>34</sup> ]PYY, [Pro <sup>34</sup> ]PYY | NPY-(3-36), PYY-(3-36)                                                                    | PP                     | [Ala <sup>31</sup> ,Aib <sup>32</sup> ]NPY (Cabrele <i>et al.</i> , 2000)                                                           | –                                                  |
| Selective antagonists  | BIBO3304 (9.5, Wieland <i>et al.</i> , 1998), BIBP3226 (8.2, Gerald <i>et al.</i> , 1996)                                                | BIIE0246 (8.5, Doods <i>et al.</i> , 1999), JNJ5207787 (Bonaventure <i>et al.</i> , 2004) | –                      | L152804 (7.6, Kanatani <i>et al.</i> , 2000)                                                                                        | –                                                  |
| Probes                 | [ <sup>125</sup> I]-[Leu <sup>31</sup> ,Pro <sup>34</sup> ]NPY, [ <sup>3</sup> H]-BIBP3226 (2.1 nM)                                      | [ <sup>125</sup> I]-PYY-(3-36)                                                            | [ <sup>125</sup> I]-PP | [ <sup>125</sup> I]-[cPP(1-7),NPY(19-23),Ala <sup>31</sup> ,Aib <sup>32</sup> ,Gln <sup>34</sup> ]hPP (Dumont <i>et al.</i> , 2004) | –                                                  |

The Y<sub>1</sub> agonists indicated are selective relative to Y<sub>2</sub> receptors. BIBP3226 is selective relative to Y<sub>2</sub>, Y<sub>4</sub> and Y<sub>5</sub> receptors (Gerald *et al.*, 1996). NPY-(13-36) is Y<sub>2</sub> selective relative to Y<sub>1</sub> and Y<sub>5</sub> receptors. PYY-(3-36) is Y<sub>2</sub> selective relative to Y<sub>1</sub> receptors.

**Abbreviations:** **BIBO3304:** (R)-N-([4-{aminocarbonylaminoethyl}-phenyl]methyl)-N<sup>2</sup>-(diphenylacetyl)-argininamide trifluoroacetate; **BIBP3226:** R-N<sup>2</sup>-(diphenylacetyl)-N-(4-hydroxyphenyl)methyl-argininamide; **BIIE0246:** (S)-N<sup>2</sup>-([1-[2-(4-[(R,S)-5,11-dihydro-6(6H)-oxodibenz[b,e]azepin-11-yl]-1-piperazinyl)-2-oxoethyl]cyclopentyl]acetyl)-N-(2-[1,2-dihydro-3,5(4H)-dioxo-1,2-diphenyl-3H-1,2,4-triazol-4-yl]ethyl)-argininamide; **JNJ5207787,** N-(1-acetyl-2,3-dihydro-1H-indol-6-yl)-3-(3-cyano-phenyl)-N-[1-(2-cyclopentylethyl)piperidin-4-yl]acrylamide; **L152804:** 2-(3,3-dimethyl-1-oxo-4H-1H-xanthen-9-yl)-5,5-dimethyl-cyclohexane-1,3-dione

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# Neuropeptides B and W

**Overview:** The neuropeptide BW receptor 1 (NPBW1, provisional nomenclature) is activated by two 23-amino-acid peptides, neuropeptide W (NPW-23) and neuropeptide B (NPB-23) (Shimomura *et al.*, 2002; Fujii *et al.*, 2002). C-terminally extended forms of the peptides (NPW-30 and NPB-29) also activate NPBW1 (Brezillon *et al.*, 2003). Unique to both forms of NPB is the *N*-terminal bromination of the first tryptophan residue. des-Br-NPB-23 and des-Br-NPB-29 were not found to be major components of bovine hypothalamic tissue extracts. The NPBW2 receptor is activated by the short and C-terminal extended forms of NPB and NPW (Brezillon *et al.*, 2003).

|                        |                                                                    |                                                                    |
|------------------------|--------------------------------------------------------------------|--------------------------------------------------------------------|
| Nomenclature           | NPBW1                                                              | NPBW2                                                              |
| Other names            | GPR7                                                               | GPR8                                                               |
| Ensembl ID             | ENSG00000183729                                                    | ENSG00000125522                                                    |
| Principal transduction | G <sub>i/o</sub> (Mazzocchi <i>et al.</i> , 2005)                  | G <sub>i/o</sub> (Mazzocchi <i>et al.</i> , 2005)                  |
| Rank order of potency  | NPB-29 > NPB-23 > NPW-30 > NPW-23 (Brezillon <i>et al.</i> , 2003) | NPW-23 > NPW-30 > NPB-29 > NPB-23 (Brezillon <i>et al.</i> , 2003) |
| Selective agonists     | Ava-3, Ava-5 (Kanesaka <i>et al.</i> , 2007)                       | –                                                                  |
| Probes                 | [ <sup>125</sup> I]-NPW-23 (0.44 nM, Singh <i>et al.</i> , 2004)   | [ <sup>125</sup> I]-NPW-23                                         |

Potency measurements were conducted with heterologously-expressed receptors with a range of 0.14–0.57 nM (NPBW1) and 0.98–21 nM (NPBW2).

**Abbreviations:** Ava3, TrpTyrLysAvaAvaAvaGlyArgAlaAlaGlyLeuLeuSerGlyLeu-NH<sub>2</sub>; Ava5, TrpTyrLysAvaAvaAvaAvaAvaAvaGlyArgAlaAlaGlyLeuLeuSerGlyLeu-NH<sub>2</sub>

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# Neurotensin

**Overview:** Neurotensin receptors (provisional nomenclature, see Foord *et al.*, 2005) are activated by the endogenous tridecapeptide neurotensin (pGlu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu) derived from a precursor (ENSG00000133636), which also generates neuromedin N, an agonist at the NTS<sub>2</sub> receptor. A nonpeptide antagonist, SR142948A, shows high affinity (pK<sub>i</sub>~9) at both NTS<sub>1</sub> and NTS<sub>2</sub> receptors (Gully *et al.*, 1997). [<sup>3</sup>H]-Neurotensin and [<sup>125</sup>I]-neurotensin may be used to label NTS<sub>1</sub> and NTS<sub>2</sub> receptors at 0.1–0.3 and 3–5 nM concentrations, respectively.

| Nomenclature           | NTS <sub>1</sub>                                                      | NTS <sub>2</sub>                                                |
|------------------------|-----------------------------------------------------------------------|-----------------------------------------------------------------|
| Other names            | High-affinity neurotensin receptor, NTRH, NTR-1, NT <sub>1</sub>      | Low-affinity neurotensin receptor, NTRL, NTR-1, NT <sub>2</sub> |
| Ensembl ID             | ENSG00000101188                                                       | ENSG00000169006                                                 |
| Principal transduction | G <sub>q/11</sub>                                                     | G <sub>q/11</sub>                                               |
| Rank order of potency  | Neurotensin > neuromedin N (Hermans <i>et al.</i> , 1997)             | Neurotensin = neuromedin N (Mazella <i>et al.</i> , 1996)       |
| Selective agonists     | JMV449 (Souaze <i>et al.</i> , 1997)                                  | Levocobastine (Mazella <i>et al.</i> , 1996)                    |
| Selective antagonists  | SR48692 (7.5–8.2; Gully <i>et al.</i> , 1997)                         | –                                                               |
| Probes                 | [ <sup>3</sup> H]-SR48692 (3.4 nM; Labbe-Jullie <i>et al.</i> , 1995) | –                                                               |

Neurotensin appears to be a low-efficacy agonist at the NTS<sub>2</sub> receptor (Vita *et al.*, 1998), while the NTS<sub>1</sub> receptor antagonist SR48692 is an agonist at NTS<sub>2</sub> receptors (Vita *et al.*, 1998). An additional protein, provisionally termed NTS3 (also known as NTR3, gp95 and sortilin; ENSG00000134243), has been suggested to bind lipoprotein lipase and mediate its degradation (Nielsen *et al.*, 1999). It has been reported to interact with the NTS<sub>1</sub> receptor (Martin *et al.*, 2002) and has been implicated in hormone trafficking and/or neurotensin uptake.

**Abbreviations:** **JMV449**, *H*-Lysψ (CH<sub>2</sub>NH)-Lys-Pro-Tyr-Ile-Leu; **SR142948A**, 2-([5-[2,6-dimethoxyphenyl]-1-[4-(*N*-[3-dimethylaminopropyl]-*N*-methylcarbamoyl)-2-isopropylphenyl]-1*H*-pyrazole-3-carbonyl]amino)adamantane-2-carboxylic acid hydrochloride; **SR48692**, 2-([1-[7-chloro-4-quinolinyl]-5-[2,6-dimethoxyphenyl]pyrazol-3-yl]carboxylamino)tricyclo(3.3.1.1.[3.7])decan-2-carboxylic acid

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# Opioid and opioid-like

**Overview:** Opioid and opioid-like receptors are activated by a variety of endogenous peptides including [Met]enkephalin (met), [Leu]enkephalin (leu),  $\beta$ -endorphin ( $\beta$ -end),  $\alpha$ -neo-dynorphin, dynorphin A (dynA), dynorphin B (dynB), Big dynorphin (Big dyn), nociceptin/orphanin FQ (N/OFQ), and possibly endomorphin -1 and -2. The Greek letter names for the opioid receptors,  $\mu$ ,  $\delta$ , and  $\kappa$ , are well established and IUPHAR considers these names most appropriate (Foord *et al.*, 2005). The human N/OFQ receptor is considered 'opioid-related' rather than opioid because while it exhibits a high degree of structural homology with the conventional opioid receptors (Mollereau *et al.*, 1994), it displays a distinct pharmacology.

| Nomenclature           | Delta opioid receptor                                                                                                                                                                                                                    | Kappa opioid receptor                                                                                              | Mu opioid receptor                                                                                                                                                                                      | N/OFQ receptor                                                                                                                                   |
|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| Preferred abbreviation | $\delta$                                                                                                                                                                                                                                 | $\kappa$                                                                                                           | $\mu$                                                                                                                                                                                                   | NOP                                                                                                                                              |
| Other names            | OP <sub>1</sub> , DOP, DOR                                                                                                                                                                                                               | OP <sub>2</sub> , KOP, KOR                                                                                         | OP <sub>3</sub> , MOP, MOR                                                                                                                                                                              | ORL1, OP <sub>4</sub>                                                                                                                            |
| Ensembl ID             | ENSG00000116329                                                                                                                                                                                                                          | ENSG00000082556                                                                                                    | ENSG00000112038                                                                                                                                                                                         | ENSG00000125510                                                                                                                                  |
| Principal transduction | G <sub>i/o</sub>                                                                                                                                                                                                                         | G <sub>i/o</sub>                                                                                                   | G <sub>i/o</sub>                                                                                                                                                                                        | G <sub>i/o</sub>                                                                                                                                 |
| Rank order of potency  | $\beta$ -End = leu = met > dynA                                                                                                                                                                                                          | Big dyn > dynA >> $\beta$ -end > leu > met                                                                         | $\beta$ -End > met $\geq$ leu $\geq$ dynA                                                                                                                                                               | N/OFQ >> dynA                                                                                                                                    |
| Selective agonists     | DPDPE (Mosberg <i>et al.</i> , 1983), DSBULET (Delay-Goyet <i>et al.</i> , 1988), [DAla <sup>2</sup> ]deltorphin I or II (Erspamer <i>et al.</i> , 1989), SNC80 (Bilsky <i>et al.</i> , 1995)                                            | U69593 (Lahti <i>et al.</i> , 1985), CI977 (Hunter <i>et al.</i> , 1990), Salvinorin A (Roth <i>et al.</i> , 2002) | Endomorphin-1 and -2 (Zadina <i>et al.</i> , 1997), morphine (Goldstein and Naidu, 1989), DAMGO (Handa <i>et al.</i> , 1981), sufentanil (Yeadon and Kitchen, 1988), PL017 (Costa <i>et al.</i> , 1992) | N/OFQ, N/OFQ-(1-13)-NH <sub>2</sub> (Guerrini <i>et al.</i> , 1997), Ro646198 (Jenck <i>et al.</i> , 2000), UFP-112 (Rizzi <i>et al.</i> , 2007) |
| Selective antagonists  | Naltrindole (Portoghesi <i>et al.</i> , 1988), naltriben (Sofuoglu <i>et al.</i> , 1991)                                                                                                                                                 | Nor-binaltorphimine (Portoghesi <i>et al.</i> , 1987), GNTI (Stevens <i>et al.</i> , 2000)                         | CTAP (Pelton <i>et al.</i> , 1986)                                                                                                                                                                      | J113397 (8.3, Kawamoto <i>et al.</i> , 1999), SB612111 (9.5, Zaratin <i>et al.</i> , 2004), UFP101 (7.2, Calo' <i>et al.</i> , 2002)             |
| Probes                 | [ <sup>3</sup> H]-DPDPE (Goldstein and Naidu, 1989), [ <sup>3</sup> H]-naltrindole (Yamamura <i>et al.</i> , 1992), [ <sup>3</sup> H]-deltorphin II (Gomes <i>et al.</i> , 2000), [ <sup>3</sup> H]-naltriben (Lever and Scheffel, 1998) | [ <sup>3</sup> H]-U69593 (Lahti <i>et al.</i> , 1985), [ <sup>3</sup> H]-CI977 (Simonin <i>et al.</i> , 2001)      | [ <sup>3</sup> H]-DAMGO (Goldstein and Naidu, 1989), [ <sup>3</sup> H]-PL017 (Hawkins <i>et al.</i> , 1987)                                                                                             | [ <sup>3</sup> H]-N/OFQ (Dooley and Houghten, 1996), [ <sup>3</sup> H]-Leu-N/OFQ, [ <sup>125</sup> I]-Tyr <sup>14</sup> -N/OFQ                   |

Subtypes of  $\mu$  ( $\mu_1$ ,  $\mu_2$ ),  $\delta$  ( $\delta_1$ ,  $\delta_2$ ) and  $\kappa$  ( $\kappa_1$ ,  $\kappa_2$ ,  $\kappa_3$ ) receptor have been proposed based primarily on binding studies with poorly selective ligands or results from *in vivo* studies. Only three naloxone-sensitive opioid receptors have been cloned, and while the  $\mu$ -receptor in particular may be subject to extensive alternative splicing, these putative isoforms have not been definitively correlated with any of the proposed subtypes. A distinct met-enkephalin receptor lacking structural resemblance to the opioid receptors listed has been identified (ENSG00000060491) and termed an opioid growth factor receptor. Opioid receptor subtypes may reflect hetero-dimerization of opioid receptors with each other or with other GPCR, and while there is increasing evidence for heterodimers in native cells, the consequences this heterodimerization for signalling remains largely unknown. For  $\mu$ -opioid receptors at least, dimerization does not seem to be required for signalling (Kuszk *et al.*, 2009).

Two areas of increasing importance in defining opioid receptor function are the presence of functionally relevant single nucleotide polymorphisms in human  $\mu$ -receptors (see Oertel *et al.*, 2009) and the identification of biased signalling by opioid receptor ligands, in particular, compounds previously characterized as antagonists (Bruchas *et al.*, 2007). As ever, the mechanisms underlying the acute and long term regulation of opioid receptor function are the subject of intense investigation and debate.

**Abbreviations:** CI977, (5R)-(5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ )-(-)-N-methyl-N-(7-[1-pyrrolidinyl]-1-oxaspiro[4,5]dec-8-yl)-4-benzofuranacetamide hydrochloride; CTAP, D-Phe-cyc[Cys-Tyr-D-Trp-Arg-Thr-Pen]-Thr-NH<sub>2</sub>; DAMGO, Tyr-DAla-Gly-[NMePhe]-NH(CH<sub>2</sub>)<sub>2</sub>; DPDPE, cyc[DPen<sup>2</sup>, DPen<sup>3</sup>]enkephalin; DSBULET, Tyr-DSer(OtBu)-Gly-Phe-Leu-Thr; GNTI, 5'-guanidinyl-17-(cyclopropylmethyl)-6,7-dehydro-4,5 $\alpha$ -epoxy-3,14-dihydroxy-6,7-2',3'-indolomorphinan; ICI174864, N,N-diallyl-Tyr-Aib-Phe-Leu-OH (Aib is aminoisobutyric acid); J113397, 1-[(3*r*,4*r*)-1-cyclooctylmethyl-3-hydroxymethyl-4-piperidyl]-3-ethyl-1,3-dihydro-2*H*-benzimidazol-2-one; PL017, [N-MePhe<sup>3</sup>,DPro<sup>4</sup>]morphiceptin; Ro646198, (1*S*,3*aS*)-8-(2,3,3*a*,4,5,6-hexahydro-1*H*-phenalen-1-yl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one; SB612111, (-)-*cis*-1-methyl-7-[[4-(2,6-dichlorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5*H*-benzocyclohept-5-ol; SNC80, (+)-4-[( $\alpha$ R)- $\alpha$ -(2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl]-3-methoxybenzyl]-N,N-diethylbenzamide; U69593, 5 $\alpha$ ,7 $\alpha$ ,8 $\beta$ -(+)-N-methyl-N-(7-[1-pyrrolidinyl]-1-oxaspiro(4,5)dec-8-yl)benzene acetamide; UFP101, [Nphe<sup>1</sup>,Arg<sup>14</sup>,Lys<sup>15</sup>]nociceptin-NH<sub>2</sub>; UFP-112, [(pF)Phe<sup>4</sup>Aib<sup>7</sup>Arg<sup>14</sup>Lys<sup>15</sup>]N/OFQ-NH<sub>2</sub>

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# Orexin

**Overview:** Orexin receptors (provisional nomenclature) are activated by the endogenous polypeptides orexin-A and orexin-B (also known as hypocretin-1 and -2; 33 and 28 aa) derived from a common precursor, preproorexin or orexin precursor (ENSG00000161610), by proteolytic cleavage (Sakurai *et al.*, 1998). Binding to both receptors may be accomplished with [<sup>125</sup>I]-orexin A (Holmqvist *et al.*, 2001).

|                        |                                                                                                 |                                                                                                                                                   |
|------------------------|-------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature           | OX <sub>1</sub>                                                                                 | OX <sub>2</sub>                                                                                                                                   |
| Other names            | Hypocretin receptor type 1                                                                      | Hypocretin receptor type 2                                                                                                                        |
| Ensembl ID             | ENSG00000121764                                                                                 | ENSG00000137252                                                                                                                                   |
| Principal transduction | G <sub>q/11</sub>                                                                               | G <sub>q/11</sub>                                                                                                                                 |
| Rank order of potency  | Orexin-A > orexin-B                                                                             | Orexin-A = orexin-B                                                                                                                               |
| Selective agonists     | –                                                                                               | [Ala <sup>11</sup> ,D-Leu <sup>15</sup> ]orexin-B (Asahi <i>et al.</i> , 2003)                                                                    |
| Selective antagonists  | SB408124 (7.5, Langmead <i>et al.</i> , 2004), SB334867A (7.2–7.3, Porter <i>et al.</i> , 2001) | EMPA (8.6–9.0, Malherbe <i>et al.</i> , 2009), JNJ10397049 (7.9–8.3, McAtee <i>et al.</i> , 2004), compound 29 (7.4; Hirose <i>et al.</i> , 2003) |

The primary coupling of orexin receptors to G<sub>q/11</sub> proteins is rather speculative and based on the strong activation of phospholipase C. Coupling of both receptors to G<sub>i/o</sub> and G<sub>s</sub> has also been reported (Kukkonen and Åkerman, 2005; Ramanjaneya *et al.*, 2009); for most cellular responses observed, the G protein pathway is unknown. The rank order of endogenous agonist potency may depend on the cellular signal transduction machinery. The synthetic [Ala<sup>11</sup>,D-Leu<sup>15</sup>]orexin-B may show poor OX<sub>2</sub> receptor selectivity (Putula *et al.*, 2011).

Loss-of-function mutations in the gene encoding the OX<sub>2</sub> receptor underlie canine hereditary narcolepsy (Lin *et al.*, 1999).

**Abbreviations:** **compound 29**, N-acyl 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline; **EMPA**, N-ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulphonyl)-amino]-N-pyridin-3-ylmethyl-acetamide; **JNJ10397049**, 1-(2,4-dibromo-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea; **SB334867A**, 1-(2-methylbenzoxazol-6-yl)-3-[1,5]naphthyridin-4-yl-urea hydrochloride; **SB408124**, 1-(6,8-difluoro-2-methyl-quinolin-4-yl)-3-(4-dimethylamino-phenyl)-urea

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# P2Y

**Overview:** P2Y receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on P2Y Receptors, Abbracchio *et al.*, 2003; 2006) are activated by the endogenous ligands ATP, ADP, UTP, UDP and UDP-glucose. The relationship of many of the cloned receptors to endogenously expressed receptors is not yet established and so it might be appropriate to use wording such as 'UTP-preferring (or ATP-, etc.) P2Y receptor' or 'P2Y<sub>1</sub>-like', etc., until further, as yet undefined, corroborative criteria can be applied.

| Nomenclature           | P2Y <sub>1</sub>                                                                                                                                                   | P2Y <sub>2</sub>                                                                                                                                                       | P2Y <sub>4</sub>                                                                | P2Y <sub>6</sub>                                                                                     |
|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| Ensembl ID             | ENSG00000169860                                                                                                                                                    | ENSG00000175591                                                                                                                                                        | ENSG00000186912                                                                 | ENSG00000171631                                                                                      |
| Principal transduction | G <sub>q/11</sub>                                                                                                                                                  | G <sub>q/11</sub>                                                                                                                                                      | G <sub>q/11</sub>                                                               | G <sub>q/11</sub>                                                                                    |
| Rank order of potency  | ADP > ATP                                                                                                                                                          | UTP = ATP                                                                                                                                                              | UTP > ATP (at rat recombinant receptors, UTP = ATP)                             | UDP >> UTP > ATP                                                                                     |
| Selective agonists     | 2-MeSADP, ADPβS, MRS2365 (Bourdon <i>et al.</i> , 2006)                                                                                                            | UTPγS (Lazarowski <i>et al.</i> , 1996), Ap <sub>4</sub> A (Castro <i>et al.</i> , 1992), 2-thioUTP (El-Tayeb <i>et al.</i> , 2006), MRS2768 (Ko <i>et al.</i> , 2008) | UTPγS (Lazarowski <i>et al.</i> , 1996), MRS4062 (Maruoka <i>et al.</i> , 2011) | UDP, 3-phenacylUDP (PSB0474, El-Tayeb <i>et al.</i> , 2006), 5-iodoUDP (Besada <i>et al.</i> , 2006) |
| Selective antagonists  | MRS2500 (8.8, Kim <i>et al.</i> , 2003), MRS2279 (8.0, Waldo <i>et al.</i> , 2002), MRS2179 (7.0, Boyer <i>et al.</i> , 1996), PIT (6.8, Gao <i>et al.</i> , 2004) | –                                                                                                                                                                      | ATP (6.2, Kennedy <i>et al.</i> , 2000)                                         | MRS2578 (pIC <sub>50</sub> 7.4, Mamedova <i>et al.</i> , 2004)                                       |
| Probes                 | [ <sup>3</sup> H]-MRS2279 (8 nM, Waldo <i>et al.</i> , 2002), [ <sup>35</sup> S]-ADPβS, [ <sup>35</sup> S]-ATPαS, [ <sup>35</sup> S]-dATPαS                        | –                                                                                                                                                                      | –                                                                               | –                                                                                                    |

| Nomenclature           | P2Y <sub>11</sub>                                                                                                                                                                | P2Y <sub>12</sub>                              | P2Y <sub>13</sub>                  | P2Y <sub>14</sub>                 |
|------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|------------------------------------|-----------------------------------|
| Other names            | –                                                                                                                                                                                | P2Y <sub>ADP</sub> , P <sub>2T</sub>           | GPR86, GPR94, SP174                | KIAA000001, gpr105                |
| Ensembl ID             | ENSG00000244165                                                                                                                                                                  | ENSG00000169313                                | ENSG00000181631                    | ENSG00000174944                   |
| Principal transduction | G <sub>s</sub> , G <sub>q/11</sub>                                                                                                                                               | G <sub>i/o</sub>                               | G <sub>i/o</sub>                   | G <sub>q/11</sub>                 |
| Rank order of potency  | ATP > UTP                                                                                                                                                                        | ADP >> ATP                                     | ADP >> ATP                         | UDP-glucose                       |
| Selective agonists     | ARC67085 (Communi <i>et al.</i> , 1999), NAD <sup>+</sup> (Moreschi <i>et al.</i> , 2006), NAADP <sup>+</sup> (Moreschi <i>et al.</i> , 2008), NF546 (Meis <i>et al.</i> , 2010) | ADP, 2-MeSADP                                  | –                                  | MRS2690 (Ko <i>et al.</i> , 2007) |
| Selective antagonists  | NF157 (Ullmann <i>et al.</i> , 2005)                                                                                                                                             | ATP, ARL66096 (Humphries <i>et al.</i> , 1995) | MRS2211 (Kim <i>et al.</i> , 2005) | –                                 |

ARC69931MX shows selectivity for P2Y<sub>12</sub> and P2Y<sub>13</sub> receptors compared to other P2Y receptors (Marteau *et al.* 2003; Takasaki *et al.*, 2001). NF157 also has antagonist activity at P2X<sub>1</sub> receptors (Ullmann *et al.*, 2005). UDP has been reported to be an antagonist at the P2Y<sub>14</sub> receptor (Fricks *et al.*, 2008).

An orphan GPCR suggested to be a 'P2Y<sub>15</sub>' receptor (Inbe *et al.*, 2004) appears not to be a genuine nucleotide receptor (see Abbracchio *et al.*, 2006), but rather responds to dicarboxylic acids (He *et al.*, 2004). Further P2Y-like receptors have been cloned from non-mammalian sources; a clone from chick brain, termed a p2y<sub>3</sub> receptor (ENSGALG00000017327), couples to the G<sub>q/11</sub> family of G proteins and shows the rank order of potency ADP > UTP > ATP = UDP (Webb *et al.*, 1996a). In addition, human sources have yielded a clone with a preliminary identification of p2y5 (ENSG00000139679) and contradictory evidence of responses to ATP (King and Townsend-Nicholson, 2000; Webb *et al.*, 1996b). This protein is now classified as LPA<sub>4</sub>, a receptor for lysophosphatidic acid (Pasternack *et al.*, 2008; Yanagida *et al.*, 2009) (see Page S76). The clone p2y7 (ENSG00000196943), originally suggested to be a P2Y receptor (Akbar *et al.*, 1996), has been shown to encode a leukotriene receptor (Yokomizo *et al.*, 1997). A P2Y receptor that was initially termed a p2y8 receptor (P79928) has been cloned from *Xenopus laevis*; it shows the rank order of potency ADPβS > ATP = UTP = GTP = CTP = TTP = ITP > ATPγS and elicits a Ca<sup>2+</sup>-dependent Cl<sup>-</sup> current in *Xenopus* oocytes (Bogdanov *et al.*, 1997). The p2y10 clone (ENSG00000078589) lacks functional data. Diadenosine polyphosphates also have effects on as yet uncloned P2Y-like receptors with the rank order of potency of Ap<sub>4</sub>A > Ap<sub>5</sub>A > Ap<sub>3</sub>A, coupling via G<sub>q/11</sub> (Castro *et al.*, 1992). P2Y-like receptors have recently been described on mitochondria (Belous *et al.*, 2004). CysLT<sub>1</sub> and CysLT<sub>2</sub> leukotriene receptors respond to nanomolar concentrations of UDP, although they are activated principally by leukotrienes C<sub>4</sub> and D<sub>4</sub> (Mellor *et al.*, 2001; 2003); Human (ENSG00000144230) and rat GPR17, which are structurally related to CysLT and P2Y receptors, are also activated by leukotrienes as well as UDP and UDP-glucose (Ciana *et al.*, 2006). Activity at the rat GPR17 is inhibited by submicromolar concentrations of MRS2179 and ARL69931 (Ciana *et al.*, 2006).

**Abbreviations:** ARC67085, 2-propylthio- $\beta$ -dichloromethylene-ATP; AR-C69931MX,  $N^6$ -(2-methylthioethyl)-2-(3,3,3-trifluoropropylthio)- $\beta$ -dichloromethylene-ATP, also known as cangrelor; 2-MeSADP, 2-methylthio-adenosine-5'-diphosphate; 2-MeSATP, 2-methylthio-adenosine-5'-triphosphate; ARL66096, 2-propylthio- $\beta$ -difluoromethylene ATP (previously FPL66096); ATP $\gamma$ S, adenosine 5'-(3-thio)triphosphate; MRS2179,  $N^6$ -methyl-2'-deoxyadenosine-3',5'-bisphosphate; MRS2211, pyridoxal-5'-phosphate-6-azo (2-chloro-5-nitrophenyl)-2,4-disulfonate; MRS2279, 2-chloro- $N^6$ -methyl-(*N*)-methanocarba-2'-deoxyadenosine-3',5'-bisphosphate; MRS2365, (*N*)-methanocarba-2-MeSADP; MRS2500,  $N^6$ -methyl-(*N*)-methanocarba-2'-deoxyadenosine-3',5-bisphosphate; MRS2578,  $N,N''$ -1,4-butanediyl bis( $N'$ -[3-isothiocyanatophenyl]) thiourea; MRS2690, 2-thiouridine-5'-diphosphoglucose; MRS2768, uridine-5'-tetrakisphosphate  $\delta$ -phenyl ester; MRS4062,  $N^4$ -phenylpropoxycytidine-5'-triphosphate; NF157, 8,8'-[carbonylbis(imino-3,1-phenylenecarbonylimino(4-fluoro-3,1-phenylene)carbonylimino)]bis-1,3,5-naphthalene trisulfonic acid hexasodium salt; NF546, 4,4'-(carbonylbis(imino-3,1-phenylene-carbonylimino-3,1-(4-methyl-phenylene)-carbonylimino))-bis(1,3-xylylene- $\alpha,\alpha'$ -diphosphonic acid); PTT, 2,2'-pyridylisatogen tosylate

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# Parathyroid hormone and parathyroid hormone-related peptide

**Overview:** Parathyroid hormone (PTH) and parathyroid hormone-related peptide (PTHrP) receptors (provisional nomenclature) are activated by precursor-derived peptides: PTH (84 amino acids, ENSG00000152266), PTHrP (141 amino-acids and related peptides (PTHrP-1-36, PTHrP-38-94 and osteostatin (PTHrP-107-139) (ENSG00000087494) and TIP39 (39 amino acids, ENSG00000142538). [<sup>125</sup>I]-PTH may be used to label both PTH<sub>1</sub> and PTH<sub>2</sub> receptors.

| Nomenclature           | PTH <sub>1</sub>                   | PTH <sub>2</sub>                        |
|------------------------|------------------------------------|-----------------------------------------|
| Other names            | PTH/PTHrP, PPR                     | –                                       |
| Ensembl ID             | ENSG00000160801                    | ENSG00000144407                         |
| Principal transduction | G <sub>s</sub> , G <sub>q/11</sub> | G <sub>s</sub> , G <sub>q/11</sub>      |
| Rank order of potency  | PTH = PTHrP                        | TIP39, PTH >> PTHrP                     |
| Selective agonists     | –                                  | TIP39 (Hoare <i>et al.</i> , 2000)      |
| Selective antagonists  | –                                  | TIP-9-39 (Jonsson <i>et al.</i> , 2001) |

Although PTH is an agonist at human PTH<sub>2</sub> receptors, it fails to activate the rodent orthologues. TIP39 is a weak antagonist at PTH<sub>1</sub> receptors (Jonsson *et al.*, 2001).

**Abbreviations:** PTH, parathyroid hormone; PTHrP, parathyroid hormone-related peptide; TIP39, tuberoinfundibular protein of 39 residues

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# Platelet-activating factor

**Overview:** Platelet-activating factor (PAF, 1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine) is a biologically active phospholipid mediator. PAF acts by binding to a unique G protein-coupled receptor (PAF-R) and activates multiple intracellular signaling pathways by coupling to the G<sub>q/11</sub> and G<sub>i/o</sub> families of G proteins. PAF-R is activated by PAF and its metabolically stable analogue mc-PAF. Other suggested endogenous ligands are oxidized phosphatidylcholine (Marathe *et al.*, 1999) and lysophosphatidylcholine (Ogita *et al.*, 1997). It may also be activated by bacterial lipopolysaccharide (Nakamura *et al.*, 1992).

|                        |                                                                                 |
|------------------------|---------------------------------------------------------------------------------|
| Nomenclature           | PAF-R                                                                           |
| Ensembl ID             | ENSG00000169403                                                                 |
| Principal transduction | G <sub>q/11</sub> , G <sub>i</sub> , G <sub>o</sub>                             |
| Selective agonists     | mc-PAF                                                                          |
| Selective antagonists  | CV-6209 (9.5), SR27417 (10.0), WEB2086 (8.0), L659989 (8.1), ginkgolide B (6.4) |
| Radioligand            | [ <sup>3</sup> H]-PAF (1.6 nM, Fukunaga <i>et al.</i> , 2001)                   |

Note that a previously recommended radioligand ([<sup>3</sup>H]-WEB2086; K<sub>d</sub> 44.6 nM) is currently unavailable.

**Abbreviations:** CV-6209, 2-(*N*-acetyl-*N*-[2-methoxy-3-octadecylcarbamoyloxypropoxycarbamoyl]aminomethyl)-1-ethylpyridinium chloride; L659989, *trans*-2-(3-methoxy-5-methylsulfonyl-4-propoxyphenyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran; mc-PAF, 1-*O*-alkyl-2-*N*-methylcarbamoyl-*sn*-glycero-3-phosphocholine; also known as (methyl)carbam(o)yl-PAF or c-PAF; SR27417, *N*-(2-dimethylaminoethyl)-*N*-(3-pyridinylmethyl)(4-[2,4,6-triisopropylphenyl]thiazol-2-yl)amine; WEB2086, 3-(4-[2-chlorophenyl]-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine-2-yl)-1-(4-morpholinyl)-1-propanone; also known as apafant

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# Proteinase-activated

**Overview:** Proteinase-activated receptors (PARs, nomenclature as agreed by NC-IUPHAR Subcommittee on Proteinase-activated Receptors, see Hollenberg and Compton, 2002) are unique members of the GPCR superfamily activated by proteolytic cleavage of their amino terminal exodomains. Agonist proteinase-induced hydrolysis unmask a tethered ligand at the exposed amino terminus, which acts intramolecularly at the binding site in the body of the receptor to effect transmembrane signalling. Tethered ligand sequences at human PAR1–4 are SFLLRN, SLIGKV, TFRGAP and GYPGQV, respectively. With the exception of PAR3, these synthetic peptide sequences (as carboxyl terminal amides) are able to act as agonists at their respective receptors. Several proteinases, including neutrophil elastase, cathepsin G and chymotrypsin can have inhibitory effects at the PAR1 and PAR2 such that they cleave the exodomain of the receptor without inducing activation, thereby preventing activation by activating proteinases but not by agonist peptides. The role of such an action *in vivo* is unclear.

| Nomenclature           | PAR <sub>1</sub>                                                                                                                         | PAR <sub>2</sub>                                                                                                                                                                                                                                                       | PAR <sub>3</sub>                           | PAR <sub>4</sub>                                                         |
|------------------------|------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|--------------------------------------------------------------------------|
| Other names            | Thrombin receptor, PAR-1, PAR <sub>1</sub>                                                                                               | PAR-2, PAR <sub>2</sub>                                                                                                                                                                                                                                                | Thrombin receptor, PAR-3, PAR <sub>3</sub> | Thrombin receptor, PAR-4, PAR <sub>4</sub>                               |
| Ensembl ID             | ENSG00000181104                                                                                                                          | ENSG00000164251                                                                                                                                                                                                                                                        | ENSG00000164220                            | ENSG00000127533                                                          |
| Principal transduction | G <sub>q</sub> /11/G <sub>i/o</sub> /G <sub>12/13</sub>                                                                                  | G <sub>q</sub> /11/G <sub>i/o</sub> /G <sub>12/13</sub>                                                                                                                                                                                                                | G <sub>q</sub> /11/G <sub>i/o</sub>        | G <sub>q</sub> /11/G <sub>i/o</sub>                                      |
| Agonist proteases      | Thrombin, activated protein C, matrix metalloproteinase 2                                                                                | Trypsin, tryptase, TF/VIIa, Xa                                                                                                                                                                                                                                         | Thrombin                                   | Thrombin, trypsin, cathepsin G                                           |
| Selective agonists     | TFLLR-NH <sub>2</sub>                                                                                                                    | 2-Furoyl-LIGRLO-NH <sub>2</sub> (McGuire <i>et al.</i> , 2004), SLIGRL-NH <sub>2</sub> , SLIGKV-NH <sub>2</sub>                                                                                                                                                        | –                                          | AYPGKF-NH <sub>2</sub> , GYPGQV-NH <sub>2</sub> , GYPGKF-NH <sub>2</sub> |
| Selective antagonists  | RWJ56110 (Andrade-Gordon <i>et al.</i> , 1999), SCH530348 (Chackalamannil <i>et al.</i> , 2008), E5555 (Serebruany <i>et al.</i> , 2009) | –                                                                                                                                                                                                                                                                      | –                                          | –                                                                        |
| Probes                 | [ <sup>3</sup> H]-haTRAP (Ahn <i>et al.</i> , 1997)                                                                                      | <i>Trans</i> -cinnamoyl-LIGRLO[N- <sup>3</sup> H]-propionyl]-NH <sub>2</sub> (Al Ani <i>et al.</i> , 1999), 2-furoyl-LIGRL[N- <sup>3</sup> H]propionyl]-O-NH <sub>2</sub> and 2-furoyl-LIGRL[N-(Alexa Fluor 594)-O]-NH <sub>2</sub> (Hollenberg <i>et al.</i> , 2008). | –                                          | –                                                                        |

TFLLR-NH<sub>2</sub> is selective relative to the PAR<sub>2</sub> receptor (Blackhart *et al.*, 1996; Kawabata *et al.*, 1999). Thrombin is inactive at the PAR<sub>2</sub> receptor.

Endogenous serine proteinases (EC 3.4.21.) active at the proteinase-activated receptors include: thrombin, generated by the action of Factor X (ENSG00000126218) on liver-derived prothrombin (ENSG00000180210); trypsin, generated by the action of enterokinase (ENSG00000154646) on pancreatic-derived trypsinogen (ENSG00000204983); tryptase, a family of enzymes ( $\alpha$ / $\beta$ 1 ENSG00000172236;  $\gamma$ 1 ENSG00000116176;  $\delta$ 1 ENSG00000095917) secreted from mast cells; cathepsin G (ENSG00000100448) generated from leukocytes; liver-derived protein C (ENSG00000115718) generated in plasma by thrombin and matrix metalloproteinase 1 (see Page S317).

**Abbreviations:** [<sup>3</sup>H]-haTRAP, Ala-*p*-fluoroPhe-Ala-Arg-cyclohexylAla-homoArg-[<sup>3</sup>H]-Tyr-amide; RWJ56110, ( $\alpha$ S)-N-([1S]-3-amino-1-[[[(phenylmethyl)amino]propyl]- $\alpha$ -[[[(1-[2,6-dichlorophenyl)methyl]-3-[1-pyrrolidinylmethyl]-1H-indol-6-yl)amino]carbonyl]amino)-3,4-difluoro-benzenepropanamide; SCH530348 (chemical name); E5555 (chemical name)

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# Prostanoid

**Overview:** Prostanoid receptors (nomenclature agreed by the NC-IUPHAR Subcommittee on Prostanoid Receptors, see Coleman *et al.*, 1994) are activated by the endogenous ligands prostaglandin (PG) D<sub>2</sub> (D), PGE<sub>2</sub> (E), PGF<sub>2α</sub> (F), PGH<sub>2</sub> (H), prostacyclin [PGI<sub>2</sub> (I)] and thromboxane A<sub>2</sub> (T). Measurement of the potency of PGI<sub>2</sub> and TXA<sub>2</sub> is hampered by their instability in physiological salt solution; they are often replaced by cicaprost and U46619, respectively, in receptor characterization studies.

| Nomenclature           | DP <sub>1</sub>                                                                                                                        | DP <sub>2</sub>                                                                                                                   | FP                                                                                       | IP                                                           | TP                                                                                                                                   |
|------------------------|----------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|--------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| Other names            | –                                                                                                                                      | CRTh2, GPR44                                                                                                                      | –                                                                                        | –                                                            | –                                                                                                                                    |
| Ensembl ID             | ENSG00000168229                                                                                                                        | ENSG00000183134                                                                                                                   | ENSG00000122420                                                                          | ENSG00000160013                                              | ENSG00000006638                                                                                                                      |
| Principal transduction | G <sub>s</sub>                                                                                                                         | G <sub>i/o</sub>                                                                                                                  | G <sub>q/11</sub>                                                                        | G <sub>s</sub>                                               | G <sub>q/11</sub>                                                                                                                    |
| Rank order of potency  | D >> E > F > I, T                                                                                                                      | D >> F, E > I, T                                                                                                                  | F > D > E > I, T                                                                         | I >> D, E, F > T                                             | T = H >> D, E, F, I                                                                                                                  |
| Selective agonists     | L644698, BW245C, ZK118182, RS93520, SQ27986                                                                                            | 13,14-Dihydro-15-oxo PGD <sub>2</sub> , 15R-15-methyl PGD <sub>2</sub> (Hata <i>et al.</i> , 2003; Monneret <i>et al.</i> , 2003) | Fluprostenol, latanoprost free acid, AL12180 (Sharif <i>et al.</i> , 2006)               | Cicaprost, AFP07, BM45778 (Seiler <i>et al.</i> , 1997)      | U46619, STA <sub>2</sub> , I-BOP, AGN192093                                                                                          |
| Selective antagonists  | BWA868C (9.3, Giles <i>et al.</i> , 1989), S5751 (8.8, Arimura <i>et al.</i> , 2001), laropiprant (10.1, Sturino <i>et al.</i> , 2007) | Ramatroban (Sugimoto <i>et al.</i> , 2003), CAY10471 (Royer <i>et al.</i> , 2007)                                                 | AS604872 (Cirillo <i>et al.</i> , 2007)                                                  | RO1138452 (8.8), RO3244794 (8.5) (Bley <i>et al.</i> , 2006) | BMS180291 (9.3–10.0), ONO-3708 (8.9), GR32191 (8.3–9.4, Lumley <i>et al.</i> , 1989), SQ29548 (8.1–9.1, Swayne <i>et al.</i> , 1988) |
| Probes                 | [ <sup>3</sup> H]-PGD <sub>2</sub> (13–34 nM)                                                                                          | [ <sup>3</sup> H]-PGD <sub>2</sub> (6–11 nM)                                                                                      | [ <sup>3</sup> H]-PGF <sub>2α</sub> (2–4 nM), [ <sup>3</sup> H]-(-)-fluprostenol (34 nM) | [ <sup>3</sup> H]-Iloprost (1–20 nM)                         | [ <sup>3</sup> H]-SQ29548 (5–40 nM), [ <sup>125</sup> I]-SAP (0.2–1.0 nM), [ <sup>125</sup> I]-I-BOP (0.3–5.0 nM)                    |

Ramatroban is also a TP receptor antagonist. Cicaprost exhibits moderate EP<sub>4</sub> receptor agonist potency (Abramovitz *et al.*, 2000). Iloprost also binds to EP<sub>1</sub> receptors. The TP receptor exists in  $\alpha$  and  $\beta$  isoforms due to alternative splicing of the cytoplasmic tail (Raychowdhury *et al.*, 1994).

| Nomenclature           | EP <sub>1</sub>                                                            | EP <sub>2</sub>                                                           | EP <sub>3</sub>                                              | EP <sub>4</sub>                                                                                                                                                                                                          |
|------------------------|----------------------------------------------------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ensembl ID             | ENSG00000160951                                                            | ENSG00000125384                                                           | ENSG00000050628                                              | ENSG00000171522                                                                                                                                                                                                          |
| Principal transduction | G <sub>q/11</sub>                                                          | G <sub>s</sub>                                                            | G <sub>i/o</sub>                                             | G <sub>s</sub>                                                                                                                                                                                                           |
| Rank order of potency  | E > F, I > D, T                                                            | E > F, I > D, T                                                           | E > F, I > D, T                                              | E > F, I > D, T                                                                                                                                                                                                          |
| Selective agonists     | 17-Phenyl-PGE <sub>2</sub> , ONO-DI-004                                    | Butaprost-free acid, CP533536 (Cameron <i>et al.</i> , 2009), ONO-AE1–259 | Sulprostone, SC46275, ONO-AE-248                             | ONO-AE1–329, L902688 (Young <i>et al.</i> , 2004), CP734432 (Prasanna <i>et al.</i> , 2009)                                                                                                                              |
| Selective antagonists  | ONO8711 (9.2), GW848687X (9.1, Giblin <i>et al.</i> , 2007), SC51322 (8.8) | –                                                                         | L798106 (7.7), ONO-AE3-240 (8.8, Amano <i>et al.</i> , 2003) | GW627368 (9.2), ONO-AE3–208 (8.5), L161982 (8.5), BGC201531 (7.8, Maubach <i>et al.</i> , 2009), CJ042794 (8.6, Murase <i>et al.</i> , 2008), ER819762 (Chen <i>et al.</i> , 2010), MK2894 (Blouin <i>et al.</i> , 2010) |
| Probes                 | [ <sup>3</sup> H]-PGE <sub>2</sub> (1–25 nM)                               | [ <sup>3</sup> H]-PGE <sub>2</sub> (5–22 nM)                              | [ <sup>3</sup> H]-PGE <sub>2</sub> (0.3–7 nM)                | [ <sup>3</sup> H]-PGE <sub>2</sub> (0.6–24 nM)                                                                                                                                                                           |

17-Phenyl-PGE<sub>2</sub> also shows agonist activity at EP<sub>3</sub> receptors. Sulprostone also has affinity for EP<sub>1</sub> receptors. Butaprost and SC46275 may require de-esterification within tissues to attain full agonist potency. There is evidence for subtypes of FP (Liljebris *et al.*, 1995), IP (Takechi *et al.*, 1996; Wise *et al.*, 1995; Wilson *et al.*, 2011) and TP (Krauss *et al.*, 1996) receptors. mRNA for the EP<sub>1</sub> and EP<sub>3</sub> receptors undergo alternative splicing to produce two (Okuda-Ashitaka *et al.*, 1996) and at least six variants, respectively, which can interfere with signalling (Okuda-Ashitaka *et al.*, 1996) or generate complex patterns of G-protein (G<sub>i/o</sub>, G<sub>q/11</sub>, G<sub>s</sub> and G<sub>12/13</sub>) coupling (e.g. Kotani *et al.*, 1995; Negishi *et al.*, 1995). The possibility of additional receptors for the isoprostanes has been suggested (Pratico *et al.*, 1996). Receptors (prostamide F, which as yet lack a molecular correlate) that preferentially recognize PGF<sub>2α</sub>-1-ethanolamide and its analogues (e.g. bimatoprost) have been identified, together with moderate-potency antagonists (e.g. AGN 211334) (see Woodward *et al.*, 2008).

**Abbreviations:** AFP07, 7,7-difluoro-16S,20-dimethyl-18,19-didehydro-PGE<sub>2</sub>; AGN192093, (Z)-7-([1 $\alpha$ ,5 $\alpha$ ,6 $\alpha$ ,7 $\beta$ ]-7-[[1E,3S]-3-hydroxy-1-octenyl]-3-oxo-2,4-dioxobicyclo[3.2.1]oct-6-yl)-5-heptenol; AH23848, (1 $\alpha$ z),2 $\beta$ ,5 $\alpha$ -( $\pm$ )-7-(5-[(1,1'-biphenyl)-4-yl]methoxy]-2-[4-morpholinyl]-3-oxocyclopentyl)-4-heptenoate; AL12180, 5,6-dihydro-4,5-didehydro-11-deoxy-11-oxa-16-(3-chlorophenoxy)- $\omega$ -tetranor-PGF<sub>2 $\alpha$</sub> ; AS604872, (2S)-3-([1,1'-biphenyl]-4-ylsulphonyl-N-[(R)-phenyl(2-pyridinyl)-methyl]-1,3-thiazolidine-2-carboxamide; BGC201531, (N-(4-[4-(5-methoxypyridin-2-yl)phenoxy]methyl)-5-methylfuran-2-carbonyl)-2-methylbenzenesulphonamide; BMS180291, (1S-(1 $\alpha$ ,2 $\alpha$ ,3 $\alpha$ ,4 $\alpha$ )-2-[(3-[4-((pentylamino)carbonyl)-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl)methyl]benzenepropanoic acid; also known as ifetroban; BMY45778, 3-(4-[4,5-diphenyl-2-oxazolyl]-5-oxazolyl)phenoxyacetic acid; BW245C, 5-(6-carboxyhexyl)-1-(3-cyclohexyl-3-hydroxypropyl)hydantoin; BW848687, 6-[2-(5-chloro-2-[(2,4-difluorophenyl)methyl]oxy)phenyl]-1-cyclopenten-1-yl]-2-pyridinecarboxylic acid; BWA868C, 3-benzyl-5-(6-carboxyhexyl)-1-(2-cyclohexyl-2-hydroxyethylamino)hydantoin; CAY10471, (+)-3-([4-fluorophenyl]sulfonyl)methylamino)-1,2,3,4-tetrahydro-9H-carbazole-9-acetic acid; CJ042794, 4-[(1S)-1-[(5-chloro-2-[(4-fluorophenyl)oxy]phenyl)carbonyl]amino]ethyl benzoic acid; CP533536, N-(4-*t*-butylbenzyl)-pyridyl-3-yl-sulphonamidomethylphenoxyacetic acid; CP734432, 5-[3-[(2S)-2-[(3R)-3-hydroxy-4-[3-(trifluoromethyl)phenyl]butyl]-5-oxopyrrolidin-1-yl]propyl]thiophene-2-carboxylate; ER819762, (S)-1'-(3,5-dimethylbenzyl)-2-ethyl-7,9-dimethoxy-10-methyl-5,10-dihydrospiro [benzo[e]imidazo [1,5-a]azepine-1,4'-piperidin]-3(2H)-one; GR32191, [1R-[1(Z),2 $\alpha$ ,3 $\beta$ ,5]]-(+)-7-[5-[[1,1'-biphenyl]-4-yl]methoxy]-3-hydroxy-2-(1-piperidinyl)cyclopentyl]-4-heptenoic acid; GW627368, N-(2-[4-[9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl]-acetyl)benzenesulphonamide; GW848687X, 6-[2-[5-chloro-2-[(2,4-difluorophenyl)methoxy]phenyl]cyclopenten-1-yl]pyridine-2-carboxylic acid; I-BOP, (1S-[1 $\alpha$ ,2 $\beta$ [5z],3 $\alpha$ [1e,3s],4 $\alpha$ ]-7-(3-[hydroxy-4-[4'-iodophenoxy]-1-butenyl]-7-oxabicyclo[2.2.1]hept-2-yl)-5-heptanoate; L161982, 5-butyl-2,4-dihydro-[[2'-[N-(5-methyl-2-thiophenecarbonyl)sulphamoyl]biphenyl-4-yl]methyl]-2-[(2-trifluoromethyl)phenyl]-1,2,4-triazol-3-one; L644698, 4-(3-[3-hydroxyoctyl]-4-oxo-2-thiazolidinyl)propyl]benzoate racemate; L798106, 5-bromo-2-methoxy-N-[3-(naphthalen-2-yl-methyl)phenyl]-acryloyl]-benzenesulphonamide; L902688, 8-aza-1-decarboxy-11-deoxy-16,16-difluoro-16-phenyl- $\omega$ -tetranor-1-(5-tetrazolo) PGE<sub>2</sub>; MK2894, 4-[1-[(2,5-Dimethyl-4-[4-(trifluoromethyl)benzyl]-3-thienyl)carbonyl]amino]cyclopropyl]benzoic acid; ONO3708, (9,11)-(11,12)-dideoxa-9 $\alpha$ ,11 $\alpha$ -dimethylmethano-11,12-methano-13,14-dihydro-13-aza-14-oxo-15-cyclopentyl-16,17,18,19,20-pentano-15-epi-TXA<sub>2</sub>; ONO8711, 6-[(2S,3S)-3-(4-chloro-2-methylphenylsulphonylaminomethyl)-bicyclo[2.2.2]octan-2-yl]-5Z-hexenoic acid; ONO-DI-004, 17S-[17,20-dimethyl-2,5-ethano-6-oxo PGE<sub>2</sub>; ONO-AE-248, 11,15-O-dimethyl-PGE<sub>2</sub>; ONO-AE1-259, 16S-9-deoxy-9 $\beta$ -chloro-15-deoxy-16-hydroxy-17,17-propano-19,20-didehydro-PGE<sub>2</sub>; ONO-AE1-329, 16-(3-methoxymethyl)phenyl- $\omega$ -tetranor-3,7-dithia-PGE<sub>2</sub>; ONO-AE3-208, 2-(2-(2-methyl-2-naphth-1-ylacetyl)amino)-phenylmethyl)-benzoic acid; ONO-AE3-240, 2-(2-[3-naph-1-yl-3-sec-butyl-propionylamino]-4-[pyrazol-1-ylmethyl]phenylmethyl)-benzoic acid; RO1138452, 4,5-dihydro-1H-imidazol-Z-yl)-[4-(4-isopropoxybenzyl)phenyl]amine; RO3244794, R-3-(4-fluorophenyl)-2-[5-(4-fluorophenyl)-benzofuran-2-ylmethoxycarbonylamino]-propionic acid; RS93520, Z-4-[(C3'S,1R,2R,3S,6R)-2C3'-cyclohexyl-3'-hydroxyprop-1-ynyl]-3-hydroxybicyclo[4.2.0]oct-7-ylidene butyrate; SAP, 7-[(1R,2S,3S,5R)-6,6-dimethyl-3-benzenesulphonamino-bicyclo[3.1.1]hept-2-yl)-5Z-heptenoic acid; SC46275, methyl-7-(2 $\beta$ -[6-(1-cyclopenten-1-yl)-4R-hydroxy-4-methyl-1e,5e-hexadienyl]-3 $\alpha$ -hydroxy-5-oxo-1R,1 $\alpha$ -cyclopentyl)-4Z-heptenoic acid; SC51322, 8-chlorodibenz[b,f][1,4]oxazepine-10(11H)-carboxylic acid, 2-[3-[furanylmethyl]-thio]-1-oxopropyl]hydrazide; SQ29548, (1S-[1 $\alpha$ ,2 $\beta$ [5z],3 $\beta$ ,4 $\beta$ ]-7-(3-[[2-(phenylamino)carbonyl]hydrazino]methyl)-7-oxabicyclo[2.2.1]hept-2-yl-5-heptenoate; S5751, ((Z)-7-[1R,2R,3S,5S]-2-(5-hydroxybenzo[b]thiophen-3-ylcarbonylamino)-10-norpinan-3-yl]hept-5-enoic acid); SQ27986, [1S-[1B,2B(5Z),3A(1E,3S)4B]]-7-[3-(3-cyclohexyl-3-hydroxy-1-propenyl)-7-oxabicyclo[2.2.1]hept-2-yl]5-heptenoic acid; STA<sub>2</sub>, 11 $\alpha$ -carba-9 $\alpha$ ,11 $\beta$ -thia-Txa<sub>2</sub>; U46619, 11 $\alpha$ ,9 $\alpha$ -epoxymethano-PGH<sub>2</sub>; ZK 118182, (5Z,13E)-(9R,11R,15S)-9-chloro-15-cyclohexyl-11,15-dihydroxy-2-oxa-16,17,18,19,20-pentano-5,13-prostadienoic acid; ZK138357, (5Z)-7-[(2RS,4S,5S)-2-[2-chlorophenyl]-5-[[1E]-[3R,S]-3-hydroxy-3-cyclohexyl-1-propenyl]-1,3-dioxolan-4-yl)-5-heptanoic acid

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# Prokineticin

**Overview:** Prokineticin receptors (provisional nomenclature, see Foord *et al.*, 2005) respond to the cysteine-rich 81-86 amino-acid peptides prokineticin 1 (PROK1, also known as endocrine-gland-derived vascular endothelial growth factor, mambakine, ENSG00000143125) and prokineticin 2 (PROK2, protein Bv8 homolog, ENSG00000163421). An orthologue of PROK1 from black mamba (*Dendroaspis polylepis*) venom, mamba intestinal toxin 1 (MIT1, Schweitz *et al.*, 1999) is a potent, non-selective agonist at prokineticin receptors (Masuda *et al.*, 2002), while Bv8, an orthologue of PROK2 from amphibians (*Bombina sp.*, Mollay *et al.*, 1999), is equipotent at recombinant PK<sub>1</sub> and PK<sub>2</sub> receptors (Negri *et al.*, 2005), and has high potency in macrophage chemotaxis assays, which are lost in PK<sub>1</sub>-null mice (Martucci *et al.*, 2006).

| Nomenclature           | PK <sub>1</sub>                                                                                                                  | PK <sub>2</sub>                                                                                                |
|------------------------|----------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| Other names            | PK-R1, GPR73 (Lin <i>et al.</i> , 2002; Soga <i>et al.</i> , 2002), G-protein coupled receptor ZAQ (Masuda <i>et al.</i> , 2002) | PK-R2, GPR73a (Lin <i>et al.</i> , 2002), GPRg2 (Soga <i>et al.</i> , 2002), ISE (Masuda <i>et al.</i> , 2002) |
| Ensembl ID             | ENSG00000169618                                                                                                                  | ENSG00000101292                                                                                                |
| Principal transduction | G <sub>q/11</sub> (Lin <i>et al.</i> , 2002; Masuda <i>et al.</i> , 2002)                                                        | G <sub>q/11</sub> (Lin <i>et al.</i> , 2002; Masuda <i>et al.</i> , 2002)                                      |
| Rank order of potency  | PROK2 ≥ PROK1 (Lin <i>et al.</i> , 2002; Masuda <i>et al.</i> , 2002; Soga <i>et al.</i> , 2002)                                 | PROK2 ≥ PROK1 (Lin <i>et al.</i> , 2002; Masuda <i>et al.</i> , 2002; Soga <i>et al.</i> , 2002)               |

**Abbreviations:** PROK1, prokineticin 1; PROK2, prokineticin 2

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# Relaxin family peptide

**Overview:** Relaxin family peptide receptors (RXFP, nomenclature as recommended by the NC-IUPHAR committee on relaxin family peptide receptors, Bathgate *et al.* 2006) may be divided into two groups RXFP1/2 and RXFP3/4. Endogenous agonists at these receptors are a number of heterodimeric peptide hormones analogous to insulin: H1 relaxin [ENSG00000107018], H2 relaxin [ENSG00000107014], H3 relaxin [also known as INSL7, ENSG00000171136], insulin-like peptide (INSL) 3 [OTTHUMG00000070952] and INSL5 [ENSG00000172410].

Species homologues of relaxin have distinct pharmacology – H2 relaxin interacts with RXFP1, RXFP2 and RXFP3, whereas mouse and rat relaxin selectively bind to and activate RXFP1 (Scott *et al.*, 2005a) and porcine relaxin may have a higher efficacy than H2 relaxin (Halls *et al.*, 2005). H3 relaxin has differential affinity for RXFP2 receptors between species; mouse and rat RXFP2 have a higher affinity for H3 relaxin (Scott *et al.*, 2005b). At least two binding sites have been identified on RXFP1 and RXFP2 receptors: a high-affinity site in the leucine-rich repeat region of the ectodomain and a somewhat lower-affinity site located in the surface loops of the transmembrane (Halls *et al.*, 2005; Sudo *et al.*, 2003). The unique N-terminal LDLa module of RXFP1 and RXFP2 is essential for receptor signalling (Scott *et al.*, 2006).

| Nomenclature           | RXFP1                                                                                                                                | RXFP2                                                                                                                                                                                                |
|------------------------|--------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Other names            | Relaxin receptor, LGR7, leucine-rich repeat-containing G-protein-coupled receptor 7, RX1                                             | INSL3 receptor, LGR8, leucine-rich repeat-containing G-protein-coupled receptor 8, GREAT, RX2                                                                                                        |
| Ensembl ID             | ENSG00000171509                                                                                                                      | ENSG00000133105                                                                                                                                                                                      |
| Principal transduction | G <sub>s</sub> , G <sub>αo8</sub> , G <sub>α13</sub> (Halls <i>et al.</i> , 2006, 2009a; Hsu <i>et al.</i> , 2002)                   | G <sub>s</sub> , G <sub>αo8</sub> (Halls <i>et al.</i> , 2006; Kumagai <i>et al.</i> , 2002)                                                                                                         |
| Rank order of potency  | H2 relaxin > H3 relaxin >> INSL3 (Sudo <i>et al.</i> , 2003)                                                                         | INSL3 > H2 relaxin >> H3 relaxin (Kumagai <i>et al.</i> , 2002; Sudo <i>et al.</i> , 2003)                                                                                                           |
| Antagonists            | LGR7-truncate (Scott <i>et al.</i> , 2006), B13/17K H2 relaxin (Hossain <i>et al.</i> , 2010)                                        | INSL3 B-chain analog (Del Borgo <i>et al.</i> , 2006), (des 1-8) A-chain INSL3 analog (Bullesbach and Schwabe, 2005), INSL3 B chain dimer (Shabanpoor <i>et al.</i> , 2011).                         |
| Probes                 | [ <sup>33</sup> P]-H2 relaxin (0.2 nM; Sudo <i>et al.</i> , 2003), Europium-labelled H2 relaxin (1 nM; Hossain <i>et al.</i> , 2009) | [ <sup>33</sup> P]-H2 relaxin (1.06 nM; Sudo <i>et al.</i> , 2003), [ <sup>125</sup> I]-INSL3 (0.1 nM; Muda <i>et al.</i> , 2005), Europium-labelled INSL3 (0.9 nM; Shabanpoor <i>et al.</i> , 2008) |

Mutations in *INSL3* and *LGR8* (RXFP2) have been reported in populations of patients with cryptorchidism (Ferlin *et al.*, 2003). Numerous splice variants of the human RXFP1 and RXFP2 receptors have been identified, none of which bind relaxin family peptides (Muda *et al.*, 2005). Splice variants of RXFP1 encoding the N-terminal LDLa module act as antagonists of RXFP1 signalling (Scott *et al.*, 2005b; 2006). cAMP elevation appears to be a major signalling pathway for RXFP1 and RXFP2 (Hsu *et al.*, 2000; Hsu *et al.*, 2002) but RXFP1 also activates MAP kinases, nitric oxide signalling and interacts with tyrosine kinases and glucocorticoid receptors (Halls *et al.*, 2007). RXFP1 signalling involves lipid rafts, residues in the C-terminus of the receptor and activation of phosphatidylinositol-3-kinase (Halls *et al.*, 2009a). More recent studies provide evidence that RXFP1 is pre-assembled in signalosomes with other signalling proteins including G<sub>αs</sub>, G<sub>βγ</sub> and adenylyl cyclase 2 that display constitutive activity and are exquisitely sensitive to sub-picomolar concentrations of relaxin (Halls and Cooper, 2010). The cAMP signalling pattern is highly dependent on the cell type in which RXFP1 is expressed (Halls *et al.*, 2009b).

| Nomenclature           | RXFP3                                                                                                                                                                                                                                   | RXFP4                                                                                                                                                                                                                    |
|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Other names            | Relaxin 3 receptor, GPCR135, somatostatin and angiotensin-like peptide receptor SALPR, RX3                                                                                                                                              | INSL5 receptor, GPCR142, GPR100, relaxin 3 receptor 2, RX4                                                                                                                                                               |
| Ensembl ID             | ENSG00000182631                                                                                                                                                                                                                         | ENSG00000173080                                                                                                                                                                                                          |
| Principal transduction | G <sub>i/o</sub> (Matsumoto <i>et al.</i> , 2000; Van der Westhuizen <i>et al.</i> , 2007)                                                                                                                                              | G <sub>i/o</sub> (Liu <i>et al.</i> , 2003b)                                                                                                                                                                             |
| Rank order of potency  | H3 relaxin > H3 relaxin B chain (Liu <i>et al.</i> , 2003a), also H2 relaxin (see below)                                                                                                                                                | INSL5 = H3 relaxin > H3 relaxin B chain (Liu <i>et al.</i> , 2003b; 2005a)                                                                                                                                               |
| Antagonists            | INSL5 (Liu <i>et al.</i> , 2005a), R3(BΔ23-27)R/I5 chimeric peptide (Kuei <i>et al.</i> , 2007), R3 B1-22R (Haugaard-Kedström <i>et al.</i> , 2011)                                                                                     | R3(BΔ23-27)R/I5 chimeric peptide (Kuei <i>et al.</i> , 2007)                                                                                                                                                             |
| Probes                 | [ <sup>125</sup> I]-H3 relaxin (0.3 nM; Liu <i>et al.</i> , 2003a), [ <sup>125</sup> I]-H3-B/INSL5 A chimera (0.5 nM; Liu <i>et al.</i> , 2005b), Europium-labelled H3-B/INSL5 A chimera (5 nM; Haugaard-Kedstrom <i>et al.</i> , 2011) | [ <sup>125</sup> I]-H3 relaxin (0.2 nM; Liu <i>et al.</i> , 2003b), [ <sup>125</sup> I]-H3-B/INSL5 A chimera (1.2 nM; Liu <i>et al.</i> , 2005b), Europium-labelled INSL5 (5 nM; Haugaard-Kedstrom <i>et al.</i> , 2011) |

H3 relaxin acts as an agonist at both RXFP3 and RXFP4 whereas INSL5 is an agonist at RXFP4 and an antagonist at RXFP3. Unlike RXFP1 and RXFP2 both RXFP3 and RXFP4 are encoded by a single exon and therefore no splice variants exist. The rat RXFP3 sequence has two potential start codons that encode RXFP3L and RXFP3S with the longer variant having an additional 7 amino-acids at the N-terminus. It is not known which variant is expressed. Rat and dog RXFP4 sequences are pseudogenes (Wilkinson *et al.*, 2005). Recent studies suggest that H2 relaxin also interacts with RXFP3 to cause a pattern of activation of signalling pathways that are a subset of those activated by H3 relaxin. The two patterns of signaling observed in several cell types expressing RXFP3 are strong inhibition of forskolin-stimulated cAMP accumulation, ERK1/2 activation and nuclear factor NFκ-B reporter gene activation with H3 relaxin, and weaker activity with H2 relaxin, porcine relaxin, or insulin-like peptide

(INSL) 3 and a strong stimulation of activator protein (AP)-1 reporter genes with H2 relaxin, and weaker activation with H3 or porcine relaxin (Van der Westhuizen *et al.*, 2010). Two distinct ligand binding sites were also identified on RXFP3-expressing cells using two different radioligands. <sup>125</sup>I-INSL5 A-chain/relaxin-3 B-chain chimera binds with high affinity with competition by H3 relaxin or a H3 relaxin B-chain peptide, whereas <sup>125</sup>I-H2 relaxin binding is competed for by H2 relaxin, H3 relaxin, or INSL3 and weakly by porcine relaxin. Thus at RXFP3, H2 relaxin is a biased ligand compared to the cognate ligand H3 relaxin.

**Abbreviations:** H2 relaxin, human gene 2 relaxin; H3 relaxin, human gene 3 relaxin; INSL3, insulin-like peptide 3; INSL5, insulin-like peptide 5

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# Somatostatin

**Overview:** Somatostatin (somatotropin release inhibiting factor) is an abundant neuropeptide, which acts on five subtypes of somatostatin receptor (sst1–sst5; nomenclature approved by the NC-IUPHAR Subcommittee on Somatostatin Receptors, see Hoyer *et al.*, 2000). Activation of these receptors produces a wide range of physiological effects throughout the body including inhibiting the secretion of many hormones. The relationship of the cloned receptors to endogenously expressed receptors is not yet well established in some cases. Endogenous ligands for these receptors are somatostatin-14 (SRIF-14) and somatostatin-28 (SRIF-28). Cortistatin (CST-14) has also been suggested to be an endogenous ligand for somatostatin receptors (Delecea *et al.*, 1996).

| Nomenclature           | sst <sub>1</sub>                                                                | sst <sub>2</sub>                                                                            | sst <sub>3</sub>                              | sst <sub>4</sub>                              | sst <sub>5</sub>                                            |
|------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------|-------------------------------------------------------------|
| Alternative names      | SSTR1, SRIF <sub>2A</sub> , SRIF <sub>2A</sub>                                  | SSTR2, SRIF <sub>1</sub> , SRIF <sub>1A</sub>                                               | SSTR3, SRIF <sub>1</sub> , SRIF <sub>1C</sub> | SSTR4, SRIF <sub>2</sub> , SRIF <sub>2B</sub> | SSTR5, SRIF <sub>1</sub> , SRIF <sub>1B</sub>               |
| Ensembl ID             | ENSG00000139874                                                                 | ENSG00000180616                                                                             | ENSG00000183473                               | ENSG00000132671                               | ENSG00000162009                                             |
| Principal transduction | G <sub>i</sub>                                                                  | G <sub>i</sub>                                                                              | G <sub>i</sub>                                | G <sub>i</sub>                                | G <sub>i</sub>                                              |
| Selective agonists     | des-Ala <sup>1,2,5</sup> -[DTrp <sup>8</sup> , lamp <sup>9</sup> ]SRIF, L797591 | Octreotide, seglitide, BIM23027, L054522                                                    | L796778                                       | NNC269100, L803087                            | BIM23268, BIM23052, L817818                                 |
| Selective antagonists  | SRA880                                                                          | Cyanamid 154806 (7.7–8.0)                                                                   | NVP ACQ090                                    | –                                             | BIM23627 (7.1)                                              |
| Probes                 | –                                                                               | [ <sup>125</sup> I]-[Tyr <sup>3</sup> ]octreotide (0.13 nM)<br>[ <sup>125</sup> I]-BIM23027 | –                                             | –                                             | [ <sup>125</sup> I]-[Tyr <sup>3</sup> ]octreotide (0.23 nM) |

[<sup>125</sup>I]-[Tyr<sup>11</sup>]SRIF-14, [<sup>125</sup>I]-LTT-SRIF-28, [<sup>125</sup>I]-CGP23996 and [<sup>125</sup>I]-[Tyr<sup>10</sup>]CST-14 may be used to label somatostatin receptors nonselectively; BIM23052 is said to be selective in rat but not human receptor (Patel and Srikant, 1994). A number of nonpeptide subtype-selective agonists have been synthesised (see Rohrer *et al.*, 1998).

**Abbreviations:** BIM23027, *cyc*(N-Me-Ala-Tyr-D-Trp-Lys-Abu-Phe); BIM23052, DPhe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH<sub>2</sub>; BIM23056, DPhe-Phe-Tyr-D-Trp-Lys-Val-Phe-dNal-NH<sub>2</sub>; BIM23268, *cyc*(Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys)-NH<sub>2</sub>; CGP23996, *cyc*(Asn-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Tyr-Thr-Ser); Cyanamid 154806, Ac-(4-NO<sub>2</sub>-Phe)-*cyc*(D-Cys-Tyr-D-Trp-Lys-Thr-Cys)-D-Tyr-NH<sub>2</sub>; L797591, (2R)-N-(6-amino-2,2,4-trimethylhexyl)-3-(1-naphthyl)-2-(((2-phenylethyl)2-pyridin-2-ylethyl)amino)carbonylamino)propanamide; L054522, tert-butyl (bS)-b-methyl-N-[[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]carbonyl]-D-tryptophyl-L-lysinate; L796778, methyl (2S)-6-amino-2-(((2R)-2-(((1S)-1-benzyl-2-[(4-nitrophenyl)amino]-2-oxoethyl)amino)carbonylamino)hexanoyl)amino)hexanoate; L803087, methyl (2S)-5-[[amino(imino)methyl]amino]-2-[[4-(5,7-difluoro-2-phenyl-1H-indol-3-yl)butanoyl]amino]pentanoate; L817818, (2R)-2-aminopropyl N2-[[2-(2-naphthyl)-1H-benzo[g]indo-3-yl]acetyl]-L-lysinate; LTT-SRIF-28, [Leu<sup>8</sup>,DTrp<sup>22</sup>,DTyr<sup>25</sup>]SRIF-28; NNC269100, 1-[3-[N-(5-bromopyridin-2-yl)-N-(3,4-dichlorobenzyl)amino]propyl]-3-[3-(<sup>1</sup>H-imidazol-1-yl)propyl]thiourea

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# Sphingosine 1-phosphate

**Overview:** Sphingosine 1-phosphate (S1P) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Lysophospholipid receptors; see Chun *et al.*, 2010) are activated by the endogenous lipid derivatives S1P and sphingosylphosphorylcholine (SPC). Originally identified as members of the endothelial differentiation gene (*edg*) family along with lysophosphatidic acid receptors, the gene names have recently been updated to *S1PR1*, etc. to reflect the receptor function of these proteins. S1P has also been described to act at intracellular sites (see Takabe *et al.*, 2008), although most cellular phenomena ascribed to S1P can be explained by receptor-mediated mechanisms. The relationship between recombinant and endogenously expressed receptors is unclear. Radioligand binding has been conducted in heterologous expression systems using [<sup>32</sup>P]-S1P (e.g. Okamoto *et al.*, 1998). In native systems, analysis of binding data is complicated by metabolism and high levels of nonspecific binding. Targeted deletion of several S1P receptors and key enzymes involved in S1P biosynthesis or degradation has clarified signalling pathways and physiological roles.

| Nomenclature           | S1P <sub>1</sub>                                                               | S1P <sub>2</sub>                                                               | S1P <sub>3</sub>                                       | S1P <sub>4</sub>                                            | S1P <sub>5</sub>                                  |
|------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------|-------------------------------------------------------------|---------------------------------------------------|
| Other names            | edg1, <i>lp</i> <sub>B1</sub>                                                  | edg5, <i>lp</i> <sub>B2</sub> , AGR16, H218                                    | edg3, <i>lp</i> <sub>B3</sub>                          | edg6, <i>lp</i> <sub>C1</sub>                               | edg8, <i>lp</i> <sub>B4</sub> , NRG-1             |
| Ensembl ID             | ENSG00000170989                                                                | ENSG00000175898                                                                | ENSG00000186354                                        | ENSG00000125910                                             | ENSG00000180739                                   |
| Principal transduction | G <sub>i/o</sub>                                                               | G <sub>q</sub> , G <sub>12/13</sub> , G <sub>s</sub>                           | G <sub>q</sub> , G <sub>i/o</sub> , G <sub>s</sub>     | G <sub>i/o</sub> , G <sub>12/13</sub> , G <sub>s</sub>      | G <sub>i/o</sub> , G <sub>12/13</sub>             |
| Rank order of potency  | S1P > dihydro-S1P > SPC (Okamoto <i>et al.</i> , 1998, Ancellin and Hla, 1999) | S1P > dihydro-S1P > SPC (Okamoto <i>et al.</i> , 1998, Ancellin and Hla, 1999) | S1P > dihydro-S1P > SPC (Okamoto <i>et al.</i> , 1998) | S1P > dihydro-S1P > SPC (Van Brocklyn <i>et al.</i> , 2000) | S1P > dihydro-S1P > SPC (Im <i>et al.</i> , 2000) |
| Selective agonists     | SEW2871 (Sanna <i>et al.</i> , 2004), AUY954 (Pan <i>et al.</i> , 2006)        | –                                                                              | –                                                      | –                                                           | –                                                 |
| Selective antagonists  | W146 (Sanna <i>et al.</i> , 2006)                                              | JTE013 (Osada <i>et al.</i> , 2002)                                            | –                                                      | –                                                           | –                                                 |

The immunomodulator fingolimod (FTY720) may be phosphorylated *in vivo* (Albert *et al.*, 2005) to generate a relatively potent agonist with activity at S1P<sub>1</sub>, S1P<sub>3</sub>, S1P<sub>4</sub> and S1P<sub>5</sub> receptors (Brinkmann *et al.*, 2002; Mandala *et al.*, 2002). VPC23019 and VPC44116 have antagonist activity at S1P<sub>1</sub> and S1P<sub>3</sub> receptors (see Marsolais and Rosen, 2009). This compound has received world-wide approval as the first oral therapy for relapsing forms of Multiple Sclerosis, with a novel mechanism of action (Cohen and Chun, 2011; Choi *et al.*, 2011).

**Abbreviations:** AUY954, an aminocarboxylate analog of fingolimod; JTE013, pyrazolopyridine analog; SEW2871, 5-(4-phenyl-5-trifluoromethylthiophen-2-yl)-3-(3-trifluoromethylphenyl)-(1,2,4)-oxadiazole; S1P, sphingosine 1-phosphate; VPC23019, (*R*)-phosphoric acid mono-[2-amino-2-(3-octyl-phenylcarbamoyl)-ethyl] ester; VPC44116, [3-amino-3-(3-octylphenylcarbamoyl)propyl]-phosphonic acid; W146, (*R*)-3-amino-(3-hexylphenylamino)-4-oxobutylphosphonic acid

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# Tachykinin

**Overview:** Tachykinin receptors (provisional nomenclature, see Foord *et al.*, 2005) are activated by the endogenous peptides substance P (SP), neurokinin A (NKA; previously known as substance K, neurokinin  $\alpha$ , neuromedin L), neurokinin B (NKB; previously known as neurokinin  $\beta$ , neuromedin K), neuropeptide K and neuropeptide  $\gamma$  (N-terminally extended forms of neurokinin A). The neurokinins (A and B) are mammalian members of the tachykinin family, which includes peptides of mammalian and nonmammalian origin containing the consensus sequence: Phe-x-Gly-Leu-Met. Marked species differences in pharmacology exist for all three receptors, in particular with nonpeptide ligands.

| Nomenclature           | NK <sub>1</sub>                                                                                                                                                                                                       | NK <sub>2</sub>                                                                                                         | NK <sub>3</sub>                                                                                                |
|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| Other names            | Substance P                                                                                                                                                                                                           | Substance K                                                                                                             | Neurokinin B, neuromedin K                                                                                     |
| Ensembl ID             | ENSG00000115353                                                                                                                                                                                                       | ENSG00000075073                                                                                                         | ENSG00000169836                                                                                                |
| Principal transduction | G <sub>q/11</sub>                                                                                                                                                                                                     | G <sub>q/11</sub>                                                                                                       | G <sub>q/11</sub>                                                                                              |
| Rank order of potency  | SP > NKA > NKB                                                                                                                                                                                                        | NKA > NKB >> SP                                                                                                         | NKB > NKA > SP                                                                                                 |
| Selective agonists     | SP methylester, [Sar <sup>9</sup> ,Met(O <sub>2</sub> ) <sup>11</sup> ]SP, [Pro <sup>9</sup> ]SP, septide                                                                                                             | [ $\beta$ -Ala <sup>8</sup> ]NKA-(4-10), [Lys <sup>5</sup> ,Me-Leu <sup>9</sup> ,Mle <sup>10</sup> ]NKA-(4-10), GR64349 | Senktide, [MePhe <sup>7</sup> ]NKB                                                                             |
| Selective antagonists  | Aprepitant (10.7; Hale <i>et al.</i> , 1998), SR140333 (9.5), LY303870 (9.4), CP99994 (9.3), RP67580 (7.6)                                                                                                            | GR94800 (9.6), GR159897 (9.5), MEN10627 (9.2), SR48968 (9.0), MEN11420 (8.6; Catalioto <i>et al.</i> , 1998)            | SR142802 (9.2), SB223412 (9.0, Sarau <i>et al.</i> , 1997), PD157672 (7.8)                                     |
| Probes                 | [ <sup>3</sup> H]- or [ <sup>125</sup> I]-SP, [ <sup>3</sup> H]- or [ <sup>125</sup> I]-BH-[Sar <sup>9</sup> ,Met(O <sub>2</sub> ) <sup>11</sup> ]SP, [ <sup>125</sup> I]-L703606 (0.3 nM), [ <sup>18</sup> F]-SPA-RQ | [ <sup>3</sup> H]-SR48968 (0.5 nM), [ <sup>3</sup> H]-GR100679, [ <sup>125</sup> I]-NKA                                 | [ <sup>3</sup> H]-Senktide, [ <sup>125</sup> I]-[MePhe <sup>7</sup> ]NKB, [ <sup>3</sup> H]-SR142801 (0.13 nM) |

The NK<sub>1</sub> receptor has also been described to couple to other G proteins (Roush and Kwatra, 1998). The hexapeptide agonist septide appears to bind to an overlapping but non-identical site to SP on the NK<sub>1</sub> receptor. There are suggestions for additional subtypes of tachykinin receptor; an orphan receptor (SwissProt P30098) with structural similarities to the NK<sub>3</sub> receptor was found to respond to NKB when expressed in *Xenopus* oocytes or Chinese hamster ovary cells (Donaldson *et al.*, 1996; Krause *et al.*, 1997).

**Abbreviations:** Aprepitant, 5-[[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl) phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (also known as Emend); CP99994, (+)-(2S,3S)-3-(2-methoxybenzylamino)-2-phenylpiperidine; [<sup>18</sup>F]-SPA-RQ, ([<sup>18</sup>F]-2-fluoromethoxy-5-(5-trifluoromethyl-tetrazol-1-yl)-benzyl)-[2S,3S]-2-phenyl-piperidin-3-yl)-amine; GR100679, cyclohexylcarbonyl-Gly-Ala-D-Trp-Phe-NMe<sub>2</sub>; GR159897, (R)-1-(2-[5-fluoro-1H-indol-3-yl]ethyl)-4-methoxy-4-([phenylsulfinyl]methyl)piperidine; GR64349, Lys-Asp-Ser-Phe-Val-Gly-(R- $\gamma$ -lactam); GR94800, N- $\alpha$ -benzoyl-Ala-Ala-D-Trp-Phe-DPro-Pro-Nle-NH<sub>2</sub>; L-703606, cis-2-(diphenylmethyl)-N-([2-iodophenyl]methyl)-1-azabicyclo[2.2.2]octan-3-amide; L-742694, 2(s)-([3,5-bis(trifluoromethyl)benzyl]-oxy)-3(S)-phenyl-4-([3-oxo-1,2,4-triazol-5-yl]methyl)morpholine; LY303870, (R)-1-[N-(2-methoxybenzyl)acetyl]amino-3-(1H-indol-3-yl)-2-(N-[2-(4-(piperidin-1-yl)piperidin-1-yl)acetyl]amino)propane; also known as lanepitant; MEN10627, cyc(2 $\beta$ -5 $\beta$ )(Met-Asp-Trp-Phe-Dap-Leu); MEN11420, cyc(2 $\beta$ -5 $\beta$ )[Asn(2-AcNH- $\beta$ -D-Glc)-Asp-Trp-Phe-Dap-Leu]; also known as nepadutant; PD157672, Boc-(s)Phe-(R) $\alpha$ MePheNH(CH<sub>2</sub>)<sub>7</sub>NHCONH<sub>2</sub>; RP67580, 3 $\alpha$ R,7 $\alpha$ R-(1-imino-2-[2-methoxyphenyl]ethyl)-7,7-diphenyl-4-perhydroisoindolone; SB223412, (s)-(-)-N-( $\alpha$ -ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide; SR140333, (s)-1-(2-[3-[3,4-dichlorophenyl]-1-[3-isopropoxyphenyl]acetyl]piperidin-3-yl)ethyl)-4-phenyl-1-azoniabicyclo(2.2.2)octane chloride; SR142801, (s)-(N)-(1-[3-[1-benzoyl-3-(3,4-dichlorophenyl)piperidin-3-yl]propyl]-4-phenylpiperidin-4-yl)-N-methylacetamide; SR48968, (s)-N-methyl-N-(4-acetyl-amino-4-phenylpiperidino)-2-(3,4-dichlorophenyl)butylbenzamide; also known as saredutant

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# Trace amine-associated

**Overview:** Trace amine-associated receptors (nomenclature as agreed by NC-IUPHAR for trace amine receptors, see Maguire *et al.*, 2009) were initially discovered as a result of a search for novel 5-HT receptors (Borowsky *et al.*, 2001), where 15 mammalian orthologues were identified and divided into two families. Emerging evidence suggests that TA<sub>1</sub> is a modulator of monoaminergic activity in the brain (Xie and Miller, 2009) with TA<sub>1</sub> and dopamine D<sub>2</sub> receptors shown to form constitutive heterodimers when co-expressed (Espinoza *et al.*, 2011).

|                        |                                                                        |                                                  |
|------------------------|------------------------------------------------------------------------|--------------------------------------------------|
| Nomenclature           | TA <sub>1</sub>                                                        | TA <sub>2</sub>                                  |
| Other names            | TAA1, TaR-1, BO111                                                     | TAA2, GPR58                                      |
| Ensembl ID             | ENSG00000146399                                                        | ENSG00000146378                                  |
| Principal transduction | G <sub>s</sub>                                                         | G <sub>s</sub>                                   |
| Potency order          | Tyramine ≥ PEA > octopamine = dopamine (Borowsky <i>et al.</i> , 2001) | PEA > tryptamine (Borowsky <i>et al.</i> , 2001) |
| Probes                 | [ <sup>3</sup> H]-Tyramine (20 nM, Borowsky <i>et al.</i> , 2001)      | –                                                |

TAAR3 (BO107, ENSMUSG00000069708, ENSRNOG00000025982), in some individuals, and TAAR4 (ENSMUSG00000069707, ENSRNOG00000029877) are pseudogenes in man, although functional in rodents. The signalling characteristics and pharmacology of TAA<sub>5</sub> (PNR, Putative Neurotransmitter Receptor, ENSG00000135569), TAA<sub>6</sub> (Trace amine receptor 4, TaR-4, ENSG00000146383), TAA<sub>8</sub> (Trace amine receptor 5, GPR102, ENSG00000146385) and TAA<sub>9</sub> (trace amine associated receptor 9, ENSG00000237110) are lacking. The thyronamines, endogenous derivatives of thyroid hormone, have been shown to have affinity for rodent cloned trace amine receptors, including TA<sub>1</sub> (Scanlan *et al.*, 2004). An antagonist EPPTB has recently been described that has a *pK<sub>i</sub>* of 9.1 at the mouse TA<sub>1</sub> but less than 5.3 for human TA<sub>1</sub> (Stalder *et al.*, 2011).

**Abbreviations:** EPPTB, N-(3-ethoxyphenyl)-4-pyrrolidin-1-yl-3-trifluoromethylbenzamide; PEA, 2-phenylethylamine

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# TRH

**Overview:** Thyrotropin-releasing hormone (TRH) receptors (provisional nomenclature) are activated by the endogenous tripeptide TRH (pGlu-His-ProNH<sub>2</sub>). TRH and TRH analogues fail to distinguish TRH<sub>1</sub> and TRH<sub>2</sub> receptors (Sun *et al.*, 2003). [<sup>3</sup>H]-TRH is able to label both TRH<sub>1</sub> and TRH<sub>2</sub> receptors with *K<sub>d</sub>* values of 13 and 9 nM, respectively.

| Nomenclature           | TRH <sub>1</sub>                                                                                       | TRH <sub>2</sub>                       |
|------------------------|--------------------------------------------------------------------------------------------------------|----------------------------------------|
| Other names            | TRH receptor, thyroliberin                                                                             | –                                      |
| Ensembl ID             | ENSG00000174417                                                                                        | ENSMUSG00000039079, ENSRNOG00000012789 |
| Principal transduction | G <sub>q</sub>                                                                                         | G <sub>q</sub>                         |
| Selective antagonists  | Midazolam (Drummond <i>et al.</i> , 1989),<br>chlordiazepoxide (Straub <i>et al.</i> , 1990), diazepam | –                                      |

The human orthologue of the rodent TRH<sub>2</sub> receptor has yet to be identified.

**Abbreviations:** MeTRH, pGlu-[N<sup>ε</sup>-methyl]His-ProNH<sub>2</sub>

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# Urotensin-II

**Overview:** The urotensin-II (U-II) receptor (UT, nomenclature as agreed by NC-IUPHAR, see Foord *et al.*, 2005, Douglas and Ohlstein, 2000) is activated by the endogenous dodecapeptide U-II, originally isolated from the urophysis, the endocrine organ of the caudal neurosecretory system of teleost fish (Bern *et al.*, 1985). Several structural forms of U-II exist in fish and amphibians. The Goby orthologue was used to identify U-II as the cognate ligand for the predicted receptor encoded by the rat gene *gpr14* (Coulouarn *et al.*, 1998; Liu *et al.*, 1999; Mori *et al.*, 1999; Nothacker *et al.*, 1999). Human U-II (derived from ENSG00000049247), an 11-amino-acid peptide (Coulouarn *et al.*, 1998), retains the cyclo-hexapeptide sequence of goby U-II that is thought to be important in ligand binding (Kinney *et al.*, 2002; Brkovic *et al.*, 2003). This sequence is also conserved in the deduced amino-acid sequence of rat (14 amino-acids) and mouse (14 amino-acids) U-II, although the N-terminal is more divergent from the human sequence (Coulouarn *et al.*, 1999). A second endogenous ligand for UT has been discovered in rat (Sugo and Mori, 2008). The urotensin II-related peptide (URP) an octapeptide, is derived from a different gene, but shares the C-terminal sequence (CFWKYCV) common to U-II from other species. Identical sequences to rat URP are predicted for the mature mouse and human peptides.

|                        |                                                                                                                                                                                                                  |
|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature           | UT                                                                                                                                                                                                               |
| Other names            | GPR14, SENR, UR-IIR                                                                                                                                                                                              |
| Ensembl ID             | ENSG00000181408                                                                                                                                                                                                  |
| Principal transduction | G <sub>q/11</sub>                                                                                                                                                                                                |
| Selective agonists     | [Pen <sup>5</sup> ]U-II-(4–11), U-II-(4–11), U-II (Grieco <i>et al.</i> , 2002), AC7954 (Lehmann <i>et al.</i> , 2005), FL104 and analogues (Lehmann <i>et al.</i> , 2006; 2007)                                 |
| Selective antagonists  | Urantide (8.3, Patacchini <i>et al.</i> , 2003), SB706375 (7.5–8.0, Douglas <i>et al.</i> , 2005), palosuran (pIC <sub>50</sub> 7.1, Clozel <i>et al.</i> , 2004), SB611812 (6.6, Rakowski <i>et al.</i> , 2005) |
| Probes                 | [ <sup>125</sup> I]-hU-II (0.24 nM, Maguire <i>et al.</i> , 2000)                                                                                                                                                |

In human vasculature, human U-II elicits both vasoconstrictor (pD<sub>2</sub> 9.3–10.1, Maguire *et al.*, 2000) and vasodilator (pIC<sub>50</sub> 10.3–10.4, Stirrat *et al.*, 2001) responses.

**Abbreviations:** [Pen<sup>5</sup>]U-II-(4–11), [pencilamine, β,β-dimethylcysteine]<sup>5</sup>U-II-(4–11); AC7954, 3-(4-chlorophenyl)-3-(2-dimethyl-aminoethyl)-isochroman-1-one HCl; FL104, (+)N-(1-[4-chlorophenyl]-3-dimethylaminopropyl)-4-phenylbenzamide oxalate; palosuran, 1-[2-(4-benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea sulphate, also known as ACT058362; SB611812, 2,6-dichloro-N-(4-chloro-3-[[2-(dimethylamino)ethyl]oxy]phenyl)-4-(trifluoromethyl)benzenesulfonamide; SB706375, 2-bromo-4,5-dimethoxy-N-[3-(R)-1-methyl-pyrrolidin-3-yloxy]-4-trifluoromethyl-phenyl-benzenesulphonamide HCl; urantide, [Pen<sup>5</sup>,DTrp<sup>7</sup>,Orn<sup>8</sup>]hU-II(4–11)

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# Vasopressin & oxytocin

**Overview:** Vasopressin (AVP) and oxytocin (OT) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on vasopressin and oxytocin receptors) are activated by the endogenous cyclic nonapeptides AVP and OT. These peptides are derived from precursors (ENSG00000101200 and ENSG00000101405, respectively), which also produce neurophysins.

| Nomenclature           | V <sub>1A</sub>                                                                                                                                                                                                                                              | V <sub>1B</sub>                                                                                                                                         | V <sub>2</sub>                                                                                                                                                                                                                                       | OT                                                                                                                                                                                                                                                                                                                                              |
|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ensembl ID             | ENSG00000166148                                                                                                                                                                                                                                              | ENSG00000198049                                                                                                                                         | ENSG00000126895                                                                                                                                                                                                                                      | ENSG00000180914                                                                                                                                                                                                                                                                                                                                 |
| Principal transduction | G <sub>q/11</sub>                                                                                                                                                                                                                                            | G <sub>q/11</sub>                                                                                                                                       | G <sub>s</sub>                                                                                                                                                                                                                                       | G <sub>q/11</sub> , G <sub>i/o</sub>                                                                                                                                                                                                                                                                                                            |
| Rank order of potency  | AVP > OT                                                                                                                                                                                                                                                     | AVP > OT                                                                                                                                                | AVP > OT                                                                                                                                                                                                                                             | OT ≥ AVP                                                                                                                                                                                                                                                                                                                                        |
| Selective agonists     | F180, [Phe <sup>2</sup> ,Orn <sup>8</sup> ]VT                                                                                                                                                                                                                | d[D-3-Pal <sup>2</sup> ]VP, d[Cha <sup>4</sup> ]AVP (Derick <i>et al.</i> , 2002), d[Leu <sup>4</sup> ,Lys <sup>8</sup> ]VP (Pena <i>et al.</i> , 2007) | d[Val <sup>4</sup> ,DArg <sup>8</sup> ]VP, OPC51803, VNA932                                                                                                                                                                                          | [Thr <sup>4</sup> ,Gly <sup>7</sup> ]OT (Elands <i>et al.</i> , 1988)                                                                                                                                                                                                                                                                           |
| Selective antagonists  | d(CH <sub>2</sub> ) <sub>5</sub> [Tyr(Me)] <sup>2</sup> , Arg <sup>8</sup> ]VP (9.0), SR49059 (8.9), YM087 (8.2)                                                                                                                                             | SSR149415 (8.4; Griebel <i>et al.</i> , 2002; Serradeil-Le Gal <i>et al.</i> , 2002)                                                                    | VPA985 (8.9, Albright <i>et al.</i> , 1998), d(CH <sub>2</sub> ) <sub>5</sub> [D-Ile <sup>2</sup> , Ile <sup>4</sup> ]AVP (8.4), SR121463A (8.4; Serradeil-Le Gal <i>et al.</i> , 1996), OPC31260 (7.6; Yamamura <i>et al.</i> , 1992), YM087 (8.96) | SSR126768A (9.3; Serradeil-Le Gal <i>et al.</i> , 2004) desGlyNH <sub>2</sub> -d(CH <sub>2</sub> ) <sub>5</sub> [Tyr(Me)] <sup>2</sup> , Thr <sup>4</sup> ,Orn <sup>8</sup> ] OT (8.5), L372662 (8.4),                                                                                                                                          |
| Probes                 | [ <sup>3</sup> H]-AVP, [ <sup>3</sup> H]-SR49059 (1.5 nM), [ <sup>3</sup> H]-d(CH <sub>2</sub> ) <sub>5</sub> [Tyr(Me)] <sup>2</sup> , Arg <sup>8</sup> ]AVP (1.1 nM), [ <sup>125</sup> I]-HO-Phaa,D-Tyr(Me)-Phe-Gln-Asn-Arg-Pro-Arg-NH <sub>2</sub> (50 pM) | [ <sup>3</sup> H]-AVP, [ <sup>3</sup> H]-SSR149415 (1 nM; Serradeil-Le Gal <i>et al.</i> 2007)                                                          | [ <sup>3</sup> H]-AVP, [ <sup>3</sup> H]-desGly-NH <sub>2</sub> [D-Ile <sup>2</sup> ,Ile <sup>4</sup> ]AVP (2.8 nM), [ <sup>3</sup> H]-d[D-Arg <sup>8</sup> ]AVP (0.8 nM), [ <sup>3</sup> H]-SR121463A (4.1 nM)                                      | [ <sup>3</sup> H]-OT, [ <sup>35</sup> S]-Non Peptide OT Antagonist (42 pM; Lemaire <i>et al.</i> , 2002), [ <sup>125</sup> I]-d(CH <sub>2</sub> ) <sub>5</sub> [Tyr(Me)] <sup>2</sup> , Thr <sup>4</sup> ,Orn <sup>8</sup> , Tyr-NH <sub>2</sub> <sup>9</sup> ]OVT (90 pM), [ <sup>111</sup> In]-DOTA-dLVT (4.5 nM; Chini <i>et al.</i> , 2003) |

The V<sub>2</sub> receptor exhibits marked species differences, such that many ligands (d(CH<sub>2</sub>)<sub>5</sub>[D-Ile<sup>2</sup>,Ile<sup>4</sup>]VP and [<sup>3</sup>H]-desGly-NH<sub>2</sub>[D-Ile<sup>2</sup>,Ile<sup>4</sup>]VP) exhibit low affinity at human V<sub>2</sub> receptors (Ala *et al.*, 1997). Similarly, [<sup>3</sup>H]-d[D-Arg<sup>8</sup>]VP is V<sub>2</sub> selective in the rat, not in the human (Saito *et al.*, 1997). The gene encoding the V<sub>2</sub> receptor is polymorphic in man, underlying nephrogenic diabetes insipidus (Bichet, 1998). YM087 display high affinity for both human V<sub>1a</sub> and V<sub>2</sub> receptors (Tahara *et al.*, 1998). d[Cha<sup>4</sup>]AVP is selective only for the human and bovine V<sub>1b</sub> receptors (Derick *et al.*, 2002), while d[Leu<sup>4</sup>,Lys<sup>8</sup>]VP has high affinity for the rat V<sub>1b</sub> receptor (Pena *et al.*, 2007).

**Abbreviations:** F180, Hmp-Phe-Ile-Hgn-Asn-Cys-Pro-Dab(Abu)-Gly-NH<sub>2</sub>; [<sup>111</sup>In]-DOTA-dLVT, [<sup>111</sup>In]-DOTA-Lys<sup>8</sup>-deamino-vasotocin; L372662, 1-(1-[4-[1-(2-methyl-1-oxidopyridin-3-ylmethyl)piperidin-4-yloxy]-2-methoxybenzoyl]piperidin-4-yl)-1,4-dihydrobenz[d][1,3]oxazin-2-one; OPC31260, 5-dimethylamino-1-(4-[2-methylbenzoylamino]benzoyl)-2,3,4,5-tetrahydro-1H-benzazepine; OPC51803, (5R)-2-(1-[2-chloro-4-{1-pyrrolidinyl}benzoyl]-2,3,4,5-tetrahydro-1H-1-benzazepin-5-yl)-N-isopropylacetamide; [<sup>35</sup>S]-non-peptide OT antagonist, [<sup>35</sup>S]-(1-(1-(2-(2,2,2-trifluoroethoxy)-4-(1-methylsulfonyl-4-piperidinyloxy)phenylacetyl)-4-piperidinyloxy)-3,4-dihydro-2(1H)-quinolinone); SR121463A, 1-(4-Boc-2-methoxybenzenesulfonyl)-5-ethoxy-3-spiro-(4-[2-morpholinoethoxy]cyclohexane)indol-2-one fumarate; equatorial isomer; SR49059, (2S)-1-([2r,3s]-[5-chloro-3-(chlorophenyl)-1-[3,4-dimethoxysulfonyl]-3-hydroxy]-2,3-dihydro-1H-indole-2-carbonyl)-pyrrolidine-2-carboxamide; SSR149415, (2S,4R)-1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]-4-hydroxy-N,N-dimethyl-2-pyrrolidine carboxamide; SSR126768A, 4-chloro-3-[(3R)-(+)-5-chloro-1-(2,4-dimethoxybenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-N-ethyl-N-(3-pyridylmethyl)-benzamide, hydrochloride; VNA932, (2-chloro-4-[3-methyl-pyrazol-1-yl]-phenyl)-(5H,11H)-pyrrolo(2,1-c)(1,4)benzodiazepin-10-yl-methanone; VPA985, 5-fluoro-2-methyl-N-(4-[5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl]-3-chlorophenyl)benzamide; YM087, (4'-[(2-methyl-1,4,5,6-tetrahydroimidazo[4,5-d][1]benzazepin-6-yl) carbonyl]-2-phenylbenzanilide monohydrochloride)

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# VIP & PACAP

**Overview:** Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating peptide (PACAP) receptors (nomenclature recommended by the NC-IUPHAR Subcommittee on Vasoactive Intestinal Peptide Receptors, Harmar *et al.*, 1998) are activated by the endogenous peptides VIP, PACAP-38, PACAP-27, peptide histidine isoleucineamide (PHI), peptide histidine methionineamide (PHM) and peptide histidine valine (PHV). 'PACAP type II receptors' (VPAC<sub>1</sub> and VPAC<sub>2</sub> receptors) display comparable affinity for PACAP and VIP, whereas PACAP-27 and PACAP-38 are >100 fold more potent than VIP as agonists of most isoforms of the PAC<sub>1</sub> receptor. However, one splice variant of the human PAC<sub>1</sub> receptor has been reported to respond to PACAP-38, PACAP-27 and VIP with comparable affinity (Dautzenberg *et al.*, 1999). PG99-465 (Moreno *et al.*, 2000) has been used as a selective VPAC<sub>2</sub> receptor antagonist in a number of physiological studies, but has been reported to have significant activity at VPAC<sub>1</sub> and PAC<sub>1</sub> receptors (Dickson *et al.*, 2006). The selective PAC<sub>1</sub> receptor agonist maxadilan, was extracted from the salivary glands of sand flies (*Lutzomyia longipalpis*) and has no sequence homology to VIP or PACAP (Moro and Lerner, 1997). Two deletion variants of maxadilan, M65 (Uchida *et al.*, 1998) and max.d.4 (Moro *et al.*, 1999) have been reported to be PAC<sub>1</sub> receptor antagonists, but these peptides have not been extensively characterised.

| Nomenclature           | VPAC <sub>1</sub>                                                                                                           | VPAC <sub>2</sub>                                                                      | PAC <sub>1</sub>                  |
|------------------------|-----------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-----------------------------------|
| Other names            | VIP <sub>1</sub> /PACAP, VIP, VIP <sub>1</sub> , PACAP type II, PVR2                                                        | VIP <sub>2</sub> /PACAP, VIP <sub>2</sub> , PACAP <sub>3</sub> , PVR2                  | PACAP, PACAP type I, PVR1         |
| Ensembl ID             | ENSG00000114812                                                                                                             | ENSG00000106018                                                                        | ENSG00000078549                   |
| Principal transduction | G <sub>s</sub>                                                                                                              | G <sub>s</sub>                                                                         | G <sub>s</sub>                    |
| Rank order of potency  | VIP, PACAP-27, PACAP-38 >> GHRH, PHI, secretin                                                                              | VIP, PACAP-38, PACAP-27 > PHI >> GHRH, secretin                                        | PACAP-27, PACAP-38 >> VIP         |
| Selective agonists     | [Ala <sup>11,22,28</sup> ]VIP, [Lys <sup>15</sup> ,Arg <sup>16</sup> ,Leu <sup>27</sup> ]VIP(1-7)/GRF(8-27)-NH <sub>2</sub> | Ro251553 (Gourlet <i>et al.</i> , 1997a, 1997b)<br>Ro251392 (Xia <i>et al.</i> , 1997) | Maxadilan (Moro and Lerner, 1997) |
| Selective antagonists  | PG97-269 (Gourlet <i>et al.</i> , 1997a)                                                                                    | –                                                                                      | –                                 |
| Probes                 | [ <sup>125</sup> I]-VIP, [ <sup>125</sup> I]-PACAP-27                                                                       | [ <sup>125</sup> I]-VIP, [ <sup>125</sup> I]-PACAP-27                                  | [ <sup>125</sup> I]-PACAP-27      |

**Abbreviations:** PG97-269, [Ac-His<sup>1</sup>,D-Phe<sup>2</sup>,Lys<sup>15</sup>,Arg<sup>16</sup>]VIP(3-7)/GRF(8-27)-NH<sub>2</sub>; Ro251392, Ac-His<sup>1</sup>[Glu<sup>8</sup>,OCH<sub>3</sub>-Tyr<sup>10</sup>,Lys<sup>12</sup>,Nle<sup>17</sup>,Ala<sup>19</sup>,Asp<sup>25</sup>,Leu<sup>26</sup>,Lys<sup>27,28</sup>]VIP (cyclo 21–25); Ro251553, Ac-His<sup>1</sup>[Glu<sup>8</sup>,Lys<sup>12</sup>,Nle<sup>17</sup>,Ala<sup>19</sup>,Asp<sup>25</sup>,Leu<sup>26</sup>,Lys<sup>27,28</sup>,Gly<sup>29,30</sup>,Thr<sup>31</sup>]VIP-NH<sub>2</sub> (cyclo 21–25)

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# LIGAND-GATED ION CHANNELS

Ligand-gated ion channels (LGICs) are integral membrane proteins that contain a pore which allows the regulated flow of selected ions across the plasma membrane. Ion flux is passive and driven by the electrochemical gradient for the permeant ions. The channels are opened, or gated, by the binding of a neurotransmitter to an orthosteric site(s) that triggers a conformational change that results in the conducting state. Modulation of gating can occur by the binding of endogenous, or exogenous, modulators to allosteric sites. LGICs mediate fast synaptic transmission, on a millisecond time scale, in the nervous system and at the somatic neuromuscular junction. Such transmission involves the release of a neurotransmitter from a pre-synaptic neurone and the subsequent activation of post-synaptically located receptors that mediate a rapid, phasic, electrical signal (the excitatory, or inhibitory, post-synaptic potential). However, in addition to their traditional role in phasic neurotransmission, it is now established that some LGICs mediate a tonic form of neuronal regulation that results from the activation of extra-synaptic receptors by ambient levels of neurotransmitter. The expression of some LGICs by non-excitable cells is suggestive of additional functions.

By convention, the LGICs comprise the excitatory, cation-selective, nicotinic acetylcholine (Millar and Gotti, 2009; Changeux, 2010), 5-HT<sub>3</sub> (Barnes *et al.*, 2009; Walstab *et al.*, 2010), ionotropic glutamate (Lodge, 2009; Traynelis *et al.*, 2010) and P2X receptors (Jarvis and Khakh, 2009; Surprenant and North, 2009) and the inhibitory, anion-selective, GABA<sub>A</sub> (Olsen and Sieghart, 2008; Belelli *et al.*, 2009) and glycine receptors (Lynch, 2009; Yevenes and Zeilhofer, 2011). The nicotinic acetylcholine, 5-HT<sub>3</sub>, GABA<sub>A</sub> and glycine receptors (and an additional zinc-activated channel) are pentameric structures and are frequently referred to as the Cys-loop receptors due to the presence of a defining loop of residues formed by a disulphide bond in the extracellular domain of their constituent subunits (Miller and Smart, 2010; Thompson *et al.*, 2010). However, the prokaryotic ancestors of these receptors contain no such loop and the term pentameric ligand-gated ion channel (pLGIC) is gaining acceptance in the literature (Hilf and Dutzler, 2009). The ionotropic glutamate and P2X receptors are tetrameric and trimeric structures, respectively. Multiple genes encode the subunits of LGICs and the majority of these receptors are heteromultimers. Such combinatorial diversity results, within each class of LGIC, in a wide range of receptors with differing pharmacological and biophysical properties and varying patterns of expression within the nervous system and other tissues. The LGICs thus present attractive targets for new therapeutic agents with improved discrimination between receptor isoforms and a reduced propensity for off-target effects. The development of novel, faster screening techniques for compounds acting on LGICs (Dunlop *et al.*, 2008) will greatly aid in the development of such agents.

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# 5-HT<sub>3</sub> (5-Hydroxytryptamine<sub>3</sub>)

**Overview:** The 5-HT<sub>3</sub> receptor [nomenclature as agreed by the NC-IUPHAR Subcommittee on 5-hydroxytryptamine (serotonin) receptors (Hoyer *et al.*, 1994; see also Peters *et al.*, 2010)] is a ligand-gated ion channel of the Cys-loop family that includes the nicotinic acetylcholine, GABA<sub>A</sub> and strychnine-sensitive glycine receptors. The receptor exists as a pentamer of 4Tm subunits that form an intrinsic cation selective channel (Barnes *et al.*, 2009). Five human 5-HT<sub>3</sub> receptor subunits have been cloned and homo-oligomeric assemblies of 5-HT3A and 5-HT3B subunits have been characterised in detail. The 5-HT3C (ENSG00000178084), 5-HT3D (ENSG00000186090) and 5-HT3E (ENSG00000186038) subunits (Karnovsky *et al.*, 2003; Niesler *et al.*, 2003), like the 5-HT3B subunit, do not form functional homomers, but are reported to assemble with the 5-HT3A subunit to influence its functional expression rather than pharmacological profile (Niesler *et al.*, 2007; Holbrook *et al.*, 2009; Walstab *et al.*, 2010a). 5-HT3A, -C, -D, and -E subunits also interact with the chaperone RIC-3 which predominantly enhances the surface expression of homomeric 5-HT<sub>3</sub>A receptor (Walstab *et al.*, 2010a). The co-expression of 5-HT3A and 5-HT3C-E subunits has been demonstrated in human colon (Kapeller *et al.*, 2011). A recombinant hetero-oligomeric 5-HT<sub>3</sub>AB receptor has been reported to contain two copies of the 5-HT3A subunit and three copies of the 5-HT3B subunit in the order B-B-A-B-A (Barrera *et al.*, 2005), but this is inconsistent with recent reports which show at least one A-A interface (Lochner and Lummis, 2010; Thompson *et al.*, 2011b). The 5-HT3B subunit imparts distinctive biophysical properties upon hetero-oligomeric 5-HT<sub>3</sub>AB *versus* homo-oligomeric 5-HT<sub>3</sub>A recombinant receptors (Davies *et al.*, 1999; Dubin *et al.*, 1999; Hanna *et al.*, 2000; Kelley *et al.*, 2003; Stewart *et al.*, 2003; Peters *et al.*, 2005; Jensen *et al.*, 2008), influences the potency of channel blockers, but generally has only a modest effect upon the apparent affinity of agonists, or the affinity of antagonists (Brady *et al.*, 2001; but see Dubin *et al.*, 1999; Das and Dillon, 2003; Deeb *et al.*, 2009) which may be explained by the orthosteric binding site residing at an interface formed between 5-HT3A subunits (Lochner and Lummis, 2010; Thompson *et al.*, 2011b). However, 5-HT<sub>3</sub>A and 5-HT<sub>3</sub>AB receptors differ in their allosteric regulation by some general anaesthetic agents, small alcohols and indoles (Solt *et al.*, 2005; R  sch *et al.*, 2007; Hu and Peoples, 2008). The potential diversity of 5-HT<sub>3</sub> receptors is increased by alternative splicing of the genes *HTR3A* and *E* (Hope *et al.*, 1993; Bruss *et al.*, 2000; Niesler *et al.*, 2007, 2008; Niesler 2011). In addition, the use of tissue-specific promoters driving expression from different transcriptional start sites has been reported for the *HTR3A*, *HTR3B*, *HTR3D* and *HTR3E* genes, which could result in 5-HT<sub>3</sub> subunits harbouring different N-termini (Tzvetkov *et al.*, 2007; Jensen *et al.*, 2008; Niesler, 2011). To date, inclusion of the 5-HT3A subunit appears imperative for 5-HT<sub>3</sub> receptor function.

|                                          |                                                                                                                                                                                                                                  |
|------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature                             | 5-HT <sub>3</sub>                                                                                                                                                                                                                |
| Former names                             | M                                                                                                                                                                                                                                |
| Ensembl ID                               | 5-HT3A ENSG00000166736, 5-HT3B ENSG00000149305                                                                                                                                                                                   |
| Selective agonists (pEC <sub>50</sub> )  | SR57227A (6.4), 3-chlorophenyl-biguanide (5.4–5.8), 2-methyl-5-HT (5.5–5.6), 1-phenylbiguanide (4.1)                                                                                                                             |
| Selective antagonists (pK <sub>i</sub> ) | (S)-Zacopride (9.0), granisetron (8.6–8.8), tropisetron (8.5–8.8), ondansetron (7.8–8.3)                                                                                                                                         |
| Channel blockers (pIC <sub>50</sub> )    | TMB-8 (5.4), diltiazem (4.1–4.8), picrotoxinin (4.9 + 5-HT3B = 4.2), bilobalide (3.3 + 5-HT3B = 2.5); ginkgolide B (3.1 + 5-HT3B > 3.0)                                                                                          |
| Radioligands (K <sub>D</sub> )           | [ <sup>3</sup> H]Ramosetron (0.15 nM), [ <sup>3</sup> H]granisetron (1.2 nM), [ <sup>3</sup> H](S)-zacopride (2.0 nM), [ <sup>3</sup> H]GR65630 (2.6 nM), [ <sup>3</sup> H]LY278584 (3 nM)                                       |
| Functional characteristics               | γ = 0.4–0.8 pS [+ 5-HT3B, γ = 16 pS]; inwardly rectifying current [+ 5-HT3B, rectification reduced]; n <sub>H</sub> 2–3 [+ 5-HT3B 1–2]; relative permeability to divalent cations reduced by co-expression of the 5-HT3B subunit |

Quantitative data in the table refer to homo-oligomeric assemblies of the human 5-HT3A subunit, or the receptor native to human tissues. Significant changes introduced by co-expression of the 5-HT3B subunit are indicated in parenthesis. Methadone, although not a selective antagonist, displays multimodal and subunit-dependent antagonism of 5-HT<sub>3</sub> receptors (Deeb *et al.*, 2009). Similarly, TMB-8, diltiazem, picrotoxin, bilobalide and ginkgolide B are not selective for 5-HT<sub>3</sub> receptors (*e.g.* Thompson *et al.*, 2011a). The anti-malarial drugs mefloquine and quinine exert a modestly more potent block of 5-HT<sub>3</sub>A *versus* 5-HT<sub>3</sub>AB receptor-mediated responses (Thompson and Lummis, 2008). Varenicline, known better as a partial agonist of nicotinic acetylcholine α4β2 receptors, is also an agonist of the 5-HT<sub>3</sub>A receptor (Lummis *et al.*, 2011). Human (Belelli *et al.*, 1995; Miyake *et al.*, 1995), rat (Isenberg *et al.*, 1993), mouse (Maricq *et al.*, 1991), guinea-pig (Lankiewicz *et al.*, 1998) ferret (Mochizuki *et al.*, 2000) and canine (Jensen *et al.*, 2006) orthologues of the 5-HT3A receptor subunit have been cloned that exhibit intraspecies variations in receptor pharmacology. Notably, most ligands display significantly reduced affinities at the guinea-pig 5-HT<sub>3</sub> receptor in comparison with other species. In addition to the agents listed in the table, native and recombinant 5-HT<sub>3</sub> receptors are subject to allosteric modulation by extracellular divalent cations, alcohols, several general anaesthetics and 5-hydroxy- and halide-substituted indoles (see reviews by Parker *et al.*, 1996; Thompson and Lummis, 2006, 2007; Walstab *et al.*, 2010b).

**Abbreviations:** GR65630, 3-(5-methyl-1H-imidazol-4-yl)-1-(1-methyl-1H-indol-3-yl)-1-propanone; LY278584, 1-methyl-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1H-indazole-3-carboxamide; SR57227A, 4-amino-(6-chloro-2-pyridyl)-1 piperidine hydrochloride, TMB-8, 8-(diethylamino)octyl-3,4,5-trimethoxybenzoate

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# Acetylcholine (nicotinic)

**Overview:** Nicotinic acetylcholine receptors are members of the Cys-loop family of transmitter-gated ion channels that includes the GABA<sub>A</sub>, strychnine-sensitive glycine and 5-HT<sub>3</sub> receptors (Sine and Engel, 2006; Albuquerque *et al.*, 2009; Millar and Gotti, 2009; Taly *et al.*, 2009, Wu and Lukas, 2011). All nicotinic receptors are pentamers in which each of the five subunits contains four  $\alpha$ -helical transmembrane domains. Genes (Ensembl family ID ENSF00000000049) encoding a total of 17 subunits ( $\alpha$ 1-10,  $\beta$ 1-4,  $\gamma$ ,  $\delta$  and  $\epsilon$ ) have been identified (Kalamida *et al.*, 2007). All subunits with the exception of  $\alpha$ 8 (present in avian species) have been identified in mammals. All  $\alpha$  subunits possess two tandem cysteine residues near to the site involved in acetylcholine binding, and subunits not named  $\alpha$  lack these residues (Millar and Gotti, 2009). The orthosteric ligand binding site is formed by residues within at least three peptide domains on the  $\alpha$  subunit (principal component), and three on the adjacent subunit (complementary component). nAChRs contain several allosteric modulatory sites. One such site, for positive allosteric modulators (PAMs) and allosteric agonists, has been proposed to reside within an intrasubunit cavity between the four transmembrane domains (Young *et al.*, 2008; Gill *et al.*, 2011; see also Hibbs and Gouaux, 2011). The high resolution crystal structure of the molluscan acetylcholine binding protein, a structural homologue of the extracellular binding domain of a nicotinic receptor pentamer, in complex with several nicotinic receptor ligands (*e.g.*, Celie *et al.*, 2004) and the crystal structure of the extracellular domain of the  $\alpha$ 1 subunit bound to  $\alpha$ -bungarotoxin at 1.94 Å resolution (Dellisanti *et al.*, 2007), has revealed the orthosteric binding site in detail (reviewed Sine and Engel, 2006; Kalamida *et al.*, 2007; Changeux and Taly, 2008; Rucktooa *et al.*, 2009). Nicotinic receptors at the somatic neuromuscular junction of adult animals have the stoichiometry ( $\alpha$ 1)<sub>2</sub> $\beta$ 1 $\delta\epsilon$ , whereas an extrajunctional ( $\alpha$ 1)<sub>2</sub> $\beta$ 1 $\gamma\delta$  receptor predominates in embryonic and denervated skeletal muscle and other pathological states. Other nicotinic receptors are assembled as combinations of  $\alpha$ (2-6) and  $\beta$ (2-4) subunits. For  $\alpha$ 2,  $\alpha$ 3,  $\alpha$ 4 and  $\beta$ 2 and  $\beta$ 4 subunits, pairwise combinations of  $\alpha$  and  $\beta$  (*e.g.*,  $\alpha$ 3 $\beta$ 4,  $\alpha$ 4 $\beta$ 2) are sufficient to form a functional receptor *in vitro*, but far more complex isoforms may exist *in vivo* (reviewed by Gotti *et al.*, 2006, 2009, Millar and Gotti, 2009). There is strong evidence that the pairwise assembly of some  $\alpha$  and  $\beta$  subunits can occur with variable stoichiometry [*e.g.*, ( $\alpha$ 4)<sub>2</sub>( $\beta$ 2)<sub>2</sub>, or ( $\alpha$ 4)<sub>3</sub>( $\beta$ 2)<sub>2</sub>] which influences the biophysical and pharmacological properties of the receptor (Millar and Gotti, 2009).  $\alpha$ 5 and  $\beta$ 3 subunits lack function when expressed alone, or pairwise, but participate in the formation of functional hetero-oligomeric receptors when expressed as a third subunit with another  $\alpha$  and  $\beta$  pair [*e.g.*,  $\alpha$ 4 $\alpha$ 5 $\alpha$ 2,  $\alpha$ 4 $\alpha$ 6 $\beta$ 2,  $\alpha$ 5 $\alpha$ 6 $\beta$ 2, see Millar and Gotti (2009) for further examples]. The  $\alpha$ 6 subunit can form a functional receptor when co-expressed with  $\beta$ 4 *in vitro*, but more efficient expression ensues from incorporation of a third partner, such as  $\beta$ 3 (Yang *et al.*, 2009). The  $\alpha$ 7,  $\alpha$ 8, and  $\alpha$ 9 subunits form functional homo-oligomers, but can also combine with a second subunit to constitute a hetero-oligomeric assembly (*e.g.*,  $\alpha$ 7 $\beta$ 2 and  $\alpha$ 9 $\alpha$ 10). For functional expression of the  $\alpha$ 10 subunit, co-assembly with  $\alpha$ 9 is necessary. The latter, along with the  $\alpha$ 10 subunit, appears to be largely confined to cochlear and vestibular hair cells. Comprehensive listings of nicotinic receptor subunit combinations identified from recombinant expression systems, or *in vivo*, are given in Millar and Gotti (2009). In addition, numerous proteins interact with nicotinic ACh receptors modifying their assembly, trafficking to and from the cell surface, and activation by ACh (reviewed by Millar, 2008; Araud *et al.*, 2010; Jones *et al.*, 2010).

The nicotinic receptor subcommittee of NC-IUPHAR has recommended a nomenclature and classification scheme for nicotinic acetylcholine (nACh) receptors based on the subunit composition of known, naturally- and/or heterologously-expressed nACh receptor subtypes (Lukas *et al.*, 1999). Headings for this table reflect abbreviations designating nACh receptor subtypes based on the predominant  $\alpha$  subunit contained in that receptor subtype. An asterisk following the indicated  $\alpha$  subunit denotes that other subunits are known to, or may, assemble with the indicated  $\alpha$  subunit to form the designated nACh receptor subtype(s). Where subunit stoichiometries within a specific nACh receptor subtype are known, numbers of a particular subunit larger than 1 are indicated by a subscript following the subunit (enclosed in parentheses – see also Collingridge *et al.*, 2009).

| Nomenclature                   | $\alpha$ 1*                                                                                                                                                                                                                                                      | $\alpha$ 2*                                                                                                                                                                          | $\alpha$ 3*                                                                                                                                                                                                                                        |
|--------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Previous names                 | Muscle-type, muscle                                                                                                                                                                                                                                              | –                                                                                                                                                                                    | Autonomic, ganglionic                                                                                                                                                                                                                              |
| Selective agonists             | Succinylcholine (selective for ( $\alpha$ 1) <sub>2</sub> $\beta$ 1 $\gamma\delta$ )                                                                                                                                                                             | –                                                                                                                                                                                    | –                                                                                                                                                                                                                                                  |
| Positive allosteric modulators | –                                                                                                                                                                                                                                                                | LY-2087101 (Broad <i>et al.</i> , 2006, also potentiates $\alpha$ 4 $\beta$ 2 and $\alpha$ 4 $\beta$ 4)                                                                              | –                                                                                                                                                                                                                                                  |
| Selective antagonists          | Waglerin-1 (selective for ( $\alpha$ 1) <sub>2</sub> $\beta$ 1 $\delta\epsilon$ ), $\alpha$ -bungarotoxin, $\alpha$ -conotoxin GI, $\alpha$ -conotoxin MI, pancuronium                                                                                           | –                                                                                                                                                                                    | $\alpha$ 3 $\beta$ 2: $\alpha$ -conotoxin MII (also blocks $\alpha$ 6-containing), $\alpha$ -conotoxin-GIC, $\alpha$ -conotoxin PnIA, $\alpha$ -conotoxin TxIA<br>$\alpha$ 3 $\beta$ 4: $\alpha$ -conotoxin AulB                                   |
| Commonly used antagonists      | ( $\alpha$ 1) <sub>2</sub> $\beta$ 1 $\gamma\delta$ and ( $\alpha$ 1) <sub>2</sub> $\beta$ 1 $\delta\epsilon$ : $\alpha$ -bungarotoxin, > pancuronium > vecuronium > rocuronium > (+)-Tc (IC <sub>50</sub> = 43–82 nM)                                           | $\alpha$ 2 $\beta$ 2: DH $\beta$ E ( $K_B$ = 0.9 $\mu$ M), (+)-Tc ( $K_B$ = 1.4 $\mu$ M)<br>$\alpha$ 2 $\beta$ 4: DH $\beta$ E ( $K_B$ = 3.6 $\mu$ M), (+)-Tc ( $K_B$ = 4.2 $\mu$ M) | $\alpha$ 3 $\beta$ 2: DH $\beta$ E ( $K_B$ = 1.6 $\mu$ M, IC <sub>50</sub> = 2.0 $\mu$ M), (+)-Tc ( $K_B$ = 2.4 $\mu$ M)<br>$\alpha$ 3 $\beta$ 4: DH $\beta$ E ( $K_B$ = 19 $\mu$ M, IC <sub>50</sub> = 26 $\mu$ M), (+)-Tc ( $K_B$ = 2.2 $\mu$ M) |
| Channel blockers               | ( $\alpha$ 1) <sub>2</sub> $\beta$ 1 $\delta\epsilon$ and ( $\alpha$ 1) <sub>2</sub> $\beta$ 1 $\gamma\delta$ : gallamine (IC <sub>50</sub> ~ 1 $\mu$ M)<br>$\alpha$ (1) <sub>2</sub> $\beta$ 1 $\delta\epsilon$ : mecamylamine (IC <sub>50</sub> ~ 1.5 $\mu$ M) | mecamylamine, hexamethonium                                                                                                                                                          | $\alpha$ 3 $\beta$ 2: mecamylamine (IC <sub>50</sub> = 7.6 $\mu$ M), hexamethonium<br>$\alpha$ 3 $\beta$ 4: mecamylamine (IC <sub>50</sub> = 0.39 $\mu$ M), hexamethonium                                                                          |
| Radioligands ( $K_D$ )         | [ <sup>3</sup> H]/[ <sup>125</sup> I]- $\alpha$ -bungarotoxin                                                                                                                                                                                                    | [ <sup>3</sup> H]/[ <sup>125</sup> I]-epibatidine (h $\alpha$ 2 $\beta$ 4, 42 pM; r $\alpha$ 2 $\beta$ 2, 10–21 pM; r $\alpha$ 2 $\beta$ 4, 84–87 pM), [ <sup>3</sup> H]-cytisine    | [ <sup>3</sup> H]/[ <sup>125</sup> I]-epibatidine (h $\alpha$ 3 $\beta$ 2, 7 pM; h $\alpha$ 3 $\beta$ 4, 230 pM; r $\alpha$ 3 $\beta$ 2, 14–34 pM, r $\alpha$ 3 $\beta$ 4, 290–304 pM), [ <sup>3</sup> H]-cytisine                                 |
| Functional characteristics     | $\alpha$ (1) <sub>2</sub> $\beta$ 1 $\gamma\delta$ : P <sub>Ca</sub> /P <sub>Na</sub> = 0.16–0.2, P <sub>i</sub> = 2.1–2.9%; $\alpha$ (1) <sub>2</sub> $\beta$ 1 $\delta\epsilon$ : P <sub>Ca</sub> /P <sub>Na</sub> = 0.65–1.38, P <sub>i</sub> = 4.1–7.2%      | $\alpha$ 2 $\beta$ 2: P <sub>Ca</sub> /P <sub>Na</sub> ~ 1.5                                                                                                                         | $\alpha$ 3 $\beta$ 2: P <sub>Ca</sub> /P <sub>Na</sub> = 1.5; $\alpha$ 3 $\beta$ 4: P <sub>Ca</sub> /P <sub>Na</sub> = 0.78–1.1, P <sub>i</sub> = 2.7–4.6%                                                                                         |

| Nomenclature                   | $\alpha 4^*$                                                                                                                                                                                                                                                                                                              | $\alpha 6^*$                                                                                                                                                                                                           | $\alpha 7^*$                                                                                                                                                                                                                                                                                                                                                                                                        |
|--------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Previous names                 | Neuronal, $\alpha$ -bungarotoxin-insensitive                                                                                                                                                                                                                                                                              | –                                                                                                                                                                                                                      | Neuronal, $\alpha$ -bungarotoxin-sensitive                                                                                                                                                                                                                                                                                                                                                                          |
| Selective agonists             | $\alpha 4\beta 2$ : TC-2559 (Chen <i>et al.</i> , 2003), TC-2403 (RJR-2403, Papke <i>et al.</i> , 2000)                                                                                                                                                                                                                   | –                                                                                                                                                                                                                      | ( $\alpha 7$ ): PNU-282987 (Bodnar <i>et al.</i> , 2005), PHA-543613 (Wishka <i>et al.</i> , 2006); PHA-709829 (Acker <i>et al.</i> , 2008), A-582941 (Bitner <i>et al.</i> , 2007, TC-5619 (Hauser <i>et al.</i> , 2009)                                                                                                                                                                                           |
| Allosteric agonists            | –                                                                                                                                                                                                                                                                                                                         | –                                                                                                                                                                                                                      | 4BP-TQS (Gill <i>et al.</i> , 2011)                                                                                                                                                                                                                                                                                                                                                                                 |
| Positive allosteric modulators | $\alpha 4\beta 2$ and $\alpha 4\beta 4$ : LY-2087101 (Broad <i>et al.</i> , 2006, also potentiates $\alpha 2^*$ ), NS9283 (Lee <i>et al.</i> , 2011)                                                                                                                                                                      | –                                                                                                                                                                                                                      | ( $\alpha 7$ ): Type 1: LY-2087101 (Broad <i>et al.</i> , 2006), NS1738 (Timmermann <i>et al.</i> , 2007; also blocks $\alpha 3\beta 4$ and $\alpha 4\beta 2$ )<br>( $\alpha 7$ ): Type 2: PNU-120596 (Hurst <i>et al.</i> , 2005), A-867744 (Malysz <i>et al.</i> , 2009; also blocks $\alpha 3\beta 4$ and $\alpha 4\beta 2$ )<br>( $\alpha 7$ ): Type 1/2 intermediate: JNJ1930942 (Dinklo <i>et al.</i> , 2011) |
| Selective antagonists          | –                                                                                                                                                                                                                                                                                                                         | $\alpha 6/\alpha 3\beta 2\beta 3$ chimera: $\alpha$ -conotoxin PIA<br>$\alpha 6\beta 2\beta 3$ : $\alpha$ -conotoxin MII [H9A, L15A]<br>$\alpha 6\beta 2^*$ : $\alpha$ -conotoxin MII (also blocks $\alpha 3\beta 2$ ) | ( $\alpha 7$ ): $\alpha$ -bungarotoxin, methyllycaconitine, $\alpha$ -conotoxin ImI, $\alpha$ -conotoxin ARIIB                                                                                                                                                                                                                                                                                                      |
| Commonly used antagonists      | $\alpha 4\beta 2$ : DH $\beta$ E ( $K_8$ = 0.1 $\mu$ M; $IC_{50}$ = 0.08–0.9 $\mu$ M), (+)-Tc ( $K_8$ = 3.2 $\mu$ M, $IC_{50}$ = 34 $\mu$ M)<br>$\alpha 4\beta 4$ : DH $\beta$ E ( $K_8$ = 0.01 $\mu$ M, $IC_{50}$ = 0.19–1.2 $\mu$ M), (+)-Tc ( $K_8$ = 0.2 $\mu$ M, $IC_{50}$ = 50 $\mu$ M)                             | $\alpha 6/\alpha 3\beta 2\beta 3$ chimera: DH $\beta$ E ( $IC_{50}$ = 1.1 $\mu$ M)                                                                                                                                     | ( $\alpha 7$ ): DH $\beta$ E ( $IC_{50}$ = 8–20 $\mu$ M)<br>( $\alpha 7$ ): (+)-Tc ( $IC_{50}$ = 3.1 $\mu$ M)                                                                                                                                                                                                                                                                                                       |
| Channel blockers               | $\alpha 4\beta 2$ : mecamylamine ( $IC_{50}$ = 3.6–4.1 $\mu$ M), hexamethonium ( $IC_{50}$ = 6.8–29 $\mu$ M)<br>$\alpha 4\beta 4$ : mecamylamine ( $IC_{50}$ = 0.33–4.9 $\mu$ M), hexamethonium ( $IC_{50}$ = 91 $\mu$ M)                                                                                                 | $\alpha 6/\alpha 3\beta 2\beta 3$ chimera: mecamylamine ( $IC_{50}$ = 11 $\mu$ M), hexamethonium                                                                                                                       | ( $\alpha 7$ ): mecamylamine ( $IC_{50}$ = 15.6 $\mu$ M)                                                                                                                                                                                                                                                                                                                                                            |
| Radioligands ( $K_d$ )         | [ $^3$ H]/[ $^{125}$ I]-epibatidine ( $\alpha 4\beta 2$ , 10–33 pM; $\alpha 4\beta 4$ , 187 pM; $\alpha 4\beta 2$ , 30–46 pM; $\alpha 4\beta 4$ , 85–94 pM), [ $^3$ H]-cytisine ( $\alpha 4\beta 2$ , 430–630 pM; $\alpha 4\beta 2$ , 100 pM; $\alpha 4\beta 4$ 100 pM), [ $^3$ H]-nicotine ( $\alpha 4\beta 2$ , 400 pM) | [ $^3$ H]-epibatidine (native $\alpha 6\beta 4^*$ , 35 pM), [ $^{125}$ I]- $\alpha$ -conotoxin MII                                                                                                                     | [ $^3$ H]-epibatidine (( $\alpha 7$ ), 0.6 pM)<br>[ $^3$ H]/[ $^{125}$ I]- $\alpha$ -bungarotoxin (( $\alpha 7$ ), 0.7–5 nM), [ $^3$ H]-methyllycaconitine (native $\alpha 7^*$ , 1.9 nM), [ $^3$ H]-A-585539 (native $\alpha 7$ , 70 pM; Anderson <i>et al.</i> , 2008), [ $^3$ H]AZ11637326 (( $\alpha 7$ ), 230 pM; Gordon <i>et al.</i> , 2010)                                                                 |
| Functional characteristics     | $\alpha 4\beta 2$ : $P_{Ca}/P_{Na}$ = 1.65, $P_i$ = 2.6–2.9%;<br>$\alpha 4\beta 4$ : $P_i$ = 1.5–3.0 %                                                                                                                                                                                                                    | –                                                                                                                                                                                                                      | $P_{Ca}/P_{Na}$ = 6.6–20, $P_i$ = 8.8–11.4%                                                                                                                                                                                                                                                                                                                                                                         |

| Nomenclature               | $\alpha 8^*$ (avian)                                                                                                             | $\alpha 9^*$                                                                                                                                                                        |
|----------------------------|----------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Previous names             | Neuronal, $\alpha$ -bungarotoxin-sensitive                                                                                       | –                                                                                                                                                                                   |
| Selective agonists         | –                                                                                                                                | –                                                                                                                                                                                   |
| Selective antagonists      | –                                                                                                                                | ( $\alpha 9$ ): $\alpha$ -bungarotoxin, strychnine, nicotine, muscarine<br>$\alpha 9\alpha 10$ : $\alpha$ -conotoxin RgIA, $\alpha$ -bungarotoxin, strychnine, nicotine, muscarine  |
| Commonly used antagonists  | ( $\alpha 8$ ): $\alpha$ -bungarotoxin > atropine $\geq$ (+)-Tc $\geq$ strychnine                                                | ( $\alpha 9$ ): $\alpha$ -bungarotoxin > methyllycaconitine > strychnine ~ tropisetron > (+)-Tc<br>$\alpha 9\alpha 10$ : $\alpha$ -bungarotoxin > tropisetron = strychnine > (+)-Tc |
| Channel blockers           | –                                                                                                                                | –                                                                                                                                                                                   |
| Radioligands ( $K_d$ )     | [ $^3$ H]-epibatidine (( $\alpha 8$ ), 0.2 nM)<br>[ $^3$ H]/[ $^{125}$ I]- $\alpha$ -bungarotoxin (native $\alpha 8^*$ , 5.5 nM) | [ $^3$ H]-methyllycaconitine ( $\alpha 9\alpha 10$ , 7.5 nM)<br>[ $^3$ H]/[ $^{125}$ I]- $\alpha$ -bungarotoxin                                                                     |
| Functional characteristics | –                                                                                                                                | ( $\alpha 9$ ): $P_{Ca}/P_{Na}$ = 9; $\alpha 9\alpha 10$ : $P_{Ca}/P_{Na}$ = 9, $P_i$ = 22%                                                                                         |

Commonly used agonists of nicotinic acetylcholine receptors that display limited discrimination in functional assays between receptor subtypes include A-85380, cytisine, DMPP, epibatidine, nicotine and the natural transmitter, ACh. A summary of their profile across differing receptors is provided in Gotti *et al.* (2006) and quantitative data across numerous assay systems are summarised in Jensen *et al.* (2005). Quantitative data presented in the table for commonly used antagonists and channel blockers for human receptors studied under voltage-clamp are from Buisson *et al.*, 1996, Chavez-Noriaga *et al.*, (1997), Papke *et al.* (2001, 2008), Paul *et al.* (2002) and Wu *et al.* (2006). Type I PAMs increase peak agonist-evoked responses but have little, or no, effect on the rate of desensitization of  $\alpha 7$  nicotinic ACh receptors whereas type II PAMs also cause a large reduction in desensitization (reviewed by Williams *et al.*, 2011).

**Abbreviations:** 4BP-TQS, 4-(4-bromophenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide; A-582941, 2-methyl-5-(6-phenyl-pyridazin-3-yl)-octahydro-pyrrolo[3,4-c]pyrrole; A-585539, (1S,4S)-2,2-dimethyl-5-(6-phenylpyridazin-3-yl)-5-aza-2-azabicyclo[2.2.1]heptane; A-867744, 4-(5-(4-chlorophenyl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide; ABT-594, (R)-5-(2-azetidylmethoxy)-2-chloropyridine; ACh, acetylcholine; AZ11637326, (5'-(2-fluoro[3,4,5(-3)H3]phenyl)-spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine, DH $\beta$ E, dihydro- $\beta$ -erythroidine; DMPP, 1,1-dimethyl-4-phenylpiperazinium; JNJ-1930942, 2-[[4-fluoro-3-(trifluoromethyl)phenyl]amino]-4-(4-pyridinyl)-5-thiazolemethanol; LY-2087101, see Broad *et al.* (2006) for structure; NS1738, 1-(5-chloro-2-hydroxy-phenyl)-3-(2-chloro-5-trifluoromethyl-phenyl)-urea; NS9283, 3-(3-(pyridine-3-yl)-1,2,4-oxadiazol-5-yl)benzonitrile; PHA-543613, N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]furo[2,3-c]pyridine-5-carboxamide; PHA-709829, N-[(3R,5R)-1-azabicyclo[3.2.1]oct-3-yl]furo[2,3-c]pyridine-5-carboxamide; PNU-120596, 1-(5-chloro-2,4-dimethoxy-phenyl)-3-(5-methyl-isoxazol-3-yl)-urea; PNU-282987, N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-chlorobenzamide hydrochloride; PSAB-OFP, (R)-(-)-5'-phenylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)furo[2,3-b]pyridine; TC-2403 (RJR-2403), (E)-N-methyl-4-(3-pyridinyl)-3-butene-1-amine; TC-2559, (E)-N-methyl-4-[3-(5-ethoxypyridinyl)]-3-buten-1-amine; TC-5619, N-[2-(pyridin-3-ylmethyl)-1-azabicyclo[2.2.2]oct-3-yl]-1-benzofuran-2-carboxamide; (+)-Tc, (+)-tubocurarine

## Further Reading

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# GABA<sub>A</sub> (γ-aminobutyric acid)

**Overview:** The GABA<sub>A</sub> receptor is a ligand-gated ion channel of the Cys-loop family that includes the nicotinic acetylcholine, 5-HT<sub>3</sub> and strychnine-sensitive glycine receptors. GABA<sub>A</sub> receptor-mediated inhibition within the CNS occurs by fast synaptic transmission, sustained tonic inhibition and temporally intermediate events that have been termed 'GABA<sub>A</sub>, slow' (Campogna and Pearce, 2011). GABA<sub>A</sub> receptors exist as pentamers of 4Tm subunits that form an intrinsic anion selective channel. Sequences of six α, three β, three γ, one δ, three ρ, one ε, one π and one θ GABA<sub>A</sub> receptor subunits (Ensembl gene family ID ENSF00000000053) have been reported in mammals (Korpi *et al.*, 2002; Whiting, 2003; Sieghart, 2006; Olsen and Sieghart, 2008, 2009). The π-subunit is restricted to reproductive tissue. Alternatively spliced versions of many subunits exist (e.g. α4- and α6- (both not functional) α5-, β2-, β3- and γ2), along with RNA editing of the α3 subunit (Daniel and Ohman, 2009). The three ρ-subunits, (ρ1-3) function as either homo- or hetero-oligomeric assemblies (Zhang *et al.*, 2001; Chebib, 2004). Receptors formed from ρ-subunits, because of their distinctive pharmacology that includes insensitivity to bicuculline, benzodiazepines and barbiturates, have sometimes been termed GABA<sub>C</sub> receptors (Zhang *et al.*, 2001), but they are classified as GABA<sub>A</sub> receptors by NC-IUPHAR on the basis of structural and functional criteria (Barnard *et al.*, 1998; Olsen and Sieghart, 2008, 2009).

Many GABA<sub>A</sub> receptor subtypes contain α-, β- and γ-subunits with the likely stoichiometry 2α.2β.1γ (Korpi *et al.*, 2002; Olsen and Sieghart, 2008). It is thought that the majority of GABA<sub>A</sub> receptors harbour a single type of α- and β-subunit variant. The α1β2γ2 hetero-oligomer constitutes the largest population of GABA<sub>A</sub> receptors in the CNS, followed by the α2β3γ2 and α3β3γ2 isoforms. Receptors that incorporate the α4- α5- or α6-subunit, or the β1-, γ1-, γ3-, δ-, ε- and θ-subunits, are less numerous, but they may nonetheless serve important functions. For example, extrasynaptically located receptors that contain α6- and δ-subunits in cerebellar granule cells, or an α4- and δ-subunit in dentate gyrus granule cells and thalamic neurones, mediate a tonic current that is important for neuronal excitability in response to ambient concentrations of GABA (see Mody and Pearce, 2004; Semyanov *et al.*, 2004; Farrant and Nusser, 2005; Belelli *et al.*, 2009). GABA binding occurs at the β+/α- subunit interface and the homologous γ+/α- subunits interface creates the benzodiazepine site. A second site for benzodiazepine binding has recently been postulated to occur at the α+/β- interface (Ramerstorfer *et al.*, 2011; reviewed by Sigel and Lüscher, 2011). The particular α- and γ-subunit isoforms exhibit marked effects on recognition and/or efficacy at the benzodiazepine site. Thus, receptors incorporating either α4- or α6-subunits are not recognised by 'classical' benzodiazepines, such as flunitrazepam (but see You *et al.*, 2010). The trafficking, cell surface expression, internalisation and function of GABA<sub>A</sub> receptors and their subunits are discussed in detail in several recent reviews (Chen and Olsen, 2007; Jacob *et al.*, 2008; Lüscher *et al.*, 2011; Vithlani *et al.*, 2011) but one point worthy of note is that receptors incorporating the γ2 subunit (except when associated with α5) cluster at the postsynaptic membrane (but may distribute dynamically between synaptic and extrasynaptic locations), whereas as those incorporating the δ subunit appear to be exclusively extrasynaptic.

NC-IUPHAR (Barnard *et al.* 1998; Olsen and Sieghart, 2008) class GABA<sub>A</sub> receptors according to their subunit structure, pharmacology and receptor function. Currently, eleven native GABA<sub>A</sub> receptors are classed as conclusively identified (*i.e.*, α1β2γ2, α1βγ2, α3βγ2, α4βγ2, α4β2δ, α4β3δ, α5βγ2, α6βγ2, α6β2δ, α6β3δ and ρ) with further receptor isoforms occurring with high probability, or only tentatively (Olsen and Sieghart, 2008, 2009). It is beyond the scope of this Guide to discuss the pharmacology of individual GABA<sub>A</sub> receptor isoforms in detail; such information can be gleaned in the reviews by Barnard *et al.* (1998), Frolund *et al.* (2002), Korpi *et al.* (2002), Krosgaard-Larsen *et al.* (2002), Johnston (2005), Sieghart (2006), Möhler (2007), Olsen and Sieghart (2008, 2009) and Attack (2008, 2010). Agents that discriminate between α-subunit isoforms are noted in the table and additional agents that demonstrate selectivity between receptor isoforms, for example *via* β-subunit selectivity, are indicated in the text below. The distinctive agonist and antagonist pharmacology of ρ receptors is summarised in the table and additional aspects are reviewed by Zhang *et al.* (2001), Chebib (2004), Johnston *et al.* (2010) and Ng *et al.* (2011).

|                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-----------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature                                                                | GABA <sub>A</sub>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Ensembl Gene family ID                                                      | ENSF00000000053                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Selective agonists (GABA site)                                              | Muscimol (partial agonist at ρ subunits), isoguvacine (partial agonist at ρ subunits), THIP (gaboxadol; δ subunit preferring, antagonist at ρ subunits), piperidine-4-sulphonic acid (low efficacy at α4 and α6 subunits, antagonist at ρ subunits), isonipepicotic acid (α4 and α6 subunit selective <i>via</i> relatively high efficacy, antagonist at ρ subunits), (±)- <i>cis</i> -2-CAMP (ρ subunit selective), 5-MeIAA (ρ subunit selective)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Selective antagonists (GABA site)                                           | Bicuculline (not active at ρ subunits), gabazine (SR95531; weakly active on ρ subunits), TPMPA (ρ subunit selective), <i>cis</i> - and <i>trans</i> -3-ACPBPA (ρ subunit selective), Aza-THIP (ρ subunit selective)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Selective agonists (positive allosteric modulators) (benzodiazepine site)   | Diazepam (not α4- or α6-subunits), flunitrazepam (not α4- or α6-subunits), bretazenil (including α4- and α6-subunits, zolpidem, zaleplon and indiplon (α1 subunit selective <i>via</i> high affinity), ocinaplon (α1 subunit selective as essentially a full agonist <i>versus</i> partial agonist at α2, α3 and α5 subunit-containing receptors), L838417 (α2, α3 and α5 subunit selective as a partial agonist <i>versus</i> antagonist at α1-subunit-containing receptors), Ro154513 (selective for α4- and α6-subunit-containing receptors as an agonist <i>versus</i> inverse agonist at α1-, α2-, α3- and α5-subunit-containing receptors), TP003 (selective for α3-subunit-containing receptors as a high efficacy partial agonist <i>versus</i> essentially antagonist activity at α1- α2- and α5-subunit-containing receptors), TPA023 (selective for α2- and α3-subunit-containing receptors as a low efficacy partial agonist <i>versus</i> essentially antagonist activity at α1- and α5-subunit-containing receptors) |
| Selective antagonists (neutral allosteric modulators) (benzodiazepine site) | Flumazenil (low affinity for α4- or α6-subunits and partial agonist), ZK93426, L838417 (α1 subunit selective <i>via</i> antagonist activity <i>versus</i> partial agonist at α2-, α3- and α5-subunit subunit containing receptors)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Inverse agonists (negative allosteric modulators) (benzodiazepine site)     | DMCM, Ro194603, α3IA (α3 selective <i>via</i> higher affinity and greater inverse agonist activity <i>versus</i> α1, α2 and α5-subunit containing receptors), L655708, RY024 (α5 selective <i>via</i> high affinity), α5IA, MRK016 (α5 selective <i>versus</i> α1, α2 and α3-subunit containing receptors <i>via</i> greater inverse agonist efficacy), Ro4938581 (α5 selective <i>versus</i> α1, α2 and α3-subunit containing receptors <i>via</i> higher affinity and greater inverse agonist activity)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

|                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature                     | GABA <sub>A</sub>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Endogenous allosteric modulators | 5α-pregnan-3α-ol-20-one (potentiation), tetrahydrodeoxycorticosterone (potentiation), Zn <sup>2+</sup> (potent inhibition of receptors formed from binary combinations of α and β subunits, incorporation of a δ- or γ-subunit causes a modest, or pronounced, reduction in inhibitory potency, respectively, Krishek <i>et al.</i> , 1998), extracellular protons (subunit dependent activity, Krishek <i>et al.</i> , 1996)                                                                                                                                               |
| Channel blockers                 | Picrotoxin, TBPS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Probes                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| GABA site                        | [ <sup>3</sup> H]Muscimol, [ <sup>3</sup> H]gabazine (SR95531)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| benzodiazepine site              | [ <sup>3</sup> H]Flunitrazepam (not α4- or α6-subunit), [ <sup>3</sup> H]zolpidem (α1-subunit selective), [ <sup>3</sup> H]L655708 (α5-subunit selective), [ <sup>3</sup> H]RY80 (α5-subunit selective), [ <sup>3</sup> H]Ro154513 [selectively labels α4- and α6-subunit-containing receptors in the presence of a saturating concentration of a 'classical' benzodiazepine ( <i>e.g.</i> , diazepam)], [ <sup>3</sup> H]CGS8216, [ <sup>11</sup> C]flumazenil (PET ligand with low affinity for α4- or α6-subunits), [ <sup>18</sup> F]fluoroethylflumazenil (PET ligand) |
| Anion channel                    | [ <sup>35</sup> S]TBPS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

The potency and efficacy of many GABA agonists varies between receptor GABA<sub>A</sub> receptor isoforms (Frolund *et al.*, 2002; Krogsgaard-Larsen *et al.*, 2002). For example, THIP (gaboxadol) is a partial agonist at receptors with the subunit composition α4β3γ2, but elicits currents in excess of those evoked by GABA at the α4β3δ receptor where GABA itself is a low efficacy agonist (Brown *et al.*, 2002; Bianchi and MacDonald, 2003). The antagonists bicuculline and gabazine differ in their ability to suppress spontaneous openings of the GABA<sub>A</sub> receptor, the former being more effective (Thompson *et al.*, 1999). The presence of the γ subunit within the heterotrimeric complex reduces the potency and efficacy of agonists (Störustovu and Ebert, 2006). The GABA<sub>A</sub> receptor contains distinct allosteric sites that bind barbiturates and endogenous (*e.g.*, 5α-pregnan-3α-ol-20-one) and synthetic (*e.g.*, alphaxalone) neuroactive steroids in a diastereo- or enantio-selective manner (see Belelli and Lambert 2005; Herd *et al.*, 2007; Hosie *et al.*, 2007; Veleiro and Burton, 2009). Picrotoxinin and TBPS act at an allosteric site within the chloride channel pore to negatively regulate channel activity; negative allosteric regulation by γ-butyrolactone derivatives also involves the picrotoxinin site, whereas positive allosteric regulation by such compounds is proposed to occur at a distinct locus. Many intravenous (*e.g.*, etomidate, propofol) and inhalational (*e.g.*, halothane, isoflurane) anaesthetics and alcohols also exert a regulatory influence upon GABA<sub>A</sub> receptor activity (Bonin and Orser, 2008; Olsen and Li, 2011). Specific amino acid residues within GABA<sub>A</sub> receptor α- and β-subunits that influence allosteric regulation by anaesthetic and non-anaesthetic compounds have been identified (Hemmings *et al.*, 2005; Hosie *et al.*, 2007). Photoaffinity labelling of distinct amino acid residues within purified GABA<sub>A</sub> receptors by the etomidate derivative, [<sup>3</sup>H]-azietomidate, has also been demonstrated (Li *et al.*, 2006) and this binding subject to positive allosteric regulation by anaesthetic steroids (Li *et al.*, 2009). An array of natural products including flavonoid and terpenoid compounds exert varied actions at GABA<sub>A</sub> receptors (reviewed in detail by Johnston, 2005).

In addition to the agents listed in the table, modulators of GABA<sub>A</sub> receptor activity that exhibit subunit dependent activity include: salicylidene salicylhydrazide [negative allosteric modulator selective for β1- versus β2-, or β3-subunit-containing receptors (Thompson *et al.*, 2004)]; fragrant dioxane derivatives [positive allosteric modulators selective for β1- versus β2-, or β3-subunit-containing receptors (Sergeeva *et al.*, 2010)]; loreclezole, etomidate, tracazolate mefenamic acid, etifoxine, stiripentol, valeric acid amide [positive allosteric modulators with selectivity for β2/β3- over β1-subunit-containing receptors, see Korpi *et al.* (2002), Fisher (2009), Khom *et al.*, (2010)]; tracazolate [intrinsic efficacy, *i.e.*, potentiation, or inhibition, is dependent upon the identity of the γ1-3-, δ-, or ε-subunit co-assembled with α1- and β1-subunits (Thompson *et al.*, 2002)]; amiloride [selective blockade of receptors containing an α6-subunit (Fisher, 2002)]; furosemide [selective blockade of receptors containing an α6-subunit co-assembled with β2/β3-, but not β1-subunit (see Korpi *et al.* (2002))]; La<sup>3+</sup> [potentiates responses mediated by α1β3γ2L receptors, weakly inhibits α6β3γ2L receptors, and strongly blocks α6β3δ and α4β3δ receptors (Saxena *et al.*, 1997, Brown *et al.*, 2002)]; ethanol [selectively potentiates responses mediated by α4β3δ and α6β3δ receptors *versus* receptors in which β2 replaces β3, or γ replaces δ (Wallner *et al.*, 2006, but see also Korpi *et al.*, 2007)]; DS1 and DS2 [selectively potentiate responses mediated by δ-subunit-containing receptors (Wafford *et al.*, 2009)]. It should be noted that the apparent selectivity of some positive allosteric modulators (*e.g.*, neurosteroids such as 5α-pregnan-3α-ol-20-one for δ-subunit-containing receptors (*e.g.*, α1β3δ) may be a consequence of the unusually low efficacy of GABA at this receptor isoform (Bianchi and MacDonald, 2003; Belelli *et al.*, 2009).

**Abbreviations:** 3-ACBPBA, 3-amino-cyclopentenylbutylphosphonic acid; 5-Me-IAA, 5-methyl-1H-imidazole-4-acetic acid; (±)-*cis*-2-CAMP, (±)-*cis*-2-aminomethylcyclopropane carboxylic acid; α3IA, 6-(4-pyridyl)-5-(4-methoxyphenyl)-3-carbomethoxy-1-methyl-1H-pyridin-2-one; α5IA, 3-(5-methylisoxazol-3-yl)-6-[(1-methyl-1,2,3-triazol-4-yl)methoxy]-1,2,4-triazolo[3,4-*a*]phthalazine; CACA, *cis*-aminocrotonic acid; CGS8216, 2-phenylpyrazolo[4,3-*c*]quinolin-3(5)-one; DMCM, methy-6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate; DS1, 4-chloro-N-[6,8-dibromo-2-(2-thienyl)imidazo[1,2-*a*]pyridine-3-yl benzamide; DS2, 4-chloro-N-[2-(2-thienyl)imidazo[1,2-*a*]pyridine-3-yl benzamide; L655708, ethyl(s)-(11,12,13-tetrahydro-7-methoxy-9-oxo)-imidazo[1,5-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine-1-carboxylate; L838417, 7-*tert*-butyl-3-(2,5-difluoro-phenyl)-6-(2-methyl-2H-[1,2,4]triazol-3-ylmethoxy)-[1,2,4]triazolo[4,3-*b*]pyridazine; MRK016, 3-*tert*-butyl-7-(5-methylisoxazol-3-yl)-2-(1-methyl-1H-1,2,4-triazol-5-ylmethoxy)-pyrazolo[1,5-*d*]-[1,2,4]triazine; Ro154513, ethyl-8-azido-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-*a*][1,4] benzodiazepine-3-carboxylate; Ro194603, imidazo[1,5-*a*]1,4-thienodiazepinone; Ro4938581, 3-bromo-10-difluoromethyl-9H-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate; SR95531, 2-(3'-carboxy-2'-propyl)-3-amino-6-*p*-methoxyphenylpyridazinium bromide; TBPS, *tert*-butylbicyclopophosphorothionate; TP003, 4,2'-difluoro-5'-[8-fluoro-7-(1-hydroxy-1-methylethyl)imidazo[1,2-*a*]pyridine-3-yl]biphenyl-2-carbonitrile; TPA023, 7-(1,1-dimethylethyl)-6-(2-ethyl-2H-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine; TPMPA, (1,2,5,6-tetrahydropyridine-4-yl)methylphosphonic acid; RY024, *tert*-butyl-8-ethynyl-5,6-dihydro-5-methyl-6-oxo-4H-imidazol[1,5-*a*][1,4]benzodiazepine-3-carboxylate; RY80, ethyl-8-acetylene-5, 6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5a][1, 4]benzodiazepine-3-carboxylate; ZK93423, 6-benzyloxy-4-methoxymethyl-β-carboline-3-carboxylate ethyl ester; ZK93426, 5-isopropyl-4-methyl-β-carboline-3-carboxylate ethyl ester

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# Glutamate (ionotropic)

**Overview:** The ionotropic glutamate receptors comprise members of the NMDA (*N*-methyl-D-aspartate), AMPA ( $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and kainate receptor classes, named originally according to their preferred, synthetic, agonist (Dingledine *et al.*, 1999; Lodge, 2009; Traynelis *et al.*, 2010). Receptor heterogeneity within each class arises from the homo-oligomeric, or hetero-oligomeric, assembly of distinct subunits into cation-selective tetramers. Each subunit of the tetrameric complex comprises an extracellular amino terminal domain (ATD), an extracellular ligand binding domain (LBD), a transmembrane domain (TMD) composed of three membrane spans (M1, M3 and M4) with a channel lining re-entrant 'p-loop' (M2) located between M1 and M3 and an intracellular carboxy-terminal domain (CTD) (see Mayer, 2006; Kaczor and Matosiuk, 2010; Nakagawa, 2010; Traynelis *et al.*, 2010). The X-ray structure of a homomeric ionotropic glutamate receptor (GluA2 – see below) has recently been solved at 3.6 Å resolution (Sobolevsky *et al.*, 2009) and although providing the most complete structural information current available may not be representative of the subunit arrangement of, for example, the heteromeric NMDA receptors (Karakas *et al.*, 2011). It is beyond the scope of this supplement to discuss the pharmacology of individual ionotropic glutamate receptor isoforms in detail; such information can be gleaned from Dingledine *et al.* (1999), Jane *et al.* (2000), Cull-Candy and Leszkiewicz (2004), Kew and Kemp (2005), Erreger *et al.* (2007), Paoletti and Neyton (2007), Chen *et al.* (2008), Jane *et al.* (2009) and Traynelis *et al.* (2010). Agents that discriminate between subunit isoforms are, where appropriate, noted in the tables and additional compounds that distinguish between receptor isoforms are indicated in the text below.

The classification of glutamate receptor subunits has been recently been re-addressed by NC-IUPHAR (Collingridge *et al.*, 2009). The scheme developed recommends a revised nomenclature for ionotropic glutamate receptor subunits that is adopted here.

**NMDA receptors:** NMDA receptors assemble as obligate heteromers that may be drawn from GluN1, GluN2A, GluN2B, GluN2C, GluN2D, GluN3A and GluN3B subunits. Alternative splicing can generate eight isoforms of GluN1 with differing pharmacological properties. Various splice variants of GluN2B, 2C, 2D and GluN3A have also been reported. Activation of NMDA receptors containing GluN1 and GluN2 subunits requires the binding of two agonists, glutamate to the S1 and S2 regions of the GluN2 subunit and glycine to S1 and S2 regions of the GluN1 subunit (Erreger *et al.* 2004; Chen and Wyllie, 2006). The minimal requirement for efficient functional expression of NMDA receptors *in vitro* is a di-heteromeric assembly of GluN1 and at least one GluN2 subunit variant, as a dimer of heterodimers arrangement in the extracellular domain (Furukawa *et al.*, 2005; Mayer, 2006; Karakas *et al.*, 2011). However, more complex tri-heteromeric assemblies, incorporating multiple subtypes of GluN2 subunit, or GluN3 subunits, can be generated *in vitro* and occur *in vivo*. The NMDA receptor channel commonly has a high relative permeability to  $\text{Ca}^{2+}$  and is blocked, in a voltage-dependent manner, by  $\text{Mg}^{2+}$  such that at resting potentials the response is substantially inhibited.

|                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature                           | NMDA                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Ensembl Gene family ID                 | ENSF00000000436                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Selective agonists (glutamate site)    | NMDA (GluN2D > GluN2C > GluN2B > GluN2A), L-aspartate (GluN2D = GluN2B > GluN2C = GluN2A), D-aspartate (GluN2D > GluN2C = GluN2B > GluN2A), (R,S)-(tetrazol-5-yl)glycine (GluN2D > GluN2C = GluN2B > GluN2A), homoquinolinic acid (GluN2B $\geq$ GluN2A $\geq$ GluN2D > GluN2C; partial agonist at GluN2A and GluN2C)                                                                                                                    |
| Selective antagonists (glutamate site) | D-AP5, CGS19755 (selfotel), CGP37849, LY233053, D-CCPene (GluN2A = GluN2B > GluN2C = GluN2D), UBP141 (GluN2D > GluN2D > GluN2A > GluN2A, Morley <i>et al.</i> , 2005), NVP-AAM077 (GluN2A > GluN2B (human), Auberson <i>et al.</i> 2002; but weakly selective for rat GluN2A <i>versus</i> GluN2B Feng <i>et al.</i> , 2004; Frizelle <i>et al.</i> , 2006; Neyton and Paoletti, 2006), conantokin-G (GluN2B > GluN2D = GluN2C = GluN2A) |
| Selective agonists (glycine site)      | Glycine (GluN2D > GluN2C > GluN2B > GluN2A), D-serine (GluN2D > GluN2C > GluN2B > GluN2A), (+)-HA966 (partial agonist, GluN2B > GluN2A)                                                                                                                                                                                                                                                                                                  |
| Selective antagonists (glycine site)   | 5,7-Dichlorokynurenate, L689560, L701324, GV196771A                                                                                                                                                                                                                                                                                                                                                                                      |
| Channel blockers                       | $\text{Mg}^{2+}$ (GluN2A = GluN2B > GluN2C = GluN2D), (+)-MK801, ketamine, phencyclidine, memantine (GluN2C $\geq$ GluN2D $\geq$ GluN2B > GluN2A), amantadine (GluN2C = GluN2D $\geq$ GluN2B $\geq$ GluN2A), N <sup>1</sup> -dansyl-spermine (GluN2A = GluN2B >> GluN2C = GluN2D)                                                                                                                                                        |
| Probes                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Glutamate site                         | [ <sup>3</sup> H]CPP, [ <sup>3</sup> H]CGS19755, [ <sup>3</sup> H]CGP39653                                                                                                                                                                                                                                                                                                                                                               |
| Glycine site                           | [ <sup>3</sup> H]Glycine, [ <sup>3</sup> H]L689560, [ <sup>3</sup> H]MDL105519, [ <sup>3</sup> H]CGP61594 (photoaffinity ligand)                                                                                                                                                                                                                                                                                                         |
| Cation channel                         | [ <sup>3</sup> H]-MK801 (dizocilpine)                                                                                                                                                                                                                                                                                                                                                                                                    |

Potency orders unreferenced in the table are from Kuner and Schoepfer (1996), Dravid *et al.* (2007), Erreger *et al.* (2007), Paoletti and Neyton (2007), Chen *et al.* (2008) and Traynelis *et al.* (2010). In addition to the glutamate and glycine binding sites documented in the table, physiologically important inhibitory modulatory sites exist for  $\text{Mg}^{2+}$ ,  $\text{Zn}^{2+}$ , and protons (see Dingledine *et al.*, 1999; Cull-Candy and Leszkiewicz, 2004; Traynelis *et al.*, 2010). Voltage-independent inhibition by  $\text{Zn}^{2+}$  binding with high affinity within the ATD is highly subunit selective (GluN2A >> GluN2B > GluN2C  $\geq$  GluN2D; Paoletti and Neyton, 2007, Traynelis *et al.*, 2010). The receptor is also allosterically modulated, in both positive and negative directions, by endogenous neuroactive steroids in a subunit dependent manner (Malayev *et al.*, 2002, Horak *et al.*, 2006). Tonic proton blockade of NMDA receptor function is alleviated by polyamines and the inclusion of exon 5 within GluN1 subunit splice variants, whereas the non-competitive antagonists ifenprodil and CP101606 (traxoprodil) increase the fraction of receptors blocked by protons at ambient concentration. Inclusion of exon 5 also abolishes potentiation by polyamines and inhibition by  $\text{Zn}^{2+}$  that occurs through binding in the ATD (Traynelis *et al.*, 1998). Ifenprodil, CP101606, haloperidol, felbamate and Ro84304 discriminate between recombinant NMDA receptors assembled from GluN1 and either GluN2A, or GluN2B, subunits by acting as selective, non-competitive, antagonists of hetero-oligomers incorporating GluN2B through a binding site at the ATD GluN1/GluN2B subunit interface (Karakas *et al.*, 2011). LY233536 is a competitive antagonist that also displays selectivity for GluN2B over GluN2A subunit-containing receptors. Similarly, CGP61594 is a photoaffinity label that interacts selectively with receptors incorporating GluN2B *versus* GluN2A, GluN2D and, to a lesser extent, GluN2C subunits. In addition to influencing the pharmacological profile of the NMDA receptor, the identity of the GluN2 subunit co-assembled with GluN1 is an

important determinant of biophysical properties that include sensitivity to block by  $Mg^{2+}$ , single-channel conductance and maximal open probability and channel deactivation time (Cull-Candy and Leszkiewicz, 2004; Erreger *et al.*, 2004; Gielen *et al.*, 2009). Incorporation of the GluN3A subunit into tri-heteromers containing GluN1 and GluN2 subunits is associated with decreased single-channel conductance, reduced permeability to  $Ca^{2+}$  and decreased susceptibility to block by  $Mg^{2+}$  (Cavara and Hollmann, 2008; Henson *et al.*, 2010). Reduced permeability to  $Ca^{2+}$  has also been observed following the inclusion of GluN3B in tri-heteromers. The expression of GluN3A, or GluN3B, with GluN1 alone forms, in *Xenopus laevis* oocytes, a cation channel with unique properties that include activation by glycine (but not NMDA), lack of permeation by  $Ca^{2+}$  and resistance to blockade by  $Mg^{2+}$  and NMDA receptor antagonists (Chatterton *et al.*, 2002). The function of heteromers composed of GluN1 and GluN3A is enhanced by  $Zn^{2+}$ , or glycine site antagonists, binding to the GluN1 subunit (Madry *et al.*, 2008).  $Zn^{2+}$  also directly activates such complexes. The co-expression of GluN1, GluN3A and GluN3B appears to be required to form glycine-activated receptors in mammalian cell hosts (Smothers and Woodward, 2007).

**AMPA and Kainate receptors:** AMPA receptors assemble as homomers, or heteromers, that may be drawn from GluA1, GluA2, GluA3 and GluA4 subunits. Transmembrane AMPA receptor regulatory proteins (TARPs) of class I (*i.e.*  $\gamma 2$ ,  $\gamma 3$ ,  $\gamma 4$  and  $\gamma 8$ ) act, with variable stoichiometry, as auxiliary subunits to AMPA receptors and influence their trafficking, single channel conductance gating and pharmacology (reviewed by Esteban, 2008; Milstein and Nicoll, 2008; Tomita, 2010; Jackson and Nicoll, 2011). Functional kainate receptors can be expressed as homomers of GluK1, GluK2 or GluK3 subunits. GluK1-3 subunits are also capable of assembling into heterotetramers (*e.g.* GluK1/K2; see Lerma, 2006; Pinheiro and Mulle, 2006; Perrais *et al.*, 2010). Two additional kainate receptor subunits, GluK4 and GluK5, when expressed individually, form high affinity binding sites for kainate, but lack function, but can form heteromers when expressed with GluK1-3 subunits (*e.g.* GluK2/K5; reviewed by Pinheiro and Mulle, 2006; Jane *et al.*, 2009; Perrais *et al.*, 2010). Kainate receptors may also exhibit 'metabotropic' functions (Lerma, 2006; Rodriguez-Morino and Sihra, 2007). As found for AMPA receptors, kainate receptors are modulated by auxiliary subunits (Neto proteins, see Perrais *et al.*, 2010; Lerma, 2011). An important function difference between AMPA and kainate receptors is that the latter require extracellular  $Na^+$  and  $Cl^-$  for their activation (Bowie, 2010; Plested, 2011). RNA encoding the GluA2 subunit undergoes extensive RNA editing in which the codon encoding a p-loop glutamine residue (Q) is converted to one encoding arginine (R). This Q/R site strongly influences the biophysical properties of the receptor. Recombinant AMPA receptors lacking RNA edited GluA2 subunits are: (1) permeable to  $Ca^{2+}$ ; (2) blocked by intracellular polyamines at depolarized potentials causing inward rectification (the latter being reduced by TARPs); (3) blocked by extracellular argitoxin and Joro spider toxins and (4) demonstrate higher channel conductances than receptors containing the edited form of GluA2 (Seeburg and Hartner, 2003; Isaac *et al.*, 2007). GluK1 and GluK2, but not other kainate receptor subunits, are similarly edited and broadly similar functional characteristics apply to kainate receptors lacking either an RNA edited GluK1, or GluK2, subunit (Lerma, 2006; Perrais *et al.*, 2010). Native AMPA and kainate receptors displaying differential channel conductances,  $Ca^{2+}$  permeabilities and sensitivity to block by intracellular polyamines have been identified (Cull-Candy *et al.*, 2006; Isaac *et al.*, 2007; Liu and Zukin, 2007). GluA1-4 can exist as two variants generated by alternative splicing (termed 'flip' and 'flop') that differ in their desensitization kinetics and their desensitization in the presence of cyclothiazide which stabilises the non-desensitized state. TARPs also stabilise the non-desensitized conformation of AMPA receptors and facilitate the action of cyclothiazide (Milstein and Nicoll, 2008). Splice variants of GluK1-3 also exist which affects their trafficking (Lerma, 2006; Perrais *et al.*, 2010).

| Nomenclature           | AMPA                                                                                                                                                                                                | Kainate                                                                                                                                                                                                                                                 |
|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ensembl Gene family ID | ENSF00000000118                                                                                                                                                                                     | ENSF00000000118                                                                                                                                                                                                                                         |
| Selective agonists     | AMPA, (S)-5-fluorowillardiine                                                                                                                                                                       | ATPA, (S)-4-AHCP, 8-deoxy-neodysiherbaine, (S)-5-iodowillardiine, LY339434 (all selective for receptors containing a GluK1 subunit), (2S,4R)-4-methylglutamate (SYM2081), dysiherbaine, domoic acid (inactive at GluK3), kainate (low potency at GluK3) |
| Selective antagonists  | NBQX, ATPO, LY293558, GYKI53655/LY300168 (active isomer GYKI53784/LY303070) (noncompetitive)                                                                                                        | UBP302, UBP310, ACET, LY382884, LY466195 (all selective for receptors containing a GluK1 subunit), NS3763 (non-competitive, GluK1 selective), MSVIII-19 (GluK1 selective), 2,4-epi-neodysiherbaine (GluK1 and GluK2 selective)                          |
| Positive modulators    | Pyrrolidinones (piracetam, aniracetam), benzothiadiazides (cyclothiazide, S18986, IDRA-21), benzylpiperidines (CX-516 (BDP-12), CX-546), biarylpropylsulfonamides (LY392098, LY404187 and LY503430) | Concanavalin A (GluK1 and GluK2, not GluK3)                                                                                                                                                                                                             |
| Channel blockers       | Intracellular polyamines, extracellular argitoxin, extracellular Joro toxin, (selective for channels lacking GluA2)                                                                                 | Intracellular polyamines (subtype selective; GluK3 >> GluK2)                                                                                                                                                                                            |
| Probes ( $K_d$ )       | [ $^3H$ ]AMPA, [ $^3H$ ]CNQX                                                                                                                                                                        | [ $^3H$ ]Kainate, [ $^3H$ ](2S,4R)-4-methylglutamate, [ $^3H$ ]UBP310 (GluK1, 21 nM, GluK3, 0.56 $\mu$ M, Atlason <i>et al.</i> , 2010)                                                                                                                 |

All AMPA receptors are additionally activated by kainate (and domoate) with relatively low potency, ( $EC_{50} \sim 100 \mu$ M). Inclusion of TARPs within the receptor complex increases the potency and maximal effect of kainate (Milstein and Nicoll, 2008; Jackson and Nicoll, 2011). AMPA is weak partial agonist at GluK1 and at heteromeric assemblies of GluK1/GluK2, GluK1/GluK5 and GluK2/GluK5 (Jane *et al.*, 2009). Quinoxalinediones such as CNQX and NBQX show limited selectivity between AMPA and kainate receptors. LY293558 also has kainate (GluK1) receptor activity as has GYKI53655 (GluK3 and GluK2/GluK3) (Jane *et al.*, 2009). ATPO is a potent competitive antagonist of AMPA receptors, has a weaker antagonist action at kainate receptors comprising GluK1 subunits, but is devoid of activity at kainate receptors formed from GluK2 or GluK2/GluK5 subunits. The pharmacological activity of ATPO resides with the (S)-enantiomer. ACET and UBP310 may block GluK3, in addition to GluK1 (Perrais *et al.*, 2009; Atlason *et al.*, 2010). (2S,4R)-4-methylglutamate (SYM2081) is equipotent in activating (and desensitising) GluK1

and GluK2 receptor isoforms and, *via* the induction of desensitisation at low concentrations, has been used as a functional antagonist of kainate receptors. Both (2S,4R)-4-methylglutamate and LY339434 have agonist activity at NMDA receptors. (2S,4R)-4-methylglutamate is also an inhibitor of the glutamate transporters EAAT1 and EAAT2.

**Delta subunits:** GluD1 and GluD2 comprise, on the basis of sequence homology, an 'orphan' class of ionotropic glutamate receptor subunit. They do not form a functional receptor when expressed solely, or in combination with other ionotropic glutamate receptor subunits, in transfected cells (Yuzaki, 2003). However, GluD2 subunits bind D-serine and glycine and GluD2 subunits carrying the mutation A654T form a spontaneously open channel that is closed by D-serine (Naur *et al.*, 2007).

**Abbreviations:** (S)-4-AHCP, (S)-2-amino-3-(3-hydroxy-7,8-dihydro-6H-cyclohepta[d]isoxazol-4-yl)propionic acid; ACET, (S)-1-(2-amino-2-carboxyethyl)-3-(2-carboxy-5-phenylthiophene-3-yl-methyl)-5-methylpyrimidine-2,4-dione; AMPA, (RS)- $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; APTA, (RS)-2-amino-3-(3-hydroxy-5-*tert*-butylisoxazol-4-yl)propionic acid; ATPO, (RS)-2-amino-3-(3-[5-*tert*-butyl-3-(phosphonomethoxy)-4-isoxazolyl]propionic acid; CGP37849, (RS)-(E)-2-amino-4-methyl-5-phosphono-3-pentenoic acid; CGP39653, (RS)-(E)-2-amino-4-propyl-5-phosphono-3-pentenoic acid; CGS19755, ( $\pm$ )-*cis*-4-phosphonomethylpiperidine-2-carboxylic acid; CGP 61594, ( $\pm$ )-*trans*-4-[2-(4-azidophenyl)-acetylaminol]-5,7-dichloro-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid; CNQX, 6-cyano-7-nitroquinoline-2,3-dione; CP101606, (1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanol; CPP, (R)-3-(2-carboxypiperazine-4-yl)propyl-1-phosphonic acid; CX-516; 1-(quinoxalin-6-yl-carbonyl)piperidine; CX-546, 1-(1,4-benzodioxan-6-ylcarbonyl)piperidine; d-AP5, (R)-2-amino-5-phosphonopentanoate; d-CCPene, (R)-(E)-3-(2-carboxypiperazine-4-yl)propenyl-1-phosphonic acid; GV196771A, E-4,6-dichloro-3-(2-oxo-1-phenylpyrrolidin-3-ylidenemethyl)-1H-indole-2-carboxylic acid; GYKI53655, ( $\pm$ )-1-(4-aminophenyl)-3-methylcarbamoyl-4-methyl-3,4-dihydro-7,8-(methylenedioxy)-5H-2,3-benzodiazepine; also known as LY300168; GYKI53784, (-)-1-(4-aminophenyl)-3-methylcarbamoyl-4-methyl-3,4-dihydro-7,8-(methylenedioxy)-5H-2,3-benzodiazepine, also known as LY303070; HA966, 3-amino-1-hydroxypyrrolidin-2-one; IDRA-21, 7-chloro-3-methyl-3,4-dihydro-2H-1,2,4-benzothiadiazine-5,5-dioxide; L689560, *trans*-2-carboxy-5,7-dichloro-4-phenylaminocarbonylamino-1,2,3,4-tetrahydroquinoline; L701324, 7-chloro-4-hydroxy-3-(3-phenoxy)phenyl-2(H)quinoline; LY233053, ( $\pm$ )-*cis*-4-[(2H-tetrazol-5-yl)methyl]piperidine-2-carboxylic acid; LY233536, ( $\pm$ )-6-(1H-tetrazol-5-ylmethyl)decahydroisoquinoline-3-carboxylic acid; LY293558, (3S,4aR,6R,8aR)-6-[2-(1H-tetrazol-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid; LY339434, (2S,4R,6E)-2-amino-4-carboxy-7-(2-naphthyl)hept-6-enoic acid; LY382884, (3S,4aR,6S,8aR)-6-[(4-carboxyphenyl)methyl-1,2,3,4,4a,5,6,7,8a-decahydroisoquinoline-3-carboxylic acid; LY392098, propane-2-sulfonic acid [2-(4-thiophen-3-yl-phenyl)propyl]amide; LY404187, propane-2-sulfonic acid [2-(4'-cyanobiphenyl-4-yl)propyl]amide; LY466195, (3S,4aR,6S,8aR)-6-[(2S)-2-carboxy-4,4-difluoro-1-pyrrolidinyl]-methyl]decahydro-3-isoquinolinecarboxylic acid; LY503430, (R)-4'-[1-fluoro-1-methyl-2-(propane-2-sulfonylamino)ethyl]biphenyl-4-carboxylic acid methylamide; MDL105519, (E)-3-(2-phenyl-2-carboxyethenyl)-4,6-dichloro-1H-indole-2-carboxylic acid; MSVIII-19, (2R,3aR,7aR)-2-[(2S)-2-amino-2-carboxyethyl]-hexahydro-furo-[3,2-*b*]pyran-2-carboxylic acid; NBQX, 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo(f)quinoline; NS3763, 5-carboxy-2,4-di-benzamidobenzoic acid; NVP-AAM077, (R)-[(S)-1-(4-bromophenyl)ethylamino]-(2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-5-yl)methyl]phosphonic acid; Ro8-4304, 4-[4-(4-fluorophenyl)-3,6-dihydro-2H-pyridin-1-yl]-2-hydroxypropoxybenzamide; S18986, (S)-2,3-dihydro-[3,4]cyclopentano-1,2,4-benzothiadiazine-1,1-dioxide; UBP141, (2R\*,3S\*)-1-(phenanthrenyl-3-carbonyl)piperazine-2,3-dicarboxylic acid; UBP302, (S)-1-(2-amino-2-carboxyethyl)-3-(2-carboxybenzyl)pyrimidine-2,4-dione, UBP310, (S)-1-(2-amino-2-carboxyethyl)-3-(2-carboxythiophene-3-yl-methyl)-5-methylpyrimidine-2,4-dione

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# Glycine

**Overview:** The inhibitory glycine receptor [nomenclature as agreed by the NC-IUPHAR sub-committee on glycine receptors (Lynch, 2009a)] is a member of the Cys-loop superfamily of transmitter-gated ion channels that includes the GABA<sub>A</sub>, nicotinic acetylcholine and 5-HT<sub>3</sub> receptors (Lynch 2009b). The receptor is expressed either as a homo-pentamer of  $\alpha$  subunits, or a complex now thought to harbour 2 $\alpha$  and 3 $\beta$  subunits (Grudzinska *et al.*, 2005; Betz and Laube, 2006), that contain an intrinsic anion channel. Four differentially expressed isoforms of the  $\alpha$ -subunit ( $\alpha 1$ – $\alpha 4$ ) and one variant of the  $\beta$ -subunit ( $\beta 1$ , ENSG00000109738) have been identified by genomic and cDNA cloning. Further diversity originates from alternative splicing of the primary gene transcripts for  $\alpha 1$  ( $\alpha 1^{\text{INS}}$  and  $\alpha 1^{\text{del}}$ ),  $\alpha 2$  ( $\alpha 2A$  and  $\alpha 2B$ ),  $\alpha 3$  ( $\alpha 3S$  and  $\alpha 3L$ ) and  $\beta$  ( $\beta \Delta 7$ ) subunits and by mRNA editing of the  $\alpha 2$  and  $\alpha 3$  subunit (Meier *et al.*, 2005; Oertel *et al.*, 2007; Eichler *et al.*, 2008). Both  $\alpha 2$  splicing and  $\alpha 3$  mRNA editing can produce subunits (*i.e.*,  $\alpha 2B$  and  $\alpha 3P185L$ ) with enhanced agonist sensitivity. Predominantly, the mature form of the receptor contains  $\alpha 1$  (or  $\alpha 3$ ) and  $\beta$  subunits while the immature form is mostly composed of only  $\alpha 2$  subunits. RNA transcripts encoding the  $\alpha 4$ -subunit have not been detected in adult humans. The N-terminal domain of the  $\alpha$ -subunit contains both the agonist and strychnine binding sites that consist of several discontinuous regions of amino acids. Inclusion of the  $\beta$ -subunit in the pentameric glycine receptor contributes to agonist binding, reduces single channel conductance and alters pharmacology. The  $\beta$ -subunit also anchors the receptor, *via* an amphipathic sequence within the large intracellular loop region, to gephyrin. The latter is a cytoskeletal attachment protein that binds to a number of subsynaptic proteins involved in cytoskeletal structure and thus clusters and anchors hetero-oligomeric receptors to the synapse (see Moss and Smart, 2001; Kirsch, 2006; Kneussel and Loeblich, 2007). G-protein  $\beta\gamma$  subunits enhance the open state probability of native and recombinant glycine receptors by association with domains within the large intracellular loop (Yevenes *et al.*, 2003; 2006). Intracellular chloride concentration modulates the kinetics of native and recombinant glycine receptors (Pitt *et al.*, 2008). Intracellular Ca<sup>2+</sup> appears to increase native and recombinant glycine receptor affinity, prolonging channel open events, by a mechanism that does not involve phosphorylation (Fucile *et al.*, 2000).

| Nomenclature                                                  | $\alpha 1$                                                                                                                                                                                                                                                                                                                                                                                                        | $\alpha 2$                                                                                                                                                                                                                                                                                                                                                                                                             | $\alpha 3$                                                                                                                                                                                               |
|---------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ensembl ID                                                    | ENSG00000145888                                                                                                                                                                                                                                                                                                                                                                                                   | ENSG00000101958                                                                                                                                                                                                                                                                                                                                                                                                        | ENSG00000145451                                                                                                                                                                                          |
| Selective agonists (potency order)                            | Glycine > $\beta$ -alanine > taurine                                                                                                                                                                                                                                                                                                                                                                              | Glycine > $\beta$ -alanine > taurine                                                                                                                                                                                                                                                                                                                                                                                   | Glycine > $\beta$ -alanine > taurine                                                                                                                                                                     |
| Selective antagonists and modulators with subunit selectivity | Strychnine, PMBA, bilobalide (IC <sub>50</sub> = 20 $\mu$ M + $\beta$ = 204 $\mu$ M), pregnenolone sulphate ( $K_i$ = 1.9 $\mu$ M; + $\beta$ = 2.7 $\mu$ M), tropisetron ( $K_i$ = 84 $\mu$ M), colchicine (IC <sub>50</sub> = 324 $\mu$ M), nifedepine (IC <sub>50</sub> = 3.3 $\mu$ M + $\beta$ = 1.2 $\mu$ M), ginkgolide X (IC <sub>50</sub> = 0.76 $\mu$ M + $\beta$ > 300 $\mu$ M), HU308 (weak inhibition) | Strychnine, PMBA, bilobalide (8 $\mu$ M + $\beta$ = 50 $\mu$ M), pregnenolone sulphate ( $K_i$ = 5.5 $\mu$ M; + $\beta$ = 10.1 $\mu$ M), tropisetron ( $K_i$ = 13 $\mu$ M + $\beta$ = 5.4 $\mu$ M), colchicine (IC <sub>50</sub> = 64 $\mu$ M), DCKA (IC <sub>50</sub> = 188 $\mu$ M), ginkgolide X (IC <sub>50</sub> = 2.8 $\mu$ M + $\beta$ > 300 $\mu$ M), HU210 (90 nM), HU308 (1.1 $\mu$ M), WIN55,212-2 (220 nM) | Strychnine, nifedepine (IC <sub>50</sub> = 29.2 $\mu$ M + $\beta$ = 11.4 $\mu$ M), HU210 (50 nM), HU 308 (97 nM), WIN55212-2 (97 nM), (12E,20Z,18S)-8-hydroxyvariabilin (IC <sub>50</sub> = 7.0 $\mu$ M) |
| Selective potentiators (EC <sub>50</sub> )                    | HU210 (270 nM), anandamide (38 nM), $\Delta^9$ -tetrahydrocannabinol (~3 $\mu$ M, ~1500% potentiation)                                                                                                                                                                                                                                                                                                            | $\Delta^9$ -tetrahydrocannabinol (~1 $\mu$ M, ~230% potentiation)                                                                                                                                                                                                                                                                                                                                                      | $\Delta^9$ -tetrahydrocannabinol (~5 $\mu$ M, ~1500% potentiation)                                                                                                                                       |
| Endogenous potentiators (EC <sub>50</sub> )                   | Zn <sup>2+</sup> (37 nM) (not affected by $\beta$ )                                                                                                                                                                                                                                                                                                                                                               | Zn <sup>2+</sup> (540 nM) (not affected by $\beta$ )                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                          |
| Endogenous inhibitors (IC <sub>50</sub> )                     | Zn <sup>2+</sup> (15 $\mu$ M; + $\beta$ = 13 $\mu$ M), Cu <sup>2+</sup> (4–15 $\mu$ M) (not affected by $\beta$ ), H <sup>+</sup>                                                                                                                                                                                                                                                                                 | Zn <sup>2+</sup> (360 $\mu$ M; + $\beta$ = 180 $\mu$ M), Cu <sup>2+</sup> (17 $\mu$ M)                                                                                                                                                                                                                                                                                                                                 | Zn <sup>2+</sup> (150 $\mu$ M), Cu <sup>2+</sup> (9 $\mu$ M)                                                                                                                                             |
| Channel blockers (IC <sub>50</sub> )                          | cyanotriphenylborate (1.3 $\mu$ M + $\beta$ = 2.8 $\mu$ M), picrotoxin (6.3 $\mu$ M + $\beta$ = 219 $\mu$ M), picrotoxinin (5.1 $\mu$ M + $\beta$ = 27 $\mu$ M), picrotin (5.2 $\mu$ M + $\beta$ = 27 $\mu$ M), ginkgolide B (0.6–8.0 $\mu$ M + $\beta$ = 0.18–2.5 $\mu$ M),                                                                                                                                      | cyanotriphenylborate (>>20 $\mu$ M; + $\beta$ = 7.5 $\mu$ M), picrotoxin (2.3 $\mu$ M + $\beta$ = 29.7 $\mu$ M), picrotoxinin (0.41 $\mu$ M), picrotin (13.1 $\mu$ M), ginkgolide B (3.7–11.4 $\mu$ M + $\beta$ = 0.14–0.8 $\mu$ M)                                                                                                                                                                                    | picrotoxin (+ $\beta$ weakens block), picrotoxinin (0.43 $\mu$ M + $\beta$ = 8.9 $\mu$ M), picrotin (6.0 $\mu$ M + $\beta$ = 24 $\mu$ M), ginkgolide B (1.8 $\mu$ M + $\beta$ = 0.55 $\mu$ M)            |
| Probes                                                        | [ <sup>3</sup> H]strychnine                                                                                                                                                                                                                                                                                                                                                                                       | [ <sup>3</sup> H]strychnine                                                                                                                                                                                                                                                                                                                                                                                            | [ <sup>3</sup> H]strychnine                                                                                                                                                                              |
| Functional characteristics                                    | $\gamma$ = 86 pS (main state) (+ $\beta$ = 44 pS)                                                                                                                                                                                                                                                                                                                                                                 | $\gamma$ = 111 pS (main state) (+ $\beta$ = 54 pS)                                                                                                                                                                                                                                                                                                                                                                     | $\gamma$ = 105 pS (main state) (+ $\beta$ = 48)                                                                                                                                                          |

Data in the table refer to homo-oligomeric assemblies of the  $\alpha$ -subunit, significant changes introduced by co-expression of the  $\beta 1$  subunit are indicated in parenthesis. Not all glycine receptor ligands are listed within the table, but some that may be useful in distinguishing between glycine receptor isoforms are indicated (see Lynch (2009a) for a more comprehensive listing). Pregnenolone sulphate, tropisetron and colchicine, for example, although not selective antagonists of glycine receptors, are included for this purpose. Strychnine is a potent and selective competitive glycine receptor antagonist with affinities in the range 5–15 nM. RU5135 demonstrates comparable potency, but additionally blocks GABA<sub>A</sub> receptors. There are conflicting reports concerning the ability of cannabinoids to inhibit (Lozovaya *et al.*, 2005), or potentiate and at high concentrations activate (Hejazi *et al.*, 2006; Yang *et al.*, 2008; Ahrens *et al.*, 2009; Demir *et al.*, 2009; Xiong *et al.*, 2011) glycine receptors. Nonetheless, cannabinoid analogues may hold promise in distinguishing between glycine receptor subtypes (Yang *et al.*, 2008). In addition, potentiation of glycine receptor activity by cannabinoids has been claimed to contribute to cannabis-induced analgesia relying on Ser296/307 ( $\alpha 1/\alpha 3$ ) in M3 (Xiong *et al.*, 2011). Several analogues of muscimol and piperidine act as agonists and antagonists of both glycine and GABA<sub>A</sub> receptors. Picrotoxin acts as an allosteric inhibitor that appears to bind within the pore, and shows strong selectivity towards homomeric receptors. While its components, picrotoxinin and picrotin, have equal potencies at  $\alpha 1$  receptors, their potencies at  $\alpha 2$  and  $\alpha 3$  receptors differ modestly and may allow some distinction between different receptor types (Yang *et al.*, 2007). Binding of picrotoxin within the pore has recently been demonstrated in the crystal structure of the related *C. elegans* GluCl Cys-loop receptor (Hibbs and Gouaux, 2011). In addition to the

compounds listed in the table, numerous agents act as allosteric regulators of glycine receptors (comprehensively reviewed by Laube *et al.*, 2002; Lynch, 2004; Webb and Lynch, 2007; Yevenes and Zeilhofer, 2011).  $\text{Zn}^{2+}$  acts through distinct binding sites of high- and low-affinity to allosterically enhance channel function at low (<10  $\mu\text{M}$ ) concentrations and inhibits responses at higher concentrations in a subunit selective manner (Miller *et al.*, 2005). The effect of  $\text{Zn}^{2+}$  is somewhat mimicked by  $\text{Ni}^{2+}$ . Endogenous  $\text{Zn}^{2+}$  is essential for normal glycinergic neurotransmission mediated by  $\alpha 1$  subunit-containing receptors (Hirzel *et al.*, 2006). Elevation of intracellular  $\text{Ca}^{2+}$  produces fast potentiation of glycine receptor-mediated responses. Dideoxyforskolin (4  $\mu\text{M}$ ) and tamoxifen (0.2–5  $\mu\text{M}$ ) both potentiate responses to low glycine concentrations (15  $\mu\text{M}$ ), but act as inhibitors at higher glycine concentrations (100  $\mu\text{M}$ ). Additional modulatory agents that enhance glycine receptor function include inhalational, and several intravenous general anaesthetics (*e.g.* minaxolone, propofol and pentobarbitone) and certain neurosteroids. Ethanol and higher order *n*-alcohols also enhance glycine receptor function although whether this occurs by a direct allosteric action at the receptor (Mascia *et al.*, 2000), or through G-protein  $\beta\gamma$  subunits (Yevenes *et al.*, 2010) is debated. Recent crystal structures of the bacterial homologue, GLIC, have identified transmembrane binding pockets for both anaesthetics (Nury *et al.*, 2011) and alcohols (Howard *et al.*, 2011). Solvents inhaled as drugs of abuse (*e.g.* toluene, 1-1-1-trichloroethane) may act at sites that overlap with those recognising alcohols and volatile anaesthetics to produce potentiation of glycine receptor function. The function of glycine receptors formed as homomeric complexes of  $\alpha 1$  or  $\alpha 2$  subunits, or hetero-oligomers of  $\alpha 1/\beta$  or  $\alpha 2/\beta$  subunits, is differentially affected by the 5-HT<sub>3</sub> receptor antagonist tropisetron (ICS 205-930) which may evoke potentiation (which may occur within the femtomolar range at the homomeric glycine  $\alpha 1$  receptor), or inhibition, depending upon the subunit composition of the receptor and the concentrations of the modulator and glycine employed. Potentiation and inhibition by tropeines involves different binding modes (Maksay *et al.*, 2009). Additional tropeines, including atropine, modulate glycine receptor activity.

**Abbreviations:** DCKA, dichlorokynurenic acid, HU210, (6aR,10aR)-9-(hydroxymethyl)-6,6-dimethyl-3-(2-methyloctan-2-yl)-6a,7,10,10a-tetrahydrobenzo[c]chromen-1-ol; HU308, [(1R,2R,5R)-2-[2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl]-6,6-dimethyl-4-bicyclo[3.1.1]hept-3-enyl]methanol; PMBA, 3-[2'-phosphonomethyl[1,1'-biphenyl]-3-yl]alanine; RU5135, 3 $\alpha$ -hydroxy-16-imino-5 $\beta$ -17-azaandrostan-11-one, WIN55212-2, (R)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo-[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone mesylate

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# P2X

**Overview:** P2X receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on P2X Receptors, Collingridge *et al.*, 2009; Khakh *et al.*, 2001) are ligand-gated ion channels with a trimeric topology (Jiang *et al.*, 2003; Kawate *et al.*, 2009; Nicke *et al.*, 1998), gating primarily Na<sup>+</sup>, K<sup>+</sup> and Ca<sup>2+</sup>, exceptionally Cl<sup>-</sup> with two putative TM domains, where the endogenous ligand is ATP. The Nomenclature Subcommittee has recommended that for P2X receptors, structural criteria should be the initial criteria for nomenclature where possible. The P2X receptor nomenclature recommended below reflects the newly accepted format for ligand-gated ion channels (see Collingridge *et al.*, 2009). Functional P2X receptors exist as polymeric transmitter-gated channels; the native receptors may occur as either homopolymers (e.g. P2X1 in smooth muscle) or heteropolymers (e.g. P2X2:P2X3 in the nodose ganglion and P2X1:P2X5 in mouse cortical astrocytes, Lalo *et al.*, 2008). P2X2, P2X4 and P2X7 receptors have been shown to form functional homopolymers which, in turn, activate pores permeable to low molecular weight solutes (see Surprenant and North, 2009). The hemi-channel pannexin-1 has been implicated in the pore formation induced by P2X7 (Pelegri and Surprenant, 2009), but not P2X2 (Chaumont and Khakh, 2008), receptor activation.

| Nomenclature       | P2X1                                                                                                                                                                                                  | P2X2            | P2X3                                                                                                                                                                                                                          | P2X4            |
|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| Ensembl ID         | ENSG00000108405                                                                                                                                                                                       | ENSG00000187848 | ENSG00000109991                                                                                                                                                                                                               | ENSG00000135124 |
| Potent agonists    | L-βγ-meATP, αβ-meATP, BzATP                                                                                                                                                                           | –               | αβ-meATP, BzATP                                                                                                                                                                                                               | –               |
| Potent antagonists | TNP-ATP (pIC <sub>50</sub> 8.9, Virginio <i>et al.</i> , 1998), Ip <sub>s</sub> I (pIC <sub>50</sub> 8.5), NF023 (pIC <sub>50</sub> 6.7); NF449 (pIC <sub>50</sub> 6.3, Kassack <i>et al.</i> , 2004) | –               | TNP-ATP (pIC <sub>50</sub> 8.9, Virginio <i>et al.</i> , 1998), AF353 (pIC <sub>50</sub> 8.0, Gever <i>et al.</i> , 2010), A317491 (7.5, Jarvis <i>et al.</i> , 2002), RO3 (pIC <sub>50</sub> 7.5, Ford <i>et al.</i> , 2006) | –               |

A317491 and RO3 also block the P2X2:P2X3 heteromultimer (Jarvis *et al.*, 2002; Ford *et al.*, 2006). NF449, A317491 and RO3 are more than 10-fold selective for P2X1 and P2X3 receptors, respectively.

| Nomenclature       | P2X5            | P2X6            | P2X7                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|--------------------|-----------------|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Other names        | –               | –               | P <sub>2Z</sub>                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Ensembl ID         | ENSG00000083454 | ENSG00000099957 | ENSG00000089041                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Potent antagonists | –               | –               | Brilliant Blue G (pIC <sub>50</sub> 8.0, Jiang <i>et al.</i> , 2000), A804598 (pIC <sub>50</sub> 8.0), A839977 (pIC <sub>50</sub> 7.7, Donnelly-Roberts and Jarvis, 2007; Donnelly-Roberts <i>et al.</i> , 2009, Honore <i>et al.</i> , 2009), decavanadate (pA <sub>2</sub> 7.4, Michel <i>et al.</i> , 2006a), KN62 (Gargett and Wiley, 1997), A740003 (pIC <sub>50</sub> 7.4), A438079 (pIC <sub>50</sub> 6.9, Donnelly-Roberts and Jarvis, 2007) |

Agonists listed show selectivity within recombinant P2X receptors of *ca.* one order of magnitude. A804598, A839977, A740003 and A438079 are at least 10-fold selective for P2X7 receptors and show similar affinity across human and rodent receptors (Donnelly-Roberts and Jarvis, 2007, Donnelly-Roberts *et al.*, 2009; Honore *et al.*, 2009).

Several P2X receptors (particularly P2X1 and P2X3) may be inhibited by desensitisation using stable agonists (e.g. αβ-meATP); suramin and PPADS are non-selective antagonists at r & hP2X1–3,5 and hP2X4, but not rP2X4,6,7 (Buell *et al.*, 1996), and can also inhibit ATPase activity (Crack *et al.*, 1994). Ip<sub>s</sub>I is inactive at rP2X2, an antagonist at rP2X3 (pIC<sub>50</sub> 5.6) and enhances agonist responses at rP2X4 (King *et al.*, 1999). Antagonist potency of NF023 at recombinant P2X2, P2X3 and P2X5 is two orders of magnitude lower than that at P2X1 receptors (Soto *et al.*, 1999). The P2X7 receptor may be inhibited in a non-competitive manner by the protein kinase inhibitors KN62 and chelerythrine (Shemon *et al.*, 2004), while the p38 MAP kinase inhibitor SB202190 and the cyclic imide AZ11645373 show a species-dependent non-competitive action (Donnelly-Roberts *et al.*, 2004; Michel *et al.*, 2006b; Stokes *et al.*, 2006; Michel, 2009). The pH-sensitive dye used in culture media, phenol red, is also reported to inhibit P2X1 and P2X3 containing channels (King *et al.*, 2005). Some recombinant P2X receptors expressed to high density bind [<sup>35</sup>S]-ATPγS and [<sup>3</sup>H]-αβ-meATP, although the latter can also bind to 5'-nucleotidase (Michel *et al.*, 1995). [<sup>3</sup>H]-A317491 and [<sup>3</sup>H]-A804598 have been used as high affinity antagonist radioligands for P2X3 (and P2X2/3) and P2X7 receptors, respectively (Donnelly-Roberts *et al.*, 2009).

**Abbreviations:** αβ-meATP, αβ-methylene-adenosine 5'-triphosphate; βγ-meATP, βγ-methylene-adenosine 5'-triphosphate; A317491, 5-((3-phenoxybenzyl)[(1S)-1,2,3,4-tetrahydro-1-naphthalenyl]amino)carbonyl)-1,2,4-benzenetricarboxylic acid; A438079, 3-(5-(2,3-dichlorophenyl)-1H-tetrazol-1-yl) methyl pyridine; A740003, (N-(1-[[[cyanoimino](5-quinolinylamino) methyl]amino]-2,2-dimethylpropyl)-2-(3,4-dimethoxyphenyl)acetamide; A839977, 1-(2,3-dichlorophenyl)-N-[2-(pyridin-2-yloxy)benzyl]-1H-tetrazol-5-amine; A804598, (S)-1-(1-(4-bromophenyl)ethyl)-2-cyano-3-(quinoline-5-yl)guanidine; AF353, (5-(5-iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine; ATPγS, adenosine 5'-(3-thio)triphosphate; AZ11645373, 3-[1-[4-(3-nitrophenyl)phenoxy]-4-pyridin-4-ylbutan-2-yl]-1,3-thiazolidine-2,4-dione; Ip<sub>s</sub>I, diinosine-5',5''-pentaphosphate; KN62, 1-(N,O-bis[5-isoquinolinesulphonyl]-N-methyl-L-tyrosyl)-4-phenylpiperazine; NF023, 8,8'-(carbonylbis[imino-3,1-phenylene carbonylimino])bis-1,3,5-naphthalenetrisulfonic acid; NF449, 4,4',4''-(carbonylbis[imino-5,1,3-benzenetriyl-bis(carbonylimino)])tetrakisbenzene-1,3-disulfonic acid octasodium salt; PPADS, pyridoxalphosphate-6-azophenyl-2',4'-disulphonate; RO3, 5-(methyl[2-methylethyl-4,5-dimethoxyphenyl]-2,4-pyridinediamine; SB202190, 4-[4-(4-fluorophenyl)-5-pyridin-4-yl]-1H-imidazol-2-yl]phenol; TNP-ATP, 2',3'-O-(2,4,6-trinitrophenyl)-ATP

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# ZAC (Zinc-activated channel)

**Overview:** The zinc-activated channel [ZAC, nomenclature as agreed by the NC-IUPHAR Subcommittee for the zinc activated channel (Hales and Peters (2010))] is a member of the Cys-loop family that includes the nicotinic acetylcholine, 5-HT<sub>3</sub>, GABA<sub>A</sub> and strychnine-sensitive glycine receptors (Davies *et al.*, 2003; Houtani *et al.*, 2005). The channel is likely to exist as a homopentamer of 4TM subunits that form an intrinsic cation selective channel displaying constitutive activity that can be blocked by (+)-tubocurarine (Davies *et al.*, 2003). ZAC is present in the human, chimpanzee, dog, cow and opossum genomes, but is functionally absent from mouse, or rat, genomes (Davies *et al.*, 2003; Houtani *et al.*, 2005).

|                                            |                                                                                  |
|--------------------------------------------|----------------------------------------------------------------------------------|
| Nomenclature                               | ZAC                                                                              |
| Other names                                | L2                                                                               |
| Ensembl ID                                 | ENSG00000186919                                                                  |
| Selective agonists (pEC <sub>50</sub> )    | Zn <sup>2+</sup> (3.3 )                                                          |
| Selective antagonists (pIC <sub>50</sub> ) | (+)-Tubocurarine (5.2)                                                           |
| Functional characteristics                 | Outwardly rectifying current (both constitutive and evoked by Zn <sup>2+</sup> ) |

Although tabulated as an antagonist, it is possible that (+)-tubocurarine acts as a channel blocker.

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# ION CHANNELS

**Overview:** Ion channels are pore-forming proteins that allow the flow of ions across membranes, either plasma membranes or the membranes of intracellular organelles (Hille, 2001). Many ion channels (such as most Na, K Ca and some Cl channels) are gated by voltage but others (such as certain K and Cl channels, TRP channels, ryanodine receptors and IP<sub>3</sub> receptors) are relatively voltage-insensitive and are gated by second messengers and other intracellular and/or extracellular mediators. As such, there is some blurring of the boundaries between 'ion channels' and 'ligand-gated channels' which are compiled separately in this guide.

Resolution of ion channel structures, beginning with K channels (Doyle *et al.*, 1998) then Cl channels (Dutzler *et al.*, 2002) and most recently Na channels (Payandeh *et al.*, 2011) has greatly improved understanding of the structural basis behind ion channel function. Many ion channels (e.g., K, Na, Ca, HCN and TRP channels) share several structural similarities. These channels are thought to have evolved from a common ancestor and have been classified together as the 'voltage-gated-like (VGL) ion channel chanome' (see Yu *et al.*, 2005). Other ion channels, however, such as Cl channels, aquaporins and connexins, have completely different structural properties to the VGL channels, having evolved quite separately.

Currently, ion channels (including ligand-gated ion channels) represent the second largest target for existing drugs after G protein-coupled receptors (Overington *et al.*, 2006). However, the advent of novel, faster screening techniques for compounds acting on ion channels (Dunlop *et al.*, 2008) suggests that these proteins represent promising targets for the development of additional, novel therapeutic agents in the near future.

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# Acid-sensing (proton-gated) ion channels (ASICs)

**Overview:** Acid-sensing ion channels (ASICs, provisional nomenclature; see Wemmie *et al.*, 2006; Lingueglia, 2007) are members of a Na<sup>+</sup> channel superfamily that includes the epithelial Na<sup>+</sup> channel (ENaC), the FMRF-amide activated channel (FaNaC) of invertebrates, the degenerins (DEG) of *Caenorhabditis elegans*, channels in *Drosophila melanogaster* and 'orphan' channels that include BLINaC (Sakai *et al.*, 1999) and INaC (Schaefer *et al.* 2000). ASIC subunits contain two TM domains and assemble as homo- or hetero-trimers (Jasti *et al.*, 2007; Gonzales *et al.*, 2009) to form proton-gated, voltage-insensitive, Na<sup>+</sup> permeable, channels (reviewed by Gründer and Chen (2010)). Splice variants of ASIC1 [provisionally termed ASIC1a (ASIC, ASIC $\alpha$ , BNaC2 $\alpha$ ) (Waldmann *et al.* 1997a), ASIC1b (ASIC $\beta$ , BNaC2 $\beta$ ) (Chen *et al.*, 1998) and ASIC1b2 (ASIC $\beta$ 2) (Ugawa *et al.*, 2001); note that ASIC1a is also permeable to Ca<sup>2+</sup>] and ASIC2 [provisionally termed ASIC2a (MDEG1, BNaC1 $\alpha$ , BNC1a) (Price *et al.*, 1996; Waldmann *et al.*, 1996; Garcia-Anoveros *et al.*, 1997) and ASIC2b (MDEG2, BNaC1 $\beta$ ); (Lingueglia *et al.*, 1997)] have been cloned. Unlike ASIC2a (listed in table), heterologous expression of ASIC2b alone does not support H<sup>+</sup>-gated currents. A third member, ASIC3 (DRASIC, TNaC1) (Waldmann *et al.*, 1997b), has been identified. A fourth mammalian member of the family (ASIC4/SPASIC) does not support a proton-gated channel in heterologous expression systems and is reported to down regulate the expression of ASIC1a and ASIC3 (Akopian *et al.* 2000; Grunder *et al.*, 2000; Donier *et al.*, 2008). ASIC channels are primarily expressed in central and peripheral neurons including nociceptors where they participate in neuronal sensitivity to acidosis. They have also been detected in taste receptor cells (ASIC1-3), photoreceptors and retinal cells (ASIC1-3), cochlear hair cells (ASIC1b), testis (hASIC3), pituitary gland (ASIC4), lung epithelial cells (ASIC1a and -3), urothelial cells, adipose cells (ASIC3), vascular smooth muscle cells (ASIC1-3), immune cells (ASIC1,-3 and -4) and bone (ASIC1-3). The activation of ASIC1a within the central nervous system contributes to neuronal injury caused by focal ischemia (Xiong *et al.*, 2007) and to axonal degeneration in autoimmune inflammation in a mouse model of multiple sclerosis (Friesse *et al.*, 2007). However, activation of ASIC1a can terminate seizures (Ziemann *et al.*, 2008). Peripheral ASIC3-containing channels play a role in post-operative pain (Deval *et al.*, 2011). Further proposed roles for centrally and peripherally located ASICs are reviewed in Wemmie *et al.* (2006) and Lingueglia (2007). The relationship of the cloned ASICs to endogenously expressed proton-gated ion channels is becoming established (Escoubas *et al.*, 2000; Sutherland *et al.*, 2001; Wemmie *et al.*, 2002, 2003, 2006; Diochot *et al.*, 2004, 2007; Lingueglia *et al.*, 2006; Lingueglia, 2007; Hattori *et al.*, 2009). Heterologously expressed heteromultimers form ion channels with altered kinetics, ion selectivity, pH- sensitivity and sensitivity to blockers that resemble some of the native proton activated currents recorded from neurones (Lingueglia *et al.*, 1997; Babinski *et al.*, 2000, Escoubas *et al.*, 2000, Baron *et al.*, 2008).

| Nomenclature                 | ASIC1                                                                                                                                                                                                                                                                                                                                                                                                                                             | ASIC2                                                                                                                                                                     | ASIC3                                                                                                                                                                                                                                                                                                                                                                                     |
|------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Other names                  | ASIC; BNaC2                                                                                                                                                                                                                                                                                                                                                                                                                                       | BNC1; BNaC1; MDEG                                                                                                                                                         | DRASIC, TNaC1                                                                                                                                                                                                                                                                                                                                                                             |
| Ensembl ID                   | ENSG00000110881                                                                                                                                                                                                                                                                                                                                                                                                                                   | ENSG00000108684                                                                                                                                                           | ENSG00000213199                                                                                                                                                                                                                                                                                                                                                                           |
| Endogenous activators        | Extracellular H <sup>+</sup> (ASIC1a, pEC <sub>50</sub> ~ 6.2–6.8; ASIC1b, pEC <sub>50</sub> ~ 5.1–6.2)                                                                                                                                                                                                                                                                                                                                           | Extracellular H <sup>+</sup> (pEC <sub>50</sub> ~ 4.1–5.0)                                                                                                                | Extracellular H <sup>+</sup> (transient component pEC <sub>50</sub> ~ 6.2–6.7) (sustained component pEC <sub>50</sub> ~ 3.5–4.3), agmatine (EC <sub>50</sub> ~ 9.8 mM @ pH 7.4, aracaine (EC <sub>50</sub> ~ 1.2 mM @ pH 7.4), GMQ (largely non-desensitizing; pEC <sub>50</sub> ~ 3.0 @ pH 7.4)                                                                                          |
| Blockers (IC <sub>50</sub> ) | ASIC1a: Psalmotoxin 1 (PcTx1) (0.9 nM), Zn <sup>2+</sup> (~7 nM), A-317567 (~2 μM), Pb <sup>2+</sup> (~4 μM), Ni <sup>2+</sup> (~0.6 mM), amiloride (10 μM), EIPA, benzamil (10 μM), nafamostat (~13 μM), diarylamidines (~3 μM), ibuprofen/ flurbiprofen (350 μM) ASIC1b: Amiloride (21–23 μM); Pb <sup>2+</sup> (~1.5 μM), diarylamidines                                                                                                       | Amiloride (28 μM), A-317567 (~30 μM), nafamostat (~70 μM), Cd <sup>2+</sup> (~1 mM), diarylamidines                                                                       | APETx2 (63 nM) (transient component only), nafamostat (2.5 ~ μM) (transient component), amiloride (16–63 μM) (transient component only – sustained component enhanced by 200 μM amiloride @ pH 4), A-317567 (~10 μM), aspirin/diclofenac (92 μM – sustained component), salicylic acid (260 μM – sustained component), Gd <sup>3+</sup> (40 μM), Zn <sup>2+</sup> (61 μM), diarylamidines |
| Functional characteristics   | ASIC1a: $\gamma$ ~14pS; P <sub>Na</sub> /P <sub>K</sub> = 5–13, P <sub>Na</sub> /P <sub>Ca</sub> = 2.5; rapid activation rate (5.8–13.7 ms) rapid inactivation rate (1.2–4 s) @ pH 6.0, slow recovery (5.3–13 s) @ pH 7.4 ASIC1b: $\gamma$ ~ 19 pS; P <sub>Na</sub> /P <sub>K</sub> = 14.0; P <sub>Na</sub> >> P <sub>Ca</sub> ; rapid activation rate (9.9 ms); rapid inactivation rate (0.9–1.7 s) @ pH 6.0, slow recovery (4.4–7.7 s) @ pH 7.4 | $\gamma$ ~10.4–13.4 pS; P <sub>Na</sub> /P <sub>K</sub> = 10, P <sub>Na</sub> /P <sub>Ca</sub> = 20; rapid activation rate, moderate inactivation rate (3.3–5.5 s) @ pH 5 | $\gamma$ ~ 13–15 pS; biphasic response consisting of rapidly inactivating transient and sustained components; very rapid activation (<5 ms) and inactivation (0.4 s); fast recovery (0.4–0.6 s) @ pH 7.4, transient component partially inactivated at pH 7.2                                                                                                                             |
| Probes                       | [ <sup>125</sup> I]-PcTx1 (ASIC1a K <sub>D</sub> = 213 pM)                                                                                                                                                                                                                                                                                                                                                                                        | –                                                                                                                                                                         | –                                                                                                                                                                                                                                                                                                                                                                                         |

Psalmotoxin 1 (PcTx1) inhibits ASIC1a by modifying activation and desensitization by H<sup>+</sup>, but promotes ASIC1b opening. PcTx1 has little effect upon ASIC2a, ASIC3, or ASIC1a expressed as a heteromultimer with either ASIC2a, or ASIC3 (Escoubas *et al.*, 2000; Diochot *et al.*, 2007) but does block ASIC1a expressed as a heteromultimer with ASIC2b (Sherwood *et al.*, 2011). Spermine, which apparently competes with PcTx1 for binding to ASIC1a, selectively enhances the function of the channel (Duan *et al.*, 2011). Blockade of ASIC1a by PcTx1 activates the endogenous enkephalin pathway and has very potent analgesic effects in rodents (Mazzuca *et al.*, 2007). APETx2 most potently blocks homomeric ASIC3 channels, but also ASIC2b+ASIC3, ASIC1b+ASIC3, and ASIC1a+ASIC3 heteromeric channels with IC<sub>50</sub> values of 117 nM, 900 nM and 2 μM, respectively. APETx2 has no effect on ASIC1a, ASIC1b, ASIC2a, or ASIC2a+ASIC3 (Diochot *et al.*, 2004; 2007). IC<sub>50</sub> values for A-317567 are inferred from blockade of ASIC channels native to dorsal root ganglion neurones (Dube *et al.*, 2005). The pEC<sub>50</sub> values for proton activation of ASIC channels are influenced by numerous factors including extracellular di- and poly-valent ions, Zn<sup>2+</sup>, protein kinase C and serine proteases (reviewed by Lingueglia *et al.*, 2006). Rapid acidification is required for activation of ASIC1 and ASIC3 due to fast inactivation/desensitization.

pEC<sub>50</sub> values for H<sup>+</sup>-activation of either transient, or sustained, currents mediated by ASIC3 vary in the literature and may reflect species and/or methodological differences (Waldmann *et al.*, 1997b; de Weille *et al.*, 1998; Babinski *et al.*, 1999). The transient and sustained current components mediated by rASIC3 are selective for Na<sup>+</sup> (Waldmann *et al.*, 1997b); for hASIC3 the transient component is Na<sup>+</sup> selective ( $P_{Na}/P_K > 10$ ) whereas the sustained current appears non-selective ( $P_{Na}/P_K = 1.6$ ) (de Weille *et al.*, 1998; Babinski *et al.*, 1999). The reducing agents dithiothreitol (DTT) and glutathione (GSH) increase ASIC1a currents expressed in CHO cells and ASIC-like currents in sensory ganglia and central neurons (Andrey *et al.*, 2005; Chu *et al.*, 2006) whereas oxidation, through the formation of intersubunit disulphide bonds, reduces currents mediated by ASIC1a (Zha *et al.*, 2009). ASIC1a is also irreversibly modulated by extracellular serine proteases, such as trypsin, through proteolytic cleavage (Vukicevic *et al.*, 2006). Non-steroidal anti-inflammatory drugs (NSAIDs) are direct blockers of ASIC currents at therapeutic concentrations (reviewed by Voilley, 2004). Extracellular Zn<sup>2+</sup> potentiates proton activation of homomeric and heteromeric channels incorporating ASIC2a, but not homomeric ASIC1a or ASIC3 channels (Baron *et al.*, 2001). However, removal of contaminating Zn<sup>2+</sup> by chelation reveals a high affinity block of homomeric ASIC1a and heteromeric ASIC1a+ASIC2 channels by Zn<sup>2+</sup> indicating complex biphasic actions of the divalent (Chu *et al.*, 2004). Nitric oxide potentiates submaximal currents activated by H<sup>+</sup> mediated by ASIC1a, ASIC1b, ASIC2a and ASIC3 (Cadiou *et al.*, 2007). Ammonium activates ASIC channels (most likely ASIC1a) in midbrain dopaminergic neurones: that may be relevant to neuronal disorders associated with hyperammonemia (Pidoplichko and Dani, 2006). The positive modulation of homomeric, heteromeric and native ASIC channels by the peptide FMRFamide and related substances, such as neuropeptides FF and SF, is reviewed in detail by Lingueglia *et al.* (2006). Inflammatory conditions and particular pro-inflammatory mediators induce overexpression of ASIC-encoding genes, enhance ASIC currents (Mamet *et al.*, 2002), and in the case of arachidonic acid directly activate the channel (Smith *et al.*, 2007; Deval *et al.*, 2008). The sustained current component mediated by ASIC3 is potentiated by hypertonic solutions in a manner that is synergistic with the effect of arachidonic acid (Deval *et al.*, 2008). Selective activation of ASIC3 by GMQ at a site separate from the proton binding site is potentiated by mild acidosis and reduced extracellular Ca<sup>2+</sup> (Yu *et al.*, 2010).

**Abbreviations:** A-317567 C-[6-[2-(1-Isopropyl-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-cyclopropyl]-naphthalen-2-yl]-methanedi-amine, EIPA, ethylisopropylamiloride; GMQ, 2-guanidine-4-methylquinazoline; FMRFamide, Phe-Met-Arg-Phe-amide; Neuropeptide FF, Phe-Leu-Phe-Gln-Pro-Gln-Arg-Phe-amide; Neuropeptide SF, Ser-Leu-Ala-Pro-Gln-Arg-Phe-amide

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# Aquaporins

**Overview:** Aquaporins and aquaglyceroporins are membrane channels that allow the permeation of water and certain other small solutes across the cell membrane. Since the isolation and cloning of the first aquaporin (AQP1) (Preston *et al.*, 1992), 12 additional members of the family have been identified, although little is known about the functional properties of two of these (AQP11 (ENSG00000178301) and AQP12 (ENSG00000184945)). The other 11 aquaporins can be divided into two families (aquaporins and aquaglyceroporins) depending on whether they are permeable to glycerol (King *et al.*, 2004). One or more members of this family of proteins have been found to be expressed in almost all tissues of the body. Individual AQP subunits have six transmembrane domains with an inverted symmetry between the first three and last three domains (Castle, 2005). Functional AQPs exist as tetramers but, unusually, each subunit contains a separate pore, so each channel has four pores.

| Nomenclature | AQP0             | AQP1                                    | AQP2             | AQP3                       |
|--------------|------------------|-----------------------------------------|------------------|----------------------------|
| Ensembl ID   | ENSG00000135517  | ENSG00000240583                         | ENSG00000167580  | ENSG00000165272            |
| Activators   | –                | cGMP                                    | –                | –                          |
| Inhibitors   | Hg <sup>2+</sup> | Hg <sup>2+</sup> , TEA, Ag <sup>+</sup> | Hg <sup>2+</sup> | Hg <sup>2+</sup> , acid pH |
| Permeability | Water (low)      | Water (high)                            | Water (high)     | Water (high), glycerol     |

| Nomenclature | AQP4            | AQP5             | AQP6                | AQP7                   |
|--------------|-----------------|------------------|---------------------|------------------------|
| Ensembl ID   | ENSG00000171885 | ENSG00000161798  | ENSG00000086159     | ENSG00000165269        |
| Activators   | –               | –                | Acid pH             | –                      |
| Inhibitors   | PKC activation  | Hg <sup>2+</sup> | Hg <sup>2+</sup>    | Hg <sup>2+</sup>       |
| Permeability | Water (high)    | Water (high)     | Water (low), anions | Water (high), glycerol |

| Nomenclature | AQP8             | AQP9                         | AQP10                 |
|--------------|------------------|------------------------------|-----------------------|
| Ensembl ID   | ENSG00000103375  | ENSG00000103569              | ENSG00000143595       |
| Activators   | –                | –                            | –                     |
| Inhibitors   | Hg <sup>2+</sup> | Hg <sup>2+</sup> , phloretin | Hg <sup>2+</sup>      |
| Permeability | Water (high)     | Water (low), glycerol        | Water (low), glycerol |

AQP6 is an intracellular channel permeable to anions as well as water (Yasui *et al.* 1999).

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# Calcium (voltage-gated)

**Overview:** Calcium ( $\text{Ca}^{2+}$ ) channels are voltage-gated ion channels present in the membrane of most excitable cells. The nomenclature for  $\text{Ca}^{2+}$  channels was proposed by Ertel *et al.* (2000) and approved by the NC-IUPHAR subcommittee on  $\text{Ca}^{2+}$  channels (Catterall *et al.*, 2005).  $\text{Ca}^{2+}$  channels form hetero-oligomeric complexes. The  $\alpha 1$  subunit is pore-forming and provides the extracellular binding site(s) for practically all agonists and antagonists. The 10 cloned  $\alpha$ -subunits can be grouped into three families: (1) the high-voltage activated dihydropyridine-sensitive (L-type,  $\text{Ca}_v1.x$ ) channels; (2) the high-voltage activated dihydropyridine-insensitive ( $\text{Ca}_v2.x$ ) channels and (3) the low-voltage-activated (T-type,  $\text{Ca}_v3.x$ ) channels. Each  $\alpha 1$  subunit has four homologous repeats (I–IV), each repeat having six transmembrane domains and a pore-forming region between transmembrane domains S5 and S6. Gating is thought to be associated with the membrane-spanning S4 segment, which contains highly conserved positive charges. Many of the  $\alpha 1$ -subunit genes give rise to alternatively spliced products. At least for high-voltage activated channels, it is likely that native channels comprise co-assemblies of  $\alpha 1$ ,  $\beta$  and  $\alpha 2$ - $\delta$  subunits. The  $\gamma$  subunits have not been proven to associate with channels other than  $\alpha 1$ s. The  $\alpha 2$ - $\delta 1$  and  $\alpha 2$ - $\delta 2$  subunits bind gabapentin and pregabalin.

| Nomenclature               | $\text{Ca}_v1.1$                                                                 | $\text{Ca}_v1.2$                                                                | $\text{Ca}_v1.3$                                                                | $\text{Ca}_v1.4$                                                              | $\text{Ca}_v2.1$                                                                                                                                             |
|----------------------------|----------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Alternative names          | L-type, $\alpha_{1S}$ , skeletal muscle L                                        | L-type, $\alpha_{1C}$ , cardiac or smooth muscle L                              | L-type, $\alpha_{1D}$                                                           | L-type, $\alpha_{1F}$                                                         | P-type, Q-type, $\alpha_{1A}$                                                                                                                                |
| Ensembl ID                 | ENSG00000081248                                                                  | ENSG00000151067                                                                 | ENSG00000157388                                                                 | ENSG00000102001                                                               | ENSG00000141837                                                                                                                                              |
| Activators                 | (-)-(S)-BayK8644<br>SZ(+)-(S)-202-791<br>FPL64176                                | (-)-(S)-BayK8644<br>SZ(+)-(S)-202-791<br>FPL64176                               | (-)-(S)-BayK8644                                                                | (-)-(S)-BayK8644                                                              |                                                                                                                                                              |
| Blockers                   | dihydropyridine antagonists, e.g. nifedipine, diltiazem, verapamil, calciseptine | dihydropyridine antagonists, e.g. nifedipine diltiazem, verapamil, calciseptine | Less sensitive to dihydropyridine antagonists verapamil                         | Less sensitive to dihydropyridine antagonists                                 | $\omega$ -Agatoxin IVA (P: $\text{IC}_{50} \sim 1 \text{ nM}$ ) (Q: $\text{IC}_{50} \sim 90 \text{ nM}$ ) $\omega$ -Agatoxin IVB, $\omega$ -Conotoxin, MVIIC |
| Functional characteristics | High voltage-activated, slow inactivation                                        | High voltage-activated, slow inactivation ( $\text{Ca}^{2+}$ dependent)         | Low-moderate voltage-activated, slow inactivation ( $\text{Ca}^{2+}$ dependent) | Moderate voltage-activated, slow inactivation ( $\text{Ca}^{2+}$ independent) | Moderate voltage-activated, moderate inactivation                                                                                                            |

| Nomenclature               | $\text{Ca}_v2.2$                                    | $\text{Ca}_v2.3$                                               | $\text{Ca}_v3.1$                                                | $\text{Ca}_v3.2$                                                 | $\text{Ca}_v3.3$                                                |
|----------------------------|-----------------------------------------------------|----------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------------------------------------|-----------------------------------------------------------------|
| Alternative names          | N-type, $\alpha_{1B}$                               | R-type, $\alpha_{1E}$                                          | T-type, $\alpha_{1G}$                                           | T-type, $\alpha_{1H}$                                            | T-type, $\alpha_{1I}$                                           |
| Ensembl ID                 | ENSG00000148408                                     | ENSG00000198216                                                | ENSG00000006283                                                 | ENSG00000196557                                                  | ENSG00000100346                                                 |
| Blockers                   | $\omega$ -Conotoxin GVIA, $\omega$ -Conotoxin MVIIC | SNX482 (may not be completely specific), high $\text{Ni}^{2+}$ | Mibefradil, low sens. to $\text{Ni}^{2+}$ , kurtoxin, SB-209712 | Mibefradil, high sens. to $\text{Ni}^{2+}$ , kurtoxin, SB-209712 | Mibefradil, low sens. to $\text{Ni}^{2+}$ , kurtoxin, SB-209712 |
| Functional characteristics | High voltage-activated, moderate inactivation       | Moderate voltage-activated, fast inactivation                  | Low voltage-activated, fast inactivation                        | Low voltage-activated, fast inactivation                         | Low voltage-activated, moderate inactivation                    |

In many cell types, P and Q current components cannot be adequately separated and many researchers in the field have adopted the terminology 'P/Q-type' current when referring to either component. Ziconotide (a synthetic peptide equivalent to  $\omega$ -conotoxin) has been approved for the treatment of chronic pain (Williams *et al.*, 2008).

**Abbreviations:** FPL64176, 2,5-dimethyl-4-[2(phenylmethyl)benzoyl]-H-pyrrole-3-carboxylate; SB-209712, (1,6-bis{1-[4-(3-phenylpropyl)piperidinyl]}hexane); (-)-(S)-BAYK8664, (-)-(S)-methyl-1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl)-pyridine-5-carboxylate; SNX482, 41 amino acid peptide-(GVDKAGCRYMFGGCSVNDCCPRLGCHSLFSYCAWDLTFSD); SZ(+)-(S)-202-791, isopropyl 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-5-nitro-3-pyridinecarboxylate

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# CatSper channels

**Overview:** CatSper channels (CatSper1-4; nomenclature as agreed by NC-IUPHAR, Clapham and Garbers, 2005) are putative 6TM, voltage-gated, calcium permeant channels that are presumed to assemble as a tetramer of  $\alpha$ -like subunits and mediate the current  $I_{\text{CatSper}}$ . In mammals, CatSper subunits are structurally most closely related to individual domains of voltage-activated calcium channels ( $\text{Ca}_v$ ) (Ren *et al.*, 2001). CatSper1 (Ren *et al.*, 2001), CatSper2 (Quill *et al.*, 2001) and CatSper3 and 4 (Lobley *et al.*, 2003; Lin *et al.*, 2005; Qi *et al.*, 2007), in common with a recently identified putative 2TM auxiliary CatSper $\beta$  protein (Liu *et al.*, 2007) and two putative 1TM associated CatSper $\gamma$  and CatSper $\delta$  proteins (Wang *et al.*, 2009; Chung *et al.*, 2011), are restricted to the testis and localised to the principle piece of sperm tail.

| Nomenclature               | CatSper1                                                                                                                                                                                                                                                                                                                                                                                    | CatSper2                          | CatSper3                          | CatSper4                          |
|----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| Ensembl ID                 | ENSG00000175294                                                                                                                                                                                                                                                                                                                                                                             | ENSG00000166762                   | ENSG00000152705                   | ENSG00000188782                   |
| Activators                 | Constitutively active, weakly facilitated by membrane depolarisation, strongly augmented by intracellular alkalinisation. In human, but not mouse, spermatozoa progesterone ( $\text{EC}_{50} \sim 8 \text{ nM}$ ) also potentiates the CatSper current ( $I_{\text{CatSper}}$ ).                                                                                                           | –                                 | –                                 | –                                 |
| Blockers                   | $\text{Cd}^{2+}$ (200 $\mu\text{M}$ ), $\text{Ni}^{2+}$ (300 $\mu\text{M}$ ), ruthenium red (10 $\mu\text{M}$ ), NNC55-0396 (2–10 $\mu\text{M}$ ), HC-056456 (20 $\mu\text{M}$ ), mibefradil (30 $\mu\text{M}$ )                                                                                                                                                                            | –                                 | –                                 | –                                 |
| Functional characteristics | Calcium selective ion channel ( $\text{Ba}^{2+} > \text{Ca}^{2+} > \text{Mg}^{2+} > \text{Na}^{+}$ ); quasilinear monovalent cation current in the absence of extracellular divalent cations; alkalinization shifts the voltage-dependence of activation towards negative potentials [ $V_{1/2}$ @ pH 6.0 = +87 mV (mouse); $V_{1/2}$ @ pH 7.5 = +11 mV (mouse) or pH 7.4 = +85 mV (human)] | Required for $I_{\text{CatSper}}$ | Required for $I_{\text{CatSper}}$ | Required for $I_{\text{CatSper}}$ |

CatSper channel subunits expressed singly, or in combination, fail to functionally express in heterologous expression systems (Ren *et al.*, 2001; Quill *et al.*, 2001). The properties of CatSper1 tabulated above are derived from whole cell voltage-clamp recordings comparing currents endogenous to spermatozoa isolated from the *corpus epididymis* of wild-type and *Catsper1*<sup>(-/-)</sup> mice (Kirichok *et al.*, 2006) and also mature human sperm (Lishko *et al.*, 2011; Strünker *et al.*, 2011).  $I_{\text{CatSper}}$  is also undetectable in the spermatozoa of *Catsper2*<sup>(-/-)</sup>, *Catsper3*<sup>(-/-)</sup>, or *Catsper4*<sup>(-/-)</sup> mice and CatSper 1 associates with CatSper 2, 3, or 4 in heterologous expression systems (Qi *et al.*, 2007). Moreover, targeted disruption of *Catsper1*, 2, 3, or 4 genes results in an identical phenotype in which spermatozoa fail to exhibit the hyperactive movement (whip-like flagellar beats) necessary for penetration of the egg *cumulus* and *zona pellucida* and subsequent fertilization. Such disruptions are associated with a deficit in alkalinization and depolarization-evoked  $\text{Ca}^{2+}$  entry into spermatozoa (Carlson *et al.*, 2003, 2005; Qi *et al.*, 2007). Thus, it is likely that the CatSper pore is formed by a heterotetramer of CatSper1-4 (Qi *et al.*, 2007) in association with the auxiliary subunits ( $\beta$ ,  $\gamma$ ,  $\delta$ ) that are also essential for function (Chung *et al.*, 2011). CatSper channels are required for the increase in intracellular  $\text{Ca}^{2+}$  concentration in sperm evoked by egg *zona pellucida* glycoproteins (Xia and Ren, 2009). The driving force for  $\text{Ca}^{2+}$  entry is principally determined by a mildly outwardly rectifying  $\text{K}^{+}$  channel (KSper) that, like CatSper, is activated by intracellular alkalinization (Navarro *et al.*, 2007). Mouse KSper is encoded by *mSlo3*, a protein detected only in testis (Navarro *et al.*, 2007; Martinez-Lopez *et al.*, 2009; Zeng *et al.*, 2011). In human sperm, such alkalinization may result from the activation of  $\text{H}_2\text{O}$ , a proton channel (Lishko and Kirichok, 2010). Mutations in CatSper are associated with syndromic and non-syndromic male infertility (Hildebrand *et al.*, 2010). In human ejaculated spermatozoa, progesterone (<50 nM) potentiates the CatSper current by a non-genomic mechanism and acts synergistically with intracellular alkalinization (Lishko *et al.*, 2011; Strünker *et al.*, 2011). In addition, certain prostaglandins (e.g.  $\text{PGF}_{1\alpha}$ ,  $\text{PGE}_1$ ) also potentiate CatSper mediated currents (Lishko *et al.*, 2011; Strünker *et al.*, 2011).

**Abbreviations:** HC-056456, (3,4-bis(2-thienylcarbonyl)-1,2,5-oxadiazole-2-ium-2-olate); NNC55-0396, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl cyclopropanecarboxylate

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# Chloride channels

**Overview:** Chloride channels are a functionally and structurally diverse group of anion selective channels involved in processes including the regulation of the excitability of neurones, skeletal, cardiac and smooth muscle, cell volume regulation, transepithelial salt transport, the acidification of internal and extracellular compartments, the cell cycle and apoptosis (reviewed by Duran *et al.*, 2010). Excluding the transmitter-gated GABA<sub>A</sub> and glycine receptors (see separate tables), well characterised chloride channels can be classified as certain members of the voltage-sensitive ClC subfamily, calcium-activated channels, high (maxi) conductance channels, the cystic fibrosis transmembrane conductance regulator (CFTR) and volume regulated channels (Verkman and Galletta, 2009). No official recommendation exists regarding the classification of chloride channels. Functional chloride channels that have been cloned from, or characterised within, mammalian tissues are listed with the exception of several classes of intracellular channels (e.g. CLIC) that are reviewed by Edwards and Kahl (2010).

**ClC-family:** The mammalian ClC family (reviewed by Chen, 2005; Dutzler, 2007; Jentsch, 2008; Accardi and Picollo, 2010; Duran *et al.*, 2010) contains 9 members that fall, on the basis of sequence homology, into three groups; ClC-1, ClC-2, hClC-Ka (rClC-K1) and hClC-Kb (rClC-K2); ClC-3 to ClC-5, and ClC-6 and -7. ClC-1 and ClC-2 are plasma membrane chloride channels. ClC-Ka and ClC-Kb are also plasma membrane channels (largely expressed in the kidney and inner ear) when associated with barttin (ENSG00000162399), a 320 amino acid 2TM protein (Estévez *et al.*, 2001). The localisation of the remaining members of the ClC family is likely to be predominantly intracellular *in vivo*, although they may traffic to the plasma membrane in overexpression systems. Numerous recent reports indicate that ClC-4, ClC-5, ClC-6 and ClC-7 (and by inference ClC-3) function as Cl<sup>-</sup>/H<sup>+</sup> antiporters (secondary active transport), rather than classical Cl<sup>-</sup> channels (Picollo and Pusch, 2005; Scheel *et al.*, 2005; Graves *et al.*, 2008; Neagoe *et al.*, 2010; Leisle *et al.*, 2011; reviewed by Pusch *et al.*, 2006 and Accardi and Picollo, 2010). Novarino *et al.* (2010) recently reported that the activity of ClC-5 as a Cl<sup>-</sup>/H<sup>+</sup> exchanger is important for renal endocytosis. Alternative splicing increases the structural diversity within the ClC family. The crystal structure of two bacterial ClC proteins has been described by Dutzler *et al.* (2002) and a eukaryotic ClC transporter (CmCLC) has recently been described at 3.5 Å resolution (Feng *et al.*, 2010). Each ClC subunit, with a complex topology of 18 intramembrane segments, contributes a single pore to a dimeric 'double-barrelled' ClC channel that contains two independently-gated pores, confirming the predictions of previous functional and structural investigations (reviewed by Chen, 2005; Pusch *et al.*, 2006; Dutzler, 2007; Jentsch, 2008). As found for ClC-4, ClC-5, ClC-6 and ClC-7, the prokaryotic ClC homologue (ClC-ec1) and CmCLC function as H<sup>+</sup>/Cl<sup>-</sup> antiporters, rather than as ion channels (Accardi and Miller, 2004; Feng *et al.*, 2010). The generation of monomers from dimeric ClC-ec1 has firmly established that each ClC subunit is a functional unit for transport and that cross-subunit interaction is not required for Cl<sup>-</sup>/H<sup>+</sup> exchange in ClC transporters (Robertson *et al.*, 2010).

| Nomenclature               | ClC-1                                                                                                                                                                                                                                                                                                                                                                                   | ClC-2                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | ClC-Ka                                                                                                                                                                                              | ClC-Kb                                                                                                                             |
|----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| Other names                | skeletal muscle Cl <sup>-</sup> channel                                                                                                                                                                                                                                                                                                                                                 | –                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | ClC-K1 (rodent)                                                                                                                                                                                     | ClC-K2 (rodent)                                                                                                                    |
| Ensembl ID                 | ENSG00000186544                                                                                                                                                                                                                                                                                                                                                                         | ENSG00000114859                                                                                                                                                                                                                                                                                                                                                                                                                                                                | ENSG00000186510                                                                                                                                                                                     | ENSG00000184908                                                                                                                    |
| Activators                 | Constitutively active                                                                                                                                                                                                                                                                                                                                                                   | Arachidonic acid, amidation, acid-activated omeprazole, lubiprostone (SPI-0211)                                                                                                                                                                                                                                                                                                                                                                                                | Constitutively active (when co-expressed with barttin)<br>Niflumic acid (10–1000 µM)                                                                                                                | Constitutively active (when co-expressed with barttin)<br>Niflumic acid (10–1000 µM)                                               |
| Blockers                   | S-(–)CPP, S-(–)CPB, 9-AC, Cd <sup>2+</sup> , Zn <sup>2+</sup> , niflumic acid, fenofibric acid                                                                                                                                                                                                                                                                                          | GaTx2 (apparent K <sub>D</sub> = 15 pM at -100 mV), NPPB, DPC, Cd <sup>2+</sup> , Zn <sup>2+</sup>                                                                                                                                                                                                                                                                                                                                                                             | 3-phenyl-CPP, DIDS, benzofuran derivatives, niflumic acid (>1 mM)                                                                                                                                   | 3-phenyl-CPP, DIDS, benzofuran derivatives                                                                                         |
| Functional characteristics | γ = 1–1.5 pS; voltage-activated (depolarization) (by fast gating of single protopores and a slower common gate allowing both pores to open simultaneously); inwardly rectifying; incomplete deactivation upon repolarization, ATP binding to cytoplasmic cystathionine β-synthetase related (CBS) domains inhibits ClC-1 (by closure of the common gate), depending on its redox status | γ = 2–3 pS; voltage-activated by membrane hyperpolarization by fast protopore and slow cooperative gating; channels only open negative to E <sub>Cl</sub> resulting in steady-state inward rectification; voltage-dependence modulated by permeant anions; activated by cell swelling, PKA, and weak extracellular acidosis; potentiated by SGK1; inhibited by phosphorylation by p34(cdc2)/cyclin B; cell surface expression and activity increased by association with Hsp90 | γ = 26 pS; linear current-voltage relationship except at very negative potentials; no time dependence; inhibited by extracellular protons (pK = 7.1); potentiated by extracellular Ca <sup>2+</sup> | Bidirectional rectification; no time dependence; inhibited by extracellular protons; potentiated by extracellular Ca <sup>2+</sup> |

|                            |                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature               | CIC-3                                                                                                                                                                                                                                                                 | CIC-4                                                                                                                                                                                                                                                                                                                                                                                                                            | CIC-5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Ensembl ID                 | ENSG00000109572                                                                                                                                                                                                                                                       | ENSG00000073464                                                                                                                                                                                                                                                                                                                                                                                                                  | ENSG00000171365                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Activators                 | –                                                                                                                                                                                                                                                                     | –                                                                                                                                                                                                                                                                                                                                                                                                                                | –                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Blockers                   | Phloretin (30 $\mu$ M); insensitive to DIDS and NPPB and tamoxifen (10 $\mu$ M)                                                                                                                                                                                       | Zn <sup>2+</sup> (50 $\mu$ M), Cd <sup>2+</sup> (68 $\mu$ M) (IC <sub>50</sub> values; Osteen and Mindell, 2008)                                                                                                                                                                                                                                                                                                                 | Insensitive to DIDS 1 mM), DPC (1 mM), 9-AC (2 mM), NPPB (0.5 mM), niflumic acid (1 mM)                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Functional characteristics | Cl <sup>−</sup> /H <sup>+</sup> antiporter (Matsuda <i>et al.</i> , 2008); pronounced outward rectification; slow activation, fast deactivation; activity enhanced by CaM kinase II; inhibited by intracellular Ins(3,4,5,6)P <sub>4</sub> and extracellular acidosis | Cl <sup>−</sup> /H <sup>+</sup> antiporter (2Cl <sup>−</sup> :1H <sup>+</sup> ) Picollo and Pusch, 2005; Scheel <i>et al.</i> , 2005; Alekov and Fahlke, 2009); extreme outward rectification; voltage-dependent gating with midpoint of activation at +73 mV (Orhan <i>et al.</i> , 2011); rapid activation and deactivation; inhibited by extracellular acidosis; non-hydrolytic nucleotide binding required for full activity | Cl <sup>−</sup> /H <sup>+</sup> antiporter (2Cl <sup>−</sup> :1H <sup>+</sup> ) (Picollo and Pusch, 2005; Scheel <i>et al.</i> , 2005; Zifarelli and Pusch, 2009; Smith and Lippiat, 2010); extreme outward rectification; voltage-dependent gating with midpoint of activation of 116.0 mV; rapid activation and deactivation; potentiated and inhibited by intracellular and extracellular acidosis, respectively; ATP binding to cytoplasmic cystathionine $\beta$ -synthetase related (CBS) domains activates CIC-5 |

|                            |                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                      |
|----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature               | CIC-6                                                                                                                                                                   | CIC-7                                                                                                                                                                                                                                                                                                                |
| Ensembl ID                 | ENSG00000011021                                                                                                                                                         | ENSG00000103249                                                                                                                                                                                                                                                                                                      |
| Activators                 | –                                                                                                                                                                       | Active when co-expressed with Ostm1                                                                                                                                                                                                                                                                                  |
| Blockers                   | DIDS (1 mM)                                                                                                                                                             | DIDS (40 $\mu$ M), NS5818 (52 $\mu$ M); NPPB (156 $\mu$ M) (IC <sub>50</sub> values ; Schulz <i>et al.</i> , 2010)                                                                                                                                                                                                   |
| Functional characteristics | Cl <sup>−</sup> /H <sup>+</sup> antiporter (2Cl <sup>−</sup> :1H <sup>+</sup> ) (Neagoe <i>et al.</i> , 2010); outward rectification, rapid activation and deactivation | Cl <sup>−</sup> /H <sup>+</sup> antiporter (2Cl <sup>−</sup> :1H <sup>+</sup> ) (Graves <i>et al.</i> , 2008; Schulz <i>et al.</i> , 2010; Leisle <i>et al.</i> , 2011); strong outward rectification; voltage-dependent gating with a threshold more positive than ~ + 20 mV; very slow activation and deactivation |

CIC channels display the permeability sequence Cl<sup>−</sup> > Br<sup>−</sup> > I<sup>−</sup> (at physiological pH). CIC-1 has significant opening probability at resting membrane potential, accounting for 75% of the membrane conductance at rest in skeletal muscle, and is important for stabilization of the membrane potential. S-(−)CPP, 9-AC and niflumic acid act intracellularly and exhibit a strongly voltage-dependent block with strong inhibition at negative voltages and relief of block at depolarized potentials (Liantonio *et al.*, 2007 and reviewed by Pusch *et al.*, 2002). Inhibition of CIC-2 by the peptide GaTx2, from *Leiurus quinquestriatus herbareus venom*, is likely to occur through inhibition of channel gating, rather than direct open channel blockade (Thompson *et al.*, 2009). Although CIC-2 can be activated by cell swelling, it does not correspond to the VRAC channel (see below). Alternative potential physiological functions for CIC-2 are reviewed by Planells-Cases and Jentsch (2009). Functional expression of human CIC-Ka and CIC-Kb requires the presence of barttin (Estévez *et al.*, 2001; Scholl *et al.*, 2006; reviewed by Fahlke and Fischer, 2010). The properties of CIC-Ka/barttin and CIC-Kb/barttin tabulated are those observed in mammalian expression systems: in oocytes the channels display time- and voltage-dependent gating. The rodent homologue (CIC-K1) of CIC-Ka demonstrates limited expression as a homomer, but its function is enhanced by barttin which increases both channel opening probability in the physiological range of potentials (Estévez *et al.*, 2001; Scholl *et al.*, 2006; Fischer *et al.*, 2010; reviewed by Fahlke and Fischer, 2010). CIC-Ka is approximately 5 to 6-fold more sensitive to block by 3-phenyl-CPP and DIDS than CIC-Kb, while newly synthesized benzofuran derivatives showed the same blocking affinity (<10  $\mu$ M) on both CIC-K isoforms (Liantonio *et al.* 2008). The biophysical and pharmacological properties of CIC-3, and the relationship of the protein to the endogenous volume-regulated anion channel(s) VRAC (see Guan *et al.*, 2006; Alekov and Fahlke, 2008) are controversial and further complicated by the possibility that CIC-3 may function as both a Cl<sup>−</sup>/H<sup>+</sup> exchanger and an ion channel (Picollo and Pusch, 2005; Wang *et al.*, 2006; Alekov and Fahlke, 2008). The functional properties tabulated are those most consistent with the close structural relationship between CIC-3, CIC-4 and CIC-5. Activation of heterologously expressed CIC-3 by cell swelling in response to hypotonic solutions is disputed, as are many other aspects of its regulation. Dependent upon the predominant extracellular anion (*e.g.* SCN<sup>−</sup> versus Cl<sup>−</sup>), CIC-4 can operate in two transport modes: a slippage mode in which behaves as an ion channel and an exchanger mode in which unitary transport rate is 10-fold lower (Alekov and Fahlke, 2009). Similar findings have been made for CIC-5 (Zdebek *et al.* 2008). CIC-7 associates with a  $\beta$  subunit, Ostm1, which increases the stability of the former (Lange *et al.*, 2006) and is essential for its function (Leisle *et al.*, 2011).

**CFTR:** CFTR, a 12TM, ABC transporter-type protein (see Page S214), is a cAMP-regulated epithelial cell membrane Cl<sup>−</sup> channel involved in normal fluid transport across various epithelia. Of the 1700 mutations identified in CFTR, the most common is the deletion mutant  $\Delta$ F508 (a class 2 mutation) which results in impaired trafficking of CFTR and reduces its incorporation into the plasma membrane causing cystic fibrosis (reviewed by Cuthbert, 2011). Channels carrying the  $\Delta$ F508 mutation that do traffic to the plasma membrane demonstrate gating defects. Thus, pharmacological restoration the function of the  $\Delta$ F508 mutant would require a compound that embodies 'corrector' (*i.e.* facilitates folding and trafficking to the cell surface) and 'potentiator' (*i.e.* promotes opening of channels at the cell surface) activities (see Cuthbert, 2011). In addition to acting as an anion channel *per se*, CFTR may act as a regulator of several other conductances including inhibition of the epithelial Na channel (ENaC), calcium activated chloride channels (CaCC) and volume regulated anion channel (VRAC), activation of the outwardly rectifying chloride channel (ORCC), and enhancement of the sulphonylurea sensitivity of the renal outer medullary potassium channel (ROMK2), (reviewed by Nilius and Droogmans, 2003). CFTR also regulates TRPV4, which provides the Ca<sup>2+</sup> signal for regulatory volume decrease in airway epithelia (Arniges *et al.*, 2004). The activities of CFTR and the chloride-bicarbonate exchangers SLC26A3 (DRA) and SLC26A6 (PAT1) are mutually enhanced by a physical association between the regulatory (R) domain of CFTR and the STAS domain of the SCL26 transporters, an effect facilitated by PKA-mediated phosphorylation of the R domain of CFTR (Ko *et al.*, 2004).

|                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature               | CFTR                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Other names                | ABCC7                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Ensembl ID                 | ENSG00000001626                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Potentiators               | VX-770, flavones (e.g. UCCF-339, UCCF-029, apigenin, genistein), benzimidazolones (e.g. UCCF-853, NS004), benzoquinolines (e.g. CBIQ), 1,4-dihydropyridines (e.g. felopidine, nimodipine), capsaicin, phenylglycines (e.g. 2-[(2-1 <i>H</i> -indol-3-yl-acetyl)-methylamino]- <i>N</i> -(4-isopropylphenyl)-2-phenylacetamide), sulfonamides (e.g. 6-(ethylphenylsulfamoyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid cycloheptylamide)                                             |
| Blockers                   | GaTx-1, GlyH-101 (extracellular application causes channel block), CFTR <sub>inh</sub> -172 (intracellular application prolongs mean closed time), malonic acid hydrazide conjugates (see Verkman and Galletta, 2009), glibenclamide (non-selective)                                                                                                                                                                                                                                   |
| Functional characteristics | $\gamma = 6-10$ pS; permeability sequence = $\text{Br}^- \geq \text{Cl}^- > \text{I}^- > \text{F}^-$ ; ( $P_{\text{I}}/P_{\text{Cl}} = 0.1-0.85$ ); slight outward rectification; phosphorylation necessary for activation by ATP binding at binding nucleotide binding domains (NBD)1 and 2; positively regulated by PKC and PKGII (tissue specific); regulated by several interacting proteins including syntaxin 1A, Munc18 and PDZ domain proteins such as NHERF (EBP50) and CAP70 |

In addition to the agents listed in the table, the novel small molecule, ataluren, induces translational read through of nonsense mutations in CFTR (reviewed by Sloane and Rowe, 2010). Corrector compounds that aid the folding of  $\Delta F508$ CFTR to increase the amount of protein expressed and potentially delivered to the cell surface include VX-532 (which is also a potentiator), VRT-325, KM11060, Corr-3a and Corr-4a (see Verkman and Galletta (2009) for details and structures of Corr-3a and Corr-4a). Inhibition of CFTR by intracellular application of the peptide GaTx1, from *Leiurus quinquestriatus herbareus venom*, occurs preferentially for the closed state of the channel (Fuller *et al.*, 2007). CFTR contains two cytoplasmic nucleotide binding domains (NBDs) that bind ATP. A single open-closing cycle is hypothesised to involve, in sequence: binding of ATP at the N-terminal NBD1, ATP binding to the C-terminal NBD2 leading to the formation of an intramolecular NBD1-NBD2 dimer associated with the open state, and subsequent ATP hydrolysis at NBD2 facilitating dissociation of the dimer and channel closing, and the initiation of a new gating cycle (Aleksandrov *et al.*, 2007; Muallem and Vergani, 2009). Phosphorylation by PKA at sites within a cytoplasmic regulatory (R) domain facilitates the interaction of the two NBD domains. PKC (and PKGII within intestinal epithelial cells *via* guanylin-stimulated cGMP formation) positively regulate CFTR activity.

**Calcium activated chloride channel:** Chloride channels activated by intracellular calcium (CaCC) are widely expressed in excitable and non-excitable cells where they perform diverse functions (Hartzell *et al.*, 2005). The molecular nature of CaCC has been uncertain with both *CLCA*, *TWEETY* and *BEST* genes having been considered as likely candidates (Loewen and Forsyth, 2005; Hartzell *et al.*, 2008; Duran *et al.*, 2010). It is now accepted that *CLCA* expression products are unlikely to form channels *per se* and probably function as cell adhesion proteins, or are secreted (Patel *et al.*, 2009). Similarly, *TWEETY* gene products do not recapitulate the properties of endogenous CaCC. The bestrophins encoded by genes *BEST1-4* have a topology more consistent with ion channels (see Hartzell *et al.*, 2008) and form chloride channels that are activated by physiological concentrations of  $\text{Ca}^{2+}$ , but whether such activation is direct is not known (Hartzell *et al.*, 2008). However, currents generated by bestrophin over-expression do not resemble native CaCC currents. The evidence for and against bestrophin proteins forming CaCC is critically reviewed by Duran *et al.* (2010). Recently, a new gene family, TMEM16 (anoctamin) consisting of 10 members (TMEM16A-K; anoctamin 1–10) has been identified and there is firm evidence that some of these members form chloride channels (Duran and Hartzell, 2011; Kunzelmann *et al.*, 2011). TMEM16A (anoctamin 1; Ano 1) produces  $\text{Ca}^{2+}$ -activated  $\text{Cl}^-$  currents with kinetics similar to native CaCC currents recorded from different cell types (Caputo *et al.*, 2008; Schroeder *et al.*, 2008; Yang *et al.*, 2008; Rock *et al.*, 2009). Knockdown of TMEM16A greatly reduces currents mediated by calcium-activated chloride channels in submandibular gland cells (Yang *et al.*, 2008) and smooth muscle cells from pulmonary artery (Manoury *et al.*, 2010). In TMEM16A<sup>(-/-)</sup> mice secretion of  $\text{Ca}^{2+}$ -dependent  $\text{Cl}^-$  secretion by several epithelia is reduced (Ousingsawat *et al.*, 2009; Rock *et al.*, 2009). Alternative splicing regulates the voltage- and  $\text{Ca}^{2+}$ -dependence of TMEM16A and such processing may be tissue-specific manner and thus contribute to functional diversity (Ferrera *et al.*, 2009). There are also reports that TMEM16B (anoctamin 2; Ano 2) supports CaCC activity (e.g. Pifferi *et al.*, 2009) and in TMEM16B<sup>(-/-)</sup> mice Ca-activated  $\text{Cl}^-$  currents in the main olfactory epithelium (MOE) and in the vomeronasal organ are virtually absent (Billig *et al.*, 2011).

|                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature               | CaCC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Other names                | $\text{Ca}^{2+}$ -activated $\text{Cl}^-$ channel                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Activators                 | intracellular $\text{Ca}^{2+}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Blockers                   | niflumic acid, flufenamic acid, DCDPC, DIDS, SITS, NPPB, A-9-C, Ins(3,4,5,6)P <sub>4</sub> , mibefradil, fluoxetine, tannic acid                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Functional characteristics | $\gamma = 0.5-5$ pS; permeability sequence, $\text{SCN}^- > \text{NO}_3^- > \text{I}^- > \text{Br}^- > \text{Cl}^- > \text{F}^-$ ; relative permeability of $\text{SCN}^-:\text{Cl}^- \sim 8$ . $\text{I}^-:\text{Cl}^- \sim 3$ , aspartate: $\text{Cl}^- \sim 0.15$ , outward rectification (decreased by increasing $[\text{Ca}^{2+}]_i$ ); sensitivity to activation by $[\text{Ca}^{2+}]_i$ decreased at hyperpolarized potentials; slow activation at positive potentials (accelerated by increasing $[\text{Ca}^{2+}]_i$ ); rapid deactivation at negative potentials, deactivation kinetics modulated by anions binding to an external site; modulated by redox status |

Blockade of  $\text{I}_{\text{Cl(Ca)}}$  by niflumic acid, DIDS and 9-AC is voltage-dependent whereas block by NPPB is voltage-independent (Hartzell *et al.*, 2005). Extracellular niflumic acid; DCDPC and A-9-C (but not DIDS) exert a complex effect upon  $\text{I}_{\text{Cl(Ca)}}$  in vascular smooth muscle, enhancing and inhibiting inwardly and outwardly directed currents in a manner dependent upon  $[\text{Ca}^{2+}]_i$  (see Leblanc *et al.*, 2005 for summary). Considerable crossover in pharmacology with large conductance  $\text{Ca}^{2+}$ -activated  $\text{K}^+$  channels also exists (see Greenwood and Leblanc, 2007 for overview). Two novel compounds, CaCC<sub>inh</sub>-A01 and CaCC<sub>inh</sub>-B01 have recently been identified as blockers of calcium-activated chloride channels in T84 human intestinal epithelial cells (see De La Fuente *et al.* (2008) for structures). Significantly, other novel compounds totally block currents mediated by TMEM16A, but have only a modest effect upon total current mediated by CaCC native to T84 cells or human bronchial epithelial cells, suggesting that TMEM16A is not the predominant CaCC in such cells (Namkung *et al.*, 2011). CaMKII modulates CaCC in a tissue dependent manner (reviewed by Hartzell *et al.*, 2005; Leblanc *et al.*, 2005). CaMKII inhibitors block activation of  $\text{I}_{\text{Cl(Ca)}}$  in T<sub>84</sub> cells but have no effect in parotid acinar cells. In tracheal and arterial smooth muscle cells, but not portal vein myocytes, inhibition of CaMKII reduces inactivation of  $\text{I}_{\text{Cl(Ca)}}$ . Intracellular Ins(3,4,5,6)P<sub>4</sub> may act as an endogenous negative regulator of CaCC channels activated by  $\text{Ca}^{2+}$ , or CaMKII. Smooth muscle CaCC are also regulated positively by  $\text{Ca}^{2+}$ -dependent phosphatase, calcineurin (see Leblanc *et al.*, 2005 for summary).

**Maxi chloride channel:** Maxi  $\text{Cl}^-$  channels are high conductance, anion selective, channels initially characterised in skeletal muscle and subsequently found in many cell types including neurones, glia, cardiac muscle, lymphocytes, secreting and absorbing epithelia, macula densa cells of the kidney and human placenta syncytiotrophoblasts (Sabirov and Okada, 2009). The physiological significance of the maxi  $\text{Cl}^-$  channel is uncertain, but roles in cell volume regulation and apoptosis have been claimed. Evidence suggests a role for maxi  $\text{Cl}^-$  channels as a conductive pathway in the swelling-induced release of ATP from mouse mammary C127i cells that may be important for autocrine and paracrine signalling by purines (Sabirov *et al.*, 2001; Dutta *et al.*, 2002). A similar channel mediates ATP release from macula densa cells within the thick ascending of the loop of Henle in response to changes in luminal NaCl concentration (Bell *et al.*, 2003). A family of human high conductance  $\text{Cl}^-$  channels (TTYH1-3) that resemble Maxi  $\text{Cl}^-$  channels has been cloned (Suzuki and Mizuno, 2004), but alternatively, Maxi  $\text{Cl}^-$  channels have also been suggested to correspond to the voltage-dependent anion channel, VDAC, expressed at the plasma membrane (Bahamonde *et al.*, 2003; Okada *et al.*, 2004).

|                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature               | Maxi $\text{Cl}^-$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Other names                | High conductance anion channel, volume- and voltage-dependent ATP-conductive large conductance (VDACL) anion channel                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Activators                 | G-protein-coupled receptors, cytosolic GTP $\gamma$ S, extracellular triphenylethylene anti-oestrogens (tamoxifen, toremifene), extracellular chlorpromazine and trifluorpromazine, cell swelling                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Blockers                   | SITS, DIDS, NPPB, DPC, intracellular arachidonic acid, extracellular $\text{Zn}^{2+}$ and $\text{Gd}^{3+}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Functional characteristics | $\gamma = 280\text{--}430$ pS (main state); permeability sequence, $\text{I} > \text{Br} > \text{Cl} > \text{F} > \text{gluconate}$ ( $\text{P}_{\text{Cl}}/\text{P}_{\text{F}} = \sim 1.5$ ); ATP is a voltage dependent permeant blocker of single channel activity ( $\text{P}_{\text{ATP}}/\text{P}_{\text{Cl}} = 0.08\text{--}0.1$ ); channel activity increased by patch-excision; channel opening probability (at steady-state) maximal within approximately $\pm 20$ mV of 0 mV, opening probability decreased at more negative and (commonly) positive potentials yielding a bell-shaped curve; channel conductance and opening probability regulated by annexin 6 |

Differing ionic conditions may contribute to variable estimates of  $\gamma$  reported in the literature. Inhibition by arachidonic acid (and cis-unsaturated fatty acids) is voltage-independent, occurs at an intracellular site, and involves both channel shut down ( $K_d = 4\text{--}5$   $\mu\text{M}$ ) and a reduction of  $\gamma$  ( $K_d = 13\text{--}14$   $\mu\text{M}$ ). Blockade of channel activity by SITS, DIDS,  $\text{Gd}^{3+}$  and arachidonic acid is paralleled by decreased swelling-induced release of ATP (Sabirov *et al.*, 2001; Dutta *et al.*, 2002). Channel activation by anti-oestrogens in whole cell recordings requires the presence of intracellular nucleotides and is prevented by pre-treatment with  $17\beta$ -oestradiol, dibutyl cAMP, or intracellular dialysis with GDP $\beta$ S (Diaz *et al.*, 2001). Activation by tamoxifen is suppressed by low concentrations of okadaic acid, suggesting that a dephosphorylation event by protein phosphatase PP2A occurs in the activation pathway (Diaz *et al.*, 2001). In contrast,  $17\beta$ -estradiol and tamoxifen appear to directly inhibit the maxi  $\text{Cl}^-$  channel of human placenta reconstituted into giant liposomes and recorded in excised patches (Riquelme, 2009).

**Volume regulated chloride channels:** Volume activated chloride channels (also termed VSOAC, volume-sensitive organic osmolyte/anion channel; VRC, volume regulated channel and VSOR, volume expansion-sensing outwardly rectifying anion channel) participate in regulatory volume decrease (RVD) in response to cell swelling. VRAC may also be important for several other processes including the regulation of membrane excitability, transcellular  $\text{Cl}^-$  transport, angiogenesis, cell proliferation, necrosis, apoptosis, glutamate release from astrocytes, insulin release from pancreatic  $\beta$  cells and resistance to the anti-cancer drug, cisplatin (reviewed by Nilius and Droogmans, 2003; Mulligan and MacVicar, 2006; Okada *et al.*, 2009; Best *et al.*, 2010). VRAC may not be a single entity, but may instead represent a number of different channels that are expressed to a variable extent in different tissues and are differentially activated by cell swelling. In addition to CIC-3 expression products (see above) several former VRAC candidates including MDRL P-glycoprotein, Icln, Band 3 anion exchanger and phospholemman are also no longer considered likely to fulfil this function (see reviews by Nilius and Droogmans, 2003; Sardini *et al.*, 2003).

|                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature               | VRAC (volume regulated anion channel), VSOAC (volume-sensitive organic osmolyte/anion channel), VRC (volume regulated channel), VSOR (volume expansion-sensing outwardly rectifying anion channel)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Activators                 | cell swelling; low intracellular ionic strength; GTP $\gamma$ S                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Blockers                   | NS3728, DCPIB, clomiphene, nafoxidine, mefloquine, tamoxifen, gossypol, arachidonic acid, mibefradil, NPPB, quinine, quinidine, chromones, NDGA, A-9-C, DIDS, 1,9-dideoxyforskolin, oxalon dye (diBA-(5)-C4), carbenoxolone, IAA-94, extracellular nucleotides, nucleoside analogues, intracellular $\text{Mg}^{2+}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Functional characteristics | $\gamma = 10\text{--}20$ pS (negative potentials), $50\text{--}90$ pS (positive potentials); permeability sequence $\text{SCN} > \text{I} > \text{NO}_3^- > \text{Br}^- > \text{Cl}^- > \text{F}^- > \text{gluconate}$ ; outward rectification due to voltage dependence of $\gamma$ ; inactivates at positive potentials in many, but not all, cell types; time dependent inactivation at positive potentials; intracellular ionic strength modulates sensitivity to cell swelling and rate of channel activation; rate of swelling-induced activation is modulated by intracellular ATP concentration; ATP dependence is independent of hydrolysis and modulated by rate of cell swelling; inhibited by increased intracellular free $\text{Mg}^{2+}$ concentration; swelling induced activation of several intracellular signalling cascades may be permissive of, but not essential to, the activation of VRAC including: the Rho-Rho kinase-MLCK; Ras-Raf-MEK-ERK; PIK3-NOX- $\text{H}_2\text{O}_2$ and Src-PLC $\gamma$ - $\text{Ca}^{2+}$ pathways; regulation by PKC $\alpha$ required for optimal activity; cholesterol depletion enhances activity; activated by direct stretch of $\beta 1$ -integrin |

In addition to conducting monovalent anions, in many cell types the activation of VRAC by a hypotonic stimulus can allow the efflux of organic osmolytes such as amino acids and polyols that may contribute to RVD.

**Other chloride channels:** In addition to some intracellular chloride channels that are not considered here, plasma membrane channels other than those listed have been functionally described. Many cells and tissues contain outwardly rectifying chloride channels (ORCC) that may correspond to VRAC active under isotonic conditions. A cAMP-activated  $\text{Cl}^-$  channel that does not correspond to CFTR has been described in intestinal Paneth cells (Tsumura *et al.*, 1998). A  $\text{Cl}^-$  channel activated by cGMP with a dependence on raised intracellular  $\text{Ca}^{2+}$  has been recorded in various vascular smooth muscle cells types, which has a pharmacology and biophysical characteristics very different from the 'conventional'

CaCC (see Matchkov *et al.*, 2004; Piper and Large, 2004). It has been proposed that bestrophin-3 is an essential component of the cGMP-activated channel (Matchkov *et al.*, 2008). A proton-activated, outwardly rectifying anion channel has also been described (Lambert and Oberwinkler, 2005).

**Abbreviations:** A-9-C, anthracene-9-carboxylic acid; CBIQ, 4-chlorobenzo[F]isoquinoline; CFTR<sub>inh</sub>-172, 3-[(3-trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone; S-(-)CPP, S-(-)-2-(4-chlorophenoxy)propionic acid; S-(-)CPB, S-(-)-2-(4-chlorophenoxy)butyric acid; DCPIB, 4-(2-butyl-6,7-dichloro-2-cyclopentyl-indan-1-on-5-yl) oxybutyric acid; diBA-(5)-C4, bis-(1,3-dibutylbarbituric acid)pentamethine oxanol; DIDS, 4,4'-diisothiocyanostilbene-2,2'-disulphonic acid; DNDS, 4,4'-dinitrostilbene-2,2'-disulphonic acid; GlyH-101, N-(2-naphthalenyl)-[(3,5-dibromo-2,4-dihydroxyphenyl)methylene]glycine hydrazide; IAA-94, indanyloxyacetic acid 94; NDGA, nordihydroguaric acid; DPC, diphenylamine carboxylic acid; DPDP, dichloro-diphenylamine 2-carboxylic acid; KM11060, 7-chloro-4-[4-[(4-chlorophenyl)sulfonyl]piperazino]quinoline; NPA, N-phenylanthracilic acid; NPPB, 5-nitro-2-(3-phenylpropylamino)benzoic acid; NS004, 5-trifluoromethyl-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-2H-benzimidazole-2-one; NS3728, N-[3,5-bis(trifluoromethyl)-phenyl]-N'[4-bromo-2-(1H-tetrazol-5-yl)-phenyl]urea; NS5818, N-(3,5-dichloro-phenyl)-N'-[2-(1H-tetrazol-5-yl)-biphenyl-4-yl-4'-carboxylic acid dimethylamide] urea; SITS, 4'-isothiocyanostilbene-2,2'-disulphonic acid; UCCF-029, 2-(4-pyridinium)benzo[h]4H-chromen-4-one bisulfate; UCCF-180, 3-(3-butynyl)-5-methoxy-1-phenylpyrazole-4-carbaldehyde; UCCF-853, 1-(3-chlorophenyl)-5-trifluoromethyl-3-hydroxybenzimidazol-2-one, VRT-325, 4-cyclohexyloxy-2-[1-[4-(4-methoxy-benzenesulfonyl)piperazin-1-yl]ethyl]quinazoline VX-532, 4-methyl-2-(5-phenyl-1H-pyrazol-3-yl)-phenol; VX-770, N-(2,4-Di-*tert*-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide

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# Connexins and pannexins

**Overview:** Gap junctions are essential for many physiological processes including cardiac and smooth muscle contraction, regulation of neuronal excitability and epithelial electrolyte transport (see Evans and Martin 2002, Bruzzone *et al.*, 2003, Connors and Long 2004). Gap junction channels allow the passive diffusion of molecules of up to 1,000 Daltons which can include nutrients, metabolites and second messengers (such as IP<sub>3</sub>) as well as cations and anions. 21 connexin genes (Cx23, Cx25, Cx26, Cx30, Cx30.2, Cx30.3, Cx31, Cx31.1, Cx31.9, Cx32, Cx36, Cx37, Cx40, Cx40.1, Cx43, Cx45, Cx46, Cx47, Cx50, Cx59, Cx62) and 3 pannexin genes (Px1, Px2, Px3; which are structurally related to the invertebrate innexin genes) code for gap junction proteins in humans. Each connexin gap junction comprises 2 hemichannels or 'connexons' which are themselves formed from 6 connexin molecules. The various connexins have been observed to combine into both homomeric and heteromeric combinations, each of which may exhibit different functional properties. It is also suggested that individual hemichannels formed by a number of different connexins might be functional in at least some cells (see Herve *et al.*, 2007). Connexins have a common topology, with four  $\alpha$ -helical transmembrane domains, two extracellular loops, a cytoplasmic loop, and N- and C-termini located on the cytoplasmic membrane face. In mice, the most abundant connexins in electrical synapses in the brain seem to be Cx36, Cx45 and Cx57 (Sohl *et al.*, 2005). Mutations in connexin genes are associated with the occurrence of a number of pathologies, such as peripheral neuropathies, cardiovascular diseases and hereditary deafness. The pannexin genes Px1 and Px2 are widely expressed in the mammalian brain (Vogt *et al.*, 2005). Like the connexins, at least some of the pannexins can form hemichannels (Bruzzone *et al.*, 2003, Pelegrin and Surprenant, 2007).

|              | Connexins                                                                                                                              | Pannexins                                                                                  |
|--------------|----------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| Nomenclature | Cx23, Cx25, Cx26, Cx30, Cx30.2, Cx30.3, Cx31, Cx31.1, Cx31.9, Cx32, Cx36, Cx37, Cx40, Cx40.1, Cx43, Cx45, Cx46, Cx47, Cx50, Cx59, Cx62 | Px1, Px2, Px3                                                                              |
| Ensembl ID   | ENSG00000159248 (Cx36)*                                                                                                                | ENSG00000110218 (Px1)<br>ENSG00000073150 (Px2)<br>ENSG00000154143 (Px3)                    |
| Inhibitors   | carbenoxolone<br>flufenamic acid<br>octanol<br>raising external calcium                                                                | carbenoxolone<br>little block by flufenamic acid<br>unaffected by raising external calcium |

Connexins are most commonly named according to their molecular weights, so, for example, Cx23 is the connexin protein of 23 kDa. This can cause confusion when comparing between species – for example, the mouse connexin Cx57 is orthologous to the human connexin Cx62. No natural toxin or specific inhibitor of junctional channels has been identified yet however two compounds often used experimentally to block connexins are carbenoxolone and flufenamic acid (Salameh and Dhein, 2005). At least some pannexin hemichannels are more sensitive to carbenoxolone than connexins but much less sensitive to flufenamic acid (Bruzzone *et al.*, 2005). It has been suggested that 2-aminoethoxydiphenyl borate (2-APB) may be a more effective blocker of some connexin channel subtypes (Cx26, Cx30, Cx36, Cx40, Cx45, Cx50) compared to others (Cx32, Cx43, Cx46, Bai *et al.*, 2006).

\*Due to space constraints, the Ensembl ID for only Cx36 is given. Ensembl information for the other connexins can be found from links therein.

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# Cyclic nucleotide-gated channels

**Overview:** Cyclic nucleotide-gated (CNG) channels are responsible for signalling in the primary sensory cells of the vertebrate visual and olfactory systems. A standardised nomenclature for CNG channels has been proposed by the NC-IUPHAR subcommittee on voltage-gated ion channels (see Hofmann *et al.*, 2005).

CNG channels are voltage-independent cation channels formed as tetramers. Each subunit has 6TM, with the pore-forming domain between TM5 and TM6. CNG channels were first found in rod photoreceptors (Fesenko *et al.*, 1985; Kaupp *et al.*, 1989), where light signals through rhodopsin and transducin to stimulate phosphodiesterase and reduce intracellular cGMP level. This results in a closure of CNG channels and a reduced 'dark current'. Similar channels were found in the cilia of olfactory neurons (Nakamura and Gold, 1987) and the pineal gland (Dryer and Henderson, 1991). The cyclic nucleotides bind to a domain in the C terminus of the subunit protein: other channels directly binding cyclic nucleotides include HCN, eag and certain plant potassium channels.

| Nomenclature               | CNGA1                                                                            | CNGA2                                                                                  | CNGA3                                                                            |
|----------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Other names                | CNG1, CNG $\alpha$ 1, RCNC1                                                      | CNG2, CNG $\alpha$ 3, OCNC1                                                            | CNG3, CNG $\alpha$ 2, CCNC1                                                      |
| Ensembl ID                 | ENSG00000198515                                                                  | ENSG00000183862                                                                        | ENSG00000144191                                                                  |
| Activators                 | Intracellular cyclic nucleotides:<br>cGMP ( $EC_{50} \approx 30 \mu M$ ) >> cAMP | Intracellular cyclic nucleotides:<br>cGMP $\approx$ cAMP ( $EC_{50} \approx 1 \mu M$ ) | Intracellular cyclic nucleotides:<br>cGMP ( $EC_{50} \approx 30 \mu M$ ) >> cAMP |
| Inhibitors                 | L- <i>cis</i> diltiazem                                                          | –                                                                                      | L- <i>cis</i> diltiazem                                                          |
| Functional characteristics | $\gamma = 25\text{--}30 \text{ pS}$<br>$P_{Ca}/P_{Na} = 3.1$                     | $\gamma = 35 \text{ pS}$<br>$P_{Ca}/P_{Na} = 6.8$                                      | $\gamma = 40 \text{ pS}$<br>$P_{Ca}/P_{Na} = 10.9$                               |

CNGA1, CNGA2 and CNGA3 express functional channels as homomers. Three additional subunits CNGA4 (ENSG00000132259), CNGB1 (ENSG00000070729) and CNGB3 (ENSG00000170289) do not, and are referred to as auxiliary subunits. The subunit composition of the native channels is believed to be as follows. Rod: CNGA1<sub>3</sub>/CNGB1<sub>1</sub>; Cone: CNGA3<sub>2</sub>/CNGB3<sub>2</sub>; Olfactory neurons: CNGA2<sub>2</sub>/CNGA4/CNGB1<sub>1</sub> (Weitz *et al.*, 2002; Zheng *et al.*, 2002; Zhong *et al.*, 2002; Peng *et al.*, 2004; Zheng and Zagotta, 2004).

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# Epithelial sodium channels (ENaC)

**Overview:** The epithelial sodium channels (ENaC) mediates sodium reabsorption in the aldosterone-sensitive distal part of the nephron and the collecting duct of the kidney. ENaC is found on other tight epithelial tissues such as the airways, distal colon and exocrine glands. ENaC activity is tightly regulated in the kidney by aldosterone, angiotensin II, vasopressin, insulin and glucocorticoids; this fine regulation of ENaC is essential to maintain sodium balance between daily intake and urinary excretion of sodium, circulating volume and blood pressure. ENaC expression is also vital for clearance of foetal lung fluid, and to maintain air-surface-liquid. (Hummler *et al.*, 1996; Loffing and Korbmacher, 2009). Sodium reabsorption is suppressed by the 'potassium-sparing' diuretics amiloride and triamterene. ENaC is a heteromultimeric channel made of homologous  $\alpha$  and  $\gamma$  subunits. The primary structure of  $\alpha$ ENaC subunit was identified by expression cloning (Canessa *et al.*, 1993);  $\beta$  and  $\gamma$ ENaC were identified by functional complementation of the  $\alpha$  subunit (Canessa *et al.*, 1994). Each ENaC subunit contains 2 TM  $\alpha$  helices connected by a large extracellular loop and short cytoplasmic amino- and carboxy-termini. The stoichiometry of the epithelial sodium channel in the kidney and related epithelia is, by homology with the structurally related channel ASIC1a, thought to be a heterotrimer of  $1\alpha:1\beta:1\gamma$  subunits (Gonzales *et al.*, 2009).

|                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|--------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature                   | Epithelial sodium channel (ENaC)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Ensembl ID                     | Human $\alpha$ subunit, ENSG00000111319; human $\beta$ subunit, ENSG00000168447; human $\gamma$ subunit, ENSG00000166828; human $\delta$ subunit, ENSG00000162572                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Activators (EC <sub>50</sub> ) | S3969 (1.2 $\mu$ M) (Lu <i>et al.</i> , 2008)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Blockers (IC <sub>50</sub> )   | Amiloride (100-200 nM), benzamil (~10 nM), triamterene (~5 $\mu$ M) (Canessa <i>et al.</i> , 1994; Kellenberger <i>et al.</i> , 2003), P552-02 (7.6 nM; Hirsch <i>et al.</i> , 2008)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Functional characteristics     | $\gamma \approx 4-5$ pS, $P_{Na}/P_K > 20$ ; tonically open at rest; expression and ion flux regulated by circulating aldosterone-mediated changes in gene transcription. The action of aldosterone, which occurs in 'early' (1.5–3 h) and 'late' (6–24 hr) phases is competitively antagonised by spironolactone, its active metabolites and eplerenone. Glucocorticoids are important functional regulators in lung/airways and this control is potentiated by thyroid hormone; but the mechanism underlying such potentiation is unclear (Barker <i>et al.</i> , 1990; Sayegh, <i>et al.</i> , 1999; Richard <i>et al.</i> , 2004). The density of channels in the apical membrane, and hence $G_{Na}$ , can be controlled via both serum and glucocorticoid-regulated kinases (SGK1, 2 and 3) (Debonneville <i>et al.</i> , 2001; Friedrich <i>et al.</i> , 2003) and via cAMP/PKA (Morris and Schafer, 2002); and these protein kinases appear to act by inactivating Nedd4/2, a ubiquitin ligase that normally targets the ENaC channel complex for internalization and degradation (Debonneville <i>et al.</i> , 2001, Boarse <i>et al.</i> 2011). ENaC is constitutively activated by soluble and membrane-bound serine proteases, such as furin, prostatic (CAP1), plasmin and elastase (Planes and Caughey, 2007; Rotin and Schild, 2008; Kleyman <i>et al.</i> , 2009; Rossier and Stutts, 2009; Kitamura and Tomita, 2010). The activation of ENaC by proteases is blocked by a protein, SPLUNC1, secreted by the airways and which binds specifically to ENaC to prevent its cleavage (Garcia-Caballero <i>et al.</i> , 2009). Pharmacological inhibitors of proteases ( <i>e.g.</i> camostat acting upon prostatic) reduce the activity of ENaC (Maekawa <i>et al.</i> , 2009). Phosphatidylinositides such as $PI(4,5)P_2$ and $PI(3,4,5)P_3$ stabilise channel gating probably by binding to the $\beta$ and $\gamma$ ENaC subunits, respectively (Ma <i>et al.</i> , 2007; Pochynyuk <i>et al.</i> , 2008), whilst C terminal phosphorylation of $\beta$ and $\gamma$ -ENaC by ERK1/2 has been reported to inhibit the withdrawal of the channel complex from the apical membrane (Yang <i>et al.</i> , 2006). This effect may contribute to the cAMP-mediated increase in sodium conductance. |

Data in the table refer to the  $\alpha\beta\gamma$  heteromer. There are several human diseases resulting from mutations in ENaC subunits. Liddle's syndrome (including features of salt-sensitive hypertension and hypokalemia), is associated with gain of function mutations in the  $\beta$  and  $\gamma$  subunits leading to defective ENaC ubiquitylation and increased stability of active ENaC at the cell surface (Staub *et al.*, 1996; Rotin and Schild, 2008; Schild, 2010). Enzymes that deubiquitylate ENaC increase its function *in vivo*. Pseudohypoaldosteronism type 1 (PHA-1) can occur through either mutations in the gene encoding the mineralocorticoid receptor, or loss of function mutations in genes encoding ENaC subunits (see Bonny and Hummler, 2000). Regulation of ENaC by phosphoinositides may underlie insulin-evoked renal  $Na^+$  retention that can complicate the clinical management of type 2 diabetes using insulin-sensitizing thiazolidinedione drugs (Guan *et al.* 2005).

**Abbreviations:** P552-02, N-(3,5-diamino-6-chloropyrazine-2-carbonyl)-N'-4-[4-(2,3-dihydroxypropoxy)phenyl]butyl-guanidine methanesulfonate; S3969, N-(2-hydroxyethyl)-4-methyl-2-(4-methyl-1H-indol-3-ylthio)pentanamide

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# Hyperpolarisation-activated, cyclic nucleotide-gated (HCN)

**Overview:** The hyperpolarisation-activated, cyclic nucleotide-gated (HCN) channels are cation channels that are activated by hyperpolarisation at voltages negative to  $-50$  mV. The cyclic nucleotides cAMP and cGMP directly activate the channels and shift the activation curves of HCN channels to more positive voltages, thereby enhancing channel activity. HCN channels underlie pacemaker currents found in many excitable cells including cardiac cells and neurons (DiFrancesco, 1993; Pape, 1996). In native cells, these currents have a variety of names, such as  $I_h$ ,  $I_q$  and  $I_i$ . The four known HCN channels have six transmembrane domains and form tetramers. It is believed that the channels can form heteromers with each other, as has been shown for HCN1 and HCN4 (Altomare *et al.*, 2003). A standardised nomenclature for HCN channels has been proposed by the NC-IUPHAR subcommittee on voltage-gated ion channels (see Hofmann *et al.*, 2005).

| Nomenclature | HCN1                                 | HCN2                                 | HCN3                                 | HCN4                                 |
|--------------|--------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|
| Ensembl ID   | ENSG00000164588                      | ENSG00000099822                      | ENSG00000143630                      | ENSG00000138622                      |
| Activators   | cAMP > cGMP (both weak)              | cAMP > cGMP                          | –                                    | cAMP > cGMP                          |
| Inhibitors   | Cs <sup>+</sup> , ZD7288, ivabradine | Cs <sup>+</sup> , ZD7288, ivabradine | Cs <sup>+</sup> , ZD7288, ivabradine | Cs <sup>+</sup> , ZD7288, ivabradine |

HCN channels are permeable to both Na<sup>+</sup> and K<sup>+</sup> ions, with a Na<sup>+</sup>/K<sup>+</sup> permeability ratio of about 0.2. Functionally, they differ from each other in terms of time constant of activation with HCN1 the fastest, HCN4 the slowest and HCN2 and HCN3 intermediate. The compounds ZD7288 (BoSmith *et al.*, 1993) and ivabradine (Bucchi *et al.*, 2002) have proven useful in identifying and studying functional HCN channels in native cells. Zatebradine and cilobradine are also useful blocking agents.

**Abbreviations:** **Ivabradine (S16257-2)**, (3-(3-(((7S)-3,4-dimethoxybicyclo [4,2,0] octa-1,3,5-trien-7-yl) methyl) methylamino) propyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin-2-one hydrochloride; **ZD7288**, [4-(N-ethyl-N-phenyl-amino)-1,2-dimethyl-6-(methylamino) pyrimidinium chloride

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# IP<sub>3</sub> receptor

**Overview:** The inositol 1,4,5-trisphosphate receptors (IP<sub>3</sub>R) are ligand-gated Ca<sup>2+</sup>-release channels on intracellular Ca<sup>2+</sup> store sites (such as the endoplasmic reticulum). They are responsible for the mobilization of intracellular Ca<sup>2+</sup> stores and play an important role in intracellular Ca<sup>2+</sup> signalling in a wide variety of cell types. Three different gene products (types I–III) have been isolated, which assemble as large tetrameric structures. IP<sub>3</sub>Rs are closely associated with certain proteins: calmodulin and FKBP (and calcineurin via FKBP). They are phosphorylated by PKA, PKC, PKG and CaMKII.

| Nomenclature               | IP <sub>3</sub> R1                                                                                                                                                 | IP <sub>3</sub> R2                                                                                                | IP <sub>3</sub> R3                                                             |
|----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Other names                | INSP3R1                                                                                                                                                            | INSP3R2                                                                                                           | INSP3R3                                                                        |
| Ensembl ID                 | ENSG00000150995                                                                                                                                                    | ENSG00000123104                                                                                                   | ENSG00000096433                                                                |
| Endogenous activators      | Ins(1,4,5)P <sub>3</sub> (nM – μM), cytosolic Ca <sup>2+</sup> (<750 μM), cytosolic ATP (<mM)                                                                      | Ins(1,4,5)P <sub>3</sub> (nM–μM), cytosolic Ca <sup>2+</sup> (nM)                                                 | Ins(1,4,5)P <sub>3</sub> (nM–μM), cytosolic Ca <sup>2+</sup> (nM)              |
| Pharmacological activators | InsP <sub>3</sub> analogues including Ins(2,4,5)P <sub>3</sub> , adenophostin A (nM)                                                                               | InsP <sub>3</sub> analogues including Ins(2,4,5)P <sub>3</sub> , adenophostin A (nM)                              | –                                                                              |
| Antagonists                | Xestospongins C (μM), caffeine (mM), phosphatidylinositol 4,5-bisphosphate (μM), heparin (μg/ml), decavanadate (μM), calmodulin at high cytosolic Ca <sup>2+</sup> | Heparin (μg/ml), decavanadate (μM)                                                                                | Heparin (μg/ml), decavanadate (μM)                                             |
| Functional characteristics | Ca <sup>2+</sup> : (P <sub>8a</sub> /P <sub>K</sub> ~6) single-channel conductance ~70 pS (50 mM Ca <sup>2+</sup> )                                                | Ca <sup>2+</sup> : single-channel conductance ~70 pS (50 mM Ca <sup>2+</sup> ), ~390 pS (220 mM Cs <sup>+</sup> ) | Ca <sup>2+</sup> : single-channel conductance ~88 pS (55 mM Ba <sup>2+</sup> ) |

The absence of a modulator of a particular isoform of receptor indicates that the action of that modulator has not been determined, not that it is without effect.

**Abbreviations:** FKBP, FK506-binding protein

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# Potassium

**Overview:** Potassium channels are fundamental regulators of excitability. They control the frequency and the shape of action potential waveform, the secretion of hormones and neurotransmitters and cell membrane potential. Their activity may be regulated by voltage, calcium and neurotransmitters (and the signalling pathways they stimulate). They consist of a primary pore-forming  $\alpha$  subunit often associated with auxiliary regulatory subunits. Since there are over 70 different genes encoding K channels  $\alpha$  subunits in the human genome, it is beyond the scope of this guide to treat each subunit individually. Instead, channels have been grouped into families and subfamilies based on their structural and functional properties. The three main families are the 2TM (two transmembrane domain), 4TM and 6TM families. A standardised nomenclature for potassium channels has been proposed by the NC-IUPHAR subcommittees on potassium channels (see Goldstein *et al.*, 2005; Gutman *et al.*, 2005; Kubo *et al.*, 2005; Wei *et al.*, 2005).

## The 2TM family of K channels

The 2TM domain family of K channels are also known as the inward-rectifier K channel family. This family includes the strong inward-rectifier K channels ( $K_{IR2.x}$ ), the G-protein-activated inward-rectifier K channels ( $K_{IR3.x}$ ) and the ATP-sensitive K channels ( $K_{IR6.x}$ , which combine with sulphonylurea receptors (SUR)). The pore-forming  $\alpha$  subunits form tetramers, and heteromeric channels may be formed within subfamilies (e.g.  $K_{IR3.2}$  with  $K_{IR3.3}$ ).

| Subfamily group           | $K_{IR1.x}$                        | $K_{IR2.x}$                                                 | $K_{IR3.x}$                                  | $K_{IR4.x}$                        |
|---------------------------|------------------------------------|-------------------------------------------------------------|----------------------------------------------|------------------------------------|
| Subtypes                  | $K_{IR1.1}$ (ROMK1)                | $K_{IR2.1-2.4}$ (IRK1–4)                                    | $K_{IR3.1-3.4}$ (GIRK1–4)                    | $K_{IR4.1-4.2}$                    |
| Ensembl ID*               | ENSG00000151704<br>( $K_{IR1.1}$ ) | ENSG00000123700<br>( $K_{IR2.1}$ )                          | ENSG00000162989<br>( $K_{IR3.1}$ )           | ENSG00000177807<br>( $K_{IR4.1}$ ) |
| Activators                | –                                  | –                                                           | PIP <sub>2</sub> , G $\beta\gamma$           | –                                  |
| Inhibitors                | –                                  | [Mg <sup>2+</sup> ] <sub>i</sub> , polyamines (internal)    | –                                            | –                                  |
| Functional characteristic | Inward-rectifier current           | IK <sub>1</sub> in heart, 'strong' inward-rectifier current | G-protein-activated inward-rectifier current | Inward-rectifier current           |

| Subfamily Group           | $K_{IR5.x}$                        | $K_{IR6.x}$                                  | $K_{IR7.x}$                        |
|---------------------------|------------------------------------|----------------------------------------------|------------------------------------|
| Subtypes                  | $K_{IR5.1}$                        | $K_{IR6.1-6.2}$ ( $K_{ATP}$ )                | $K_{IR7.1}$                        |
| Ensembl ID*               | ENSG00000153822<br>( $K_{IR5.1}$ ) | ENSG00000121361<br>( $K_{IR6.1}$ )           | ENSG00000115474<br>( $K_{IR7.1}$ ) |
| Activators                | –                                  | Minoxidil, cromakalim, diazoxide, nicorandil | –                                  |
| Inhibitors                | –                                  | Tolbutamide, glibenclamide                   | –                                  |
| Functional characteristic | Inward-rectifier current           | ATP-sensitive, inward-rectifier current      | Inward-rectifier current           |
| Associated subunits       | –                                  | SUR1, SUR2A, SUR2B                           | –                                  |

\*Due to space constraints, the Ensembl ID for only one member of each subfamily is given. Ensembl information for the other subfamily members can be found from links therein or at the following link: <http://www.iuphar-db.org/DATABASE/FamilyMenuForward?familyId=74>.

## The 4TM family of K channels

The 4TM family of K channels are thought to underlie many leak currents in native cells. They are open at all voltages and regulated by a wide array of neurotransmitters and biochemical mediators. The primary pore-forming  $\alpha$  subunit contains two pore domains (indeed, they are often referred to as two-pore domain K channels or K2P) and so it is envisaged that they form functional dimers rather than the usual K channel tetramers. There is some evidence that they can form heterodimers within subfamilies (e.g.  $K_{2P3.1}$  with  $K_{2P9.1}$ ). There is no current, clear, consensus on nomenclature of 4TM K channels, nor on the division into subfamilies (see Goldstein *et al.*, 2005). The suggested division into subfamilies, below, is based on similarities in both structural and functional properties within subfamilies.

| Subfamily group | 'TWIK'                                                            | 'TREK'                                                             | 'TASK'                                                             | 'TALK'                                                              | 'THIK'                                       | 'TRESK'                             |
|-----------------|-------------------------------------------------------------------|--------------------------------------------------------------------|--------------------------------------------------------------------|---------------------------------------------------------------------|----------------------------------------------|-------------------------------------|
| Subtypes        | $K_{2P1.1}$ (TWIK1)<br>$K_{2P6.1}$ (TWIK2)<br>$K_{2P7.1}$ (KNCK7) | $K_{2P2.1}$ (TREK1)<br>$K_{2P10.1}$ (TREK2)<br>$K_{2P4.1}$ (TRAAK) | $K_{2P3.1}$ (TASK1)<br>$K_{2P9.1}$ (TASK3)<br>$K_{2P15.1}$ (TASK5) | $K_{2P16.1}$ (TALK1)<br>$K_{2P5.1}$ (TASK2)<br>$K_{2P17.1}$ (TASK4) | $K_{2P13.1}$ (THIK1)<br>$K_{2P12.1}$ (THIK2) | $K_{2P18.1}$ (TRESK1)               |
| Ensembl ID*     | ENSG00000135750<br>( $K_{2P1.1}$ )                                | ENSG00000082482<br>( $K_{2P2.1}$ )                                 | ENSG00000171303<br>( $K_{2P3.1}$ )                                 | ENSG00000164626<br>( $K_{2P5.1}$ )                                  | ENSG00000152315<br>( $K_{2P13.1}$ )          | ENSG00000186795<br>( $K_{2P18.1}$ ) |

| Subfamily group           | 'TWIK'               | 'TREK'                                                                                 | 'TASK'                                                                                                         | 'TALK'                   | 'THIK'             | 'TRESK'            |
|---------------------------|----------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|--------------------------|--------------------|--------------------|
| Activators                | –                    | Halothane (not TRAAK), riluzole, stretch, heat, arachidonic acid, acid pH <sub>i</sub> | Halothane, alkaline pH <sub>o</sub> (K <sub>2p</sub> 3.1)                                                      | Alkaline pH <sub>o</sub> | –                  | –                  |
| Inhibitors                | Acid pH <sub>i</sub> | –                                                                                      | Anandamide (K <sub>2p</sub> 3.1, K <sub>2p</sub> 9.1) ruthenium red (K <sub>2p</sub> 9.1) acid pH <sub>o</sub> | –                        | Halothane          | Arachidonic acid   |
| Functional characteristic | Background current   | Background current                                                                     | Background current                                                                                             | Background current       | Background current | Background current |

The K<sub>2p</sub>7.1, K<sub>2p</sub>15.1 and K<sub>2p</sub>12.1 subtypes, when expressed in isolation, are nonfunctional. All 4TM channels are insensitive to the classical potassium channel blockers TEA and 4-AP, but are blocked to varying degrees by Ba<sup>2+</sup> ions.

\*Due to space constraints, the Ensembl ID for only one member of each subfamily is given. Ensembl information for the other subfamily members can be found from links therein or at the following link: <http://www.iuphar-db.org/DATABASE/FamilyMenuForward?familyId=79>.

### The 6TM family of K channels

The 6TM family of K channels comprises the voltage-gated K<sub>v</sub> subfamilies, the KCNQ subfamily the EAG subfamily (which includes hERG channels), the Ca<sup>2+</sup>-activated Slo subfamily (actually with 7TM) and the Ca<sup>2+</sup>-activated SK subfamily. As for the 2TM family, the pore-forming  $\alpha$  subunits form tetramers and heteromeric channels may be formed within subfamilies (e.g. K<sub>v</sub>1.1 with K<sub>v</sub>1.2; KCNQ2 with KCNQ3).

| Subfamily group            | K <sub>v</sub> 1.x                                                                                                                                      | K <sub>v</sub> 2.x                                                                         | K <sub>v</sub> 3.x                                   | K <sub>v</sub> 4.x                      |
|----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|------------------------------------------------------|-----------------------------------------|
| Subtypes                   | K <sub>v</sub> 1.1 – K <sub>v</sub> 1.8<br>Shaker-related                                                                                               | K <sub>v</sub> 2.1–2.2<br>Shab-related                                                     | K <sub>v</sub> 3.1–3.4<br>Shal-related               | K <sub>v</sub> 4.1–4.3<br>Shaw-related  |
| Ensembl ID*                | ENSG00000111262<br>(K <sub>v</sub> 1.1)                                                                                                                 | ENSG00000158445<br>(K <sub>v</sub> 2.1)                                                    | ENSG00000129159<br>(K <sub>v</sub> 3.1)              | ENSG00000102057<br>(K <sub>v</sub> 4.1) |
| Inhibitors                 | TEA potent (1.1), TEA moderate (1.3, 1.6), 4-AP potent (1.4), $\alpha$ -dendrotoxin (1.1, 1.2, 1.6), margatoxin (1.1, 1.2, 1.3), noxiustoxin (1.2, 1.3) | TEA moderate                                                                               | TEA potent, 4-AP potent (3.1, 3.2), BDS-1 (3.4)      | –                                       |
| Functional characteristics | K <sub>v</sub> (1.1–1.3, 1.5–1.8), K <sub>A</sub> (1.4)                                                                                                 | K <sub>v</sub> (2.1)                                                                       | K <sub>v</sub> (3.1, 3.2), K <sub>A</sub> (3.3, 3.4) | K <sub>A</sub>                          |
| Associated subunits        | K <sub>v</sub> $\beta$ <sub>1</sub> , K <sub>v</sub> $\beta$ <sub>2</sub>                                                                               | K <sub>v</sub> 5.1, K <sub>v</sub> 6.1–6.4, K <sub>v</sub> 8.1–8.2, K <sub>v</sub> 9.1–9.3 | MiRP2 (K <sub>v</sub> 3.4)                           | KChIP, KChAP                            |

| Subfamily group           | K <sub>v</sub> 7.x ('KCNQ')                                                           | K <sub>v</sub> 10.x, K <sub>v</sub> 11.x, K <sub>v</sub> 12.x ('EAG')                                                 | K <sub>Ca</sub> 1.x, K <sub>Ca</sub> 4.x, K <sub>Ca</sub> 5.x ('Slo')                       | K <sub>Ca</sub> 2.x, K <sub>Ca</sub> 3.x ('SK')                                   |
|---------------------------|---------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Subtypes                  | K <sub>v</sub> 7.1–7.5 (KCNQ1-5)                                                      | K <sub>v</sub> 10.1–10.2 (eag1-2)<br>K <sub>v</sub> 11.1–11.3 (erg1-3, hERG 1-3)<br>K <sub>v</sub> 12.1–12.3 (elk1-3) | K <sub>Ca</sub> 1.1, K <sub>Ca</sub> 4.1–4.2, K <sub>Ca</sub> 5.1<br>Slo (BK), Slack, Slick | K <sub>Ca</sub> 2.1–2.3 (SK1–SK3)<br>K <sub>Ca</sub> 3.1 (SK4, IK)                |
| Ensembl ID*               | ENSG00000053918<br>(K <sub>v</sub> 7.1)                                               | ENSG00000143473<br>(K <sub>v</sub> 10.1)                                                                              | ENSG00000156113<br>(K <sub>Ca</sub> 1.1)                                                    | ENSG00000105642<br>(K <sub>Ca</sub> 2.1)                                          |
| Activators                | Retigabine (K <sub>v</sub> 7.2, –5)                                                   | –                                                                                                                     | NS004, NS1619                                                                               | –                                                                                 |
| Inhibitors                | TEA (K <sub>v</sub> 7.2, 7.4), XE991 (K <sub>v</sub> 7.1, 7.2, 7.4, 7.5), linopirdine | E-4031 (K <sub>v</sub> 11.1), astemizole (K <sub>v</sub> 11.1), terfenadine (K <sub>v</sub> 11.1)                     | TEA, charybdotoxin, iberiotoxin                                                             | Charybdotoxin (K <sub>Ca</sub> 3.1), apamin (K <sub>Ca</sub> 2.1–2.3)             |
| Functional characteristic | K <sub>v</sub> 7.1 – cardiac I <sub>Ks</sub><br>K <sub>v</sub> 7.2/7.3 – M current    | K <sub>v</sub> 11.1 – cardiac I <sub>Kr</sub>                                                                         | Maxi K <sub>Ca</sub> K <sub>Na</sub> (slack & slick)                                        | SK <sub>Ca</sub> (K <sub>Ca</sub> 2.1–2.3) I <sub>KCa</sub> (K <sub>Ca</sub> 3.1) |
| Associated subunits       | minK, MiRP2 (K <sub>v</sub> 7.1)                                                      | minK, MiRP1 (erg1)                                                                                                    | –                                                                                           | –                                                                                 |

\*Due to space constraints, the Ensembl ID for only one member of each subfamily is given. Ensembl information for the other subfamily members can be found from links therein or at the following links: <http://www.iuphar-db.org/DATABASE/FamilyMenuForward?familyId=81> or <http://www.iuphar-db.org/DATABASE/FamilyMenuForward?familyId=69>

**Abbreviations:** 4-AP, 4-aminopyridine; BDS-1, blood depressing substance 1; E4031, 1-(2-(6-methyl-2-pyridyl)ethyl)-4-(4-methylsulphonyl aminobenzoyl)piperidine; NS004, 1-(2-hydroxy-5-chlorophenyl)-5-trifluoromethyl-2-benzimidazolone; NS1619, 1-(2'-hydroxy-5'-trifluoromethylphenyl)-5-trifluoromethyl-2(3H)benzimidazolone; PIP<sub>2</sub>, phosphatidylinositol 4,5, bisphosphate; TEA, tetraethylammonium; XE991, 10,10-bis(4-pyridinylmethyl)-9(10H)-anthracene

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# Voltage-gated proton channel

**Overview:** The voltage-gated proton channel (provisionally denoted H<sub>v</sub>1) is a putative 4TM proton-selective channel gated by membrane depolarization and which is sensitive to the transmembrane pH gradient (Ramsey *et al.*, 2006; Sasaki *et al.*, 2006; DeCoursey, 2008a,b; Capasso *et al.*, 2011). The structure of H<sub>v</sub>1 is homologous to the voltage sensing domain (VSD) of the superfamily of voltage-gated ion channels (*i.e.* segments S1 to S4) and contains no discernable pore region (Ramsey *et al.*, 2006; Sasaki *et al.*, 2006). Proton flux through H<sub>v</sub>1 is instead most likely mediated by a water wire completed in a crevice of the protein when the voltage-sensing S4 helix moves in response to a change in transmembrane potential (Ramsey *et al.*, 2010; Wood *et al.*, 2011). H<sub>v</sub>1 expresses largely as a dimer mediated by intracellular C-terminal coiled-coil interactions (Li *et al.*, 2010) but individual promoters nonetheless support gated H<sup>+</sup> flux *via* separate conduction pathways (Koch *et al.*, 2008; Lee *et al.*, 2008; Tombola *et al.*, 2008; Petheo *et al.*, 2010). Within dimeric structures, the two protomers do not function independently, but display co-operative interactions during gating resulting in increased voltage sensitivity, but slower activation, of the dimeric, *versus* monomeric, complexes (Gonzalez *et al.*, 2010; Tombola *et al.*, 2010).

|                              |                                                                                                                                                                                                                                                                                                                                                                                                                     |
|------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature                 | H <sub>v</sub> 1                                                                                                                                                                                                                                                                                                                                                                                                    |
| Other names                  | Voltage-gated proton channel 1 (HVCN1), Voltage-sensor only protein (VSOP)                                                                                                                                                                                                                                                                                                                                          |
| Ensembl ID                   | ENSG00000122986                                                                                                                                                                                                                                                                                                                                                                                                     |
| Activators                   | –                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Blockers (IC <sub>50</sub> ) | Zn <sup>2+</sup> (≈0.5–2.0 μM), Cd <sup>2+</sup> (≈10 μM)                                                                                                                                                                                                                                                                                                                                                           |
| Functional characteristics   | Activated by membrane depolarization mediating macroscopic currents with time-, voltage- and pH-dependence; outwardly rectifying; voltage dependent kinetics with relatively slow current activation sensitive to extracellular pH and temperature, relatively fast deactivation; voltage threshold for current activation determined by pH gradient (ΔpH = pH <sub>o</sub> - pH <sub>i</sub> ) across the membrane |

The voltage threshold ( $V_{thr}$ ) for activation of H<sub>v</sub>1 is not fixed but is set by the pH gradient across the membrane such that  $V_{thr}$  is positive to the Nernst potential for H<sup>+</sup>, which ensures that only outwardly directed flux of H<sup>+</sup> occurs under physiological conditions (DeCoursey, 2008a,b; Capasso *et al.*, 2011). Phosphorylation of H<sub>v</sub>1 within the N-terminal domain by PKC enhances the gating of the channel (Musset *et al.*, 2010a). Tabulated IC<sub>50</sub> values for Zn<sup>2+</sup> and Cd<sup>2+</sup> are for heterologously expressed human and mouse H<sub>v</sub>1 (Ramsey *et al.*, 2006; Sasaki *et al.*, 2006). Zn<sup>2+</sup> is not a conventional pore blocker, but is coordinated by two, or more, external protonation sites involving histamine residues (Ramsey *et al.*, 2006). Zn<sup>2+</sup> binding may occur at the dimer interface between pairs of histamine residues from both monomers where it may interfere with channel opening (Musset *et al.*, 2010b). Mouse knockout studies demonstrate that H<sub>v</sub>1 participates in charge compensation in granulocytes during the respiratory burst of NADPH oxidase-dependent reactive oxygen species production that assists in the clearance of bacterial pathogens (Ramsey *et al.*, 2009). Additional physiological functions of H<sub>v</sub>1 are reviewed by Capasso *et al.* (2011).

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# Ryanodine receptor

**Overview:** The ryanodine receptors (RyRs) are found on intracellular  $\text{Ca}^{2+}$  storage/release organelles. The family of RyR genes encodes three highly related  $\text{Ca}^{2+}$  release channels: RyR1, RyR2 and RyR3, which assemble as large tetrameric structures. These RyR channels are ubiquitously expressed in many types of cells and participate in a variety of important  $\text{Ca}^{2+}$  signaling phenomena (neurotransmission, secretion, etc.). In addition to the three mammalian isoforms described below, various nonmammalian isoforms of the ryanodine receptor have been identified and these are discussed in Sutko and Airey (1996). The function of the ryanodine receptor channels may also be influenced by closely associated proteins such as the tacrolimus (FK506)-binding protein, calmodulin (Yamaguchi *et al.*, 2003), triadin, calsequestrin, junctin and sorcin, and by protein kinases and phosphatases.

| Nomenclature               | RyR1                                                                                                                                                                                                | RyR2                                                                                                                                                           | RyR3                                                                                                                                                             |
|----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ensembl ID                 | ENSG00000196218                                                                                                                                                                                     | ENSG00000198626                                                                                                                                                | ENSG00000198838                                                                                                                                                  |
| Endogenous activators      | Depolarisation <i>via</i> DHP receptor, cytosolic $\text{Ca}^{2+}$ ( $\mu\text{M}$ ), cytosolic ATP (mM), luminal $\text{Ca}^{2+}$ , calmodulin at low cytosolic $\text{Ca}^{2+}$ , CaM kinase, PKA | Cytosolic $\text{Ca}^{2+}$ ( $\mu\text{M}$ ), cytosolic ATP (mM), luminal $\text{Ca}^{2+}$ , CaM kinase, PKA                                                   | Cytosolic $\text{Ca}^{2+}$ ( $\mu\text{M}$ ), cytosolic ATP (mM), calmodulin at low cytosolic $\text{Ca}^{2+}$                                                   |
| Pharmacological activators | Ryanodine (nM– $\mu\text{M}$ ), caffeine (mM), suramin ( $\mu\text{M}$ )                                                                                                                            | Ryanodine (nM– $\mu\text{M}$ ), caffeine (mM), suramin ( $\mu\text{M}$ )                                                                                       | Ryanodine (nM– $\mu\text{M}$ ), caffeine (mM)                                                                                                                    |
| Antagonists                | Cytosolic $\text{Ca}^{2+}$ (>100 $\mu\text{M}$ ), cytosolic $\text{Mg}^{2+}$ (mM), calmodulin at high cytosolic $\text{Ca}^{2+}$ , dantrolene                                                       | Cytosolic $\text{Ca}^{2+}$ (>1 mM), cytosolic $\text{Mg}^{2+}$ (mM), calmodulin at high cytosolic $\text{Ca}^{2+}$                                             | Cytosolic $\text{Ca}^{2+}$ (>1 mM), cytosolic $\text{Mg}^{2+}$ (mM), calmodulin at high cytosolic $\text{Ca}^{2+}$ , dantrolene                                  |
| Channel blockers           | Ryanodine (>100 $\mu\text{M}$ ), ruthenium red, procaine                                                                                                                                            | Ryanodine (>100 $\mu\text{M}$ ), ruthenium red, procaine                                                                                                       | Ruthenium red                                                                                                                                                    |
| Functional characteristics | $\text{Ca}^{2+}$ : ( $P_{\text{Ca}}/P_{\text{K}} \sim 6$ ) single-channel conductance: $\sim 90$ pS (50 mM $\text{Ca}^{2+}$ ), 770 pS (200 mM $\text{K}^{+}$ )                                      | $\text{Ca}^{2+}$ : ( $P_{\text{Ca}}/P_{\text{K}} \sim 6$ ) single-channel conductance: $\sim 90$ pS (50 mM $\text{Ca}^{2+}$ ), 720 pS (210 mM $\text{K}^{+}$ ) | $\text{Ca}^{2+}$ : ( $P_{\text{Ca}}/P_{\text{K}} \sim 6$ ) single-channel conductance: $\sim 140$ pS (250 mM $\text{Ca}^{2+}$ ), 777 pS (250 mM $\text{K}^{+}$ ) |

The modulators of channel function included in this table are those most commonly used to identify ryanodine-sensitive  $\text{Ca}^{2+}$  release pathways. Numerous other modulators of ryanodine receptor/channel function can be found in the reviews listed below. The absence of a modulator of a particular isoform of receptor indicates that the action of that modulator has not been determined, not that it is without effect. The potential role of cyclic ADP ribose as an endogenous regulator of ryanodine receptor channels is controversial. A region of RyR likely to be involved in ion translocation and selection has been identified (Zhao *et al.*, 1999; Gao *et al.*, 2000).

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# Sodium leak channel, non-selective

**Overview:** The sodium leak channel, non selective (NC-IUPHAR tentatively recommends the nomenclature  $\text{Na}_{\text{vi}}2.1$ , W.A. Catterall, personal communication) is structurally a member of the family of voltage-gated sodium channel family ( $\text{Na}_{\text{v}}1.1 - \text{Na}_{\text{v}}1.9$ ) (Lee *et al.*, 1999; Yu and Catterall, 2004). In contrast to the latter,  $\text{Na}_{\text{vi}}2.1$ , is voltage-insensitive (denoted in the subscript 'vi' in the tentative nomenclature) and possesses distinctive ion selectivity and pharmacological properties.  $\text{Na}_{\text{vi}}2.1$ , which is insensitive to TTX (10  $\mu\text{M}$ ), has been proposed to mediate the TTX-resistant and voltage-insensitive  $\text{Na}^+$  leak current ( $\text{I}_{\text{L-Na}}$ ) observed in many types of neurone (Lu *et al.*, 2007). However, whether  $\text{Na}_{\text{vi}}2.1$  is constitutively active has been challenged (Swayne *et al.*, 2009).  $\text{Na}_{\text{vi}}2.1$  is widely distributed within the central nervous system and is also expressed in the heart and pancreas specifically, in rodents, within the islets of Langerhans (Lee *et al.*, 1999; Lu *et al.*, 2007).

|                               |                                                                                                                                                                                                                                                                                 |
|-------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature                  | $\text{Na}_{\text{vi}}2.1$                                                                                                                                                                                                                                                      |
| Other names                   | NALCN, $\text{Nav}2.1$ , $\text{Na}_{\text{x}}$ , voltage-gated channel like 1 (VGCNL1), Rb21                                                                                                                                                                                   |
| Ensembl ID                    | ENSG00000102452                                                                                                                                                                                                                                                                 |
| Activators                    | Constitutively active (Lu <i>et al.</i> , 2007), or activated downstream of Src family tyrosine kinases (SFKs) (Lu <i>et al.</i> , 2009; Swayne <i>et al.</i> , 2009); positively modulated by decreased extracellular $\text{Ca}^{2+}$ concentration (Lu <i>et al.</i> , 2010) |
| Blockers ( $\text{IC}_{50}$ ) | $\text{Gd}^{3+}$ (1.4 $\mu\text{M}$ ), $\text{Cd}^{2+}$ (0.15 mM), $\text{Co}^{2+}$ (0.26 mM), verapamil (0.38 mM)                                                                                                                                                              |
| Functional characteristics    | $\gamma = 27 \text{ pS}$ (by fluctuation analysis), $P_{\text{Na}}/P_{\text{Cs}} = 1.3$ , $P_{\text{K}}/P_{\text{Cs}} = 1.2$ , $P_{\text{Ca}}/P_{\text{Cs}} = 0.5$ , linear current voltage-relationship, voltage-independent and non-inactivating                              |

In native and recombinant expression systems  $\text{Na}_{\text{vi}}2.1$  can be activated by stimulation of  $\text{NK}_1$  (in hippocampal neurones), neurotensin (in ventral tegmental area neurones) and M3 muscarinic acetylcholine receptors (in MIN6 pancreatic  $\beta$ -cells and) in a manner that is independent of signalling through G proteins (Lu *et al.*, 2009; Swayne *et al.*, 2009). Pharmacological and molecular biological evidence indicates such modulation to occur through a pathway that involves the activation of Src family tyrosine kinases. It is suggested that  $\text{Na}_{\text{vi}}2.1$  exists as a macromolecular complex with M3 receptors (Swayne *et al.*, 2009) and peptide receptors (Lu *et al.*, 2009), in the latter instance in association with the protein UNC-80, which recruits Src to the channel complex (Lu *et al.*, 2009; Wang and Ren, 2009). By contrast, stimulation of  $\text{Na}_{\text{vi}}2.1$  by decreased extracellular  $\text{Ca}^{2+}$  concentration is G-protein dependent and involves a  $\text{Ca}^{2+}$ -sensing G protein-coupled receptor and UNC80 which links  $\text{Na}_{\text{vi}}2.1$  to the protein UNC79 in the same complex (Lu *et al.*, 2010).  $\text{Na}_{\text{vi}}2.1$  null mutant mice have severe disturbances in respiratory rhythm and die within 24 hours of birth (Lu *et al.*, 2007).  $\text{Na}_{\text{vi}}2.1$  heterozygous knockout mice display increased serum sodium concentrations in comparison to wildtype littermates and a role for the channel in osmoregulation has been postulated (Sinke *et al.*, 2011).

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# Sodium (voltage-gated)

**Overview:** Sodium channels are voltage-gated sodium-selective ion channels present in the membrane of most excitable cells. Sodium channels comprise of one pore-forming  $\alpha$  subunit, which may be associated with either one or two  $\beta$  subunits (Isom, 2001).  $\alpha$ -Subunits consist of four homologous domains (I–IV), each containing six transmembrane segments (S1–S6) and a pore-forming loop. The positively charged fourth transmembrane segment (S4) acts as a voltage sensor and is involved in channel gating. The crystal structure of the bacterial NavAb channel has revealed a number of novel structural features compared to earlier potassium channel structures including a short selectivity filter with ion selectivity determined by interactions with glutamate side chains (Payandeh *et al.*, 2011). Interestingly, the pore region is penetrated by fatty acyl chains that extend into the central cavity which may allow the entry of small, hydrophobic pore-blocking drugs (Payandeh *et al.*, 2011). Auxiliary  $\beta$ 1,  $\beta$ 2,  $\beta$ 3 and  $\beta$ 4 subunits consist of a large extracellular N-terminal domain, a single transmembrane segment and a shorter cytoplasmic domain.

The nomenclature for sodium channels was proposed by Goldin *et al.*, (2000) and approved by the NC-IUPHAR subcommittee on sodium channels (Catterall *et al.*, 2005).

| Nomenclature              | Nav1.1                          | Nav1.2                          | Nav1.3                            | Nav1.4                                                 | Nav1.5                     |
|---------------------------|---------------------------------|---------------------------------|-----------------------------------|--------------------------------------------------------|----------------------------|
| Alternative names         | Brain type I                    | Brain type II                   | Brain type III                    | $\mu$ 1, SkM1                                          | h1, SkM II, cardiac        |
| Ensembl ID                | ENSG00000144285                 | ENSG00000136531                 | ENSG00000153253                   | ENSG00000007314                                        | ENSG00000183873            |
| Activators                | Veratridine, batrachotoxin      | Veratridine, batrachotoxin      | Veratridine, batrachotoxin        | Veratridine, batrachotoxin                             | Veratridine, batrachotoxin |
| Blockers                  | Tetrodotoxin (10 nM), saxitoxin | Tetrodotoxin (10 nM), saxitoxin | Tetrodotoxin (2–15 nM), saxitoxin | $\mu$ -Conotoxin GIIIA, tetrodotoxin (5 nM), saxitoxin | Tetrodotoxin (2 $\mu$ M)   |
| Functional characteristic | Fast inactivation (0.7 ms)      | Fast inactivation (0.8 ms)      | Fast inactivation (0.8 ms)        | Fast inactivation (0.6 ms)                             | Fast inactivation (1 ms)   |

| Nomenclature              | Nav1.6                         | Nav1.7                         | Nav1.8                    | Nav1.9                    |
|---------------------------|--------------------------------|--------------------------------|---------------------------|---------------------------|
| Alternative names         | PN4, NaCH6                     | PN1, NaS                       | SNS, PN3                  | NaN, SNS2                 |
| Ensembl ID                | ENSG00000196876                | ENSG00000169432                | ENSG00000185313           | ENSG00000168356           |
| Activators                | Veratridine, batrachotoxin     | Veratridine, batrachotoxin     | –                         | –                         |
| Blockers                  | Tetrodotoxin (6 nM), saxitoxin | Tetrodotoxin (4 nM), saxitoxin | Tetrodotoxin (60 $\mu$ M) | Tetrodotoxin (40 $\mu$ M) |
| Functional characteristic | Fast inactivation (1 ms)       | Fast inactivation (0.5 ms)     | Slow inactivation (6 ms)  | Slow inactivation (16 ms) |

Sodium channels are also blocked by local anaesthetic agents, antiarrhythmic drugs and antiepileptic drugs. There are two clear functional fingerprints for distinguishing different subtypes. These are sensitivity to tetrodotoxin (Nav1.5, Nav1.8 and Nav1.9 are much less sensitive to block) and rate of inactivation (Nav1.8 and particularly Nav1.9 inactivate more slowly).

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# Transient receptor potential (TRP) cation channels

**Overview:** The TRP superfamily of channels (nomenclature agreed by NC-IUPHAR; Clapham *et al.*, 2005; Wu *et al.*, 2010), whose founder member is the *Drosophila* Trp channel, exists in mammals as six families; TRPC, TRPM, TRPV, TRPA, TRPP and TRPML based on amino acid homologies. TRP subunits contain six putative transmembrane domains and assemble as homo- or hetero-tetramers to form cation selective channels with diverse modes of activation and varied permeation properties (reviewed by Owsianik *et al.*, 2006b). Established, or potential, physiological functions of the individual members of the TRP families are discussed in detail in the recommended reviews and a compilation edited by Islam (2011). The established, or potential, involvement of TRP channels in disease is reviewed in Kiselyov *et al.* (2007a), Nilius *et al.* (2007) and Nilius and Owsianik (2010), together with a special edition of *Biochemica et Biophysica Acta* on the subject (Nilius, 2007). The pharmacology of most TRP channels is poorly developed (Wu *et al.*, 2010). Broad spectrum agents are listed in the tables along with more selective, or recently recognised, ligands that are flagged by the inclusion of a primary reference. Most TRP channels are regulated by phosphoinositides such as  $\text{PtdIns}(4,5)\text{P}_2$  and  $\text{Ins}(1,4,5)\text{P}_3$  although the effects reported are often complex, occasionally contradictory, and likely be dependent upon experimental conditions (reviewed by Voets and Nilius, 2007; Nilius *et al.*, 2008; Rohacs, 2009). Such regulation is generally not included in the tables.

**TRPC (canonical) family:** Members of the TRPC subfamily (reviewed by Freichel *et al.*, 2005; Putney, 2005; Ambudkar and Ong, 2007; Abramowitz and Birnbaumer, 2009; Birnbaumer, 2009; Kiselyov and Patterson, 2009; Patel *et al.*, 2010; Beech, 2011) fall into the subgroups tabulated below. TRPC2 (not tabulated) is a pseudogene in man. It is generally accepted that all TRPC channels are activated downstream of  $\text{G}_{q/11}$ -coupled receptors, or receptor tyrosine kinases (reviewed by Plant and Schaefer, 2003; Trebak *et al.*, 2007; Wu *et al.*, 2010). A comprehensive listing of G-protein coupled receptors that activate TRPC channels is given in Abramowitz and Birnbaumer (2009). Hetero-oligomeric complexes of TRPC channels and their association with proteins to form signalling complexes are detailed in Ambudkar and Ong (2007) and Kiselyov *et al.* (2007b). TRPC channels have frequently been proposed to act as store-operated channels (SOCs) (or components of multimeric complexes that form SOC), activated by depletion of intracellular calcium stores (reviewed by Pedersen *et al.*, 2005; Ambudkar and Ong, 2007; Potier and Trebak, 2008; Salido *et al.*, 2009; Yuan *et al.*, 2009; Cheng *et al.*, 2011), but this is controversial. All members of the TRPC family are blocked by 2-APB and SKF96356 (Harteneck and Gollasch, 2011; Harteneck *et al.*, 2011). Activation of TRPC channels by lipids is discussed by Beech (2011).

**TRPC1/C4/C5 subgroup:** TRPC4/C5 may be distinguished from other TRP channels by their potentiation by micromolar concentrations of  $\text{La}^{3+}$ .

| Nomenclature               | TRPC1                                                                                                                                                                                                                                   | TRPC4                                                                                                                                                                         | TRPC5                                                                                                                                                                                                                                                                                                                                                                                          |
|----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Other names                | TRP1                                                                                                                                                                                                                                    | TRP4, CCE1                                                                                                                                                                    | TRP5, CCE2                                                                                                                                                                                                                                                                                                                                                                                     |
| Ensembl ID                 | ENSG00000144935                                                                                                                                                                                                                         | ENSG00000133107                                                                                                                                                               | ENSG00000072315                                                                                                                                                                                                                                                                                                                                                                                |
| Physical activators        | Membrane stretch (likely indirect)                                                                                                                                                                                                      | –                                                                                                                                                                             | Membrane stretch (likely indirect)                                                                                                                                                                                                                                                                                                                                                             |
| Chemical activators        | Activated by NO-mediated cysteine S-nitrosylation                                                                                                                                                                                       | Activated by NO-mediated cysteine S-nitrosylation, $\text{La}^{3+}$ (micromolar), potentiated by extracellular protons                                                        | NO-mediated cysteine S-nitrosylation (disputed), lysophosphatidylcholine, genesteine (independent of tyrosine kinase inhibition, Wong <i>et al.</i> , 2010), diadzein, $\text{La}^{3+}$ (micromolar), $\text{Gd}^{3+}$ (0.1 mM), $\text{Pb}^{2+}$ (5 $\mu\text{M}$ ), intracellular $\text{Ca}^{2+}$ ( $\text{EC}_{50}$ = 635 nM at negative potentials), potentiated by extracellular protons |
| Blockers                   | GsMTx-4, 2-APB, SKF96365, $\text{Gd}^{3+}$ , $\text{La}^{3+}$                                                                                                                                                                           | ML204 ( $\text{IC}_{50}$ = 2.9 $\mu\text{M}$ , Miller <i>et al.</i> , 2011), 2-APB, SKF96365, niflumic acid, $\text{La}^{3+}$ (millimolar)                                    | ML204 ( $\text{IC}_{50}$ $\approx$ 10 $\mu\text{M}$ , Miller <i>et al.</i> , 2011), GsMTx-4, SKF96365, 2-APB, KB-R7943, BTP2 (Pyr2), flufenamic acid, chlorpromazine, $\text{La}^{3+}$ (millimolar)                                                                                                                                                                                            |
| Functional characteristics | $\gamma$ = 16 pS (fluctuation analysis), conducts mono- and di-valent cations non-selectively; monovalent cation current suppressed by extracellular $\text{Ca}^{2+}$ ; non-rectifying, or mildly inwardly rectifying; non-inactivating | $\gamma$ = 30–41 pS, conducts mono- and di-valent cations non-selectively ( $\text{P}_{\text{Ca}}/\text{P}_{\text{Na}}$ = 1.1 – 7.7); dual (inward and outward) rectification | $\gamma$ = 41–63 pS; conducts mono- and di-valent cations non-selectively ( $\text{P}_{\text{Ca}}/\text{P}_{\text{Na}}$ = 1.8 – 9.5); dual rectification (inward and outward) as a homomer, outwardly rectifying when expressed with TRPC1 or TRPC4                                                                                                                                            |

**TRPC3/C6/C7 subgroup.** All members are activated by diacylglycerol independent of protein kinase C stimulation (Harteneck and Gollasch, 2011).

| Nomenclature        | TRPC3           | TRPC6                              | TRPC7           |
|---------------------|-----------------|------------------------------------|-----------------|
| Other names         | TRP3            | TRP6                               | TRP7            |
| Ensembl ID          | ENSG00000138741 | ENSG00000137672                    | ENSG00000069018 |
| Physical activators | –               | Membrane stretch (likely indirect) | –               |

|                            |                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                            |
|----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature               | TRPC3                                                                                                                                                                                                             | TRPC6                                                                                                                                                                                                                                                                                 | TRPC7                                                                                                                                                                                                                                                                                                                      |
| Chemical activators        | Diacylglycerols                                                                                                                                                                                                   | Hyperforin (Leuner <i>et al.</i> , 2007), 2,4 diahexanxoylphloroglucinol (Leuner <i>et al.</i> , 2010), diacylglycerols, lysophosphatidylcholine, flufenamate, arachidonic acid, 20-HETE                                                                                              | Diacylglycerols                                                                                                                                                                                                                                                                                                            |
| Blockers                   | Pyr3 (Kiyonaka <i>et al.</i> , 2009), 2-APB, SKF96365, ACA, KB-R7943, BTP2 (Pyr2), Gd <sup>3+</sup> , La <sup>3+</sup> , Ni <sup>2+</sup>                                                                         | GsMTx-4, SKF96365, 2-APB, amiloride, ACA, KB-R7943, ML-9, La <sup>3+</sup> (IC <sub>50</sub> $\approx$ 6 $\mu$ M), Gd <sup>3+</sup> , Cd <sup>2+</sup> , extracellular protons                                                                                                        | SKF96365, 2-APB, amiloride, La <sup>3+</sup>                                                                                                                                                                                                                                                                               |
| Functional characteristics | $\gamma$ = 66 pS; conducts mono- and di-valent cations non-selectively ( $P_{Ca}/P_{Na}$ = 1.6); monovalent cation current suppressed by extracellular Ca <sup>2+</sup> ; dual (inward and outward) rectification | $\gamma$ = 28–37 pS; conducts mono- and divalent cations with a preference for divalents ( $P_{Ca}/P_{Na}$ = 4.5–5.0); monovalent cation current suppressed by extracellular Ca <sup>2+</sup> and Mg <sup>2+</sup> , dual rectification (inward and outward), or inward rectification | $\gamma$ = 25–75 pS; conducts mono and divalent cations with a preference for divalents ( $P_{Ca}/P_{Cs}$ = 5.9); modest outward rectification (monovalent cation current recorded in the absence of extracellular divalents); monovalent cation current suppressed by extracellular Ca <sup>2+</sup> and Mg <sup>2+</sup> |

**TRPM (melastatin) family:** Members of the TRPM subfamily (reviewed by Fleig and Penner, 2004; Harteneck, 2005; Pedersen *et al.*, 2005; Zholos, 2010) fall into the five subgroups tabulated below.

**TRPM1/M3 subgroup:** TRPM1 exists as five splice variants and is involved in normal melanocyte pigmentation (Oancea *et al.*, 2009) and is also a visual transduction channel in retinal ON bipolar cells (Koike *et al.*, 2010). TRPM3 (reviewed by Oberwinkler and Philipp, 2007) exists as multiple splice variants four of which (mTRPM3 $\alpha$ 1, mTRPM3 $\alpha$ 2, hTRPM3 $\alpha$  and hTRPM3<sub>1325</sub>) have been characterised and found to differ significantly in their biophysical properties. TRPM3 has recently been found to contribute to the detection of noxious heat (Vriens *et al.*, 2011).

|                            |                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|----------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature               | TRPM1                                                                                         | TRPM3                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Other names                | LTRPC1, Melastatin                                                                            | LTRPC3                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Ensembl ID                 | ENSG00000134160                                                                               | ENSG00000083067                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Physical activators        | –                                                                                             | Heat ( $Q_{10}$ = 7.2 between 15–25°C; Vriens <i>et al.</i> , 2011), hypotonic cell swelling                                                                                                                                                                                                                                                                                                                                              |
| Chemical activators        | Pregnenolone sulphate (Lambert <i>et al.</i> , 2011)                                          | Pregnenolone sulphate (Wagner <i>et al.</i> , 2008), epipregnanolone sulphate (Majeed <i>et al.</i> , 2010), nifedipine, D-erythro-sphingosine, dihydrosphingosine                                                                                                                                                                                                                                                                        |
| Blockers                   | Zn <sup>2+</sup> (IC <sub>50</sub> = 1 $\mu$ M)                                               | Rosiglitazone, troglitazone, pioglitazone (independent of PPAR- $\gamma$ ; Majeed <i>et al.</i> , 2011), mefenamic acid, Klose <i>et al.</i> , 2011), 2-APB, La <sup>3+</sup> , Gd <sup>3+</sup> , intracellular Mg <sup>2+</sup> , extracellular Na <sup>+</sup> (TRPM3 $\alpha$ 2 only)                                                                                                                                                 |
| Functional characteristics | Conducts mono- and di-valent cations non-selectively, dual rectification (inward and outward) | TRPM3 <sub>1235</sub> : $\gamma$ = 83 pS (Na <sup>+</sup> current), 65 pS (Ca <sup>2+</sup> current); conducts mono- and di-valent cations non-selectively ( $P_{Ca}/P_{Na}$ = 1.6)<br>TRPM3 $\alpha$ 1: selective for monovalent cations ( $P_{Ca}/P_{Cs}$ = 0.1)<br>TRPM3 $\alpha$ 2: conducts mono- and di-valent cations non-selectively ( $P_{Ca}/P_{Cs}$ = 1–10)<br>Outwardly rectifying (magnitude varies between splice variants) |

**TRPM2:** TRPM2 functions as a sensor of redox status in cells and is also activated by heat (reviewed by Yamamoto *et al.*, 2010). Numerous splice variants of TRPM2 exist which differ in their activation mechanisms (Du *et al.*, 2009).

|                            |                                                                                                                                                                                                                                                                                                                                                                                                                |
|----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature               | TRPM2                                                                                                                                                                                                                                                                                                                                                                                                          |
| Other names                | (TRPC7, LTRPC2)                                                                                                                                                                                                                                                                                                                                                                                                |
| Ensembl ID                 | ENSG00000142185                                                                                                                                                                                                                                                                                                                                                                                                |
| Physical activators        | Heat $\sim$ 35°C                                                                                                                                                                                                                                                                                                                                                                                               |
| Chemical activators        | Intracellular Ca <sup>2+</sup> via calmodulin, intracellular ADP ribose (ADPR) and cyclic ADPR (cADPR); agents producing reactive oxygen (e.g. H <sub>2</sub> O <sub>2</sub> ) and nitrogen (e.g. GEA 3162) species; potentiated by arachidonic acid                                                                                                                                                           |
| Blockers                   | 2-APB, ACA, clotrimazole, miconazole, econazole, flufenamic acid, Zn <sup>2+</sup> , extracellular protons                                                                                                                                                                                                                                                                                                     |
| Functional characteristics | $\gamma$ = 52–60 pS at negative potentials, 76 pS at positive potentials; conducts mono- and di-valent cations non-selectively ( $P_{Ca}/P_{Na}$ = 0.6–0.7); non-rectifying; inactivation at negative potentials; activated by oxidative stress probably via PARP-1, PARP inhibitors reduce activation by oxidative stress, activation inhibited by suppression of APDR formation by glycohydrolase inhibitors |

$\text{Ca}^{2+}$  activates all slice variants of TRPM2, but other activators listed are effective only at the full length isoform (Du *et al.*, 2009). Inhibition of TRPM2 by clotrimazole, miconazole, econazole, flufenamic acid is largely irreversible.

**TRPM4/5 subgroup:** TRPM4 and TRPM5 are thermosensitive and have the distinction within all TRP channels of being impermeable to  $\text{Ca}^{2+}$  (Wu *et al.*, 2010). A splice variant of TRPM4 (*i.e.* TRPM4b) and TRPM5 are molecular candidates for endogenous calcium-activated cation (CAN) channels (Guinamard *et al.*, 2011). TRPM4 has been shown to be an important regulator of  $\text{Ca}^{2+}$  entry in to mast cells (Vennekens *et al.*, 2007) and dendritic cell migration (Barbet *et al.*, 2008). TRPM5 in taste receptor cells of the tongue appears essential for the transduction of sweet, amino acid and bitter stimuli (Liman, 2007).

|                            |                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                             |
|----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature               | TRPM4                                                                                                                                                                                                                                                                                                                                           | TRPM5                                                                                                                                                                                                                                                                                       |
| Other names                | LTRPC4                                                                                                                                                                                                                                                                                                                                          | TRP-T                                                                                                                                                                                                                                                                                       |
| Ensembl ID                 | ENSG00000130529                                                                                                                                                                                                                                                                                                                                 | ENSG00000070985                                                                                                                                                                                                                                                                             |
| Physical activators        | Membrane depolarization ( $V_{1/2} = -20$ to $+60$ mV dependent upon conditions) in the presence of elevated $[\text{Ca}^{2+}]_i$ , heat ( $Q_{10} = 8.5$ @ $+25$ mV between $15$ – $25^\circ\text{C}$ )                                                                                                                                        | Membrane depolarization ( $V_{1/2} = 0$ to $+120$ mV dependent upon conditions), heat ( $Q_{10} = 10.3$ @ $-75$ mV between $15$ and $25^\circ\text{C}$ )                                                                                                                                    |
| Chemical activators        | Decavanadate, whole cell current transiently activated by intracellular $\text{Ca}^{2+}$ ( $\text{EC}_{50}$ $0.3$ – $20$ $\mu\text{M}$ ), enhanced by BTP2                                                                                                                                                                                      | Rosiglitazone (Majeed <i>et al.</i> , 2011), transiently activated by intracellular $\text{Ca}^{2+}$ ( $\text{EC}_{50}$ $635$ – $840$ nM)                                                                                                                                                   |
| Blockers                   | Clotrimazole, 9-phenanthrol, intracellular nucleotides ( $\text{ATP}^{4-}$ , ADP, AMP, AMP-PNP – $\text{IC}_{50}$ range $1.3$ – $19$ $\mu\text{M}$ ) and adenosine ( $\text{IC}_{50}$ $630$ $\mu\text{M}$ ); intracellular spermine ( $\text{IC}_{50} = 35$ – $61$ $\mu\text{M}$ ) and flufenamic acid ( $\text{IC}_{50} = 2.8$ $\mu\text{M}$ ) | Intracellular spermine ( $\text{IC}_{50} = 37$ $\mu\text{M}$ ) and flufenamic acid ( $\text{IC}_{50} = 24$ $\mu\text{M}$ ), extracellular protons ( $\text{IC}_{50} = 630$ nM), (not inhibited by $\text{ATP}^{4-}$ )                                                                       |
| Functional characteristics | $\gamma = 23$ pS (within the range $60$ to $+60$ mV); permeable to monovalent cations; impermeable to $\text{Ca}^{2+}$ ; strong outward rectification; slow activation at positive potentials, rapid deactivation at negative potentials, deactivation blocked by decavanadate                                                                  | $\gamma = 15$ – $25$ pS; conducts monovalent cations selectively ( $P_{\text{Ca}}/P_{\text{Na}} = 0.05$ ); strong outward rectification; slow activation at positive potentials, rapid inactivation at negative potentials; activated and subsequently desensitized by $[\text{Ca}^{2+}]_i$ |

TRPM4 exists as multiple splice variants: data listed are for TRPM4b. The sensitivity of TRPM4b and TRPM5 to activation by  $[\text{Ca}^{2+}]_i$  demonstrates a pronounced and time-dependent reduction following excision of inside-out membrane patches (Ullrich *et al.*, 2005). The  $V_{1/2}$  for activation of TRPM4 and TRPM5 demonstrates a pronounced negative shift with increasing temperature.

**TRPM6/M7 subgroup:** TRPM6 and 7 combine channel and enzymatic activities ('chanzymes') and are involved in  $\text{Mg}^{2+}$  homeostasis (reviewed by Penner and Fleig, 2007; Bates-Withers *et al.*, 2011; Runnels, 2011).

|                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature               | TRPM6                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | TRPM7                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Other names                | –                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | TRP-PLIK, Chak1, MagNum, MIC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Ensembl ID                 | ENSG00000119121                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | ENSG00000092439                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Physical activators        | –                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | –                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Chemical activators        | Constitutively active, activated by reduction of intracellular $\text{Mg}^{2+}$ , potentiated by extracellular protons and 2-APB (micromolar)                                                                                                                                                                                                                                                                                                                                                                | Elevated cAMP and activation of PKA; potentiated by intracellular ATP; potentiated by extracellular protons, 2-APB (millimolar)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Blockers                   | Ruthenium red (voltage dependent block, $\text{IC}_{50} = 100$ nM at $-120$ mV), inward current mediated by monovalent cations blocked by $\text{Ca}^{2+}$ ( $\text{IC}_{50} = 4.8$ – $5.4$ $\mu\text{M}$ ) and $\text{Mg}^{2+}$ ( $\text{IC}_{50} = 1.1$ – $3.4$ $\mu\text{M}$ )                                                                                                                                                                                                                            | Spermine (permeant blocker), carvacrol, $\text{La}^{3+}$ , $\text{Mg}^{2+}$ , 2-APB (micromolar)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Functional characteristics | $\gamma = 40$ – $87$ pS; permeable to mono- and di-valent cations with a preference for divalents ( $\text{Mg}^{2+} > \text{Ca}^{2+}$ ; $P_{\text{Ca}}/P_{\text{Na}} = 6.9$ ), conductance sequence $\text{Zn}^{2+} > \text{Ba}^{2+} > \text{Mg}^{2+} = \text{Ca}^{2+} = \text{Mn}^{2+} > \text{Sr}^{2+} > \text{Cd}^{2+} > \text{Ni}^{2+}$ ; strong outward rectification abolished by removal of extracellular divalents, inhibited by intracellular $\text{Mg}^{2+}$ ( $\text{IC}_{50} = 0.5$ mM) and ATP | $\gamma = 40$ – $105$ pS at negative and positive potentials respectively; conducts mono- and di-valent cations with a preference for monovalents ( $P_{\text{Ca}}/P_{\text{Na}} = 0.34$ ); conductance sequence $\text{Ni}^{2+} > \text{Zn}^{2+} > \text{Ba}^{2+} = \text{Mg}^{2+} > \text{Ca}^{2+} = \text{Mn}^{2+} > \text{Sr}^{2+} > \text{Cd}^{2+}$ ; outward rectification, decreased by removal of extracellular divalent cations; inhibited by intracellular $\text{Mg}^{2+}$ , $\text{Ba}^{2+}$ , $\text{Sr}^{2+}$ , $\text{Zn}^{2+}$ , $\text{Mn}^{2+}$ and $\text{Mg}$ .ATP (disputed); activated by and intracellular alkalinization; sensitive to osmotic gradients |

**TRPM8:** Is a channel activated by cooling and pharmacological agents evoking a 'cool' sensation and participates in the thermosensation of cold temperatures (Bautista *et al.*, 2007; Colburn *et al.*, 2007; Dhaka *et al.*, 2007; reviewed by Voets *et al.* (2007), Liu and Qin (2011), Knowlton and McKemy (2011), Mätkiä *et al.* (2011).

|                            |                                                                                                                                                                                                                                                                                                                                |
|----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature               | TRPM8                                                                                                                                                                                                                                                                                                                          |
| Other names                | CMR1, TRP-p8                                                                                                                                                                                                                                                                                                                   |
| Ensembl ID                 | ENSG00000144481                                                                                                                                                                                                                                                                                                                |
| Physical activators        | Depolarization ( $V_{1/2} \approx +50$ mV at 15°C), cooling (<22–26°C)                                                                                                                                                                                                                                                         |
| Chemical Activators        | WS-12, (-)-menthol (inhibited by intracellular $Ca^{2+}$ ), icilin (requires intracellular $Ca^{2+}$ as a co-factor for full agonist activity); agonist activities are temperature dependent and potentiated by cooling                                                                                                        |
| Blockers                   | AMTB (Lashinger <i>et al.</i> , 2008), 5-benzoyloxytryptamine, clotrimazole, BCTC, capsaizepine, 2-APB, $La^{3+}$ , ACA, anandamide, NADA, linoleic acid, cannabinoids ( <i>e.g.</i> , cannabidiol, THC); insensitive to ruthenium red                                                                                         |
| Functional characteristics | $\gamma = 40$ –83 pS at positive potentials; conducts mono- and di-valent cations non-selectively ( $P_{Ca}/P_{Na} = 1.0$ –3.3); pronounced outward rectification; demonstrates desensitization to chemical agonists and adaptation to a cold stimulus in the presence of $Ca^{2+}$ ; modulated by lysophospholipids and PUFAs |

Activation of TRPM8 by depolarization is strongly temperature-dependent *via* a channel-closing rate that decreases with decreasing temperature. The  $V_{1/2}$  is shifted in the hyperpolarizing direction both by decreasing temperature and by exogenous agonists, such as menthol (Voets *et al.*, 2004) whereas antagonists produce depolarizing shifts in  $V_{1/2}$  (Mätkiä *et al.*, 2007). The  $V_{1/2}$  for the native channel is far more positive than that of heterologously expressed TRPM8 (Mätkiä *et al.*, 2007). It should be noted that menthol and structurally related compounds can elicit release of  $Ca^{2+}$  from the endoplasmic reticulum independent of activation of TRPM8 (Mahieu *et al.*, 2007). Intracellular pH modulates activation of TRPM8 by cold and icilin, but not menthol (Andersson *et al.*, 2004).

**TRPA (ankyrin) family:** TRPA1 is the sole mammalian member of this group (reviewed by Garcia-Anoveros and Nagata, 2007). In some (Story *et al.*, 2003; Bandell *et al.*, 2004; Sawada *et al.*, 2007; Karashima *et al.*, 2009), but not other (Jordt *et al.*, 2004; Nagata *et al.*, 2005), studies TRPA1 is activated by noxious cold. One study suggests that activation of TRPA1 is secondary to a cold-induced elevation of  $[Ca^{2+}]_i$  (Zurborg *et al.*, 2007), but this has been refuted (Karashima *et al.*, 2009). Additionally, TRPA1 has been proposed to be a component of a mechanosensitive transduction channel of vertebrate hair cells (Corey *et al.*, 2004; Nagata *et al.*, 2005), but TRPA1<sup>-/-</sup> mice demonstrate no impairment in hearing, or vestibular function (Bautista *et al.* 2006; Kwan *et al.*, 2006). There is consensus that TRPA1 acts as a nociceptor for environmental irritants (Baraldi *et al.*, 2010).

|                            |                                                                                                                                                                                                               |
|----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature               | TRPA1                                                                                                                                                                                                         |
| Other names                | ANKTM1, p120, TRPN1                                                                                                                                                                                           |
| Ensembl ID                 | ENSG00000104321                                                                                                                                                                                               |
| Physical activators        | Cooling (<17°C) (disputed)                                                                                                                                                                                    |
| Chemical Activators        |                                                                                                                                                                                                               |
| Covalent                   | <i>e.g.</i> Isothiocyanates, cinnamaldehyde, allicin, acrolein, formalin, chlorobenzylidene malononitrile                                                                                                     |
| Non-covalent               | <i>e.g.</i> URB597 ( $EC_{50} = 24$ $\mu$ M, Niforatus <i>et al.</i> , 2007), nicotine ( $EC_{50} \approx 20$ $\mu$ M), icilin (-)-menthol (1–100 $\mu$ M), thymol (1–100 $\mu$ M), THC, 1,4-dihydropyridines |
| Blockers ( $IC_{50}$ )     | AP18 (3.1 $\mu$ M, Petrus <i>et al.</i> , 2007), HC030031 (6.2 $\mu$ M, McNamara <i>et al.</i> , 2007), ruthenium red ( $IC_{50} < 1$ –3 $\mu$ M)                                                             |
| Functional characteristics | $\gamma = 87$ –100 pS; conducts mono- and di-valent cations non-selectively ( $P_{Ca}/P_{Na} = 0.84$ ); outward rectification; activated by elevated intracellular $Ca^{2+}$ .                                |

Agents activating TRPA1 in a covalent manner are thiol reactive electrophiles that bind to cysteine and lysine residues within the cytoplasmic domain of the channel (Hinman *et al.*, 2006; Macpherson *et al.*, 2007). TRPA1 is activated by a wide range of endogenous and exogenous compounds and only a few representative examples are mentioned in the table: an exhaustive listing can be found in Baraldi *et al.* (2010). In addition, TRPA1 is potently activated by intracellular zinc ( $EC_{50} = 8$  nM) (Andersson *et al.*, 2009; Hu *et al.*, 2009).

**TRPV (vanilloid) family:** Members of the TRPV family (reviewed by Vennekens *et al.*, 2008) can broadly be divided into the thermosensitive, non-selective cation channels, TRPV1–4 and the calcium selective channels TRPV5 and TRPV6.

**TRPV1–V4 subfamily:** TRPV1 is involved in the development of thermal hyperalgesia following inflammation and may contribute to the detection of noxious heat (reviewed by Pringle *et al.*, 2007; Starowicz *et al.*, 2007; Szallasi *et al.*, 2007). Numerous splice variants of TRPV1 have been described, some of which modulate the activity of TRPV1, or act in a dominant negative manner when co-expressed with TRPV1 (see Schumacher and Eilers, 2010). The pharmacology of TRPV1 channels is discussed in detail in Gunthorpe and Chizh (2009) and Vriens *et al.* (2009). TRPV2 is probably not a thermosensor in man (Park *et al.*, 2011), but has recently been implicated in innate immunity (Link *et al.*, 2010). TRPV3 and TRPV4 are both thermosensitive, with the latter also having a mechanosensing function (Eveaerts *et al.*, 2010a).

|                     |                                                                                   |                                          |
|---------------------|-----------------------------------------------------------------------------------|------------------------------------------|
| Nomenclature        | TRPV1                                                                             | TRPV2                                    |
| Other names         | VR1, vanilloid/capsaicin receptor, OTRPC1                                         | VRL-1, OTRPC2, GRC                       |
| Ensembl ID          | ENSG00000043316                                                                   | ENSG00000154039                          |
| Physical activators | Depolarization ( $V_{1/2} \approx 0$ mV at 35°C), noxious heat (>43°C at pH 7.4), | Noxious heat (>53°C, rodent, not human), |

|                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                            |
|----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature               | TRPV1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | TRPV2                                                                                                                                                                                                                                                                                                                                                      |
| Chemical Activators        | DkTx (irreversible), extracellular protons ( $pEC_{50} = 5.4$ at $37^{\circ}\text{C}$ ), capsaicin, resiniferatoxin, vanillotoxins, phenylacetyltrivanil, olvanil, anandamide, camphor, allicin, some eicosanoids ( <i>e.g.</i> , 12-(S)-HPETE, 15-(S)-HPETE, 5-(S)-HETE, leukotriene $B_4$ ), NADA, 2-APB, DPBA, activated by NO-mediated cysteine S-nitrosylation                                                                                                                                                              | Probenecid, 2-APB (rodent, not human), DPBA, cannabidiol, THC                                                                                                                                                                                                                                                                                              |
| Blockers ( $IC_{50}$ )     | Ruthenium red (0.09–0.22 $\mu\text{M}$ ), 5'-iodoresiniferatoxin (3.9 nM), 6-iodo-nordihydrocapsaicin (10 nM), BCTC (6–35 nM), capsazepine (40–280 nM), A-425619 (5 nM), A-778317 (5 nM), AMG517 (0.9 nM), AMG 628 (3.7 nM), JNJ17203212 (65 nM), JYL1421 (9.2 nM), SB366791 (18 nM), SB452533, SB-705498 (3–6 nM)                                                                                                                                                                                                               | Ruthenium red (0.6 $\mu\text{M}$ ), SKF96365, amiloride, TRIM, $\text{La}^{3+}$                                                                                                                                                                                                                                                                            |
| Probes ( $K_D$ )           | $[^3\text{H}]$ -A-778317 (3.4 nM), $[^3\text{H}]$ -resiniferatoxin, $[^{125}\text{I}]$ -resiniferatoxin                                                                                                                                                                                                                                                                                                                                                                                                                          | –                                                                                                                                                                                                                                                                                                                                                          |
| Functional characteristics | $\gamma = 35$ pS at $-60$ mV; 77 pS at $+60$ mV, conducts mono- and di-valent cations with a selectivity for divalents ( $P_{\text{Ca}}/P_{\text{Na}} = 9.6$ ); voltage- and time- dependent outward rectification; potentiated by ethanol; activated/potentiated/upregulated by PKC stimulation; extracellular acidification facilitates activation by PKC; desensitisation inhibited by PKA; inhibited by $\text{Ca}^{2+}$ /calmodulin; cooling reduces vanilloid-evoked currents; may be tonically active at body temperature | Conducts mono- and di-valent cations ( $P_{\text{Ca}}/P_{\text{Na}} = 0.9\text{--}2.9$ ); dual (inward and outward) rectification; current increases upon repetitive activation by heat; translocates to cell surface in response to IGF-1 to induce a constitutively active conductance, translocates to the cell surface in response to membrane stretch |

|                            |                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature               | TRPV3                                                                                                                                                                                                         | TRPV4                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Other names                | –                                                                                                                                                                                                             | VRL-2, OTRPC4, VR-OAC, TRP12                                                                                                                                                                                                                                                                                                                                                                                                              |
| Ensembl ID                 | ENSG00000167723                                                                                                                                                                                               | ENSG00000111199                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Physical activators        | Depolarization ( $V_{1/2} \sim +80$ mV, reduced to more negative values following heat stimuli), heat ( $23^{\circ}\text{--}39^{\circ}\text{C}$ , temperature threshold reduces with repeated heat challenge) | Constitutively active, heat ( $> 24\text{--}32^{\circ}\text{C}$ ), mechanical stimuli                                                                                                                                                                                                                                                                                                                                                     |
| Chemical activators        | 6-tert-butyl-m-cresol, carvacrol, eugenol, thymol, camphor, menthol, incensole acetate, 2-APB, DPBA, NO-mediated cysteine S-nitrosylation                                                                     | GSK1016790A ( $EC_{50} = 2.1$ nM, Thorne et al., 2008), RN1747 ( $EC_{50} = 0.77$ $\mu\text{M}$ , Vincent et al., 2009), bisandrographolide A, 4 $\alpha$ -PDH, 4 $\alpha$ -PDD, PMA, epoxyeicosatrienoic acids, NO-mediated cysteine S-nitrosylation                                                                                                                                                                                     |
| Blockers                   | Ruthenium red ( $<1$ $\mu\text{M}$ ), DPTHF (6–10 $\mu\text{M}$ )                                                                                                                                             | HC067047 ( $IC_{50} = 17$ nM, Everaerts et al., 2010b), RN1734 ( $IC_{50} = 2.3$ $\mu\text{M}$ , Vincent et al., 2009), ruthenium red (voltage dependent block), $\text{La}^{3+}$ , $\text{Gd}^{3+}$                                                                                                                                                                                                                                      |
| Functional characteristics | $\gamma = 197$ pS at $+40$ to $+80$ mV, 48 pS at negative potentials; conducts mono- and di-valent cations; outward rectification; potentiated by arachidonic acid                                            | $\gamma = \sim 60$ pS at $-60$ mV, $\sim 90\text{--}100$ pS at $+60$ mV; conducts mono- and di-valent cations with a preference for divalents ( $P_{\text{Ca}}/P_{\text{Na}} = 6\text{--}10$ ); dual (inward and outward) rectification; potentiated by intracellular $\text{Ca}^{2+}$ via $\text{Ca}^{2+}$ /calmodulin; inhibited by elevated intracellular $\text{Ca}^{2+}$ via an unknown mechanism ( $IC_{50} = 0.4$ $\mu\text{M}$ ); |

Activation of TRPV1 by depolarisation is strongly temperature-dependent *via* a channel opening rate that increases with increasing temperature. The  $V_{1/2}$  is shifted in the hyperpolarizing direction both by increasing temperature and by exogenous agonists (Voets *et al.*, 2004). The sensitivity of TRPV4 to heat, but not 4 $\alpha$ -PDD, is lost upon patch excision. TRPV4 is activated by anandamide and arachidonic acid following P450 epoxygenase-dependent metabolism to 5',6'-epoxyeicosatrienoic acid (reviewed by Nilius *et al.*, 2004). Activation of TRPV4 by cell swelling, but not heat, or phorbol esters, is mediated *via* the formation of epoxyeicosatrienoic acids. Phorbol esters bind directly to TRPV4.

**TRPV5/V6 subfamily:** Under physiological conditions, TRPV5 and TRPV6 are calcium selective channels involved in the absorption and reabsorption of calcium across intestinal and kidney tubule epithelia (reviewed by Wissenbach and Niemeyer, 2007; de Groot *et al.*, 2008).

|              |                                                                                  |                                                                                                        |
|--------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Nomenclature | TRPV5                                                                            | TRPV6                                                                                                  |
| Other names  | ECaC, ECaC1, CaT2, OTRPC3                                                        | ECaC2, CaT1, CaT-L                                                                                     |
| Ensembl ID   | ENSG00000127412                                                                  | ENSG00000165125                                                                                        |
| Activators   | Constitutively active (with strong buffering of intracellular $\text{Ca}^{2+}$ ) | Constitutively active (with strong buffering of intracellular $\text{Ca}^{2+}$ ), potentiated by 2-APB |

|                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature               | TRPV5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | TRPV6                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Blockers                   | Ruthenium red ( $IC_{50} = 121$ nM), econazole, miconazole, $Pb^{2+} = Cu^{2+} = Gd^{3+} > Cd^{2+} > Zn^{2+} > La^{3+} > Co^{2+} > Fe^{2+}$ ; $Mg^{2+}$                                                                                                                                                                                                                                                                                                                                | Ruthenium red ( $IC_{50} = 9$ $\mu$ M), $Cd^{2+}$ , $Mg^{2+}$ , $La^{3+}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Functional characteristics | $\gamma = 59$ – $78$ pS for monovalent ions at negative potentials, conducts mono- and di-valents with high selectivity for divalents ( $P_{Ca}/P_{Na} > 107$ ); voltage- and time- dependent inward rectification; inhibited by intracellular $Ca^{2+}$ promoting fast inactivation and slow downregulation; feedback inhibition by $Ca^{2+}$ reduced by calcium binding protein 80-K-H; inhibited by extracellular and intracellular acidosis; upregulated by 1,25-dihydrovitamin D3 | $\gamma = 58$ – $79$ pS for monovalent ions at negative potentials, conducts mono- and di-valents with high selectivity for divalents ( $P_{Ca}/P_{Na} > 130$ ); voltage- and time-dependent inward rectification; inhibited by intracellular $Ca^{2+}$ promoting fast and slow inactivation; gated by voltage-dependent channel blockade by intracellular $Mg^{2+}$ ; slow inactivation due to $Ca^{2+}$ -dependent calmodulin binding; phosphorylation by PKC inhibits $Ca^{2+}$ -calmodulin binding and slow inactivation; upregulated by 1,25-dihydroxyvitamin D3 |

TRPV5 preferentially conducts  $Ca^{2+}$  under physiological conditions, but in the absence of extracellular  $Ca^{2+}$ , conducts monovalent cations. Single channel conductances listed for TRPV5 and TRPV6 were determined in divalent cation-free extracellular solution.  $Ca^{2+}$ -induced inactivation occurs at hyperpolarized potentials when  $Ca^{2+}$  is present extracellularly. Single channel events cannot be resolved (probably due to greatly reduced conductance) in the presence of extracellular divalent cations. Measurements of  $P_{Ca}/P_{Na}$  for TRPV5 and TRPV6 are dependent upon ionic conditions due to anomalous mole fraction behaviour. Blockade of TRPV5 and TRPV6 by extracellular  $Mg^{2+}$  is voltage-dependent. Intracellular  $Mg^{2+}$  also exerts a voltage dependent block that is alleviated by hyperpolarization and contributes to the time-dependent activation and deactivation of TRPV6 mediated monovalent cation currents. TRPV5 and TRPV6 differ in their kinetics of  $Ca^{2+}$ -dependent inactivation and recovery from inactivation. TRPV5 and TRPV6 function as homo- and hetero-tetramers.

**TRPML (mucolipin) family:** The TRPML family (see Qian and Noben-Trauth, 2005; Zeevi *et al.*, 2007; Puertollano and Kiselyov, 2009) consists of three mammalian members (TRPML1-3). TRPML channels are probably restricted to intracellular vesicles and mutations in the gene (*MCOLN1*) encoding TRPML1 (mucolipin-1) are the cause of the neurodegenerative disorder mucopolipidosis type IV (MLIV) in man. TRPML1 is a cation selective ion channel that is important for sorting/transport of endosomes in the late endocytotic pathway and specifically fusion between late endosome-lysosome hybrid vesicles. TRPML2 (*MCLN2*) remains to be functionally characterised in detail. TRPML3 is important for hair cell maturation, stereocilia maturation and intracellular vesicle transport. A naturally occurring gain of function mutation in TRPML3 (*i.e.* A419P) results in the varitint waddler (*Va*) mouse phenotype (reviewed by Qian and Noben-Trauth, 2005; Nilius *et al.*, 2007).

|                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature               | TRPML1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | TRPML2                                                                                                                                        | TRPML3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Other names                | MCLN1, mucolipin-1 (ML1)                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | MCLN2                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Ensembl ID                 | ENSG00000090674                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | ENSG00000153898                                                                                                                               | ENSG00000055732                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Activators                 | TRPML1 <sup>Va</sup> : Constitutively active, current potentiated by extracellular acidification (equivalent to intralysosomal acidification)                                                                                                                                                                                                                                                                                                                                               | TRPML2 <sup>Va</sup> : Constitutively active, current potentiated by extracellular acidification (equivalent to intralysosomal acidification) | TRPML3 <sup>Va</sup> : Constitutively active, current inhibited by extracellular acidification (equivalent to intralysosomal acidification)<br>Wild type TRPML3: Activated by $Na^+$ -free extracellular (extracytosolic) solution and membrane depolarization, current inhibited by extracellular acidification (equivalent to intralysosomal acidification)                                                                                                                                                                                                                                                                     |
| Blockers                   | –                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | –                                                                                                                                             | $Gd^{3+}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Functional characteristics | TRPML1 <sup>Va</sup> : $\gamma = 40$ pS and 76–86 pS at very negative holding potentials with $Fe^{2+}$ and monovalent cations as charge carriers, respectively; conducts $Na^+ \cong K^+ > Cs^+$ and divalent cations ( $Ba^{2+} > Mn^{2+} > Fe^{2+} > Ca^{2+} > Mg^{2+} > Ni^{2+} > Co^{2+} > Cd^{2+} > Zn^{2+} > Cu^{2+}$ ) but not $Fe^{3+}$ , impermeable to protons; monovalent cation flux suppressed by divalent cations ( <i>e.g.</i> $Ca^{2+}$ , $Fe^{2+}$ ); inwardly rectifying | TRPML1 <sup>Va</sup> : Conducts $Na^+$ ; monovalent cation flux suppressed by divalent cations; inwardly rectifying                           | TRPML3 <sup>Va</sup> : $\gamma = 49$ pS at very negative holding potentials with monovalent cations as charge carrier; conducts $Na^+ > K^+ > Cs^+$ with maintained current in the presence of $Na^+$ , conducts $Ca^{2+}$ and $Mg^{2+}$ , but not $Fe^{2+}$ , impermeable to protons; inwardly rectifying<br>Wild type TRPML3: $\gamma = 59$ pS at negative holding potentials with monovalent cations as charge carrier; conducts $Na^+ > K^+ > Cs^+$ and $Ca^{2+}$ ( $P_{Ca}/P_K \cong 350$ ), slowly inactivates in the continued presence of $Na^+$ within the extracellular (extracytosolic) solution; outwardly rectifying |

Data in the table are for TRPML proteins mutated (*i.e.* TRPML1<sup>Va</sup>, TRPML2<sup>Va</sup> and TRPML3<sup>Va</sup>) at loci equivalent to TRPML3 A419P to allow plasma membrane expression when expressed in HEK-293 cells and subsequent characterisation by patch-clamp recording (Grimm *et al.*, 2007; Kim

*et al.*, 2007; Xu *et al.*, 2007; Dong *et al.*, 2008; Nagata *et al.*, 2008). Data for wild type TRPML3 are also tabulated (Kim *et al.*, 2007, 2008; Xu *et al.*, 2007; Nagata *et al.*, 2008). It should be noted that alternative methodologies, particularly in the case of TRPML1, have resulted in channels with differing biophysical characteristics (reviewed by Puertollano and Kiselyov, 2009).

**TRPP (polycystin) family:** The TRPP family (reviewed by Delmas *et al.*, 2004a, Delmas, 2005; Giamarchi *et al.* 2006; Witzgall, 2007; Hofherr and Kötting, 2011) subsumes the polycystins that are divided into two structurally distinct groups, polycystic kidney disease 1-like (PKD1-like) and polycystic kidney disease 2-like (PKD2-like). Members of the PKD1-like group, in mammals, include PKD1 (reclassified as TRPP1), PDKREJ, PKD1L1, PKD1L2 and PKD1L3. The PKD2-like members comprise PKD2, PKD2L1 and PKD2L2, which have renamed TRPP2, TRPP3 and TRPP5, respectively (Moran *et al.*, 2004). PDKREJ (ENSG00000130943), PKD1L1 (ENSG00000158683), PKD1L2 (ENSMUS00000034416), PKD1L3 (ENSG00000187008) and TRPP5 (ENSG00000078795) are not listed in the table due to lack of functional data. Similarly, TRPP1 (ENSG00000008710) is also omitted because although one study (Babich *et al.*, 2004) has reported the induction of a cation conductance in CHO cells transfected with TRPP1, there is no unequivocal evidence that TRPP1 is a channel *per se* and in other studies (*e.g.* Hanaoka *et al.*, 2000, Delmas *et al.*, 2004b) TRPP1 is incapable of producing currents.

| Nomenclature                 | TRPP2                                                                                                                                         | TRPP3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Other names                  | Polycystin-2 (PC2), polycystic kidney disease 2 (PKD2)                                                                                        | Polycystic kidney disease 2-like 1 protein (PKD2L1)                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Ensembl ID                   | ENSG00000118762                                                                                                                               | ENSG00000107593                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Activators                   | Constitutive activity, suppressed by co-expression of TRPP1                                                                                   | Low constitutive activity, enhanced by membrane depolarization; changes in cell volume affect voltage-dependent gating (increased channel opening probability with cell swelling)                                                                                                                                                                                                                                                                                                          |
| Blockers (IC <sub>50</sub> ) | Amiloride, La <sup>3+</sup> , Gd <sup>3+</sup>                                                                                                | Phenamil (0.14 µM), benzamil (1.1 µM), EIPA (10.5 µM), amiloride (143 µM), flufenamate, La <sup>3+</sup> , Gd <sup>3+</sup> ,                                                                                                                                                                                                                                                                                                                                                              |
| Functional characteristics   | γ = 123–177 pS (with K <sup>+</sup> as charge carrier); P <sub>Na</sub> /P <sub>K</sub> = 0.14–1.1; conducts both mono- and di-valent cations | γ = 105–137 pS (outward conductance) 184–399 pS (inward conductance), conducts mono- and di-valent cations with a preference for divalents (P <sub>Ca</sub> /P <sub>Na</sub> = 4.0–4.3); steady state currents rectify outwardly, whereas instantaneous currents show strong inward rectification; activated and subsequently inactivated by intracellular Ca <sup>2+</sup> (human, but not mouse); inhibited by extracellular acidification and potentiated by extracellular alkalization |

Data in the table are extracted from Delmas *et al.* (2004a), Dai *et al.* (2007) and Shimizu *et al.* (2009). Broadly similar single channel conductance, mono- and di-valent cation selectivity and sensitivity to blockers are observed for TRPP2 co-expressed with TRPP1 (Delmas, 2004b). Ca<sup>2+</sup>, Ba<sup>2+</sup> and Sr<sup>2+</sup> permeate TRPP3, but reduce inward currents carried by Na<sup>+</sup>. Mg<sup>2+</sup> is largely impermeant and exerts a voltage dependent inhibition that increases with hyperpolarization.

**Abbreviations:** 2-APB, 2-amino ethoxyphenylborate; **4α-PDD**, 4α-phorbol 12,13-didecanoate; **4α-PDH**, 4α-phorbol 12,13-dihexanoate; **5-(S)-HETE**, 5-(S)-hydroxyeicosatetraenoic acid; **12-(S)-HPETE** and **15-(S)-HPETE**, 12- and 15-(S)-hydroperoxyeicosatetraenoic acids; **20-HETE**, 20-hydroxyeicosatetraenoic acid; **A-425619**, 1-isoquinolin-5-yl-3-(4-trifluoromethyl-benzyl)urea; **A-778317**, 1-((R)-5-*tert*-butyl-indan-1-yl)-3-isoquinolin-5-yl-urea; **ACA**, N-(p-aminocinnamoyl)anthranilic acid; **AMG 517**, N-{4-[6-(4-trifluoromethyl-phenyl)-pyrimidin-4-yloxy]-benzothiazol-2-yl}-acetamide; **AMG628**, (R)-N-(4-(6-(4-(1-(4-fluorophenyl)ethyl)piperazin-1-yl)pyrimidin-4-yloxy)benzo[d]thiazol-2-yl)acetamide; **AMTB**, N-(3-aminopropyl)-2-[[[(3-methylphenyl) methyl]oxy]-N-(2-thienylmethyl)benzamide; **AP18**, 4-(4-chlorophenyl)-3-methyl-3-buten-2-one oxime; **BCTC**, N-(4-*tert*-butylphenyl)-4-(3-chloropyridin-2-yl)tetrahydropyrazine-1(2*H*)-carboxamide; **BTP2**, 4-methyl-4'-[3,5-bis(trifluoromethyl)-1*H*-pyrazol-1-yl]-1,2,3-thiadiazole-5-carboxanilide; **DPBA**, diphenylboronic anhydride; **DPTHF**, diphenyltetrahydrofuran; **GEA3162**, 1,2,3,4-oxatriazolium-5-amino-3-(3,4-dichlorophenyl)-chloride; **GSK1016790A** N-((1S)-1-[[4-((2S)-2-[[2,4-dichlorophenyl)sulfonyl]amino]-3-hydroxypropanoyl]-1-piperazinyl]carbonyl]-3-methylbutyl)-1-benzothiophene-2-carboxamide; **HC030031**, 2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)-N-(4-isopropylphenyl)acetamide; **HC067047**, 2-methyl-1-[3-(4-morpholinyl)propyl]-5-phenyl-N-[3-(trifluoromethyl)phenyl]-1*H*-pyrrole-3-carboxamide; **JYL1421**, N-(4-*tert*-butylbenzyl)-N'-[3-fluoro-4-(methylsulfonylamino)benzyl]thiourea; **JNJ17203212**, 4-(3-trifluoromethyl-pyridin-2-yl)-piperazine-1-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide; **KB-R7943**, 2-[2-[4-(4-nitrobenzyloxy)phenyl]ethyl]isothiurea methanesulfonate; **ML-9**, 1-(5-chloronaphthalene-1-sulphonyl)homopiperazine; **ML204**, structure not available; **NADA**, N-arachidonoyl dopamine; **PMA**, phorbol 12 myristate 13-acetate; **Pyr3**, ethyl-1-(4-(2,3,3-trichloroacrylamide)phenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate; **RN1734**, 2,4-dichloro-N-isopropyl-N-(2-isopropylaminoethyl)benzenesulfonamide; **RN1747**, 1-(4-chloro-2-nitrophenyl)sulfonyl-4-benzylpiperazine; **SB366791**, N-(3-methoxyphenyl)-4-chlorocinnamide; **SB705498**, N-(2-bromophenyl)-N'-[((R)-1-(5-trifluoromethyl-2-pyridyl)pyrrolidin-3-yl)]urea; **SDZ249665**, 1-[4-(2-aminoethoxy)-3-methoxy-benzyl]-3-(4-*tert*-butyl-benzyl)-urea; **SKF96265**, 1-(β-(3-(4-methoxyphenyl)propoxy)-4-methoxyphenethyl)-1*H*-imidazole hydrochloride; **THC**, Δ<sup>9</sup>-tetrahydrocannabinol; **TRIM**, 1-(2-(trifluoromethyl)phenyl)imidazole; **URB597**, 3'-carbamoilbiphenyl-3-yl cyclohexylcarbamate; **WS-12**, 2-isopropyl-5-methyl-cyclohexanecarboxylic acid (4-methoxy-phenyl)-amide

## Further Reading

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# NUCLEAR RECEPTORS

**Overview:** Nuclear receptors are specialised transcription factors with commonalities of sequence and structure, which bind as homo- or heterodimers to specific consensus sequences of DNA (response elements) in the promoter region of particular target genes. They regulate (either promoting or repressing) transcription of these target genes in response to a variety of endogenous ligands. Endogenous agonists are hydrophobic entities which, when bound to the receptor promote conformational changes in the receptor to allow recruitment (or dissociation) of protein partners, generating a large multiprotein complex.

Two major subclasses of nuclear receptors with identified endogenous agonists can be identified: steroid and non-steroid hormone receptors. Steroid hormone receptors function typically as dimeric entities and are thought to be resident outside the nucleus in the unliganded state in a complex with chaperone proteins, which are liberated upon agonist binding. Migration to the nucleus and interaction with other regulators of gene transcription, including RNA polymerase, acetyltransferases and deacetylases, allows gene transcription to be regulated. Non-steroid hormone receptors typically exhibit a greater distribution in the nucleus in the unliganded state and interact with other nuclear receptors to form heterodimers, as well as with other regulators of gene transcription, leading to changes in gene transcription upon agonist binding.

Selectivity of gene regulation is brought about through interaction of nuclear receptors with particular consensus sequences of DNA, which are arranged typically as repeats or inverted palindromes to allow accumulation of multiple transcription factors in the promoter regions of genes.

## Further Reading

Germain P, Staels B, Dacquet C, Spedding M, Laudet V (2006). Overview of nomenclature of nuclear receptors. *Pharmacol Rev* 58: 685–704.

# Orphan nuclear receptors

In man, 48 nuclear receptors have been identified from sequence analysis of the genome (see Benoit *et al.*, 2006; Germain *et al.*, 2006), only half of which have been 'assigned' a ligand by Nomenclature Committees of NC-IUPHAR. 19 families of nuclear receptors have been identified, allowing a systematic nomenclature of the format NRXYZ, where NR represents nuclear receptor, X the subfamily (1, 2, 3, 4, 5, 6 or 0), Y the group (A, B, C, D, E, H or I) and Z the individual member.

## Preliminary pairings

Listed below are a number of putative nuclear receptors identified by NC-IUPHAR, for which only preliminary evidence for an endogenous ligand has been published.

| Common nomenclature | Systematic nomenclature | Other names                                          | Ensembl ID      | Putative endogenous ligand                                     | Comment                                                                       |
|---------------------|-------------------------|------------------------------------------------------|-----------------|----------------------------------------------------------------|-------------------------------------------------------------------------------|
| Rev-erb $\alpha$    | NR1D1                   | EAR1, hRev                                           | ENSG00000126368 | Haem (Raghuram <i>et al.</i> , 2007; Yin <i>et al.</i> , 2007) | A synthetic agonist, GSK4112, has been described (Grant <i>et al.</i> , 2010) |
| Rev-erb $\beta$     | NR1D2                   | EAR1 $\beta$ , RVR, BD73                             | ENSG00000174738 | Haem (Raghuram <i>et al.</i> , 2007; Yin <i>et al.</i> , 2007) | A synthetic agonist, GSK4112, has been described (Grant <i>et al.</i> , 2010) |
| HNF4 $\alpha$       | NR2A1                   | Hepatocyte nuclear factor 4- $\alpha$ , MODY1, TCF14 | ENSG00000101076 | Linoleic acid (Yuan <i>et al.</i> , 2009)                      | –                                                                             |
| TR4                 | NR2C2                   | Testicular receptor 4, TAK1                          | ENSG00000177463 | Retinol, retinoic acid (Zhou <i>et al.</i> , 2011)             | Forms a heterodimer with TR2 (Young <i>et al.</i> , 1998)                     |

## Orphan nuclear receptors

| Common nomenclature | Systematic nomenclature | Other names                                                               | Ensembl ID      | Comments                                                                                                                                                             |
|---------------------|-------------------------|---------------------------------------------------------------------------|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| HNF4 $\gamma$       | NR2A2                   | Hepatocyte nuclear factor 4- $\gamma$                                     | ENSG00000164749 | –                                                                                                                                                                    |
| TR2                 | NR2C1                   | Testicular receptor 2                                                     | ENSG00000120798 | Forms a heterodimer with TR4 (Young <i>et al.</i> , 1998); gene disruption appears without effect on testicular development or function (Shyr <i>et al.</i> , 2002)) |
| TLX                 | NR2E1                   | Tailless homolog, TLL                                                     | ENSG00000112333 | Gene disruption is associated with abnormal brain development (Monaghan <i>et al.</i> , 1997; Land and Monaghan, 2003)                                               |
| PNR                 | NR2E3                   | Photoreceptor-specific nuclear receptor, retina-specific nuclear receptor | ENSG00000031544 | –                                                                                                                                                                    |
| COUP-TFI            | NR2F1                   | COUP $\alpha$ , EAR3, SVP44                                               | ENSG00000175745 | Gene disruption is perinatally lethal (Qiu <i>et al.</i> , 1997)                                                                                                     |
| COUP-TFII           | NR2F2                   | COUP $\beta$ , ARP1, SVP40                                                | ENSG00000185551 | Gene disruption is embryonically lethal (Pereira <i>et al.</i> , 1999)                                                                                               |
| EAR2                | NR2F6                   | V-erb-related gene                                                        | ENSG00000160113 | Gene disruption impairs CNS development (Warnecke <i>et al.</i> , 2005)                                                                                              |

| Common nomenclature | Systematic nomenclature | Other names                                                                                                                                               | Ensembl ID      | Comments                                                                                                                                                                                                                                                               |
|---------------------|-------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ERR $\alpha$        | NR3B1                   | ESRL1, estrogen-related receptor $\alpha$ , estrogen receptor-like 1                                                                                      | ENSG00000173153 | Activated by some dietary flavonoids (Suetsugi <i>et al.</i> , 2003); activated by the synthetic agonist GSK4716 (Zuercher <i>et al.</i> , 2005) and blocked by XCT790 (Willy <i>et al.</i> , 2004)                                                                    |
| ERR $\beta$         | NR3B2                   | ESRL2, estrogen-related receptor $\beta$ , estrogen receptor-like 2                                                                                       | ENSG00000119715 | May be activated by DY131 (Yu and Forman, 2005)                                                                                                                                                                                                                        |
| ERR $\gamma$        | NR3B3                   | ESRL3, estrogen-related receptor $\gamma$ , estrogen receptor-like 3                                                                                      | ENSG00000196482 | May be activated by DY131 (Yu and Forman, 2005)                                                                                                                                                                                                                        |
| Nur77               | NR4A1                   | Nerve growth factor 1B, NGFI-B, NAK1, ST59, TR3, HMR                                                                                                      | ENSG00000123358 | An exogenous agonist, cytosporone B, has been described (Zhan <i>et al.</i> , 2008), although structural analysis and molecular modelling has not identified a ligand binding site (Baker <i>et al.</i> , 2003; Flaig <i>et al.</i> , 2005; Wang <i>et al.</i> , 2003) |
| NURR1               | NR4A2                   | Immediate-early response protein NOT, transcriptionally-inducible nuclear receptor, TINUR, RNR-1                                                          | ENSG00000153234 | –                                                                                                                                                                                                                                                                      |
| NOR1                | NR4A3                   | Neuron-derived orphan receptor, mitogen-induced nuclear orphan receptor                                                                                   | ENSG00000119508 | –                                                                                                                                                                                                                                                                      |
| SF1                 | NR5A1                   | Steroidogenic factor 1, adrenal 4-binding protein, steroid hormone receptor Ad4BP, Fushi tarazu factor homolog 1                                          | ENSG00000136931 | Reported to be inhibited by AC45594 (Del Tredici <i>et al.</i> , 2008) and SID7969543 (Madoux <i>et al.</i> , 2008)                                                                                                                                                    |
| LRH-1               | NR5A2                   | Liver receptor homolog 1, $\alpha$ 1-fetoprotein transcription factor, hepatocytic transcription factor, B1-binding factor, CYP7A promoter-binding factor | ENSG00000116833 | –                                                                                                                                                                                                                                                                      |
| GCNF                | NR6A1                   | Germ cell nuclear factor, retinoid receptor-related testis-specific receptor, RTR                                                                         | ENSG00000148200 | –                                                                                                                                                                                                                                                                      |
| DAX-1               | NR0B1                   | AHCH                                                                                                                                                      | ENSG00000169297 | –                                                                                                                                                                                                                                                                      |
| SHP                 | NR0B2                   | Small heterodimer partner                                                                                                                                 | ENSG00000131910 | –                                                                                                                                                                                                                                                                      |

**Abbreviations:** AC45594, 4-heptoxyphenol; DY131, N-(4-(diethylaminobenzylidenyl)-N'-(4-hydroxybenzoyl)-hydrazine; GSK4112, 1,1-dimethylethyl-N-[(4-chlorophenyl)methyl]-N-[(5-nitro-2-thienyl)methyl]glycinate, also known as SR6452; GSK4716, 4-hydroxy-2-[(1E)-[4-(1-methylethyl)phenyl]methylene]hydrazide; SID7969543, ethyl 2-[2-[2-(2,3-dihydro-1,4-benzodioxin-7-ylamino)-2-oxoethyl]-1-oxoisquinolin-5-yl]oxypropanoate; XCT790, (E)-3-[4-[[2,4-bis(trifluoromethyl)phenyl]methoxy]-3-methoxyphenyl]-2-cyano-N-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]prop-2-enamide

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# Liver X and farnesoid X

**Overview:** Liver X and farnesoid X receptors (LXR and FXR, nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, see Moore *et al.*, 2006) are members of a steroid analogue-activated nuclear receptor subfamily (ENSF00000000720), which form heterodimers with members of the retinoid X receptor family. Endogenous ligands for LXRs include hydroxycholesterols (OHC), while FXRs appear to be activated by bile acids.

| Nomenclature            | LXR $\alpha$                                                              | LXR $\beta$                                                               | FXR $\alpha$                                                                                                              | FXR $\beta$                            |
|-------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| Systematic nomenclature | NR1H3                                                                     | NR1H2                                                                     | NR1H4                                                                                                                     | NR1H5                                  |
| Other names             | Oxysterols receptor $\alpha$                                              | Oxysterols receptor $\beta$ , ubiquitously expressed nuclear receptor     | Bile acid receptor                                                                                                        | Lanosterol receptor                    |
| Ensembl ID              | ENSG000000025434                                                          | ENSG000000131408                                                          | ENSG00000012504                                                                                                           | ENSMUSG00000048938 (pseudogene in man) |
| Potency order           | 20s-OHC, 22R-OHC, 24s-OHC > 25-OHC, 27-OHC (Lehmann <i>et al.</i> , 1997) | 20s-OHC, 22R-OHC, 24s-OHC > 25-OHC, 27-OHC (Lehmann <i>et al.</i> , 1997) | Chenodeoxycholate > lithocholate, deoxycholate (Makishima <i>et al.</i> , 1999; Parks <i>et al.</i> , 1999)               | –                                      |
| Selective agonists      | –                                                                         | –                                                                         | ECDCA (Pellicciari <i>et al.</i> , 2002), fexaramine (Downes <i>et al.</i> , 2003), GW4064 (Maloney <i>et al.</i> , 2000) | Lanosterol (Otte <i>et al.</i> , 2003) |
| Selective antagonists   | –                                                                         | –                                                                         | Guggulsterone (Urizar <i>et al.</i> , 2002)                                                                               | –                                      |

TO901317 (Repa *et al.*, 2000) and GW3965 (Collins *et al.*, 2002) are synthetic agonists acting at both LXR $\alpha$  and LXR $\beta$  with less than 10-fold selectivity.

**Abbreviations:** ECDCA, 6 $\alpha$ -ethyl-chenodeoxycholate, also known as INT747; **guggulsterone**, *trans*-4,17(20)-pregnadiene-3,16-dione; **GW3965**, 3-(3-[N-[2-chloro-3-trifluoromethylbenzyl]-[2,2-diphenylethyl]amino]propyloxy)phenylacetic acid hydrochloride; **GW4064**, 3-[(E)-2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-propan-2-yl-1,2-oxazol-4-yl]methoxy]phenyl]ethenyl]benzoic acid; **OHC**, hydroxycholesterol; **TO901317**, N-(2,2,2-trifluoroethyl)-N-(4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl)-benzenesulfonamide

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# Peroxisome proliferator-activated

**Overview:** Peroxisome proliferator-activated receptors (PPARs, nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, see Michalik *et al.*, 2006) are nuclear hormone receptors of the NR1C family, with diverse roles regulating lipid homeostasis, cellular differentiation, proliferation and the immune response. PPARs have many potential endogenous agonists (see Michalik *et al.*, 2006), including 15-deoxy- $\Delta^{12,14}$ -prostaglandin  $J_2$ , prostacyclin, many fatty acids and their oxidation products, lysophosphatidic acid (McIntyre *et al.*, 2003), 13-HODE, 15-HETE, Paz-PC, azelaoyl-PAF, and leukotriene  $B_4$ . These receptors also bind hypolipidaemic drugs (PPAR $\alpha$ ) and anti-diabetic thiazolidinediones (PPAR $\gamma$ ), as well as many non-steroidal anti-inflammatory drugs, such as sulindac and indomethacin. Once activated by a ligand, the receptor forms a heterodimer with members of the retinoid X receptor family and can act as a transcription factor. Although radioligand binding assays have been described for all three receptors, the radioligands are not commercially available. Commonly, receptor occupancy studies are conducted using fluorescent ligands and truncated forms of the receptor limited to the ligand binding domain.

| Nomenclature            | PPAR $\alpha$                                                       | PPAR $\beta$                           | PPAR $\gamma$                                                                                                                                                                                           |
|-------------------------|---------------------------------------------------------------------|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Systematic nomenclature | NR1C1                                                               | NR1C2                                  | NR1C3                                                                                                                                                                                                   |
| Other names             | –                                                                   | PPAR $\delta$ , NUC1, FAAR             | –                                                                                                                                                                                                       |
| Ensembl ID              | ENSG00000100406                                                     | ENSG00000112033                        | ENSG00000132170                                                                                                                                                                                         |
| Selective agonists      | GW7647, WY14643, clofibrate, fenofibrate, ciprofibrate, gemfibrozil | L165041, GW501516, GW0742              | Rosiglitazone, ciglitazone, troglitazone, pioglitazone, CDDO, GW1929                                                                                                                                    |
| Selective antagonists   | GW6471 (Xu <i>et al.</i> , 2002)                                    | GSK0660 (Shearer <i>et al.</i> , 2008) | GW9662 (Huang <i>et al.</i> , 1999), CDDO-Me (Wang <i>et al.</i> , 2000), diclofenac (6.2, Adamson <i>et al.</i> , 2002), BADGE (4.0, Wright <i>et al.</i> , 2000), T0070907 (Lee <i>et al.</i> , 2002) |

As with the estrogen receptor antagonists, many agents show tissue-selective efficacy (e.g. Bishop-Bailey, 2000; Rocchi *et al.*, 2001; Nakamura *et al.*, 2002). Agonists with mixed activity at PPAR $\alpha$  and PPAR $\gamma$  have also been described (e.g. Doeber *et al.*, 2004; Guo *et al.*, 2004; Xu *et al.*, 2004).

**Abbreviations:** 13-HODE, 13-hydroxyoctadecadienoic acid; 15-HETE, 15-hydroxyeicosatetraenoic acid; azelaoyl-PAF, 1-O-hexadecyl-2-O-(9-carboxyoctanoyl)-sn-glycerol-3-phosphocholine; BADGE, bisphenol A diglycidyl ether; CDDO, 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid; CDDO-Me, 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid methyl ester; GSK0660, ; GW1929, (2S)-[2-benzoylphenyl]amino-3-(4-[2-(methylpyridin-2-ylamino)ethoxy]phenyl)propionic acid; GW501516, 2-methyl-4-[[[4-methyl-2-[4-trifluoromethylphenyl]-1,3-thiazol-5-yl)methyl]sulfanyl]phenoxy]acetic acid; GW7647, 2-[[4-[2-[[[cyclohexylamino]carbonyl][4-cyclohexylbutyl]amino]ethyl]phenyl]thio]-2-methylpropanoic acid; GW9662, 2-chloro-5-nitro-N-phenylbenzamide; L165041, (4-[3-[4-acetyl-3-hydroxy-2-propylphenoxy]propoxy]phenoxy)acetic acid; Paz-PC, 1-palmitoyl-2-azelaoyl-sn-glycerol-3-phosphocholine; T0070907, 2-chloro-5-nitro-N-(4-pyridyl)benzamide; WY14643, N-(3-[2-quinolinylmethoxy]phenyl)-trifluoromethanesulphonamide

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# Retinoic acid, retinoid X and retinoic acid-related orphan

**Overview:** Cytoplasmic cellular retinoid binding proteins I (ENSG00000114115), II (ENSG00000114113), III (ENSG00000139194) and IV (ENSG00000162444) are thought to control the levels of intracellular retinoids available for interaction with their receptors (Li, 1999). [<sup>3</sup>H]-ATRA and [<sup>3</sup>H]-9-*cis*-retinoic acid have been used to label RARs and RXRs, respectively.

Retinoic acid receptors (nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, see Germain *et al.*, 2006a) are nuclear hormone receptors of the NR1B family activated by the vitamin A-derived agonists all-*trans* retinoic acid (ATRA) and 9-*cis*-retinoic acid, and the RAR-selective synthetic agonists TTNPB and adapalene.

| Nomenclature            | RAR $\alpha$                               | RAR $\beta$                                                                  | RAR $\gamma$                       |
|-------------------------|--------------------------------------------|------------------------------------------------------------------------------|------------------------------------|
| Systematic nomenclature | NR1B1                                      | NR1B2                                                                        | NR1B3                              |
| Other names             | –                                          | HBV-activated protein                                                        | –                                  |
| Ensembl ID              | ENSG00000131759                            | ENSG00000077092                                                              | ENSG00000172819                    |
| Selective agonists      | Ro406055 (Delescluse <i>et al.</i> , 1991) | AC261066 (Lund <i>et al.</i> , 2005),<br>AC55649 (Lund <i>et al.</i> , 2005) | AHPN (Martin <i>et al.</i> , 1992) |
| Selective antagonists   | Ro415253 (Apfel <i>et al.</i> , 1992)      | –                                                                            | MM11253 (Le <i>et al.</i> , 2000)  |

Ro415253 has been suggested to be a PPAR $\gamma$  agonist (Schupp *et al.*, 2007). LE135 is an antagonist with selectivity for RAR $\alpha$  and RAR $\beta$  compared to RAR $\gamma$  (Li *et al.*, 1999).

Retinoid X receptors (nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, see Germain *et al.*, 2006b) are NR2B family members activated by 9-*cis*-retinoic acid and the RXR-selective agonists LGD1069 and LG100268, sometimes referred to as rexinoids. These receptors form RXR–RAR heterodimers and RXR–RXR homodimers (Mangelsdorf and Evans, 1995; Chambon, 1996).

| Nomenclature            | RXR $\alpha$                         | RXR $\beta$     | RXR $\gamma$    |
|-------------------------|--------------------------------------|-----------------|-----------------|
| Systematic nomenclature | NR2B1                                | NR2B2           | NR2B3           |
| Ensembl ID              | ENSG00000078380                      | ENSG00000112472 | ENSG00000143171 |
| Selective agonists      | CD3254 (Nahoum <i>et al.</i> , 2007) | –               | –               |

UVI3003 has been described as a pan-RXR antagonist (Nahoum *et al.*, 2007).

Retinoic acid-related orphan receptors (ROR, nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, see Benoit *et al.*, 2006) have yet to be assigned a definitive endogenous ligand, although ROR $\alpha$  may be synthesised with a ‘captured’ agonist such as cholesterol (Kallen *et al.*, 2002; 2004).

| Nomenclature            | ROR $\alpha$                                                          | ROR $\beta$     | ROR $\gamma$    |
|-------------------------|-----------------------------------------------------------------------|-----------------|-----------------|
| Systematic nomenclature | NR1F1                                                                 | NR1F2           | NR1F3           |
| Other names             | RZR $\alpha$                                                          | RZR $\beta$     | RZR $\gamma$    |
| Ensembl ID              | ENSG00000069667                                                       | ENSG00000198963 | ENSG00000143365 |
| Selective agonists      | Cholesterol sulfate, cholesterol, 7-OHC (Bitsch <i>et al.</i> , 2003) | –               | –               |

ATRA shows selectivity for ROR $\beta$  within the ROR family (Stehlin-Gaon *et al.*, 2003). ROR $\alpha$  has been suggested to be a nuclear receptor responding to melatonin (Wiesenberg *et al.*, 1995).

**Abbreviations:** 7-OHC, 7-hydroxycholesterol; AC261066, 4-(4-[2-butoxyethoxy]-5-methyl-2-thiazolyl)-2-fluorobenzoic acid; AC55649, 4'-octyl-[1,1'-biphenyl]-4-carboxylic acid; AHPN, 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid, also known as CD437; ATRA, all-*trans*-retinoic acid; CD1530, 4-(6-hydroxy-7-tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-yl-2-naphthalenyl)benzoic acid; CD3254, (E)-3-[4-hydroxy-3-(3,5,5,8,8-pentamethyl-6, 7-dihydronaphthalen-2-yl)phenyl]prop-2-enoic acid; LE135, 4-(7,8,9,10-tetrahydro-5,7,7,10,10-pentamethyl-5H-benzo[e]naphtho[2,3-*b*][1,4]diazepin-13-yl)benzoic acid; LG100268, 6-(1-[3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl]cyclopropyl) nicotinic acid; LGD1069, 4-(1-[3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl]ethenyl) benzoic acid; MM11253, 6-(2-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl]-1,3-dithiolan-2-yl)-2-naphthalenecarboxylic acid; Ro406055, 4-([5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl]carboxamido)benzoic acid (also known as AM580); Ro415253, 4-[2-(7-heptoxy-4,4-dimethyl-1,1-dioxo-2,3-dihydrothiochromen-6-yl)prop-1-enyl]benzoic acid, also known as LG629; TTNPB, (E)-4-(2-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl]-1-propenyl)benzoic acid; UVI3003, 3-(4-hydroxy-3-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(pentyloxy)-2-naphthalenyl]phenyl)-2-propenoic acid

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# Steroid hormone

**Overview:** Steroid hormone receptors (nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, see Dahlman-Wright *et al.*, 2006; Lu *et al.*, 2006) are nuclear hormone receptors of the NR3 class, with endogenous agonists that may be divided into 3-hydroxysteroids (oestrone and oestradiol) and 3-ketosteroids (5 $\alpha$ -dihydrotestosterone [DHT], aldosterone, cortisol, corticosterone, progesterone and testosterone). These receptors exist as dimers coupled with chaperone molecules (such as HSP90 [ENSG00000166598] and immunophilin FKBP52 [ENSG00000004478]), which are shed on binding the steroid hormone. Although rapid signalling phenomena are observed (see Levin, 2008; Prossnitz and Maggiolini, 2009), the principal signalling cascade appears to involve binding of the activated receptors to nuclear hormone response elements of the genome, with a 15-nucleotide consensus sequence AGAACAnnnTGTCT (i.e. an inverted palindrome) as homo- or heterodimers. They also affect transcription by protein–protein interactions with other transcription factors, such as activator protein 1 (AP-1) and nuclear factor  $\kappa$ B (NF- $\kappa$ B). Splice variants of each of these receptors can form functional or nonfunctional monomers that can dimerize to form functional or non-functional receptors. For example, alternative splicing of PR mRNA produces A and B monomers that combine to produce functional AA, AB and BB receptors with distinct characteristics (Vegeto *et al.*, 1993).

A 7TM receptor responsive to estrogen (GPE, also known as GPR30, ENSG00000164850, see Prossnitz *et al.*, 2008) has been described. Human orthologues of 7TM ‘membrane progesterin receptors’ (ENSG00000182749, ENSG00000170915 and ENSG00000137819), initially discovered in fish (Zhu *et al.*, 2003a; 2003b), appear to localize to intracellular membranes and appear to respond to ‘non-genomic’ progesterone analogues independently of G proteins (Smith *et al.*, 2008).

| Nomenclature            | Glucocorticoid                                                                           | Mineralocorticoid                                                                    | Progesterone                        | Androgen                                                                     |
|-------------------------|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-------------------------------------|------------------------------------------------------------------------------|
| Preferred abbreviation  | GR                                                                                       | MR                                                                                   | PR                                  | AR                                                                           |
| Systematic nomenclature | NR3C1                                                                                    | NR3C2                                                                                | NR3C3                               | NR3C4                                                                        |
| Other names             | Type II glucocorticoid receptor                                                          | Type I glucocorticoid receptor, aldosterone receptor                                 | –                                   | dihydrotestosterone receptor                                                 |
| Ensembl ID              | ENSG00000113580                                                                          | ENSG00000151623                                                                      | ENSG00000082175                     | ENSG00000169083                                                              |
| Rank order of potency   | Cortisol, corticosterone >> aldosterone, deoxycortisone (Rupprecht <i>et al.</i> , 1993) | Corticosterone, cortisol, aldosterone, progesterone (Rupprecht <i>et al.</i> , 1993) | Progesterone                        | DHT > testosterone                                                           |
| Selective agonists      | RU28362, RU26988                                                                         | Aldosterone                                                                          | ORG2058, progesterone               | DHT, mibolerone, R1881                                                       |
| Selective antagonists   | Mifepristone, ZK112993, onapristone                                                      | RU28318, ZK112993, onapristone                                                       | Mifepristone, ZK112993, onapristone | Hydroxyflutamide, nilutamide                                                 |
| Probes                  | [ <sup>3</sup> H]-Dexamethasone                                                          | [ <sup>3</sup> H]-Aldosterone                                                        | [ <sup>3</sup> H]-ORG2058           | [ <sup>3</sup> H]-DHT, [ <sup>3</sup> H]-mibolerone, [ <sup>3</sup> H]-R1881 |

[<sup>3</sup>H]-Dexamethasone also binds to MR *in vitro*. PR antagonists have been suggested to subdivide into Type I (e.g. onapristone) and Type II (e.g. ZK112993) groups. These groups appear to promote binding of PR to DNA with different efficacies and evoke distinct conformational changes in the receptor, leading to a transcription-neutral complex (Gass *et al.*, 1998; Leonhardt *et al.*, 1998). Mutations in AR underlie testicular feminization and androgen insensitivity syndromes, spinal and bulbar muscular atrophy (Kennedy’s disease).

| Nomenclature            | Oestrogen $\alpha$                                                  | Oestrogen $\beta$                                                                                             |
|-------------------------|---------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| Preferred abbreviation  | ER $\alpha$                                                         | ER $\beta$                                                                                                    |
| Systematic nomenclature | NR3A1                                                               | NR3A2                                                                                                         |
| Other names             | Estradiol                                                           | Estradiol                                                                                                     |
| Ensembl ID              | ENSG00000091831                                                     | ENSG00000140009                                                                                               |
| Selective agonists      | PPT (Kraichely <i>et al.</i> , 2000; Stauffer <i>et al.</i> , 2000) | DPN (Meyers <i>et al.</i> , 2001), WAY200070 (Malamas <i>et al.</i> , 2004)                                   |
| Selective antagonists   | MPP (Sun <i>et al.</i> , 2002)                                      | PHTPP (Compton <i>et al.</i> , 2004), <i>R,R</i> -THC (Meyers <i>et al.</i> , 1999; Sun <i>et al.</i> , 1999) |

*R,R*-THC exhibits partial agonist activity at ER $\alpha$  (Meyers *et al.*, 1999; Sun *et al.*, 1999). Estrogen receptors may be blocked non-selectively by tamoxifen and raloxifene, and labelled by [<sup>3</sup>H]-estradiol and [<sup>3</sup>H]-tamoxifen. Many agents thought initially to be antagonists at estrogen receptors appear to have tissue-specific efficacy (e.g. tamoxifen is an antagonist at estrogen receptors in the breast, but is an agonist at estrogen receptors in the uterus), hence the descriptor SERM (selective estrogen receptor modulator) or SnuRM (selective nuclear receptor modulator). Y134 has been suggested to be an ER $\alpha$ -selective estrogen receptor modulator (Ning *et al.*, 2007).

Additional ‘orphan’ estrogen-receptor-related proteins have been described (ERR $\alpha$  ENSG00000173153; ERR $\beta$  ENSG00000119715; ERR $\gamma$  ENSG00000057103); DY131 is an agonist with selectivity for ERR $\beta$  and ERR $\gamma$  compared to ERR $\alpha$ , ER $\alpha$  and ER $\beta$  (Yu and Forman, 2005).

**Abbreviations:** DHT, 5 $\alpha$ -dihydrotestosterone; DPN, 2,3-bis(4-hydroxyphenyl)propionitrile; DY131, *N'*-([1E]-[4-(diethylamino)phenyl]methylene)-4-hydroxybenzohydrazide; MPP, 1,3-bis(4-hydroxyphenyl)-4-methyl-5-(4-[2-piperidinylethoxy]phenol)-1H-pyrazole; ORG2058, 16- $\alpha$ -ethyl-21-hydroxy-19-norpregn-4-ene-3,20-dione; PPT, 4,4',4''-(4-propyl-[1H]-pyrazole-1,3,5-triyl)trisphenol; PHTPP, 4-(2-phenyl-5,7-bis[trifluoromethyl]pyrazolo[1,5-a]pyrimidin-3-yl)phenol; R1881, 17 $\beta$ -hydroxy-17 $\alpha$ -methyl-estra-4,9,11-triene-3-one, also known as methyl-trienolone; *r,r*-THC, *R,R*-tetrahydrochrysene; RU26988, 11 $\beta$ ,17 $\beta$ -dihydroxy-21-methyl-17 $\alpha$ -pregna-1,4,6-trien-20-yl-3-on; RU28318, 3-oxo-7-

propyl-17-hydroxy-androstan-4-en-17-yl; RU28362, 11 $\beta$ ,17 $\beta$ -dihydroxy-6-methyl-17-(1-propionyl)androsta-1,4,6-triene-3-one; Y134, (6-hydroxy-2-[4-hydroxyphenyl]-benzo[b]thiophen-3-yl)-(4-[4-isopropylpiperazin-1-yl]-phenyl)methanone; WAY200070, 7-bromo-2-(4-hydroxyphenyl)-1,3-benzoxazol-5-ol; ZK112993, 11 $\beta$ -(4-acetylphenyl)-17 $\beta$ -hydroxyl-17 $\alpha$ -(1-propinyl)-4,8-estradiene-3-one

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# Thyroid hormone

**Overview:** Thyroid hormone receptors (TRs, nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, see Flamant *et al.*, 2006) are nuclear hormone receptors of the NR1A family, with diverse roles regulating macronutrient metabolism, cognition and cardiovascular homeostasis. TRs are activated by thyroxine (T4) and thyroid hormone (T3). Once activated by a ligand, the receptor acts as a transcription factor either as a monomer, homodimer or heterodimer with members of the retinoid X receptor family.

|                         |                                   |                                      |
|-------------------------|-----------------------------------|--------------------------------------|
| Nomenclature            | TR $\alpha$                       | TR $\beta$                           |
| Systematic nomenclature | NR1A1                             | NR1A2                                |
| Other names             | THRA, erbA $\alpha$ , erbA1, EAR7 | THRB, erbA $\beta$ , erbA2           |
| Ensembl ID              | ENSG00000126351                   | ENSG00000151090                      |
| Rank order of potency   | T3 > T4                           | T3 > T4                              |
| Selective agonists      | –                                 | GC1 (Chiellini <i>et al.</i> , 1998) |

An interaction with integrin  $\alpha V\beta 3$  has been suggested to underlie plasma membrane localization of thyroid hormone receptors and non-genomic signalling (Bergh *et al.*, 2005). One splice variant, TR $\alpha_2$ , lacks a functional DNA-binding domain and appears to act as a transcription suppressor.

Although radioligand binding assays have been described for these receptors, the radioligands are not commercially available. NH-3 has been described as an antagonist at thyroid hormone receptors with modest selectivity for TR $\beta$  (Nguyen *et al.*, 2002).

**Abbreviations:** GC1, (3,5-dimethyl-4-[4-hydroxy-3-isopropylbenzyl]phenoxy)acetate; NH-3, (4-[4-hydroxy-3-isopropyl-5-{4-nitrophenylethynyl}-benzyl]-3,5-dimethylphenoxy)acetate

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# Vitamin D, Pregnane X and Constitutive Androstane

**Overview:** Vitamin D (VDR), Pregnane X (PXR) and Constitutive Androstane (CAR) receptors (nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, Moore *et al.*, 2006) are members of the NR11 family of nuclear receptors, which form heterodimers with members of the retinoid X receptor family. PXR and CAR are activated by a range of exogenous compounds, with no established endogenous physiological agonists, although high concentrations of bile acids and bile pigments activate PXR and CAR (see Moore *et al.*, 2006).

| Nomenclature            | Vitamin D                                                                     | Pregnane X                                                                                                                                                                                                                               | Constitutive Androstane                                                                                 |
|-------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|
| Systematic nomenclature | NR111                                                                         | NR112                                                                                                                                                                                                                                    | NR113                                                                                                   |
| Other names             | 1,25-dihydroxyvitamin D3 receptor                                             | Orphan nuclear receptor PAR1, pregnane-activated receptor, steroid and xenobiotic receptor, SXR                                                                                                                                          | Constitutive activator of retinoid response, constitutive active response, orphan nuclear receptor MB67 |
| Ensembl ID              | ENSG00000111424                                                               | ENSG00000144852                                                                                                                                                                                                                          | ENSG00000143257                                                                                         |
| Selective agonists      | 1,25-Dihydroxyvitamin D <sub>3</sub> , EB1089 (Colston <i>et al.</i> , 1992)  | 5 $\beta$ -Pregnane-3,20-dione, estradiol (Jones <i>et al.</i> , 2000), hyperforin (Wentworth <i>et al.</i> , 2000), lovastatin (Lehmann <i>et al.</i> , 1998), rifampicin (Blumberg <i>et al.</i> , 1998; Lehmann <i>et al.</i> , 1998) | TCPOBOP (Tzameli <i>et al.</i> , 2000), CITCO (Maglich <i>et al.</i> , 2003)                            |
| Selective antagonists   | TEI9647 (Miura <i>et al.</i> , 1999), ZK159222 (Herdick <i>et al.</i> , 2000) | –                                                                                                                                                                                                                                        | –                                                                                                       |

**Abbreviations:** CITCO, 6-(4-chlorophenyl)imidazo[2,1-b][1,3]thiazole-5-carbaldehyde-O-(3,4-dichlorobenzyl)oxime; EB1089, (1R,3S,5Z)-5-[(2E)-2-[(1R,3aS,7aR)-1-[(1R,2E,4E)-6-ethyl-6-hydroxy-1-methyl-2,4-octadien-1-yl]-octahydro-7 $\alpha$ -methyl-4H-inden-4-ylidene]ethylidene]-4-methylene-1,3-cyclohexanediol, also known as seocalcitol; TEI9647, (23S)-25-dehydro-1 $\alpha$  hydroxyvitamin D<sub>3</sub>-26,23-lactone; TCPOBOP, 1,4-bis-[2-(3,5-dichloropyridyloxy)]benzene; ZK159222, butyl 1-[(E,1R,4R)-4-[(1R,3aS,4E,7aR)-4-[(2Z)-2-[(3S,5R)-3,5-dihydroxy-2-methylidenecyclohexylidene]ethylidene]-7 $\alpha$ -methyl-2,3,3a,5,6,7-hexahydro-1H-inden-1-yl]-1-hydroxypent-2-enyl]cyclopropane-1-carboxylate

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# CATALYTIC RECEPTORS

Catalytic receptors are cell-surface proteins, usually dimeric in nature, which encompass ligand binding and functional domains typically in one polypeptide chain. The ligand binding domain is placed on the extracellular surface of the plasma membrane and separated from the functional domain by a single transmembrane-spanning domain of 20–25 hydrophobic amino acids. The functional domain on the intracellular face of the plasma membrane has catalytic activity, or interacts with particular enzymes, giving the superfamily of receptors its name. Endogenous agonists of the catalytic receptor superfamily are peptides or proteins, the binding of which may induce dimerization of the receptor, which is the functional version of the receptor.

Amongst the catalytic receptors, particular subfamilies may be readily identified dependent on the function of the enzymatic portion of the receptor. The smallest group is the particulate guanylyl cyclases of the natriuretic peptide receptor family. The most widely recognized group is probably the receptor tyrosine kinase (RTK) family, epitomized by the neurotrophin receptor family, where a crucial initial step is the activation of a signalling cascade by autophosphorylation of the receptor on intracellular tyrosine residue(s) catalyzed by enzyme activity intrinsic to the receptor. A third group is the extrinsic protein tyrosine kinase receptors, where the catalytic activity resides in a separate protein from the binding site. Examples of this group include the GDNF and ErbB receptor families, where one, catalytically silent, member of the heterodimer is activated upon binding the ligand, causing the second member of the heterodimer, lacking ligand binding capacity, to initiate signaling through tyrosine phosphorylation. A fourth group, the receptor threonine/serine kinase (RTSK) family, exemplified by TGF- $\beta$  and BMP receptors, has intrinsic serine/threonine protein kinase activity in the heterodimeric functional unit. The fifth and final group are the receptor tyrosine phosphatases (RTP), which appear to lack cognate ligands, but may be triggered by events such as cell:cell contact and have identified roles in the skeletal, hematopoietic and immune systems.

NC-IUPHAR is currently considering nomenclature of catalytic receptors. It is recommended that nomenclature from the Human Genome Organisation Gene Nomenclature Committee (HGNC) is adopted where the precise complement of receptors is known (e.g. using heterologous expression). The alternative nomenclature recommended in the Guide to Receptors and Channels, Fifth Edition, may be considered as provisional.

# Cytokine receptor family

**Overview:** Cytokines are not a clearly defined group of agents, other than having an impact on immune signalling pathways, although many cytokines have effects on other systems, such as in development. A feature of some cytokines, which allows them to be distinguished from hormones, is that they may be produced by 'non-secretory' cells, for example, endothelial cells. Within the cytokine receptor family, some subfamilies may be identified, which are described elsewhere in the Guide to Receptors and Channels, receptors for the TNF family (see Page S211), the TGF- $\beta$  family (see Page S200) and the chemokines (see Page S39). Within this group of records are described Type I cytokine receptors, typified by interleukin receptors, and Type II cytokine receptors, exemplified by interferon receptors. An unusual feature of this group of agents is the existence of soluble and decoy receptors. These bind cytokines without allowing signalling to occur. A further attribute is the production of endogenous antagonist molecules, which bind to the receptors selectively and prevent signalling.

A commonality of these families of receptors is the ligand-induced homo- or hetero-oligomerization, which results in the recruitment of intracellular protein partners to evoke cellular responses, particularly in inflammatory or haematopoietic signalling. Although not an exclusive signalling pathway, a common feature of the majority of cytokine receptors is activation of the JAK/STAT pathway. This cascade is based around the protein tyrosine kinase activity of the Janus kinases (JAK, ENSFM00250000000777), which phosphorylate the receptor and thereby facilitate the recruitment of signal transducers and activators of transcription (STATs, ENSFM00500000269705, ENSFM00500000269817). The activated homo- or heterodimeric STATs function principally as transcription factors in the nucleus.

## Type I cytokine receptors

The **IL-2 family** of cytokines bind to heterodimeric receptors with ligand-selective  $\alpha$  or  $\beta$  chains, and a common  $\gamma$  chain ( $\gamma_c$ ) (IL2RG, ENSG00000147168, also known as CD132, C1DX, IMD4, severe combined immunodeficiency, SCIDX1).

| Nomenclature      | Interleukin-2 $\alpha$  | Interleukin-2 $\beta$ | Interleukin-4   | Interleukin-7   | Interleukin-9   |
|-------------------|-------------------------|-----------------------|-----------------|-----------------|-----------------|
| HGNC nomenclature | IL2RA                   | IL2RB                 | IL4R            | IL7R            | IL9R            |
| Ensembl ID        | ENSG00000134460         | ENSG00000100385       | ENSG00000077238 | ENSG00000168685 | ENSG00000124334 |
| Other names       | CD25, IL2R, TAC antigen | CD122, IL15RB         | CD124, P24394   | CD127           | CD129           |
| Agonist           | IL-2                    | IL-2, IL-15           | IL-4, IL-13     | IL-7            | IL-9            |

| Nomenclature      | Interleukin-13 $\alpha$ 1 | Interleukin-13 $\alpha$ 2     | Interleukin-15 $\alpha$ | Interleukin-21  | TSLP            |
|-------------------|---------------------------|-------------------------------|-------------------------|-----------------|-----------------|
| HGNC nomenclature | IL13RA1                   | IL13RA2                       | IL15RA                  | IL21R           | TSLPR           |
| Ensembl ID        | ENSG00000131724           | ENSG00000123496               | ENSG00000134470         | ENSG00000103522 | ENSG00000205755 |
| Other names       | CD213a1, IL-13Ra, NR4     | CD213a2, CT19, IL-13R, IL13BP | –                       | –               | CRLF2           |
| Agonist           | IL-13                     | IL-13                         | IL-15                   | IL-21           | TSLP            |

IL13RA2 acts as a substitute for  $\gamma_c$  producing a non-signalling complex; a decoy receptor.

Endogenous agonists include IL-2 (ENSG00000109471, also known as T-cell growth factor, TCGF, aldesleukin), IL-4 (ENSG00000113520, also known as B-cell stimulatory factor 1, lymphocyte stimulatory factor 1, binetrakin, pitrakinra), IL-7 (ENSG00000104432), IL-9 (ENSG00000145839, also known as HP40, P40), IL-13 (ENSG00000169194), IL-15 (ENSG00000164136), IL-21 (ENSG00000138684, also known as ZA11) and thymic stromal lymphopoietin (TSLP, ENSG00000145777).

Ro264550 has been described as a selective IL-2 receptor antagonist, which binds to IL-2 (Tilley *et al.* 1997).

The **IL-3 family** signal through a receptor complex comprising of a ligand-specific  $\alpha$  subunit and a common  $\beta$  chain (CSF2RB, ENSG00000100368, also known as CD131, IL3RB or IL5RB), which is shared between all members of this cytokine family.

| Nomenclature      | Interleukin-3   | Interleukin-5       | Granulocyte macrophage colony-stimulating factor |
|-------------------|-----------------|---------------------|--------------------------------------------------|
| HGNC nomenclature | IL3RA           | IL5RA               | CSF2RA                                           |
| Ensembl ID        | ENSG00000185291 | ENSG00000091181     | ENSG00000198223                                  |
| Other names       | CD123, A40266   | CD125, CDw125, IL5R | CD116                                            |
| Agonist           | IL-3            | IL-5                | GM-CSF                                           |

Endogenous agonists include IL-3 (ENSG00000164399, also known as multipotential colony-stimulating factor, hematopoietic growth factor, P-cell-stimulating factor, mast cell growth factor), IL-5 (ENSG00000113525, also known as EDF, TRF), GM-CSF (ENSG00000164400), and G-CSF (ENSG00000108342).

YM90709 has been described as a selective IL-5 receptor antagonist (Morokata *et al.*, 2002).

**The IL-6 family** signal through a ternary receptor complex consisting of the cognate receptor and a homodimer of the IL-6 signal transducer gp130 (IL6ST, ENSG00000134352, also known as CD130, oncostatin M receptor), which then activates the JAK/STAT, Ras/Raf/MAPK and PI 3-kinase /PKB signalling modules.

| Nomenclature      | Interleukin-6   | Interleukin-11 $\alpha$ | Interleukin-31                        |
|-------------------|-----------------|-------------------------|---------------------------------------|
| HGNC nomenclature | IL6R            | IL11RA                  | IL31RA                                |
| Ensembl ID        | ENSG00000160712 | ENSG00000137070         | ENSG00000164509                       |
| Other names       | CD126           | –                       | CRL, CRL3, gp130-like monocyte, GLM-R |
| Agonist           | IL-6            | IL-11                   | IL-31                                 |

| Nomenclature      | Ciliary neurotrophic factor $\alpha$ | Leptin          | Leukemia inhibitory factor | Oncostatin-M specific $\beta$ |
|-------------------|--------------------------------------|-----------------|----------------------------|-------------------------------|
| HGNC nomenclature | CNTFR                                | LEPR            | LIFR                       | OSMR                          |
| Ensembl ID        | ENSG00000122756                      | ENSG00000116678 | ENSG00000113594            | ENSG00000145623               |
| Other names       | CNTFR $\alpha$                       | CD295           | CD118                      | OSMR $\beta$                  |
| Agonist           | CNTF                                 | Leptin          | LIF, CTF1, OSM             | OSM                           |

Unusually amongst the cytokine receptors, the CNTF receptor is a glycerophosphatidylinositol-linked protein. CRLF1 (cytokine receptor-like factor 1, ENSG00000006016, also known as CISS, CISS1, CLF, CLF-1, NR6) acts as an endogenous antagonist for the CNTF receptor.

Endogenous agonists include IL-6 (ENSG00000136244, also known as B-cell stimulatory factor 2, interferon  $\beta$ -2, hybridoma growth factor, CTL differentiation factor), IL-11 (ENSG00000095752, also known as adipogenesis inhibitory factor), ciliary neurotrophic factor (CNTF, ENSG00000242689), cardiotrophin-1 (CTF1, ENSG00000150281, also known as B-cell stimulatory factor 3, BSF3), cardiotrophin-like cytokine (CLCF1, ENSG00000175505), leptin (LEP, ENSG00000174697, also known as OB), leukemia inhibitory factor (LIF, ENSG00000128342, also known as cholinergic differentiation factor) and Oncostatin M (OSM, ENSG00000099985).

**The IL-12 receptor family:** IL12RB1 is shared between receptors for IL-12 and IL-23; the functional agonist at IL-12 receptors is a heterodimer of IL-12A/IL-12B or homodimer of IL-12B/IL-2B subunits, while that for IL-23 receptors is a heterodimer of IL-12A/IL-23A.

| Nomenclature      | Interleukin-12 $\beta$ 1     | Interleukin-12 $\beta$ 2     | Interleukin 23  |
|-------------------|------------------------------|------------------------------|-----------------|
| HGNC nomenclature | IL12RB1                      | IL12RB2                      | IL23R           |
| Ensembl ID        | ENSG00000096996              | ENSG00000081985              | ENSG00000162594 |
| Other names       | CD212, IL12RB                | –                            | –               |
| Agonist           | IL-12A/IL-12B, IL-12B/IL-12B | IL-12A/IL-12B, IL-12B/IL-12B | IL-12A/IL-23A   |

Endogenous agonists include IL-12A (ENSG00000168811, also known as CLMF, IL-12A, NFSK, NKSF1, p35), IL-12B (ENSG00000113302, also known as natural killer cell stimulatory factor 2, cytotoxic lymphocyte maturation factor 2, p40) and IL-23 (ENSG00000110944).

**The prolactin receptor family** is made up of homodimeric receptor tyrosine kinases.

| Nomenclature       | Erythropoietin  | Granulocyte colony-stimulating factor | Growth hormone                                                | Prolactin                  | Thrombopoietin                                    |
|--------------------|-----------------|---------------------------------------|---------------------------------------------------------------|----------------------------|---------------------------------------------------|
| HGNC nomenclature  | EPOR            | CSF3R                                 | GHR                                                           | PRLR                       | TPOR                                              |
| Ensembl ID         | ENSG00000187266 | ENSG00000119535                       | ENSG00000112964                                               | ENSG00000113494            | ENSG00000117400                                   |
| Other names        | –               | CD114                                 | Somatotropin, GH-binding protein, GHBP, serum-binding protein | –                          | Myeloproliferative leukemia protein, C-mpl, CD110 |
| Endogenous agonist | Erythropoietin  | G-CSF                                 | Growth hormone 1, growth hormone 2, choriomammotropin         | Prolactin > growth hormone | Thrombopoietin                                    |

Endogenous agonists are large (~200 aa) polypeptides, and include erythropoietin (EPO, ENSG00000130427), granulocyte macrophage colony-stimulating factor (GM-CSF, ENSG00000164400, also known as colony-stimulating factor, CSF, sargramostim, molgramostin), growth hormone 1 (GH1, ENSG00000189162), growth hormone 2 (GH2, ENSG00000136488, also known as placenta-specific growth hormone), choriomam-

motropin (CSH1, ENSG00000136487, also known as lactogen), thrombopoietin (TPO, ENSG00000090534, also known as megakaryocyte colony-stimulating factor, myeloproliferative leukemia virus oncogene ligand, C-mpl ligand, megakaryocyte growth and development factor, MGDF), chorionic somatomammotropin hormone 2 (CSH2, ENSG00000213218), chorionic somatomammotropin hormone-like 1 (CSHL, ENSG00000204414, also known as lactogen-like) and granulocyte colony stimulating factor (CSF3, ENSG00000108342, also known as G-CSF, pluripoietin, filgrastim, lenograstim).

### Type II cytokine receptors

**The interferon receptor family** includes receptors for type I and type II interferons, that bind to heterodimeric receptors made up of IFNAR1/IFNAR2 or IFNGR1/IFNGR2, respectively.

| Nomenclature        | Interferon- $\alpha/\beta$ 1                                 | Interferon- $\alpha/\beta$ 2                                 | Interferon- $\gamma$ 1 | Interferon- $\gamma$ 2 |
|---------------------|--------------------------------------------------------------|--------------------------------------------------------------|------------------------|------------------------|
| HGNC nomenclature   | IFNAR1                                                       | IFNAR2                                                       | IFNGR1                 | IFNGR2                 |
| Ensembl ID          | ENSG00000142166                                              | ENSG00000159110                                              | ENSG00000027697        | ENSG00000159128        |
| Other names         | IFNAR, IFRC                                                  | IFNABR                                                       | CD119, IFNGR           | AF-1, IFNGT1           |
| Endogenous agonists | IFN- $\alpha$ , IFN- $\beta$ , IFN- $\omega$ , IFN- $\kappa$ | IFN- $\alpha$ , IFN- $\beta$ , IFN- $\omega$ , IFN- $\kappa$ | IFN- $\gamma$          | IFN- $\gamma$          |

Endogenous agonists in man include IFN- $\alpha$  (IFNA1, ENSG00000197919), IFN- $\beta$  (IFNB1, ENSG00000171855), IFN- $\gamma$  (IFNG, ENSG00000111537), IFN- $\kappa$  (IFNK, ENSG00000147896) and IFN- $\omega$  (IFNW1, ENSG00000177047).

**The IL-10 family** of receptors are heterodimeric combinations of family members: IL10RA/IL10RB responds to IL-10; IL20RA/IL20RB responds to IL-19, IL-20 and IL-24; IL22RA1/IL20RB responds to IL-20 and IL-24; IL22RA1/IL10RB responds to IL-22; IL28RA/IL10RB responds to IL-28A, IL28B and IL-29.

| Nomenclature      | Interleukin-10 $\alpha$ | Interleukin-10 $\beta$                          | Interleukin-20 $\alpha$ | Interleukin-20 $\beta$          |
|-------------------|-------------------------|-------------------------------------------------|-------------------------|---------------------------------|
| HGNC nomenclature | IL10RA                  | IL10RB                                          | IL20RA                  | IL20RB                          |
| Ensembl ID        | ENSG00000110324         | ENSG00000243646                                 | ENSG00000016402         | ENSG00000174564                 |
| Other names       | CDW210A, HIL-10R, IL10R | CDW210B, CRF2-4, CRFB4, D21S58, D21S66, IL-10R2 | IL-20R1, ZCYTOR7        | DIRS1, FNDC6, IL-20R2, MGC34923 |

| Nomenclature      | Interleukin-22 $\alpha$ 1 | Interleukin-22 $\alpha$ 2 | Interleukin-28 $\alpha$ |
|-------------------|---------------------------|---------------------------|-------------------------|
| HGNC nomenclature | IL22RA1                   | IL22RA2                   | IL28RA                  |
| Ensembl ID        | ENSG00000142677           | ENSG00000164485           | ENSG00000185436         |
| Other names       | CRF2-9, IL22R             | IL22bP, CRF2-S1           | CRF2/12, IFNLR, IL-28R1 |

Endogenous agonists are IL-10 (ENSG00000136634), IL-19 (ENSG00000142224), IL-20 (ENSG00000162891), IL-22 (ENSG00000127318), IL-24 (ENSG00000162892), IL-28A (IL28A, ENSG00000183709, also known as IFN- $\lambda$ 2), IL-28B (IL28B, ENSG00000197110, also known as IFN- $\lambda$ 3), IL-29 (ENSG00000182393).

**Immunoglobulin-like family of IL-1 receptors** are heterodimeric receptors made up of a cognate receptor subunit and an IL-1 receptor accessory protein (IL1RAP, ENSG00000196083, also known as C3orf13, IL-1RAcP, IL1R3).

| Nomenclature        | Interleukin-1, type I        | Interleukin-1 receptor-like 1           | Interleukin-1 receptor-like 2 | Interleukin-18 1        |
|---------------------|------------------------------|-----------------------------------------|-------------------------------|-------------------------|
| HGNC nomenclature   | IL1R1                        | IL1RL1                                  | IL1RL2                        | IL18R1                  |
| Ensembl ID          | ENSG00000115594              | ENSG00000115602                         | ENSG00000115598               | ENSG00000115604         |
| Other names         | CD121A, D2S1473, IL1R, IL1RA | DER4, FIT-1, IL33R, ST2, ST2L, ST2V, T1 | IL1R-rp2, IL1RRP2             | CD218a, IL-1Rrp, IL1RRP |
| Endogenous agonists | IL-1 $\alpha$ , IL-1 $\beta$ | –                                       | –                             | IL-18                   |

IL1R2, the type II IL-1 receptor (ENSG00000115590, also known as CD121b, IL1RB), is a decoy receptor, while the IL-1 receptor antagonist (IL1RN, ENSG00000136689, also known as ICIL-1RA, IL1F3, IL1RA, IRAP) prevents IL-1 binding to the receptor. Analogues of IL1RAP have been identified in the human genome: IL-1 receptor accessory protein-like 1 protein (IL1RAPL1, ENSG00000169306, also known as IL1R8, IL1RAPL, MRX10, MRX21, MRX34, OPHN4 or TIGIRR-2), X-linked IL-1 receptor accessory protein-like 2 (IL1RAPL2, ENSG00000189108, also known as IL-1R9, IL1R9, IL1RAPL-2 or TIGIRR-1) and IL-18 receptor accessory protein-like (IL18RAP, ENSG00000115607, also known as AcPL, CD218b).

Endogenous agonists are IL-1 $\alpha$  (IL1A, ENSG00000115008, also known as IL-1 or IL-1F1), IL-1 $\beta$  (ENSG00000125538, also known as IL-1F2) and IL-18 (ENSG00000150782, also known as IFN- $\gamma$ -inducing factor).

AF12198 has been described as a selective Type I IL-1 receptor antagonist (Akeson *et al.*, 1996).

The IL17 receptor family appear to represent a distinct class of cytokine receptors with incompletely defined signalling.

| Nomenclature      | Interleukin 17 $\alpha$                | Interleukin 17 $\beta$       | Interleukin 17 $\gamma$ | Interleukin 17 $\delta$ | Interleukin 17 $\epsilon$ |
|-------------------|----------------------------------------|------------------------------|-------------------------|-------------------------|---------------------------|
| HGNC nomenclature | IL17RA                                 | IL17RB                       | IL17RC                  | IL17RD                  | IL17RE                    |
| Ensembl ID        | ENSG00000177663                        | ENSG00000056736              | ENSG00000163702         | ENSG00000144730;        | ENSG00000163701           |
| Other names       | CD217, CDw217, hIL-17R, IL-17RA, IL17R | CRL4, EVI27, IL17BR, IL17RH1 | IL17-RL                 | SEF                     | –                         |

Endogenous agonists include IL-17A (ENSG00000112115, also known as cytotoxic T-lymphocyte-associated serine esterase 8; CTLA8).

**Abbreviations:** AF12198, AcPheGluTrpThrProGlyTrpTyrGlnAzeTyrAlaLeuProLeu; CSF, colony stimulating factor; EPO, erythropoietin; GH, growth hormone; G-CSF, granulocyte colony-stimulating factor; GMCSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; JAK, Janus kinase; LIF, leukemia inhibitory factor; OSM, oncostatin-M; PRL prolactin; Ro264550, N-[(3R)-1-(aminoiminomethyl)-3-piperidiny]acetyl]-4-(phenylethynyl)-L-phenylalanine methyl ester; STAT, signal transducers and activators of transcription; TPO, thrombopoietin; YM90709, 2,3-dimethoxy-6,6-dimethyl-5,6-dihydrobenzo[7,8]indolizino[2,3-b]quinoxaline

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# GDNF family

**Overview:** GDNF family receptors (ENSM00500000269996) are extrinsic tyrosine kinase receptors. Ligand binding to the extracellular domain of the glycosylphosphatidylinositol-linked cell-surface receptors (tabulated below) activates a transmembrane tyrosine kinase enzyme, Ret (Rearranged during transfection, ENSG00000165731). The endogenous ligands are typically dimeric, linked through disulphide bridges: glial cell-derived neurotrophic factor (GDNF, 211 aa, ENSG00000168621); neurturin (NRTN, 197 aa, ENSG00000171119); artemin (ARTN, 237 aa, ENSG00000117407) and persephin (PSPN, 156 aa, ENSG00000125650).

| Nomenclature           | GDNF family receptor $\alpha 1$                                                              | GDNF family receptor $\alpha 2$ | GDNF family receptor $\alpha 3$ | GDNF family receptor $\alpha 4$ |
|------------------------|----------------------------------------------------------------------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Preferred abbreviation | <b>GFR<math>\alpha 1</math></b>                                                              | <b>GFR<math>\alpha 2</math></b> | <b>GFR<math>\alpha 3</math></b> | <b>GFR<math>\alpha 4</math></b> |
| Other names            | GDNF receptor                                                                                | Neurturin receptor              | Artemin receptor                | Persephin receptor              |
| Ensembl ID             | ENSG00000151892                                                                              | ENSG00000168546                 | ENSG00000146013                 | ENSG00000125861                 |
| Potency order          | GDNF>NRTN>ARTN                                                                               | NRTN>GDNF                       | ARTN                            | PSPN                            |
| Probes                 | [ <sup>125</sup> I]-GDNF (3–63 pM, Treanor <i>et al.</i> , 1996; Klein <i>et al.</i> , 1997) | –                               | –                               | –                               |

Inhibitors of other receptor tyrosine kinases, such as semaxinib, which inhibits VEGF receptor function, may also inhibit Ret function (Mologni *et al.*, 2006). Mutations of Ret and GDNF genes may be involved in Hirschsprung's disease, which is characterized by the absence of intramural ganglion cells in the hindgut, often resulting in intestinal obstruction.

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# Natriuretic peptide

**Overview:** Natriuretic peptide receptors are a family (ENSF000000000198) of homodimeric, catalytic receptors with a single TM domain and guanylyl cyclase (EC 4.6.1.2) activity on the intracellular domain of the protein sequence. Isoforms are activated by the peptide hormones atrial natriuretic peptide (ANP, ENSG000000175206), brain natriuretic peptide (BNP, ENSG000000120937) and C-type natriuretic peptide (CNP, ENSG000000163273). Another family member is GC-C, the receptor for guanylin (ENSG000000113389) and uroguanylin (ENSG00000044012). Family members have conserved ligand-binding, catalytic (guanylyl cyclase) and regulatory domains with the exception of NPR-C which has an extracellular binding domain homologous to that of other NPRs, but with a truncated intracellular domain which appears to couple, *via* the G<sub>i/o</sub> family of G proteins to activation of phospholipase C, inwardly-rectifying potassium channels and inhibition of adenylyl cyclase activity (Murthy and Makhlof, 1999).

| Nomenclature          | NPR-A                                                                                                                                                         | NPR-B                                                                                                                                           | NPR-C                                                                                        | GC-C                                                                                             |
|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Other names           | NPR1, GC-A, ANP <sub>A</sub> receptor, ANPRA, GUCY2A                                                                                                          | NPR2, GC-B, ANP <sub>B</sub> receptor, ANPRB, GUCY2B                                                                                            | NPR3, ANPRC, <i>npr3</i> , clearance receptor                                                | STaR, GUCY2C                                                                                     |
| Ensembl ID            | ENSG000000169418                                                                                                                                              | ENSG000000159899                                                                                                                                | ENSG000000113389                                                                             | ENSG00000070019                                                                                  |
| Potency order         | ANP ≥ BNP >> CNP (Suga <i>et al.</i> , 1992)                                                                                                                  | CNP >> ANP >> BNP (Suga <i>et al.</i> , 1992)                                                                                                   | ANP > CNP ≥ BNP (Suga <i>et al.</i> , 1992)                                                  | Uroguanylin > guanylin                                                                           |
| Selective agonists    | ANP, BNP, sANP (Olson <i>et al.</i> , 1996)                                                                                                                   | CNP (Suga <i>et al.</i> , 1992)                                                                                                                 | cANF <sup>4-23</sup> (Maack <i>et al.</i> , 1987), osteocrin (Moffatt <i>et al.</i> , 2007). | <i>E. coli</i> heat-stable enterotoxin (ST <sub>a</sub> ), linacotide (Harris and Crowell, 2007) |
| Selective antagonists | A71915 (9.2–9.5, Delporte <i>et al.</i> , 1991), [Asu7,23']-β-ANP <sup>7-28</sup> (7.5, Kambayashi <i>et al.</i> , 1989), anantin (Wyss <i>et al.</i> , 1991) | Monoclonal antibody 3G12 (Drewett <i>et al.</i> , 1995), [Ser <sup>11</sup> ](N-CNP,C-ANP)pBNP <sup>2-25</sup> (Deschenes <i>et al.</i> , 2005) | AP811 (9.3, Veale <i>et al.</i> , 2000), M372049 (Hobbs <i>et al.</i> , 2004)                | –                                                                                                |
| Probes                | [ <sup>125</sup> I]-ANP                                                                                                                                       | [ <sup>125</sup> I]-CNP                                                                                                                         | [ <sup>125</sup> I]-ANP                                                                      | [ <sup>125</sup> I]-ST <sub>a</sub>                                                              |

The polysaccharide obtained from fermentation of *Aureobasidium* species, HS142-1, acts as an antagonist at both NPR-A and NPR-B receptors (Morishita *et al.*, 1991).

Gucy2D (RetGC1, GC-E, ENSG000000132518) and Gucy2F (RetGC2, GC-F, ENSG000000101890) are predominantly retinal guanylyl cyclase activities, which are inhibited by calcium ions acting through the guanylyl cyclase activating peptides GCAP1 (GUCA1A, ENSG00000048545), GCAP2 (GUCA1B, ENSG000000112599) and GCAP3 (GUCA1C, ENSG000000138472) (see Hunt *et al.*, 2010).

**Abbreviations:** A71915, ([Arg<sup>6</sup>,Cha<sup>8</sup>]ANP<sup>6-15</sup>-d-Tic-Arg-Cys-NH<sub>2</sub>; **anantin**, cyclo(Gly-Phe-Ile-Gly-Trp-Gly-Asn-β-Asp)-Ile-Phe-Gly-His-Tyr-Ser-Gly-Asp-Phe; AP811, (s)-N<sup>2</sup>-([4-((2-naphthalenylcarbonyl)amino)phenyl]acetyl)-l-arginyl-l-isoleucyl-l-α-aspartyl-N-(2-methylbutyl)-l-argininamide; [Asu7,23']-β-ANP(7–28), an antiparallel dimer linked by 7-23' and 7'-23 disulphide bonds (Asu, l-α-aminosuberic acid); cANF<sup>4-23</sup>, des[Gln<sup>18</sup>,Ser<sup>19</sup>,Gly<sup>20</sup>,Leu<sup>21</sup>,Gly<sup>22</sup>]ANP<sup>4-23</sup>-NH<sub>2</sub>; **HS142-1**, *Aureobasidium*-derived polysaccharide; **M372049**, see Chauhan *et al.* (2003) for structure; sANP, [G9T, R11S, G16R]ANP

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# Pattern recognition receptors

**Overview:** pattern recognition receptors (PRR, see Takeuchi and Akira, 2010) participate in the innate immune response to microbial agents, the stimulation of which leads to activation of intracellular enzymes and regulation of gene transcription. PRR include both cell-surface and intracellular proteins, including toll-like receptors (TLR), nucleotide-binding oligomerization domain-like receptors (NLR, also known as NOD-like receptors) and the mannose receptor family (ENSM00250000004089). PRR may be divided into signalling-associated members, identified here, and endocytic members (such as the mannose receptor family), the function of which appears to be to recognise particular microbial motifs for subsequent cell attachment, internalisation and destruction.

PRRs express multiple leucine-rich regions to bind a range of microbially-derived ligands, termed PAMPs or pathogen-associated molecular patterns, which includes peptides, carbohydrates, peptidoglycans, lipoproteins, lipopolysaccharides, and nucleic acids.

## Toll-like receptor family

Members of this family share significant homology with the interleukin-1 receptor family and appear to require dimerization either as homo- or heterodimers for functional activity. Heterodimerization appears to influence the potency of ligand binding substantially (e.g. TLR1/2 and TLR2/6, Takeuchi *et al.*, 2001; 2002). TLR1, TLR2, TLR4, TLR5, TLR6 and TLR11 are cell-surface proteins, while other members are associated with intracellular organelles, signalling through the MyD88-dependent pathways (with the exception of TLR3). As well as responding to exogenous infectious agents, it has been suggested that selected members of the family may be activated by endogenous ligands, such as hsp60 (Ohashi *et al.*, 2000).

| Nomenclature | Other names                                          | Ensembl ID         | Agonists                                                                                                          |
|--------------|------------------------------------------------------|--------------------|-------------------------------------------------------------------------------------------------------------------|
| TLR1         | Toll/interleukin-1 receptor-like protein, CD281, TIL | ENSG00000174125    | –                                                                                                                 |
| TLR2         | CD282, TIL4                                          | ENSG00000137462    | Peptidoglycan (Schwandner <i>et al.</i> , 1999; Yoshimura <i>et al.</i> , 1999)                                   |
| TLR3         | CD283                                                | ENSG00000164342    | PolyIC (Alexopoulou <i>et al.</i> , 2001)                                                                         |
| TLR4         | CD284, hToll, ARMD10                                 | ENSG00000136869    | LPS (Poltorak <i>et al.</i> , 1998), taxol (Kawasaki <i>et al.</i> , 2000)                                        |
| TLR5         | SLEB1, TIL3                                          | ENSG00000187554    | Flagellin (Hayashi <i>et al.</i> , 2001)                                                                          |
| TLR6         | CD286                                                | ENSG00000174130    | –                                                                                                                 |
| TLR7         | –                                                    | ENSG00000196664    | R848 (Hemmi <i>et al.</i> , 2002), imiquimod (Hemmi <i>et al.</i> , 2002), loxoribine (Heil <i>et al.</i> , 2003) |
| TLR8         | –                                                    | ENSG00000101916    | R848 (Hemmi <i>et al.</i> , 2002), imiquimod                                                                      |
| TLR9         | CD289                                                | ENSG00000173366    | CpG (Hemmi <i>et al.</i> , 2000)                                                                                  |
| TLR10        |                                                      | ENSG00000174123    | –                                                                                                                 |
| TLR11        |                                                      | ENSMUSG00000051969 | –                                                                                                                 |

Eritoran (E5564) is a lipid A analogue, which has been described as a TLR4 antagonist (Ingalls *et al.*, 1998).

## NOD-like receptor family

Structural analysis has identified a common motif of a mid-peptide located nucleotide-binding and oligomerization (NACHT) domain, which allows division of NOD-like receptors into three subfamilies, NLRC (or NODs), NLRP (or NALP) and IPAF (see Schroder and Tschopp, 2010). NLRC members are named on the basis of a sequence motif expressed at their N-termini, the caspase recruitment domain (CARD), while NLRP members have a pyrin domain. NLRs express C-terminal leucine-rich regions which have regulatory function and appear to recognize the microbial products to which the NLRs respond. NLRC family members recruit a serine/threonine kinase RIPK2 (receptor-interacting serine/threonine kinase 2, also known as CARD3, CARDIAK, RICK, RIP2, ENSG00000104312) leading to signalling through NF- $\kappa$ B and MAP kinase. NLRP family members, upon activation, recruit adaptor proteins (e.g. Asc also known as PYCARD, CARD5, TMS-1, ENSG00000103490). Activated NLRs associate in multiprotein complexes, known as inflammasomes (see Schroder and Tschopp, 2010), allowing the recruitment of caspases (see Page S317).

| Nomenclature | Other names                                                   | Ensembl ID      | Agonists          |
|--------------|---------------------------------------------------------------|-----------------|-------------------|
| NLRC1        | NOD1, CARD4, CLR7.1                                           | ENSG00000106100 | meso-DAP          |
| NLRC2        | NOD2, BLAU, CARD15, CD, CLR16.3, IBD1, PSORAS1                | ENSG00000167207 | Muramyl dipeptide |
| NLRC3        | NOD3, CLR16.2s                                                | ENSG00000167984 |                   |
| NLRC5        | NOD4, NOD27, CLR16.1, FLJ21709                                | ENSG00000140853 |                   |
| NLRX1        | NOD9, CLR11.3                                                 | ENSG00000160703 |                   |
| CIITA        | Class II major histocompatibility complex, C2TA, MHC2TA, NLRA | ENSG00000179583 |                   |
| NLRP1        | CARD7, CLR17.1, DEFCAP, DKFZp586O1822, KIAA0926, NAC, NALP1   | ENSG00000091592 | Muramyl dipeptide |

| Nomenclature | Other names                                                              | Ensembl ID      | Agonists                                                 |
|--------------|--------------------------------------------------------------------------|-----------------|----------------------------------------------------------|
| NLRP2        | CLR19.9, FLJ20510, NALP2, NBS1, PAN1, PYPAF2                             | ENSG00000022556 | Multiple virus particles, including Sendai and influenza |
| NLRP3        | AGTAVPRL, AII, AVP, C1orf7, CIAS1, CLR1.1, FCAS, FCU, MWS, NALP3, PYPAF1 | ENSG00000162711 |                                                          |
| NLRP4        | CLR19.5, CT58, FLJ32126, NALP4, PAN2, PYPAF4, RNH2                       | ENSG00000160505 |                                                          |
| NLRP5        | CLR19.8, MATER, NALP5, PAN11, PYPAF8                                     | ENSG00000171487 |                                                          |
| NLRP6        | CLR11.4, NALP6, PAN3, PYPAF5                                             | ENSG00000174885 |                                                          |
| NLRP7        | CLR19.4, NALP7, NOD12, PAN7, PYPAF3                                      | ENSG00000167634 |                                                          |
| NLRP8        | CLR19.2, NALP8, NOD16, PAN4                                              | ENSG00000179709 |                                                          |
| NLRP9        | CLR19.1, NALP9, NOD6, PAN12                                              | ENSG00000185792 |                                                          |
| NLRP10       | CLR11.1, NALP10, NOD8, PAN5, Pynod                                       | ENSG00000182261 |                                                          |
| NLRP11       | CLR19.6, NALP11, NOD17, PAN10, PYPAF6                                    | ENSG00000179873 |                                                          |
| NLRP12       | CLR19.3, Monarch1, NALP12, PAN6, PYPAF7, RNO2                            | ENSG00000142405 |                                                          |
| NLRP13       | CLR19.7, NALP13, NOD14, PAN13                                            | ENSG00000173572 |                                                          |
| NLRP14       | CLR11.2, GC-LRR, Nalp-iota, NALP14, NOD5, PAN8                           | ENSG00000158077 |                                                          |
| IPAF         | NOD4, NLRC4                                                              | ENSG00000091106 |                                                          |
| NAIP         | BIRC1, NLRB1                                                             | ENSG00000249437 |                                                          |

NLRP3 has also been reported to respond to host-derived products, known as danger-associated molecular patterns, or DAMPs, including uric acid (Martinon *et al.*, 2006), ATP, glucose, hyaluronan and amyloid  $\beta$  (see Schroder and Tschopp, 2010).

Loss-of-function mutations of NLRP3 are associated with cold autoinflammatory and Muckle-Wells syndromes.

**Abbreviations:** CpG, DNA enriched in cytosine:guanosine pairs; **imi**quimod, 1-(4-amino-imidazo[4,5-c]quinolin-1-yl)-2-methylpropane, also known as R837; **LPS**, lipopolysaccharide derived from Gram-negative bacteria; **meso-DAP**, meso-diaminopimeilic acid; **polyIC**, polyinosine-polycytosine; **R848**, 1-(4-amino-2-ethoxymethyl-imidazo[4,5-c]quinolin-1-yl)-2-methyl-propan-2-ol, also known as resiquimod and S28463

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# Receptor serine/threonine kinase (RSTK) family (EC 2.7.11.30)

**Overview:** receptor serine/threonine kinases (RSTK) respond to particular cytokines, the transforming growth factor  $\beta$  (TGF $\beta$ ) and bone morphogenetic protein (BMP) families, and may be divided into two subfamilies on the basis of structural similarities. Agonist binding initiates formation of a cell-surface complex of type I and type II RSTK, possibly heterotetrameric, where the type II protein phosphorylates the type I partner's kinase domain, initiating phosphorylation of particular members of the Smad family. These migrate to the nucleus and act as complexes to regulate gene transcription.

**The type I receptor serine/threonine kinases** (ENSFM00250000000213) are also known as activin receptors or activin receptor-like kinases, ALKs, for which a systematic nomenclature has been proposed (ALK1-7).

| Systematic nomenclature | HGNC nomenclature | Ensembl ID      | Other names                                                                               |
|-------------------------|-------------------|-----------------|-------------------------------------------------------------------------------------------|
| ALK1                    | ACVRL1            | ENSG00000139567 | Serine/threonine-protein kinase receptor R3, SKR3                                         |
| ALK2                    | ACVR1             | ENSG00000115170 | Activin receptor 1, serine/threonine-protein kinase receptor R1, SKR1                     |
| ALK3                    | BMPR1A            | ENSG00000107779 | BMP receptor 1A, serine/threonine-protein kinase receptor R5, SKR5, CD292                 |
| ALK4                    | ACVR1B            | ENSG00000135503 | Activin receptor 1B, ACTR-1B, serine/threonine-protein kinase receptor R2, SKR2           |
| ALK5                    | TGFR1             | ENSG00000106799 | TGF $\beta$ receptor I, TGF $\beta$ -1, serine/threonine-protein kinase receptor R4, SKR4 |
| ALK6                    | BMPR1B            | ENSG00000138696 | BMP receptor 1B, CDw293                                                                   |
| ALK7                    | ACVR1C            | ENSG00000123612 | Activin receptor 1C, ACTR-1C                                                              |

The type II receptor serine/threonine kinases (ENSFM005000000269790).

| Nomenclature                       | HGNC nomenclature | Ensembl ID      | Other names     |
|------------------------------------|-------------------|-----------------|-----------------|
| Activin receptor 2A                | ACVR2A            | ENSG00000121989 | ACTR-1IA        |
| Activin receptor 2B                | ACVR2B            | ENSG00000114739 | ACTR-1IB        |
| Anti-Müllerian hormone receptor-II | AMHR2             | ENSG00000135409 | –               |
| BMP receptor 2                     | BMPR2             | ENSG00000204217 | –               |
| TGF $\beta$ receptor II            | TGFR2             | ENSG00000163513 | TGF $\beta$ -II |
| TGF $\beta$ receptor III           | TGFR3             | ENSG00000069702 | Betaglycan      |

**Smads** were identified as mammalian orthologues of *Drosophila* genes termed 'mothers against decapentaplegic' and may be divided into Receptor-regulated Smads (R-Smads, including Smad1, Smad2, Smad3, Smad5 and Smad8), Co-mediated Smad (Co-Smad, Smad4) and Inhibitory Smads (I-Smad, Smad6 and Smad7). R-Smads form heteromeric complexes with Co-Smad. I-Smads compete for binding of R-Smad with both receptors and Co-Smad.

| Nomenclature | HGNC nomenclature | Ensembl ID      | Other names             |
|--------------|-------------------|-----------------|-------------------------|
| Smad1        | SMAD1             | ENSG00000170365 | JV4-1, MADH1, MADR1     |
| Smad2        | SMAD2             | ENSG00000175387 | JV18-1, MADH2, MADR2    |
| Smad3        | SMAD3             | ENSG00000166949 | HsT17436, JV15-2, MADH3 |
| Smad4        | SMAD4             | ENSG00000141646 | DPC4, MADH4             |
| Smad5        | SMAD5             | ENSG00000113658 | Dwfc, JV5-1, MADH5      |
| Smad6        | SMAD6             | ENSG00000137834 | HsT17432, MADH6, MADH7  |
| Smad7        | SMAD7             | ENSG00000101665 | MADH7, MADH8            |
| Smad8        | SMAD9             | ENSG00000120693 | MADH6, MADH9            |

**Endogenous agonists** are characterized by six conserved cysteine residues and are divided into two subfamilies on the basis of sequence comparison and signalling pathways activated: the TGF $\beta$ /activin/nodal subfamily and the BMP/GDF (growth/differentiation factor)/MIS (Müllerian inhibiting substance) subfamily. Ligands active at RSTKs appear to be generated as large precursors which undergo complex maturation processes (see Li and Flavell, 2008). Some are known to form disulphide-linked homo- and/or heterodimeric complexes. Thus, inhibins are  $\alpha$  subunits linked to a variety of  $\beta$  chains, while activins are combinations of  $\beta$  subunits.

Binding of TGF $\beta$  family members generate complexes of TGF $\beta$  receptor II or activin receptor 2B with ALK4, ALK5 or ALK7 and couple to Smad2 and Smad3 (see Shi and Massague, 2003). Binding of BMP family members generate complexes of BMP receptor 2, activin receptor 2A or activin receptor 2B with ALK1, ALK2, ALK3 or ALK6 and couple to Smad1, Smad5 and Smad8. Activins generate complexes of activin receptor 2A or activin receptor 2B with ALK2 (see Shi and Massague, 2003).

| Nomenclature      | HGNC nomenclature | Ensembl ID      | Other names                                                                                            |
|-------------------|-------------------|-----------------|--------------------------------------------------------------------------------------------------------|
| BMP2              | BMP2              | ENSG00000125845 | BMP2A                                                                                                  |
| BMP3              | BMP3              | ENSG00000152785 |                                                                                                        |
| BMP4              | BMP4              | ENSG00000125378 | BMP2B                                                                                                  |
| BMP5              | BMP5              | ENSG00000112175 | –                                                                                                      |
| BMP6              | BMP6              | ENSG00000153162 | VG1-related sequence, VGR1                                                                             |
| BMP7              | BMP7              | ENSG00000101144 | Osteogenic protein 1                                                                                   |
| BMP8A             | BMP8A             | ENSG00000183682 | –                                                                                                      |
| BMP8B             | BMP8B             | ENSG00000116985 | BMP8, osteogenic protein 2; op2                                                                        |
| BMP9              | GDF2              | ENSG00000128802 | Growth/differentiation factor 2                                                                        |
| BMP10             | BMP10             | ENSG00000163217 | –                                                                                                      |
| BMP11             | GDF11             | ENSG00000135414 | Growth/differentiation factor 11                                                                       |
| BMP12             | GDF7              | ENSG00000143869 | Growth differentiation factor 7                                                                        |
| BMP13             | GDF6              | ENSG00000156466 | Growth differentiation factor 6                                                                        |
| BMP14             | GDF5              | ENSG00000125965 | Growth differentiation factor 5, CDMP1                                                                 |
| BMP15             | BMP15             | ENSG00000130385 | Growth/differentiation factor 9b                                                                       |
| GDF1              | GDF1              | ENSG00000130283 | Growth/differentiation factor 1                                                                        |
| GDF3              | GDF3              | ENSG00000184344 | Growth/differentiation factor 3                                                                        |
| GDF9              | GDF9              | ENSG00000164404 | Growth/differentiation factor                                                                          |
| GDF10             | GDF10             | ENSG00000107623 | Growth/differentiation factor 10, BMP3b                                                                |
| GDF11             | GDF11             | ENSG00000130513 | TGF-PL, MIC-1, MIC1, NAG-1, PDF, PLAB, PTGFB                                                           |
| Inhibin $\alpha$  | INH A             | ENSG00000123999 | –                                                                                                      |
| Inhibin $\beta$ A | INH B A           | ENSG00000122641 | Activin $\beta$ A, follicle-stimulating hormone-releasing protein, erythroid differentiation factor    |
| Inhibin $\beta$ B | INH B B           | ENSG00000163083 | Activin $\beta$ B                                                                                      |
| Inhibin $\beta$ C | INH B C           | ENSG00000175189 | –                                                                                                      |
| Inhibin $\beta$ E | INH B E           | ENSG00000139269 | Activin, MGC4638                                                                                       |
| Myostatin         | MSTN              | ENSG00000138379 | Growth/differentiation 8, GDF8                                                                         |
| TGF $\beta$ 1     | TGFB1             | ENSG00000105329 | –                                                                                                      |
| TGF $\beta$ 2     | TGFB2             | ENSG00000092969 | Glioblastoma-derived T-cell suppressor factor, G-TSF, BSC-1 cell growth inhibitor, polyergin, cetermin |
| TGF $\beta$ 3     | TGFB3             | ENSG00000119699 | –                                                                                                      |

BMP1 is a member of the tolloid-like family (ENSMF00570000851071) of metalloproteinases and does not signal through these receptors.

TGF $\beta$  family ligand signalling may be inhibited by endogenous proteins, such as follistatin (ENSG00000134363), which binds and neutralizes activins to prevent activation of the target receptors.

An appraisal of small molecule inhibitors of TGF $\beta$  and BMP signalling concluded that TGF $\beta$  pathway inhibitors were more selective than BMP signalling inhibitors (Vogt *et al.*, 2011). The authors confirmed the selectivity of SB505124 to inhibit TGF $\beta$  signalling through ALK4, ALK5, ALK7 (Dacosta Byfield *et al.*, 2004). Dorsomorphin inhibits BMP signalling through ALK2 and ALK3; it also inhibits AMP kinase (Zhou *et al.*, 2001).

**Abbreviations:** SB505124, 2-(5-benzo[1,3]dioxol-5-yl-2-tert-butyl-3H-imidazol-4-yl)-6-methylpyridine hydrochloride

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# Receptor tyrosine kinases (E.C. 2.7.1.112)

Receptor tyrosine kinases (RTKs) are a family of 58 cell-surface receptors (see Grassot *et al.*, 2003), which transduce signals to polypeptide and protein hormones, cytokines and growth factors. RTKs are of widespread interest not only through physiological functions, but also as drug targets in many types of cancer and other disease states. A high proportion of drugs exploiting these targets are biological, acting to block the receptor or chelate the ligand, thereby preventing the biological activity. RTKs are dimeric proteins and most structurally diverse in the extracellular region, but exhibit marked similarities in the hydrophobic transmembrane region and the intracellular protein tyrosine kinase domain, often split into two regions. Binding of agonist evokes autophosphorylation leading to the stimulation of multiple signal transduction pathways, including phospholipase C- $\gamma$  (see Page S302), mitogen-activated protein kinases (see Page S310) and phosphatidylinositol 3-kinase.

## ErbB (epidermal growth factor) receptor family

**Overview:** ErbB family receptors (ENSM000410000138465) are Class I receptor tyrosine kinases (see Grassot *et al.*, 2003). ErbB2 (also known as HER-2 or NEU, ENSG00000141736) appears to act as an essential partner for the other members of the family without itself being activated by a cognate ligand (Graus-Porta *et al.*, 1997).

| Nomenclature       | ErbB1                                                                     | ErbB3            | ErbB4                                                        |
|--------------------|---------------------------------------------------------------------------|------------------|--------------------------------------------------------------|
| Ensembl ID         | ENSG00000146648                                                           | ENSG000000065361 | ENSG00000178568                                              |
| Other names        | EGF, HER1                                                                 | HER3             | HER4                                                         |
| Endogenous ligands | EGF, amphiregulin, betacellulin, epigen, epiregulin, HB-EGF, TGF $\alpha$ | NRG-1, NRG-2     | Betacellulin, epiregulin, HB-EGF, NRG-1, NRG-2, NRG-3, NRG-4 |

[<sup>125</sup>I]-EGF has been used to label the ErbB1 EGF receptor. The extracellular domain of ErbB2 can be targetted by the antibodies trastuzumab and pertuzumab to inhibit ErbB family action. The intracellular ATP-binding site of the tyrosine kinase domain can be inhibited by GW583340 (7.9–8.0, Gaul *et al.*, 2003), gefitinib, erlotinib and tyrphostins AG879 and AG1478.

Ligands of the ErbB family of receptors are peptides including EGF (ENSG00000138798), amphiregulin (also known as colorectal cell-derived growth factor, ENSG00000109321), betacellulin (ENSG00000174808), epigen (ENSG00000182585), epiregulin (ENSG00000124882), heparin-binding EGF-like growth factor (HB-EGF or diphtheria toxin receptor, ENSG00000113070), neuregulins (NRG-1, also known as Neu differentiation factor, acetylcholine receptor-inducing activity, heregulin or glial growth factor, ENSG00000157168; NRG-2, ENSG00000158458; NRG-3, ENSG00000185737 and NRG-4, ENSG00000169752) and transforming growth factor- $\alpha$  (TGF $\alpha$ , ENSG00000163235). These ligands appear to be generated by proteolytic cleavage of cell-surface peptides.

## Insulin receptor family

**Overview:** The circulating peptide hormones insulin and the related insulin-like growth factors (IGF) activate Class II receptor tyrosine kinases (see Grassot *et al.*, 2003), to evoke cellular responses, mediated through multiple intracellular adaptor proteins. Exceptionally amongst the catalytic receptors, the functional receptor in the insulin receptor family is derived from a single gene product, cleaved post-translationally into two peptides, which then cross-link via disulphide bridges to form a heterotetramer. Intriguingly, the endogenous peptide ligands are formed in a parallel fashion with post-translational processing producing a heterodimer linked by disulphide bridges. Signalling through the receptors is mediated through a rapid autophosphorylation event at intracellular tyrosine residues, followed by recruitment of multiple adaptor proteins, notably IRS1 (ENSG00000169047), IRS2 (ENSG00000185950), Shc1 (ENSG00000160691), Grb2 (ENSG00000177885) and Sos1 (ENSG00000115904).

| Nomenclature       | Insulin                   | Insulin-like growth factor I                     | INSRR                                 |
|--------------------|---------------------------|--------------------------------------------------|---------------------------------------|
| Ensembl ID         | ENSG00000171105           | ENSG00000140443                                  | ENSG00000027644                       |
| Other names        | CD220 antigen             | IGF-I receptor, CD221 antigen                    | Insulin receptor-related protein, IRR |
| Endogenous ligands | Insulin (ENSG00000129965) | IGF1 (ENSG00000017427)<br>IGF2 (ENSG00000167244) | –                                     |

There is evidence for low potency binding and activation of insulin receptors by IGF1. IGF2 also binds and activates the cation-independent mannose 6-phosphate receptor (CI-MPR, insulin-like growth factor II receptor, 300 kDa mannose 6-phosphate receptor, MPR 300, CD222 antigen ENSG00000197081), which lacks classical signalling capacity and appears to subserve a trafficking role (Macdonald *et al.*, 1988). INSRR, which has a much more discrete localization, being predominant in the kidney (Kurachi *et al.*, 1992), currently lacks a cognate ligand or evidence for functional impact.

PQ401 inhibits the insulin-like growth factor receptor (Gable *et al.*, 2006).

**PDGF (platelet-derived growth factor) receptor family**

**Overview:** PDGF receptors are Class III RTKs, which function as homo- or heterodimers.

| Nomenclature       | PDGFR $\alpha$                                                    | PDGFR $\beta$                                                                  | KIT                                                                                                                      | CSF1R                                                         | FLT3                                             |
|--------------------|-------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|--------------------------------------------------|
| Ensembl ID         | ENSG00000134853                                                   | ENSG00000113721                                                                | ENSG00000157404                                                                                                          | ENSG00000182578                                               | ENSG00000122025                                  |
| Other names        | Platelet-derived growth factor receptor $\alpha$ , CD140a, PDGFR2 | Platelet-derived growth factor receptor $\beta$ , CD140b, PDGFR1, JTK12, PDGFR | CD117, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog, C-Kit, PBT, stem cell growth factor receptor, SCFR | Colony stimulating factor 1 receptor, CD115, CSFR, C-FMS, FMS | FMS-related tyrosine kinase 3, CD135, FLK2, STK1 |
| Endogenous ligands | PDGF                                                              | PDGF                                                                           | SCF                                                                                                                      | CSF1, CSF2, CSF3                                              | FLT3L                                            |

Endogenous ligands of PDGF receptors are homo- or heterodimeric: PDGFA (PDGF1, ENSG00000197461), PDGFB (SIS, SSV, ENSG00000100311), PDGFC (fallotin, SCDGF, ENSG00000145431) and PDGFD (IEGF, MSTP036, SCDGF-B, ENSG00000170962) combine as homo- or heterodimers to activate homo- or heterodimeric PDGF receptors. SCF (stem cell factor, KITLG, ENSG00000049130) is a dimeric ligand for KIT. CSF1R may be activated by colony stimulating factor 1 (macrophage-CSF, CSF1, ENSG00000184371), CSF2 (granulocyte-macrophage CSF, GM-CSF, ENSG00000164400) and CSF3 (ENSG00000108342). FLT3L is the cognate ligand of FLT3 (ENSG00000090554).

5'-Fluorouridine diphosphate has been described as a selective FLT3 inhibitor (Choi *et al.*, 2010).

**FGF (fibroblast growth factor) receptor family**

**Overview:** Fibroblast growth factor (FGF) family receptors are members of the Ret family (ENSM0025000000009), which respond to members of the FGF family. Ret (rearranged during transfection, ENSG00000165731, also known as CDHF12, CDHR16, HSCR1, MEN2A, MEN2B, MTC1, PTC, RET51) is a signalling partner for the GDNF family of receptors (see Page S194). FGF receptors function as homo- and heterodimers.

| Nomenclature       | FGFR1                                                      | FGFR2                                                             | FGFR3                                                       | FGFR4                                                             |
|--------------------|------------------------------------------------------------|-------------------------------------------------------------------|-------------------------------------------------------------|-------------------------------------------------------------------|
| Ensembl ID         | ENSG00000077782                                            | ENSG00000066468                                                   | ENSG00000068078                                             | ENSG00000160867                                                   |
| Other names        | CD331, BFGFR, CEK, FLG, FLT2, H2, H3, H4, H5, KAL2, N-SAM  | CD332, BEK, CEK3, CFD1, ECT1, JWS, K-SAM, KGFR, TK14, TK25        | CD333, ACH, CEK2, JTK4                                      | CD334, JTK2                                                       |
| Endogenous ligands | FGF1, FGF2, FGF4 > FGF, FGF6 (Ornitz <i>et al.</i> , 1996) | FGF1 > FGF4, FGF7 FGF9 > FGF2, FGF6 (Ornitz <i>et al.</i> , 1996) | FGF1, FGF2, FGF9 > FGF4, FGF8 (Ornitz <i>et al.</i> , 1996) | FGF1, FGF2, FGF4, FGF9 > FGF6, FGF8 (Ornitz <i>et al.</i> , 1996) |

Splice variation of the receptors can influence agonist responses.

FGFR1L (ENSG00000127418) is a truncated kinase-null analogue. Mutations of Ret (and GDNF, see Page S194) genes may be involved in Hirschsprung's disease, which is characterized by the absence of intramural ganglion cells in the hindgut, often resulting in intestinal obstruction.

At least 22 members of the FGF gene family have been identified in the human genome (see Itoh and Ornitz, 2011). Within this group, subfamilies of FGF may be divided into canonical, intracellular and hormone-like FGFs. FGF1-FGF10 (ENSG00000113578, ENSG00000138685, ENSG00000186895, ENSG00000075388, ENSG00000138675, ENSG00000111241, ENSG00000140285, ENSG00000107831, ENSG00000102678, ENSG00000070193) have been identified to act through FGF receptors, while FGF11-14 appear to signal through intracellular targets. Other family members are less well characterized.

PD173074 has been described to inhibit FGFR1 and FGFR3 (Skaper *et al.*, 2000).

**VEGF (vascular endothelial growth factor) receptor family**

**Overview:** VEGF receptors (ENSM00440000236870) are homo- and heterodimeric proteins, which respond to VEGF proteins, some of which undergo proteolysis prior to receptor binding. Splice variants of VEGFR1 and VEGFR2 generate truncated proteins limited to the extracellular domains, capable of homodimerisation and binding VEGF ligands as a soluble, non-signalling entity.

|                    |                                  |                                                         |                                       |
|--------------------|----------------------------------|---------------------------------------------------------|---------------------------------------|
| Nomenclature       | VEGFR1                           | VEGFR2                                                  | VEGFR3                                |
| Ensembl ID         | ENSG00000102755                  | ENSG00000128052                                         | ENSG00000037280                       |
| Other names        | FMS-like tyrosine kinase 1, FLT1 | KDR, kinase insert domain protein receptor, CD309, FLK1 | FMS-like tyrosine kinase 4, FLT4, PCL |
| Endogenous ligands | VEGFA, VEGFB                     | VEGFA, VEGFC, VEGFE                                     | VEGFC, VEGFD, VEGFE                   |

Ligands at VEGF receptors are typically homodimeric: VEGFA (ENSG00000112715, also known as vascular permeability factor), VEGFB (ENSG00000173511, also known as VEGF-related factor or VRF), VEGFC (ENSG00000150630), VEGFD (ENSG00000165197, also known as c-fos induced growth factor, FIGF) or placental growth factor (ENSG00000119630, also known as PlGF). VEGFA is able to activate VEGFR1 homodimers, VEGFR1/2 heterodimers and VEGFR2/3 heterodimers. VEGFB and PlGF activate VEGFR1 homodimers, while VEGFC and VEGFD activate VEGFR2/3 heterodimers and VEGFR3 homodimers, and, following proteolysis, VEGFR2 homodimers.

### HGF (hepatocyte growth factor) receptor family

**Overview:** HGF receptors regulate maturation of the liver in the embryo, as well as having roles in the adult, for example, in the innate immune system.

|                    |                                               |                                                                                            |
|--------------------|-----------------------------------------------|--------------------------------------------------------------------------------------------|
| Nomenclature       | HGFR                                          | MST1R                                                                                      |
| Ensembl ID         | ENSG00000105976                               | ENSG00000164078                                                                            |
| Other names        | MET, RCCP2, hepatocyte growth factor receptor | CD136, CDw136, PTK8, RON, macrophage stimulating 1 receptor, c-met-related tyrosine kinase |
| Endogenous ligands | HGF                                           | MST1                                                                                       |

Ligands at the HGF receptor family include HGF (ENSG0000019991, also known as heparin-binding EGF-like factor 1, HB-EGF), synthesized as a single gene product, which is post-translationally processed to yield a heterodimer linked by a disulphide bridge. The maturation of HGF is enhanced by a serine proteinase, HGF activating complex (HGFAC, ENSG00000109758), and inhibited by HGF-A inhibitor 1, HAI (SPINT1, ENSG00000166145), a serine protease inhibitor. Macrophage stimulating protein 1 (MST1, ENSG00000173531, also known as hepatocyte growth factor-like) is a related gene.

SU11274 is an inhibitor of the HGF receptor (Sattler *et al.*, 2003), with the possibility of further targets (Arena *et al.*, 2007).

### Neurotrophin receptor family

**Overview:** Various isoforms of neurotrophin receptors exist, including truncated forms of trkB and trkC, which lack catalytic domains. p75, which has homologies with tumour necrosis factor receptors (see Page S211), lacks a tyrosine kinase domain, but can signal *via* ceramide release and nuclear factor  $\kappa$ B (NF- $\kappa$ B) activation. Both trkA and trkB contain two leucine-rich regions and can exist in monomeric or dimeric forms.

|                    |                                                                      |                       |                       |                                                               |
|--------------------|----------------------------------------------------------------------|-----------------------|-----------------------|---------------------------------------------------------------|
| Nomenclature       | trkA                                                                 | trkB                  | trkC                  | p75                                                           |
| Ensembl ID         | ENSG00000198400                                                      | ENSG00000148053       | ENSG00000140538       | ENSG00000064300                                               |
| Other names        | gp140 <sup>trk</sup> , high-affinity, slow-dissociating NGF receptor | gp145 <sup>trkB</sup> | gp145 <sup>trkC</sup> | p75 <sup>NTR</sup> , low-affinity neurotrophin receptor, NGFR |
| Endogenous ligands | NGF>NT3                                                              | BDNF, NT4/5>NT3       | NT3                   | NGF, BDNF, NT3, NT4/5                                         |

[<sup>125</sup>I]-NGF and [<sup>125</sup>I]-BDNF have been used to label the trkA and trkB receptor, respectively. The selectivity of small molecule peptide mimetics of NGF has not been ascertained (Massa *et al.*, 2003). There are, as yet, no selective antagonists, but activation can be blocked using anti-neurotrophin antisera or selective immunoadhesins that sequester neurotrophins (Shelton *et al.*, 1995). p75 influences the binding of NGF and NT3 to trkA. The ligand selectivity of p75 appears to be dependent on the cell type; for example, in sympathetic neurones, it binds NT3 with comparable affinity to trkC (Dechant *et al.*, 1997).

The endogenous ligands of neurotrophin receptors are small proteins (ca. 120 aa) and include nerve growth factor (NGF, ENSG00000134259), neurotrophin (NT) 3 (ENSG00000185652), NT4/5 (ENSG00000167744) and brain-derived neurotrophic factor (BDNF, ENSG00000176697).

The intracellular tyrosine kinase activity of the trkA receptor can be inhibited by GW441756 (8.7, Wood *et al.*, 2004) and tyrphostin AG879 (Ohmichi *et al.*, 1993).

### Ephrin receptor family

Ephrin receptors (ENSM00250000000121) have a role in the regulation of neuronal development. Their ligands are membrane-associated proteins, although the relationship between ligands and receptors has been incompletely defined.

|              |                  |                 |                             |                 |                         |
|--------------|------------------|-----------------|-----------------------------|-----------------|-------------------------|
| Nomenclature | EPHA1            | EPHA2           | EPHA3                       | EPHA4           | EPHA5                   |
| Ensembl ID   | ENSG00000146904  | ENSG00000142627 | ENSG00000044524             | ENSG00000116106 | ENSG00000145242         |
| Other names  | EPH, EPHT, EPHT1 | ECK             | ETK, ETK1, HEK, HEK4, TYRO4 | Hek8, TYRO1     | CEK7, EHk1, Hek7, TYRO4 |

|              |                 |                 |                 |                 |
|--------------|-----------------|-----------------|-----------------|-----------------|
| Nomenclature | EPHA6           | EPHA7           | EPHA8           | EPHA10          |
| Ensembl ID   | ENSG00000080224 | ENSG00000135333 | ENSG00000070886 | ENSG00000183317 |
| Other names  | EHK2            | EHK3, HEK11     | EEK, HEK3       | –               |

|              |                 |                              |                   |                 |                 |
|--------------|-----------------|------------------------------|-------------------|-----------------|-----------------|
| Nomenclature | EPHB1           | EPHB2                        | EPHB3             | EPHB4           | EPHB6           |
| Ensembl ID   | ENSG00000154928 | ENSG00000133216              | ENSG00000182580   | ENSG00000196411 | ENSG00000106123 |
| Other names  | EPHT2, Hek6     | DRT, EPHT3, ERK, Hek5, Tyro5 | ETK2, Hek2, Tyro6 | HTK, Tyro11     | HEP             |

Ligands at the ephrin receptors may be divided into two families, ephrin A and ephrin B. Ephrin A are glycosylphosphatidylinositol-linked proteins: EFNA1 (ENSG00000169242, ECKLG, EPLG1, LERK1, TNFAIP4), EFNA2 (ENSG00000099617, ELF-1, EPLG6, LERK6), EFNA3 (ENSG00000143590, Ehk1-L, EPLG3, LERK3), EFNA4 (ENSG00000243364, EPLG4, LERK4) and EFNA5 (ENSG00000184349, AF1, EPLG7, LERK7). Ephrin B (ENSM00250000002014) are single TM proteins: EFNb1 (ENSG00000090776), EFNb2 (ENSG00000125266) and EFNb3 (ENSG00000108947).

#### TAM (or AXL) receptor family

Members of this RTK family (ENSM00500000269872) represented a novel structural motif, when sequenced. The ligands for this family are able to bind to negatively-charged surfaces of apoptotic cells.

|                    |                                                                            |                                                                            |                                                 |
|--------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------|-------------------------------------------------|
| Nomenclature       | AXL                                                                        | TYRO3                                                                      | MERTK                                           |
| Ensembl ID         | ENSG00000167601                                                            | ENSG00000092445                                                            | ENSG00000153208                                 |
| Other names        | JTK11, UFO                                                                 | BrT, Dtk, RSE, Sky, Tif                                                    | c-mer proto-oncogene tyrosine kinase, mer, RP38 |
| Endogenous ligands | Gas6 (Nagata <i>et al.</i> , 1996), protein S (Stitt <i>et al.</i> , 1995) | Gas6 (Nagata <i>et al.</i> , 1996), protein S (Stitt <i>et al.</i> , 1995) | Gas6 (Nagata <i>et al.</i> , 1996)              |

Gas6 (ENSG00000183087, also known as growth arrest specific protein 6, AXLLG, AXSF) and protein S  $\alpha$  (ENSG00000184500) are secreted plasma proteins which undergo vitamin K-dependent post-translational modifications through the generation of carboxyglutamate-rich domains.

#### Leukocyte tyrosine kinase (LTK) receptor family

The LTK family (ENSM00500000270379) appear to lack endogenous ligands.

|              |                                 |                                   |                 |
|--------------|---------------------------------|-----------------------------------|-----------------|
| Nomenclature | LTK                             | ALK                               | ROS1            |
| Ensembl ID   | ENSG00000062524                 | ENSG00000171094                   | ENSG00000047936 |
| Other names  | Leukocyte tyrosine kinase, TYK1 | Anaplastic lymphoma kinase, CD246 | c-ros-1, MCF3   |

Crizotinib appears to be a selective ALK inhibitor acting on the tyrosine kinase activity (see Gerber and Minna, 2010).

#### TIE family of angiopoietin receptors

The TIE family (ENSM00420000140591) were initially associated with formation of blood vessels and respond to angiopoietins.

|                    |                                                                        |                                                       |
|--------------------|------------------------------------------------------------------------|-------------------------------------------------------|
| Nomenclature       | TIE1                                                                   | TIE2                                                  |
| Ensembl ID         | ENSG00000066056                                                        | ENSG00000120156                                       |
| Other names        | Tyrosine kinase with immunoglobulin-like and EGF-like domains 1, JTK14 | TEK tyrosine kinase, endothelial, CD202b, VMCM, VMCM1 |
| Endogenous ligands | –                                                                      | Angiopoietin 1, angiopoietin 4                        |

Endogenous ligands (ENSM00500000269808) are angiopoietin 1 (ANGPT1, ENSG00000154188), angiopoietin 2 (Ang2, ENSG00000091879), and angiopoietin 4 (ANGPT4 ENSG00000101280). Related sequences include angiotensin protein-like 1 (ANGPTL1, ENSG00000116194, also known as angiopoietin 3) and ANGPTL7 (ENSG00000171819, AngX, CDT6). Angiopoietin 2 appears to act as an endogenous antagonist of angiopoietin 1 function.

### DDR (collagen receptor) family

**Overview:** Collagen receptors (ENSM00260000050411) are structurally-related membrane protein tyrosine kinases activated by collagen. Collagen is probably the most abundant protein in man, with at least 29 families of genes encoding proteins, which undergo splice variation and post-translational processing, and may exist in monomeric or polymeric forms, producing a triple-stranded, twine-like structure.

|              |                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                           |
|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature | DDR1                                                                                                                                                                                                                                             | DDR2                                                                                                                                                                                                                                                      |
| Ensembl ID   | ENSG00000204580                                                                                                                                                                                                                                  | ENSG00000162733                                                                                                                                                                                                                                           |
| Other names  | Epithelial discoidin domain-containing receptor 1, epithelial discoidin domain receptor 1, neuroepithelial tyrosine kinase, cell adhesion kinase, TRK E, protein-tyrosine kinase RTK 6, HGK2, CD167 antigen-like family member A, CD167a antigen | Discoidin domain-containing receptor 2 Precursor (Discoidin domain receptor 2, receptor protein-tyrosine kinase TKT, tyrosine-protein kinase TYRO10, neurotrophic tyrosine kinase, receptor-related 3, CD167 antigen-like family member B, CD167b antigen |

In man, principal family members include COL1A1 (ENSG00000108821), COL2A1 (ENSG00000139219), COL3A1 (ENSG00000168542) and COL4A1 (ENSG00000187498).

### ROR family and other RTKs

Members of the ROR family (ENSM00510000502747) appear to be activated by ligands complexing with other cell-surface proteins.

|              |                                                         |                                                                    |                                            |                 |                   |
|--------------|---------------------------------------------------------|--------------------------------------------------------------------|--------------------------------------------|-----------------|-------------------|
| Nomenclature | ROR1                                                    | ROR2                                                               | MUSK                                       | PTK7            | RYK               |
| Ensembl ID   | ENSG00000185483                                         | ENSG00000169071                                                    | ENSG00000030304                            | ENSG00000112655 | ENSG00000163785   |
| Other names  | NTRKR1, receptor tyrosine kinase-like orphan receptor 1 | BDB, BDB1, NTRKR2, receptor tyrosine kinase-like orphan receptor 2 | Muscle, skeletal, receptor tyrosine kinase | CCK4            | JTK5, JTK5A, RYK1 |

ROR1 and ROR2 appear to be activated by Wnt5a (ENSG00000114251) binding to a Frizzled receptor (see Page S51) and forming a cell-surface multiprotein complex (Grumolato *et al.*, 2010). Agrin (AGRN, ENSG00000188157) forms a complex with LRP4 (ENSG00000134569) to activate MUSK (Kim *et al.*, 2008). PTK7 and RYK also appear to interact with the Wnt signalling system (Fradkin *et al.*, 2010; Puppo *et al.*, 2011).

**Abbreviations:** BDNF, brain-derived neurotrophic factor; **erlotinib**, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine, also known as OSI774; **gefitinib**, N-(3-chloro-4-fluoro-phenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy)quinazolin-4-amine, also known as ZD1839; **GW441756**, 1,3-dihydro-3-[(1-methyl-1H-indol-3-yl)methylene]-2H-pyrrolo[3,2-b]pyridin-2-one hydrochloride; **GW583340**, N-(3-chloro-4-[[3-fluorophenyl]methoxy]phenyl)-6-(2-[[[2-[methylsulfonyl]ethyl]amino]methyl]-4-thiazolyl]-4-quinazolinamine dihydrochloride; **IGF**, insulin-like growth factor; **NGF**, nerve growth factor; **PD173074**, 1-tert-butyl-3-[2-[4-(diethylamino)butylamino]-6-(3,5-dimethoxyphenyl)pyrido[2,3-d]pyrimidin-7-yl]urea; **PQ401**, 1-(5-chloro-2-methoxyphenyl)-3-(2-methylquinolin-4-yl)urea; **tyrphostin AG1478**, N-(3-chlorophenyl)-6,7-dimethoxyquinazolin-4-amine hydrochloride; **tyrphostin AG879**,  $\alpha$ -cyano-(3,5-di-*t*-butyl-4-hydroxy)thiocinnamide

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# Receptor tyrosine phosphatases (RTP, EC 3.1.3.48)

Overview: receptor tyrosine phosphatases (RTP) are cell-surface proteins with a single TM region and intracellular phosphotyrosine phosphatase activity. Many family members exhibit constitutive activity in heterologous expression, dephosphorylating intracellular targets such as Src tyrosine kinase (ENSG00000197122) to activate signalling cascades. Family members bind components of the extracellular matrix or cell-surface proteins indicating a role in intercellular communication.

| Nomenclature | HGNC nomenclature | Ensembl ID      | Other names                                                                                                                         |
|--------------|-------------------|-----------------|-------------------------------------------------------------------------------------------------------------------------------------|
| Type A       | PTPRA             | ENSG00000132670 | Leukocyte common antigen-related peptide, HLPR, HPTPA, LRP, PTPA, PTPRL2, RPTPA                                                     |
| Type B       | PTPRB             | ENSG00000127329 | R-PTP-beta, vascular endothelial protein tyrosine phosphatase, VEPTP                                                                |
| Type C       | PTPRC             | ENSG00000081237 | CD45, T200 leukocyte common antigen, gp180                                                                                          |
| Type D       | PTPRD             | ENSG00000153707 | HPTP, R-PTP-delta                                                                                                                   |
| Type E       | PTPRE             | ENSG00000132334 | PTPE, R-PTP-epsilon                                                                                                                 |
| Type F       | PTPRF             | ENSG00000142949 | Leukocyte antigen-related PTP receptor, LAR                                                                                         |
| Type G       | PTPRG             | ENSG00000144724 | R-PTP-gamma                                                                                                                         |
| Type H       | PTPRH             | ENSG00000080031 | Stomach cancer-associated protein tyrosine phosphatase 1, SAP1                                                                      |
| Type J       | PTPRJ             | ENSG00000149177 | R-PTP-eta, CD148, density-enhanced phosphatase 1, DEP1, susceptibility to colon cancer 1 homologue, SCC1                            |
| Type K       | PTPRK             | ENSG00000152894 | R-PTP-kappa                                                                                                                         |
| Type M       | PTPRM             | ENSG00000173482 | R-PTP-mu, PTPRL1, RPTPM, RPTPU, hR-PTPu                                                                                             |
| Type N       | PTPRN             | ENSG00000054356 | Islet cell antigen 2, IA-2                                                                                                          |
| Type N2      | PTPRN2            | ENSG00000155093 | Islet cell antigen 2β, IA-2β, phogrin, ICAAR                                                                                        |
| Type O       | PTPRO             | ENSG00000151490 | PTP-phi, PTPase U2, glomerular epithelial protein 1, GLEPP1, osteoclastic transmembrane protein-tyrosine phosphatase, NPHS6, PTP-OC |
| Type Q       | PTPRQ             | ENSG00000139304 | PTPGMC1                                                                                                                             |
| Type R       | PTPRR             | ENSG00000153233 | Ch-1 PTPase; NC-PTPCOM1; R-PTP-R; ch-1PTPase, EC-PTP, PCPTP1, PTP-SL, PTPBR7, PTPRQ                                                 |
| Type S       | PTPRS             | ENSG00000105426 | R-PTP-sigma                                                                                                                         |
| Type T       | PTPRT             | ENSG00000196090 | RPTP-rho                                                                                                                            |
| Type U       | PTPRU             | ENSG00000060656 | R-PTP-psi, pancreatic carcinoma phosphatase 2, PCP-2, PTPU2                                                                         |
| Type Z1      | PTPRZ1            | ENSG00000106278 | Phosphacan, R-PTP-zeta-2, PTP18, PTPRZ, PTPZ, RPTPB, RPTPZ2                                                                         |

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# Tumour necrosis factor (TNF) family

**Overview:** The TNF receptor superfamily (TNFRSF) displays limited homology beyond an extracellular domain rich in cysteine residues and is activated by at least 18 different human homologues of TNF referred to as the TNF superfamily (TNFSF). Some homologues lacking transmembrane and cytoplasmic domains function as decoy receptors binding ligand without inducing cell signalling. Many of these receptors and ligands function as multimeric entities. Signalling through these receptors is complex and involves interaction with cytoplasmic adaptor proteins (such as TRADD and TRAF1). Several of these receptors contain cytoplasmic motifs known as 'death domains', which upon activation serve to recruit death domain- and death effector domain-containing proteins crucial for the initiation of an apoptotic response. Additional signalling pathways include the regulation of the nuclear factor  $\kappa$ B or mitogen-activated protein kinase (see Page S310) pathways. Pharmacological manipulation of these receptors is mainly enacted through chelating the endogenous agonists with humanised monoclonal antibodies (e.g. infliximab or adalimumab) or recombinant fusion proteins of IgG and soluble receptors (e.g. etanercept). Some mutated forms of TNF ligands are capable of selecting for different receptor subtypes.

| Nomenclature | Other names                                                                                                             | Ensembl ID          | Adaptor proteins  | Endogenous ligands    |
|--------------|-------------------------------------------------------------------------------------------------------------------------|---------------------|-------------------|-----------------------|
| TNFRSF1A     | TNFR1, CD120a, p55TNFR, TNFAR, TNFR60                                                                                   | ENSG000000067182    | TRADD             | TNFSF1, TNFSF2        |
| TNFRSF1B     | TNFR2, CD120b, p75TNFR, p80, TNFBR                                                                                      | ENSG000000028137    | TRAF1, 2, 5       | TNFSF1, TNFSF2        |
| TNFRSF3      | TNFR III, LTBR, TNFCR, TNFR-RP, TNFR2-RP, CD18                                                                          | ENSG00000111321     | TRAF3, 4, 5       | TNFSF3, TNFSF14       |
| TNFRSF4      | OX-40, ACT35, TXGP1L, CD134                                                                                             | ENSG00000186827     | TRAF1, 2, 3, 5    | TNFSF4                |
| TNFRSF5      | CD40, Bp50, p50                                                                                                         | ENSG00000101017     | TRAF1, 2, 3, 5, 6 | TNFSF5                |
| TNFRSF6      | Fas, CD95, APO-1, APT1, TNFRSF6A                                                                                        | ENSG000000026103    | FADD              | TNFSF6                |
| TNFRSF7      | CD27, S152, Tp55, T14                                                                                                   | ENSG00000139193     | TRAF2, SIVA       | TNFSF7                |
| TNFRSF8      | CD30, Ki-1                                                                                                              | ENSG00000120949     | TRAF1, 2, 3, 5    | TNFSF8                |
| TNFRSF9      | 4-1BB, CDw137, ILA                                                                                                      | ENSG000000049249    | TRAF1, 2, 3       | TNFSF9                |
| TNFRSF10A    | DR4, TNF-related apoptosis-inducing ligand receptor 1, TRAIL-R1, APO-2, CD261                                           | ENSG00000104689     | FADD              | TNFSF10               |
| TNFRSF10B    | DR5, TNF-related apoptosis-inducing ligand receptor 2, TRAIL-R2, KILLER, CD262, TRICK2A, TRICKB                         | ENSG00000120889     | FADD              | TNFSF10               |
| TNFRSF11A    | Receptor activator of NF- $\kappa$ B, RANK, osteoclast differentiation factor receptor, ODFR, TRANCE-R, CD265           | ENSG00000141655     | TRAF1, 2, 3, 5, 6 | TNFSF11               |
| TNFRSF11B    | Osteoprotegerin, OPG, osteoclastogenesis inhibitory factor, OCIF, TR1                                                   | ENSG00000164761     | –                 | TNFSF11               |
| TNFRSF12     | TRS, WSL-1, LARD, WSL-LR, apoptosis-mediating receptor DR3, apoptosis-mediating receptor TRAMP, death domain receptor 3 | ENSG00000171680     | TRADD             | TNFSF15, TNFSF12      |
| TNFRSF12A    | TWEAK-R, Fn14, FGF-inducible 14, CD266 antigen                                                                          | ENSG00000006327     | TRAF1, 2, 3, 5    | TNFSF12               |
| TNFRSF13B    | Transmembrane activator and CAML interactor, TACI, CD267                                                                | ENSG00000108516     | TRAF2, 5, 6       | TNFSF13B              |
| TNFRSF13C    | B cell-activating factor receptor, BAFF-R, CD268, BR3                                                                   | ENSG00000159958     | TRAF3             | TNFSF13B              |
| TNFRSF14     | Herpesvirus entry mediator A, HVEM, tumour necrosis factor receptor-like 2, TR2, LIGHT-R, ATAR, HVEA                    | ENSG00000157873     | TRAF1,2,3,5       | TNFSF14, TNFSF1, BTLA |
| TNFRSF16     | Low affinity nerve growth factor receptor, NGF receptor, Gp80-LNGFR, p75, p75 <sup>NTR</sup> , NGF-R, NTR, CD271        | ENSG000000064300    | TRAF2, 4, 6       | NGF, BDNF, NT-3, NT-4 |
| TNFRSF17     | BCMA, BCM, TNFRSF13, TNFRSF13a, CD269                                                                                   | ENSG000000048462    | TRAF1,2,3,5,6     | TNFSF13B, TNFSF13     |
| TNFRSF18     | Glucocorticoid-induced TNFR-related protein, GITR, activation-inducible TNFR family receptor, AITR                      | ENSG00000186891     | TRAF1, 2, 3       | TNFSF18               |
| TNFRSF19     | Toxicity and JNK inducer, TAJ, TROY, TAJ- $\alpha$ , TRADE                                                              | ENSG00000127863     | TRAF1,2,3,5       |                       |
| TNFRSF19L    | Receptor expressed in lymphoid tissues, RELT                                                                            | ENSG000000054967    | TRAF1             |                       |
| TNFRSF21     | Death receptor 6, DR6                                                                                                   | ENSG00000146072     | TRADD             |                       |
| TNFRSF22     | SOBa; Tnfrh2, Tnfrsf1al2, mDcTrailr2                                                                                    | ENSMUSG00000010751  | –                 |                       |
| TNFRSF23     | mSOB, Tnfrh1, mDcTrailr1                                                                                                | ENSMUSG000000037613 | –                 |                       |
| TNFRSF27     | X-linked ectodysplasin-A2 receptor, EDA-A2 receptor                                                                     | ENSG00000131080     | –                 |                       |

TNFRSF1A is preferentially activated by the shed form of TNF ligand, whereas the membrane-bound form of TNF serves to activate TNFRSF1A and TNFRSF1B equally.

TNFRSF6B (ENSG00000026036, also known as the decoy receptor for Fas ligand (DcR3), TR6, M68) acts as a non-functional target for TNFSF14, TNFSF15 and TNFSF6. TNFRSF10C (ENSG00000173535, also known as decoy receptor 1, DcR1, decoy TRAIL receptor without death domain, TNF-related apoptosis-inducing ligand receptor 3, TRAIL-R3, LIT, TRID, CD263) and TNFRSF10D (ENSG00000173530, also known as decoy receptor 2, DcR2, TNF-related apoptosis-inducing ligand receptor 4, TRAIL-R4, TRUNDD, CD264) act as non-functional targets for TNFSF10.

The tumour necrosis factor ligand superfamily includes TNFSF1 (ENSG00000204496, TNF $\beta$ , lymphotoxin- $\alpha$ , LT $\alpha$ ), TNFSF2 (ENSG00000204490, TNF, TNF $\alpha$ , cachectin, necrosin, cytotoxin, DIF), TNFSF3 (ENSG00000206327 TNFC, LTB, lymphotoxin- $\beta$ , LT $\beta$ ), TNFSF4 (ENSG00000117586, OX-40 ligand, CD252, glycoprotein Gp34, TAX transcriptionally-activated glycoprotein 1, TXGP-1), TNFSF5 (ENSG00000102245, CD40 ligand, CD154, gp39, TNF-related activation protein, TRAP), TNFSF6 (ENSG00000117560, Fas ligand, CD95L, CD178, ApoL, Apoptosis antigen ligand), TNFSF7 (ENSG00000125726, CD70, CD27 ligand, Ki-24), TNFSF8 (ENSG00000106952, CD30 ligand, CD153), TNFSF9 (ENSG00000125657, 4-1BB ligand, CDw137L), TNFSF10 (ENSG00000121858, TRAIL, Apo-2 ligand (Apo-2L), TL2, CD253), TNFSF11 (ENSG00000120659, Receptor activator of nuclear factor  $\kappa$ B ligand, RANKL, TNF-related activation-induced cytokine, TRANCE, osteoprotegerin ligand, OPG, osteoclast differentiation factor, ODF, CD254 antigen), TNFSF12 (TNF-related weak inducer of apoptosis, TWEAK, Apo-3 ligand, Apo3L, CD255), TNFSF13 (ENSG00000161955, APRIL, TALL2, TRDL-1, ZTNF2, TNFSF13A, CD256), TNFSF13B (ENSG00000102524, zTNF4, THANK, TNF- and APOL-related leukocyte expressed ligand 1, TALL-1, B lymphocyte stimulator, BlyS, B cell-activating factor, BAFF, dendritic cell-derived TNF-like molecule, DTL, CD257 antigen), TNFSF14 (ENSG00000125735, LIGHT, LTg, TR2, Herpesvirus entry mediator-ligand, CD258), TNFSF15 (ENSG00000181634, TL1, TL1A, VEGI, vascular endothelial cell growth inhibitor, TNF ligand-related molecule 1), and TNFSF18 (ENSG00000120337, TL6, glucocorticoid-induced TNF-related ligand, activation-inducible TNF-related ligand).

**Abbreviations:** BDNF, brain-derived neurotrophic factor (ENSG00000176697); BTLA, B- and T-lymphocyte attenuator (ENSG00000186265); FADD, Fas-associated death domain (ENSG00000168040); NT-3, neurotrophin-3 (ENSG00000185652); NT-4, neurotrophin-4 (ENSG00000167744); SIVA, ENSG00000184990; TRADD, TNF receptor-associated death domain (ENSG00000102871); TRAF, TNF receptor-associated factor (ENSG00000000597)

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# TRANSPORTERS

**Overview:** The majority of biological solutes are charged organic or inorganic molecules. Cellular membranes are hydrophobic and, therefore, effective barriers to separate them allowing the formation of gradients, which can be exploited, for example, in the generation of energy. Membrane transporters carry solutes across cell membranes, which would otherwise be impermeable to them. The energy required for active transport processes is obtained from ATP turnover or by exploiting ion gradients.

ATP-driven transporters can be divided into three major classes: P-type ATPases; F-type and V-type ATPases and ATP-binding cassette transporters. The first of these, P-type ATPases, are multimeric proteins, which transport (primarily) inorganic cations. The second, F-type or V-type ATPases, are proton-coupled motors, which can function either as transporters or as motors. Last, are ATP-binding cassette transporters, heavily involved in drug disposition as well as transporting endogenous solutes.

The second largest family of membrane proteins in the human genome, after the G protein-coupled receptors, are the SLC solute carrier family. Within the solute carrier family, there are not only a great variety of solutes transported, from simple inorganic ions to amino acids and sugars to relatively complex organic molecules like haem. The solute carrier family includes 48 families of almost 400 members, many of whom remain orphan transporters, in as much as a physiological function has yet to be determined. The SLC transporters include members which function as antiports, where solute movement in one direction is balanced by a solute moving in the reverse direction. Symports allow concentration gradients of one solute to allow movement of a second solute across a membrane. A third, relatively small group are equilibrative transporters, which allow solutes to travel across membranes down their concentration gradients. A more complex family of transporters, the SLC27 fatty acid transporters also express enzymatic function. Many of the transporters also express electrogenic properties of ion channels.

# ATP-binding cassette family

**Overview:** ATP-binding cassette transporters are ubiquitous membrane proteins characterized by facilitated movement of a range of substrates, including ions, lipids, peptides, steroids. The functional transporter is probably dimeric, with individual subunits typically made up of two groups of 6TM-spanning domains, with two nucleotide-binding domains (NBD). The majority of eukaryotic ABC transporters are 'full' transporters incorporating both TM and NBD entities. Some ABCs, notably the ABCD and ABCG families, appear relatively truncated and are only functional as homo- or heterodimers. Eukaryotic ABC transporters convey substrates from the cytoplasm, either out of the cell or into intracellular organelles. Their role in the efflux of exogenous compounds, notably chemotherapeutic agents, has led to considerable interest.

## ABCA subfamily

| Systematic name | Common abbreviation | Other names                                                                                            | Ensembl ID      | Comments                                                                                                                                                             |
|-----------------|---------------------|--------------------------------------------------------------------------------------------------------|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ABCA1           | ABC1, CERP          | Cholesterol efflux regulatory protein                                                                  | ENSG00000165029 | Loss-of-function mutations are associated with Tangier disease, in which plasma HDL cholesterol levels are greatly reduced                                           |
| ABCA2           | ABC2                | –                                                                                                      | ENSG00000107331 | –                                                                                                                                                                    |
| ABCA3           | ABC3, ABCC          | –                                                                                                      | ENSG00000167972 | Loss-of-function mutations are associated with pulmonary surfactant deficiency                                                                                       |
| ABCA4           | ABCR                | Retinal-specific ATP-binding cassette transporter, RIM ABC transporter, RmP, Stargardt disease protein | ENSG00000198691 | Retinal-specific transporter of <i>N</i> -retinylPE; loss-of-function mutations are associated with Stargardt disease, a juvenile onset macular degenerative disease |
| ABCA5           | –                   | –                                                                                                      | ENSG00000154265 | –                                                                                                                                                                    |
| ABCA6           | –                   | –                                                                                                      | ENSG00000154262 | –                                                                                                                                                                    |
| ABCA7           | –                   | –                                                                                                      | ENSG00000064687 | Genome wide association studies identify ABCA7 variants as associated with Alzheimer's Disease (Hollingworth <i>et al.</i> , 2011)                                   |
| ABCA8           | –                   | KIAA0822                                                                                               | ENSG00000141338 | –                                                                                                                                                                    |
| ABCA9           | –                   | –                                                                                                      | ENSG00000154258 | –                                                                                                                                                                    |
| ABCA10          | –                   | –                                                                                                      | ENSG00000154263 | –                                                                                                                                                                    |
| ABCA12          | –                   | –                                                                                                      | ENSG00000144452 | Reported to play a role in skin ceramide formation (Zuo <i>et al.</i> , 2008)                                                                                        |
| ABCA13          | –                   | –                                                                                                      | ENSG00000179869 | –                                                                                                                                                                    |

A number of structural analogues are not found in man: ABCA14 (ENSMUSG00000062017); ABCA15 (ENSMUSG00000054746); ABCA16 (ENSMUSG00000051900) and ABCA17 (ENSMUSG00000035435).

## ABCB subfamily

| Systematic name | Common abbreviation | Other names                                                                                                                                           | Ensembl ID      | Comments                                                                                                                                          |
|-----------------|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| ABCB1           | MDR1, PGP1          | Multi-drug resistance protein 1, P-glycoprotein 1, CD243 antigen                                                                                      | ENSG00000085563 | Responsible for the cellular export of many therapeutic drugs                                                                                     |
| ABCB2           | TAP1                | Antigen peptide transporter 1, APT1, peptide transporter TAP1, peptide supply factor 1 (PSF-1), peptide transporter involved in antigen processing 1  | ENSG00000168394 | Endoplasmic reticulum, possibly as heterodimer with TAP2                                                                                          |
| ABCB3           | TAP2                | Antigen peptide transporter 2 (APT2), Peptide transporter TAP2, peptide supply factor 2 (PSF-2), peptide transporter involved in antigen processing 2 | ENSG00000204267 | Endoplasmic reticulum, possibly as heterodimer with TAP1                                                                                          |
| ABCB4           | PGY3                | Multi-drug resistance protein 3, P-glycoprotein 3                                                                                                     | ENSG00000005471 | Transports phosphatidylcholine from intracellular to extracellular face of the hepatocyte canalicular membrane (Oude Elferink and Paulusma, 2007) |
| ABCB5           | –                   | –                                                                                                                                                     | ENSG00000004846 | Multidrug resistance protein in, and marker of, melanoma cells (Schatton <i>et al.</i> 2008)                                                      |
| ABCB6           | MTABC3              | Mitochondrial ABC transporter 3, ubiquitously expressed mammalian ABC half transporter, P-glycoprotein-related protein                                | ENSG00000115657 | Mitochondrial porphyrin transporter (Krishnamurthy <i>et al.</i> , 2006)                                                                          |
| ABCB7           | ABC7                | –                                                                                                                                                     | ENSG00000131269 | Mitochondrial; reportedly essential for haematopoiesis (Pondarre <i>et al.</i> , 2007)                                                            |
| ABCB8           | MABC1               | –                                                                                                                                                     | ENSG00000197150 | Mitochondrial; suggested to play a role in chemoresistance of melanoma (Elliott and Al-Hajj, 2009)                                                |
| ABCB9           | TAPL                | TAP-like protein, hABCB9                                                                                                                              | ENSG00000150967 | Reported to be lysosomal (Kamakura <i>et al.</i> , 2008)                                                                                          |
| ABCB10          | MTABC2              | Mitochondrial ABC transporter 2                                                                                                                       | ENSG00000135776 | Mitochondrial                                                                                                                                     |
| ABCB11          | ABC16               | Bile salt export pump, BSEP, PFIC-2, PFIC2, PGY4, SPGP                                                                                                | ENSG00000073734 | Loss-of-function mutations are associated with familial intrahepatic cholestasis (Stieger, 2009)                                                  |

## ABCC subfamily

| Systematic name | Common abbreviation | Other names                                                                                                                                          | Ensembl ID      | Comments                                                                                                                                                                                                                         |
|-----------------|---------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ABCC1           | MRP1                | Multidrug resistance-associated protein 1, leukotriene C <sub>4</sub> transporter                                                                    | ENSG00000103222 | Exhibits a broad substrate specificity (Bakos and Homolya, 2007)                                                                                                                                                                 |
| ABCC2           | MRP2, cMOAT         | Multidrug resistance-associated protein 2, canalicular multispecific organic anion transporter 1, canalicular multidrug resistance protein           | ENSG00000023839 | Loss-of-function mutations are associated with Dubin-Johnson syndrome, in which plasma levels of conjugated bilirubin are elevated                                                                                               |
| ABCC3           | MRP3                | Multidrug resistance-associated protein 3, canalicular multispecific organic anion transporter 2, multi-specific organic anion transporter-D, MOAT-D | ENSG00000108846 | Transports conjugates of glutathione, sulfate or glucuronide (see Borst <i>et al.</i> , 2007)                                                                                                                                    |
| ABCC4           | MRP4                | Multidrug resistance-associated protein 4, multi-specific organic anion transporter-B, MOAT-B                                                        | ENSG00000125257 | Although reported to facilitate cellular cyclic nucleotide export, this role has been questioned (see Borst <i>et al.</i> , 2007); reported to export prostaglandins in a manner sensitive to NSAIDs (Reid <i>et al.</i> , 2003) |
| ABCC5           | MRP5                | Multidrug resistance-associated protein 5, multi-specific organic anion transporter-C, MOAT-C, pABC11, SMRP                                          | ENSG00000114770 | Although reported to facilitate cellular cyclic nucleotide export, this role has been questioned (see Borst <i>et al.</i> , 2007)                                                                                                |
| ABCC6           | MRP6                | Multidrug resistance-associated protein 6, anthracycline resistance-associated protein, multi-specific organic anion transporter-E, MOAT-E           | ENSG00000091262 | –                                                                                                                                                                                                                                |
| ABCC7           | CFTR                | Cystic fibrosis transmembrane conductance regulator, cAMP-dependent chloride channel                                                                 | ENSG00000001626 | See page S214                                                                                                                                                                                                                    |
| ABCC10          | MRP7                | Multidrug resistance-associated protein 7                                                                                                            | ENSG00000124574 | –                                                                                                                                                                                                                                |
| ABCC11          | MRP8                | Multidrug resistance-associated protein 8                                                                                                            | ENSG00000121270 | Single nucleotide polymorphisms distinguish wet vs. dry earwax; association between earwax allele and breast cancer risk in Japanese but not European populations                                                                |
| ABCC12          | MRP9                | Multidrug resistance-associated protein 9                                                                                                            | ENSG00000140798 | –                                                                                                                                                                                                                                |

ABCC8 (ENSG00000006071, also known as SUR1, sulfonylurea receptor 1) and ABCC9 (ENSG00000069431, also known as SUR2, sulfonylurea receptor 2) are unusual in that they lack transport capacity but regulate the activity of particular K<sup>+</sup> channels (K<sub>ir</sub>6.1-6.2, see Page S158), conferring nucleotide sensitivity to these channels to generate the canonical K<sub>ATP</sub> channels. ABCC13 (ENSG00000155288) is a possible pseudogene.

## ABCD subfamily of peroxisomal ABC transporters

This family of 'half-transporters' act as homo- or heterodimers to accumulate fatty acid-CoA esters into peroxisomes for oxidative metabolism (see Kemp *et al.*, 2011).

| Systematic name | Common abbreviation | Other names                                                       | Ensembl ID      | Substrates                                                                                       |
|-----------------|---------------------|-------------------------------------------------------------------|-----------------|--------------------------------------------------------------------------------------------------|
| ABCD1           | ALDP                | Adrenoleukodystrophy protein                                      | ENSG00000101986 | Coenzyme A esters of very long chain fatty acids (van Roermund <i>et al.</i> , 2008; 2011)       |
| ABCD2           | ALDR                | Adrenoleukodystrophy-related protein, adrenoleukodystrophy-like 1 | ENSG00000173208 | Coenzyme A esters of very long chain unsaturated fatty acids (van Roermund <i>et al.</i> , 2011) |
| ABCD3           | PMP70               | 70 kDa peroxisomal membrane protein, PXMP1                        | ENSG00000117528 | –                                                                                                |

ABCD4 (ENSG00000119688, also known as PMP69, PXMP1-L or P70R) appears to be located on the endoplasmic reticulum (Kashiwayama *et al.*, 2009), with an unclear function. Loss-of-function mutations in the gene encoding ALDP underlie the metabolic storage disorder X-linked adrenoleukodystrophy.

### ABCG subfamily

This family of 'half-transporters' act as homo- or heterodimers; particularly ABCG5 and ABCG8 are thought to be obligate heterodimers. They are associated with cellular export of sterols and phospholipids, as well as exogenous drugs (ABCG2).

| Systematic name | Common abbreviation | Other names                                                                                                                                                         | Ensembl ID      | Comments                                                                                                                                  |
|-----------------|---------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| ABCG1           | ABC8                | White protein homolog                                                                                                                                               | ENSG00000160179 | Transports sterols and choline phospholipids (see Kerr <i>et al.</i> , 2011)                                                              |
| ABCG2           | ABCP                | Placenta-specific ATP- binding cassette transporter, breast cancer resistance protein, BCRP, mitoxantrone resistance-associated protein, MXR, CD338 antigen, CDw338 | ENSG00000118777 | Exhibits a broad substrate specificity, including urate and haem, as well as multiple synthetic compounds (see Kerr <i>et al.</i> , 2011) |
| ABCG4           | –                   | White2                                                                                                                                                              | ENSG00000172350 | Putative functional dependence on ABCG1                                                                                                   |
| ABCG5           | –                   | White3, Sterolin-1                                                                                                                                                  | ENSG00000138075 | Transports phytosterols; forms a heterodimer with ABCG8                                                                                   |
| ABCG8           | –                   | Sterolin-2                                                                                                                                                          | ENSG00000143921 | Transports phytosterols; forms a heterodimer with ABCG5                                                                                   |

A further group of ABC transporter-like proteins have been identified to lack membrane spanning regions and are not believed to be functional transporters, but appear to have a role in protein translation (Chen *et al.*, 2006; Paytubi *et al.*, 2009): ABCE1 (ENSG00000164163, also known as OABP or 2'-5' oligoadenylate-binding protein); ABCF1 (ENSG00000204574, also known as ABC50 or TNF- $\alpha$ -stimulated ABC protein); ABCF2 (ENSG00000033050, also known as iron-inhibited ABC transporter 2) and ABCF3 (ENSG00000161204).

**Abbreviations:** ABC, ATP-binding cassette; NBD, nucleotide-binding domain; *N-retinyl*PE, *N*-retinylphosphatidylethanolamine; NSAID, non-steroidal anti-inflammatory drugs

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# F-type and V-type ATPases (EC 3.6.3.14)

The F-type (ATP synthase) and the V-type (vacuolar or vesicular proton pump) ATPases, although having distinct subcellular locations and roles, exhibit marked similarities in subunit structure and mechanism. They are both composed of a 'soluble' complex (termed F<sub>1</sub> or V<sub>1</sub>) and a membrane complex (F<sub>0</sub> or V<sub>0</sub>). Within each ATPase complex, the two individual sectors appear to function as connected opposing rotary motors, coupling catalysis of ATP synthesis or hydrolysis to proton transport.

## F-type ATPase

The F-type ATPase, also known as ATP synthase or ATP phosphohydrolase (H<sup>+</sup>-transporting), is a mitochondrial membrane-associated multimeric complex consisting of two domains, an F<sub>0</sub> channel domain in the membrane and an F<sub>1</sub> domain extending into the lumen. Proton transport across the inner mitochondrial membrane is used to drive the synthesis of ATP, although it is also possible for the enzyme to function as an ATPase. The ATP5O subunit (oligomycin sensitivity-conferring protein, OSCP, ENSG00000241837), which acts as a connector between F<sub>1</sub> and F<sub>0</sub> motors,

The F<sub>1</sub> **motor**, responsible for ATP turnover, has the subunit composition  $\alpha\beta\gamma\delta\epsilon$ .

| Nomenclature | HGNC nomenclature | Ensembl ID                          | Other names                                                                                                      |
|--------------|-------------------|-------------------------------------|------------------------------------------------------------------------------------------------------------------|
| $\alpha$     | ATP5A1;<br>ATPAF2 | ENSG00000152234;<br>ENSG00000171953 | ATP5A, ATP5AL2, ATPM, hATP1, OMR, ORM;<br>ATP synthase mitochondrial F1 complex assembly factor 2, ATP12, Atp12p |
| $\beta$      | ATP5B;<br>ATPAF1  | ENSG00000110955;<br>ENSG00000123472 | ATP5B;<br>ATP synthase mitochondrial F1 complex assembly factor 1, ATP11, Atp11p, FLJ22351                       |
| $\gamma$     | ATP5C1            | ENSG00000165629                     | ATP5C, ATP5CL1                                                                                                   |
| $\delta$     | ATP5D             | ENSG00000099624                     | –                                                                                                                |
| $\epsilon$   | ATP5E             | ENSG00000124172                     | –                                                                                                                |

The F<sub>0</sub> **motor**, responsible for ion translocation, is complex in mammals, with probably nine subunits centring on A, B, and C subunits in the membrane, together with D, E, F2, F6, G2 and 8 subunits.

| Nomenclature | HGNC nomenclature            | Ensembl ID                                              | Other names                                            |
|--------------|------------------------------|---------------------------------------------------------|--------------------------------------------------------|
| A            | MT-ATP6                      | ENSG00000198899                                         | F-ATPase protein 6                                     |
| B            | ATP5F1                       | ENSG00000116459                                         | –                                                      |
| C            | ATP5G1;<br>ATP5G2;<br>ATP5G3 | ENSG00000159199;<br>ENSG00000135390;<br>ENSG00000154518 | ATP synthase proteolipid P1, ATPase protein 9          |
| D            | ATP5H                        | ENSG00000167863                                         | ATP5JD, ATPQ                                           |
| E            | ATP5I                        | ENSG00000169020                                         | ATP5K                                                  |
| F2           | ATP5J2                       | ENSG00000241468                                         | ATP5JL                                                 |
| F6           | ATP5J                        | ENSG00000154723                                         | ATP5, ATP5A, ATPM, CF6, ATP synthase-coupling factor 6 |
| G2           | ATP5L2                       | ENSG00000249222                                         | ATP5K2                                                 |
| 8            | MT-ATP8                      | ENSG00000229604                                         | –                                                      |

Multiple pseudogenes for these proteins have been defined in the human genome.

## V-type ATPase

The V-type ATPase is most prominently associated with lysosomes in mammals, but also appears to be expressed on the plasma membrane and neuronal synaptic vesicles.

The V<sub>1</sub> **motor**, responsible for ATP turnover, has eight subunits with a composition of A-H.

| Nomenclature | HGNC nomenclature | Ensembl ID                                                                                                          | Other names                                       |
|--------------|-------------------|---------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| A            | ATP6V1A           | ENSG00000114573                                                                                                     | ATP6A1, ATP6V1A1, VA68, Vma1, VPP2                |
| B1           | ATP6V1B1          | ENSG00000116039                                                                                                     | ATP6B1, RTA1B, VATB, Vma2, VPP3                   |
| B2           | ATP6V1B2          | ENSG00000147416                                                                                                     | ATP6B2, HO57, VATB, Vma2, VPP3                    |
| C1           | ATP6V1C1          | ENSG00000155097                                                                                                     | ATP6C, ATP6D, VATC, Vma5                          |
| C2           | ATP6V1C2          | ENSG00000143882                                                                                                     | ATP6C2, VMA5                                      |
| D            | ATP6V1D           | ENSG00000100554                                                                                                     | ATP6M, VATD, VMA8                                 |
| E1           | ATP6V1E1          | ENSG00000131100                                                                                                     | ATP6E, ATP6E2, ATP6V1E, P31, Vma4                 |
| E2           | ATP6V1E2          | ENSG00000250565                                                                                                     | ATP6E1, ATP6EL2, ATP6V1EL2, MGC9341, VMA4         |
| F            | ATP6V1F           | ENSG00000128524                                                                                                     | ATP6S14, VATF, Vma7                               |
| G1           | ATP6V1G1          | ENSG00000136888                                                                                                     | ATP6G, ATP6G1, ATP6GL, ATP6J, DKFZp547P234, Vma10 |
| G2           | ATP6V1G2          | ENSG00000230900;<br>ENSG00000213760;<br>ENSG00000234668;<br>ENSG00000234920;<br>ENSG00000206445;<br>ENSG00000226850 | ATP6G, ATP6G2, Em:AC004181.3, NG38, Vma10         |
| G3           | ATP6V1G3          | ENSG00000151418                                                                                                     | ATP6G3, Vma10                                     |
| H            | ATP6V1H           | ENSG00000047249                                                                                                     | CGI-11, SFD, SFDalpha, SFDbeta, VMA13             |

The  $V_0$  motor, responsible for ion translocation, has six subunits (a–e).

| Nomenclature | HGNC nomenclature | Ensembl ID      | Other names                                                               |
|--------------|-------------------|-----------------|---------------------------------------------------------------------------|
| a1           | ATP6V0A1          | ENSG00000033627 | ATP6N1, ATP6N1A, Stv1, Vph1, VPP1                                         |
| a2           | ATP6V0A2          | ENSG00000185344 | ATP6a2, ATP6N1D, J6B7, Stv1, TJ6, TJ6M, TJ6s, Vph1                        |
| a3           | TCIRG1            | ENSG00000110719 | T-cell immune regulator 1, Atp6i, ATP6N1C, ATP6V0A3, OC-116, OC116, TIRC7 |
| a4           | ATP6V0A4          | ENSG00000105929 | ATP6N1B, ATP6N2, RDRTA2, RTA1C, RTADR, Stv1, Vph1, VPP2                   |
| b            | ATP6V0B           | ENSG00000117410 | ATP6F, HATPL, VMA16                                                       |
| c            | ATP6V0C           | ENSG00000185883 | ATP6C, ATP6L, ATPL, VATL, Vma3                                            |
| d1           | ATP6V0D1          | ENSG00000159720 | ATP6D, ATP6DV, P39, VATX, Vma6, VPATPD                                    |
| d2           | ATP6V0D2          | ENSG00000147614 | ATP6D2, FLJ38708, VMA6                                                    |
| e1           | ATP6V0E1          | ENSG00000113732 | ATP6H, ATP6V0E, M9.2                                                      |
| e2           | ATP6V0E2          | ENSG00000171130 | ATP6V0E2L, C7orf32                                                        |

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# P-type ATPases (EC 3.6.3.-)

Phosphorylation-type ATPases are associated with membranes and the transport of ions or phospholipids. A characteristic is the interconversion between E1 and E2 conformations in the activity cycle of the transporters.

## Na<sup>+</sup>/K<sup>+</sup>-ATPase (EC 3.6.3.9)

The cell-surface Na<sup>+</sup>/K<sup>+</sup>-ATPase is an integral membrane protein which regulates the membrane potential of the cell by maintaining gradients of Na<sup>+</sup> and K<sup>+</sup> ions across the plasma membrane, also making a small, direct contribution to membrane potential, particularly in cardiac cells. The active enzyme is a heteromultimer with incompletely defined stoichiometry, possibly as tetramers of heterodimers, each consisting of one of four large, ten TM domain catalytic  $\alpha$  subunits and one of three smaller single TM domain glycoprotein  $\beta$ -subunits (see table). Additional protein partners known as FXYD proteins (e.g. FXYD2, ENSG00000137731) appear to associate with and regulate the activity of the pump.

| Nomenclature | Systematic name | Ensembl ID      | Other names                                                                                                                                           |
|--------------|-----------------|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| $\alpha 1$   | ATP1A1          | ENSG00000163399 | Sodium/potassium-transporting ATPase subunit $\alpha$ -1, sodium pump subunit $\alpha$ -1, Na <sup>+</sup> /K <sup>+</sup> ATPase $\alpha$ -1 subunit |
| $\alpha 2$   | ATP1A2          | ENSG00000018625 | Sodium/potassium-transporting ATPase subunit $\alpha$ -1, sodium pump subunit $\alpha$ -1, Na <sup>+</sup> /K <sup>+</sup> ATPase $\alpha$ -1 subunit |
| $\alpha 3$   | ATP1A3          | ENSG00000105409 | Sodium/potassium-transporting ATPase subunit $\alpha$ -3, sodium pump subunit $\alpha$ -3, Na <sup>+</sup> /K <sup>+</sup> ATPase $\alpha$ -3 subunit |
| $\alpha 4$   | ATP1A4          | ENSG00000132681 | Sodium/potassium-transporting ATPase subunit $\alpha$ -4, sodium pump subunit $\alpha$ -4, Na <sup>+</sup> /K <sup>+</sup> ATPase $\alpha$ -4 subunit |
| $\beta 1$    | ATP1B1          | ENSG00000143153 | Sodium/potassium-transporting ATPase subunit $\beta$ -1                                                                                               |
| $\beta 2$    | ATP1B2          | ENSG00000129244 | Sodium/potassium-transporting ATPase subunit $\beta$ -2                                                                                               |
| $\beta 3$    | ATP1B3          | ENSG00000069849 | Sodium/potassium-transporting ATPase subunit $\beta$ -3, CD298 antigen                                                                                |

Na<sup>+</sup>/K<sup>+</sup>-ATPases are inhibited by ouabain and cardiac glycosides, such as digoxin, as well as potentially endogenous cardiotonic steroids (see Bagrov *et al.*, 2009).

## Ca<sup>2+</sup>-ATPases (EC 3.6.3.8)

The sarcoplasmic/endoplasmic reticulum Ca<sup>2+</sup>-ATPase (SERCA) is an intracellular membrane-associated pump for sequestering calcium from the cytosol into intracellular organelles, usually associated with the recovery phase following excitation of muscle and nerves.

| Nomenclature | Systematic name | Ensembl ID      | Other names                                                                                              |
|--------------|-----------------|-----------------|----------------------------------------------------------------------------------------------------------|
| SERCA1       | ATP2A1          | ENSG00000196296 | Sarcoplasmic/endoplasmic reticulum calcium ATPase 1, fast twitch skeletal muscle isoform                 |
| SERCA2       | ATP2A2          | ENSG00000174437 | Sarcoplasmic/endoplasmic reticulum calcium ATPase 2, calcium pump 2, slow twitch skeletal muscle isoform |
| SERCA3       | ATP2A3          | ENSG00000074370 | Sarcoplasmic/endoplasmic reticulum calcium ATPase 3                                                      |

The fungal toxin ochratoxin A has been described to activate SERCA in kidney microsomes (Chong and Rahimtula, 1992). Cyclopiazonic acid (Seidler *et al.*, 1989), thapsigargin (Lytton *et al.*, 1991) and BHQ are widely employed to block SERCA. Thapsigargin has also been described to block the TRPV1 vanilloid receptor (Toth *et al.*, 2002).

The plasma membrane Ca<sup>2+</sup>-ATPase (PMCA) is a cell-surface pump for extruding calcium from the cytosol, usually associated with the recovery phase following excitation of cells. The active pump is a homodimer, each subunit of which is made up of ten TM segments, with cytosolic C- and N-termini and two large intracellular loops.

| Nomenclature | Systematic name | Ensembl ID      | Other names                                                                      |
|--------------|-----------------|-----------------|----------------------------------------------------------------------------------|
| PMCA1        | ATP2B1          | ENSG00000070961 | Plasma membrane calcium ATPase isoform 1                                         |
| PMCA2        | ATP2B2          | ENSG00000157087 | Plasma membrane calcium ATPase isoform 2                                         |
| PMCA3        | ATP2B3          | ENSG00000067842 | Plasma membrane calcium ATPase isoform 3                                         |
| PMCA4        | ATP2B4          | ENSG00000058668 | Plasma membrane calcium ATPase isoform 4, matrix-remodeling-associated protein 1 |

The stoichiometry of flux through the PMCA differs from SERCA, with the PMCA transporting 1 Ca<sup>2+</sup> while SERCA transports 2 Ca<sup>2+</sup>.

Secretory pathway  $\text{Ca}^{2+}$ -ATPases (SPCA) allow accumulation of calcium and manganese in the Golgi apparatus.

| Nomenclature | Systematic name | Ensembl ID      | Other names                                              |
|--------------|-----------------|-----------------|----------------------------------------------------------|
| SPCA1        | ATP2C1          | ENSG00000017260 | ATPase 2C1, ATP-dependent $\text{Ca}^{2+}$ pump PMR1     |
| SPCA2        | ATP2C2          | ENSG00000064270 | ATPase 2C2, secretory pathway $\text{Ca}^{2+}$ -ATPase 2 |

Loss-of-function mutations in SPCA1 appear to underlie Hailey-Hailey disease (Hu *et al.*, 2000).

#### $\text{H}^{+}/\text{K}^{+}$ -ATPase (EC 3.6.3.10)

The  $\text{H}^{+}/\text{K}^{+}$  ATPase is a heterodimeric protein, made up of  $\alpha$  and  $\beta$  subunits. The  $\alpha$  subunit has 10 TM domains and exhibits catalytic and pore functions, while the  $\beta$  subunit has a single TM domain, which appears to be required for intracellular trafficking and stabilising the  $\alpha$  subunit. The ATP4A and ATP4B subunits are expressed together, while the ATP12A subunit is suggested to be expressed with the  $\beta 1$  (ATP1B1) subunit of the  $\text{Na}^{+}/\text{K}^{+}$ -ATPase (Pestov *et al.*, 2006).

| Nomenclature | Ensembl ID      | Other names                                                                                                               |
|--------------|-----------------|---------------------------------------------------------------------------------------------------------------------------|
| ATP4A        | ENSG00000105675 | Potassium-transporting ATPase $\alpha$ chain 1, gastric $\text{H}^{+}/\text{K}^{+}$ -ATPase $\alpha$ subunit, ATP6A       |
| ATP12A       | ENSG00000075673 | Potassium-transporting ATPase $\alpha$ chain 2, non-gastric $\text{H}^{+}/\text{K}^{+}$ -ATPase $\alpha$ subunit, ATP1AL1 |
| ATP4B        | ENSG00000186009 | Potassium-transporting ATPase $\beta$ chain 1, gastric $\text{H}^{+}/\text{K}^{+}$ -ATPase $\beta$ subunit                |

The gastric  $\text{H}^{+}/\text{K}^{+}$ -ATPase is inhibited by (*R*)-lansoprazole and a metabolite of (*S*)-omeprazole.

#### $\text{Cu}^{2+}$ -ATPase (EC 3.6.3.4)

Copper-transporting ATPases convey copper ions across cell-surface and intracellular membranes. They consist of eight TM domains and associate with multiple copper chaperone proteins (e.g. ATOX1, ENSG00000177556).

| Nomenclature | Ensembl ID      | Other names                                                                    |
|--------------|-----------------|--------------------------------------------------------------------------------|
| ATP7A        | ENSG00000165240 | Copper-transporting ATPase 1, copper pump 1, Menkes disease-associated protein |
| ATP7B        | ENSG00000123191 | Copper-transporting ATPase 2, copper pump 2, Wilson disease-associated protein |

#### Phospholipid-transporting ATPase (EC 3.6.3.1)

These transporters are thought to translocate the aminophospholipids phosphatidylserine and phosphatidylethanolamine from one side of the phospholipid bilayer to the other.

| Nomenclature | Ensembl ID      | Other names                                                                                                     |
|--------------|-----------------|-----------------------------------------------------------------------------------------------------------------|
| ATP8A1       | ENSG00000124406 | Probable phospholipid-transporting ATPase IA, chromaffin granule ATPase II                                      |
| ATP8A2       | ENSG00000132932 | Probable phospholipid-transporting ATPase IB, ML-1                                                              |
| ATP8B1       | ENSG00000081923 | Probable phospholipid-transporting ATPase IC, familial intrahepatic cholestasis type 1                          |
| ATP8B2       | ENSG00000143515 | Probable phospholipid-transporting ATPase ID                                                                    |
| ATP8B3       | ENSG00000130270 | Probable phospholipid-transporting ATPase IK                                                                    |
| ATP8B4       | ENSG00000104043 | Probable phospholipid-transporting ATPase IM                                                                    |
| ATP9A        | ENSG00000054793 | Probable phospholipid-transporting ATPase IIA, ATPase IIA                                                       |
| ATP9B        | ENSG00000166377 | Probable phospholipid-transporting ATPase IIB, ATPase class II type 9B                                          |
| ATP10A       | ENSG00000206190 | Probable phospholipid-transporting ATPase VA, ATPase class V type 10A, aminophospholipid translocase VA, ATP10C |
| ATP10B       | ENSG00000118322 | Probable phospholipid-transporting ATPase VB, ATPase class V type 10B                                           |
| ATP10D       | ENSG00000145246 | Probable phospholipid-transporting ATPase VD, ATPase class V type 10D                                           |
| ATP11A       | ENSG00000068650 | Probable phospholipid-transporting ATPase IH, ATPase class VI type 11A, ATPase IS                               |
| ATP11B       | ENSG00000058063 | Probable phospholipid-transporting ATPase IF, ATPase class VI type 11B, ATPase IR                               |
| ATP11C       | ENSG00000101974 | Probable phospholipid-transporting ATPase IG, ATPase class VI type 11C, ATPase IG, ATPase IQ                    |

Loss-of-function mutations in ATP8B1 are associated with type I familial intrahepatic cholestasis.

A further series of structurally-related proteins have been identified in the human genome, with as yet undefined function, including ATP13A1 (ENSG00000105726), ATP13A2 (ENSG00000159363), ATP13A3 (ENSG00000133657), ATP13A4 (ENSG00000127249) and ATP13A5 (ENSG00000187527).

**Abbreviations:** BHQ, 2,5-di-*t*-butyl-1,4 benzohydroquinone

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# The SLC superfamily of solute carriers

The SLC superfamily of solute carriers is the second largest family of membrane proteins after G protein-coupled receptors, but with a great deal fewer therapeutic drugs that exploit them. As with the ABC transporters, however, they play a major role in drug disposition and so can be hugely influential in determining the clinical efficacy of particular drugs.

48 families are identified on the basis of sequence similarities, but many of them overlap in terms of the solutes that they carry. For example, amino acid accumulation is mediated by members of the SLC1, SLC3/7, SLC6, SLC15, SLC16, SLC17, SLC32, SLC36, SLC38 and SLC43. Further members of the SLC superfamily regulate ion fluxes at the plasma membrane, or solute transport into and out of cellular organelles.

Within the SLC superfamily, there is an abundance in diversity of structure. Two families (SLC3 and SLC7) only generate functional transporters as heteromeric partners, where one partner is a single TM domain protein. Membrane topology predictions for other families suggest 3, 4, 6, 7, 8, 9, 10, 11, 12, 13, or 14 TM domains. Functionally, members may be divided into those dependent on gradients of ions (particularly sodium, chloride or protons), exchange of solutes or simple equilibrative gating. For many members, the stoichiometry of transport is not yet established. Furthermore, one family of transporters also possess enzymatic activity (SLC27), while many members function as ion channels (e.g. SLC1A7/EAAT5), which increases the complexity of function of the SLC superfamily.

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## SLC1 family of amino acid transporters

**Overview:** The SLC1 family of sodium dependent transporters includes the plasma membrane located glutamate transporters and the neutral amino acid transporters ASCT1 and ASCT2 (Amara and Arriza, 1993; Palacin *et al.*, 1998; Kanai and Hediger, 2003; 2004; Beart and O'Shea, 2007).

### Glutamate transporter subfamily

Glutamate transporters present the unusual structural motif of 8TM segments and 2 re-entrant loops (Grunwald and Kanner, 2000). The crystal structure of a glutamate transporter homologue (Glt<sub>ph</sub>) from *Pyrococcus horikoshii* supports this topology and indicates that the transporter assembles as a trimer, where each monomer is a functional unit capable of substrate permeation (Yernool *et al.*, 2004; Boudker *et al.*, 2007; Reyes *et al.*, 2009; reviewed by Jiang and Amara, 2011). These structural data are in agreement with the proposed quaternary structure for EAAT2 (Gendreau *et al.*, 2004) and several functional studies that propose the monomer is the functional unit (Ryan *et al.*, 2004; Grewer *et al.*, 2005; Koch *et al.*, 2007; Leary *et al.*, 2007). Recent evidence suggests that EAAT3 and EAAT4 may assemble as heterotrimers (Nothmann *et al.*, 2011). The activity of glutamate transporters located upon both neurones (predominantly EAAT3, 4 and 5) and glia (predominantly EAAT 1 and 2) serves, dependent upon their location, to regulate excitatory neurotransmission, maintain low ambient extracellular concentrations of glutamate (protecting against excitotoxicity) and provide glutamate for metabolism including the glutamate-glutamine cycle. The Na<sup>+</sup>/K<sup>+</sup>-ATPase (see Page S219) that maintains the ion gradients that drive transport has been demonstrated to co-assemble with EAAT1 and EAAT2 (Rose *et al.*, 2009). Recent evidence supports altered glutamate transport and novel roles in brain for splice variants of EAAT1 and EAAT2 (Gebhardt *et al.*, 2010; Lee and Pow, 2010). Three patients with dicarboxylic aminoaciduria (DA) were recently found to have loss-of-function mutations in EAAT3 (Bailey *et al.*, 2011). DA is characterized by excessive excretion of the acidic amino acids glutamate and aspartate and EAAT3 is the predominant glutamate/aspartate transporter in the kidney. Enhanced expression of EAAT2 resulting from administration of β-lactam antibiotics (e.g. ceftriaxone) is neuroprotective and occurs through NF-κB-mediated EAAT2 promoter activation (Rothstein *et al.*, 2005; Ganel *et al.*, 2006; Lee *et al.*, 2008; reviewed by Kim *et al.*, 2010). PPARγ (see Page S181) activation (e.g. by rosiglitazone) also leads to enhanced expression of EAAT through promoter activation (Romera *et al.*, 2007). In addition, several translational activators of EAAT2 have recently been described (Colton *et al.*, 2010) along with treatments that increase the surface expression of EAAT2 (e.g. Lau *et al.*, 2011; Zou *et al.*, 2011), or prevent its down-regulation (e.g. Goursaud *et al.*, 2011). A thermodynamically uncoupled Cl<sup>-</sup> flux, activated by Na<sup>+</sup> and glutamate (Kanai and Hediger, 2003; Grewer and Rauen, 2005; Machtens *et al.*, 2011) (Na<sup>+</sup> and aspartate in the case of Glt<sub>ph</sub>, Ryan and Mindell, 2007), is sufficiently large, in the instances of EAAT4 and EAAT5, to influence neuronal excitability (Veruki *et al.*, 2006; Torres-Salazar and Fahlke, 2007). Indeed, it has recently been suggested that the primary function of EAAT5 is as a slow anion channel gated by glutamate, rather than a glutamate transporter (Gameiro *et al.*, 2011).

|                     |                                     |                                     |                                     |
|---------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| Common abbreviation | EAAT1                               | EAAT2                               | EAAT3                               |
| Systematic name     | SLC1A3                              | SLC1A2                              | SCL1A1                              |
| Nomenclature        | Excitatory amino acid transporter 1 | Excitatory amino acid transporter 2 | Excitatory amino acid transporter 3 |
| Other names         | GLAST                               | GLT1                                | EAAC1                               |
| Ensembl ID          | ENSG000000079215                    | ENSG00000110436                     | ENSG00000106688                     |

|                               |                                                                                                                                             |                                                                                                                                                                                               |                                                                                                                                                  |
|-------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| Common abbreviation           | EAAT1                                                                                                                                       | EAAT2                                                                                                                                                                                         | EAAT3                                                                                                                                            |
| Endogenous substrates         | L-glutamate, L-aspartate                                                                                                                    | L-glutamate, L-aspartate                                                                                                                                                                      | L-glutamate, L-aspartate, L-cysteine (Zerangue and Kavanaugh, 1996a)                                                                             |
| Synthetic substrates          | DL- <i>threo</i> - $\beta$ -hydroxyaspartate, L- <i>trans</i> -2,4-pyrrolidine dicarboxylate                                                | DL- <i>threo</i> - $\beta$ -hydroxyaspartate, L- <i>trans</i> -2,4-pyrrolidine dicarboxylate                                                                                                  | DL- <i>threo</i> - $\beta$ -hydroxyaspartate, L- <i>trans</i> -2,4-pyrrolidine dicarboxylate                                                     |
| Inhibitors ( $K_B$ or $K_i$ ) | UCPH-101 ( $IC_{50}$ = 120 nM – membrane potential assay, Jensen <i>et al.</i> , 2009), DL-TBOA (9 $\mu$ M)                                 | WAY-213613 ( $IC_{50}$ = 130 nM), DL-TBOA (0.12 $\mu$ M), (2 <i>S</i> ,4 <i>R</i> )-4-methylglutamate (3.4 $\mu$ M), dihydrokainate (9 $\mu$ M), <i>Threo</i> -3-methylglutamate (18 $\mu$ M) | NBI-59159 ( $IC_{50}$ = 25 nM), DL-TBOA ( $IC_{50}$ = 8 $\mu$ M), L- $\beta$ -BA ( $IC_{50}$ = 0.8 $\mu$ M – [ $^3$ H]-D-aspartate uptake assay) |
| Probes                        | [ $^3$ H]-ETB-TBOA ( $K_D$ = 15.5 nM), [ $^3$ H]-[(2 <i>S</i> ,4 <i>R</i> )-4-methylglutamate, [ $^3$ H]-D-aspartate, [ $^3$ H]-L-aspartate | [ $^3$ H]-ETB-TBOA ( $K_D$ = 16.2 nM), [ $^3$ H]-[(2 <i>S</i> ,4 <i>R</i> )-4-methylglutamate, [ $^3$ H]-D-aspartate, [ $^3$ H]-L-aspartate                                                   | [ $^3$ H]-ETB-TBOA ( $K_D$ = 320 nM), [ $^3$ H]-D-aspartate, [ $^3$ H]-L-aspartate                                                               |
| Stoichiometry                 | Probably 3 Na $^+$ : 1 H $^+$ : 1 glutamate (in): 1 K $^+$ (out)                                                                            | 3 Na $^+$ : 1 H $^+$ : 1 glutamate (in): 1 K $^+$ (out) (Levy <i>et al.</i> , 1998)                                                                                                           | 3 Na $^+$ : 1 H $^+$ : 1 glutamate (in): 1 K $^+$ (out) (Zerangue and Kavanaugh, 1996b)                                                          |

|                               |                                                                                              |                                                                                              |
|-------------------------------|----------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
| Common abbreviation           | EAAT4                                                                                        | EAAT5                                                                                        |
| Systematic name               | SLC1A6                                                                                       | SLC1A7                                                                                       |
| Nomenclature                  | Excitatory amino acid transporter 4                                                          | Excitatory amino acid transporter 5                                                          |
| Ensembl ID                    | ENSG00000105143                                                                              | ENSG00000162383                                                                              |
| Endogenous substrates         | L-glutamate, L-aspartate                                                                     | L-glutamate, L-aspartate                                                                     |
| Synthetic substrates          | DL- <i>threo</i> - $\beta$ -hydroxyaspartate, L- <i>trans</i> -2,4-pyrrolidine dicarboxylate | DL- <i>threo</i> - $\beta$ -hydroxyaspartate, L- <i>trans</i> -2,4-pyrrolidine dicarboxylate |
| Inhibitors ( $K_B$ or $K_i$ ) | DL-TBOA (4.4 $\mu$ M), <i>Threo</i> -3-methylglutamate (50 $\mu$ M)                          | DL-TBOA (3.2 $\mu$ M)                                                                        |
| Probes                        | [ $^3$ H]-ETB-TBOA ( $K_D$ = 24.8 nM), [ $^3$ H]-D-aspartate, [ $^3$ H]-L-aspartate          | [ $^3$ H]-ETB-TBOA ( $K_D$ = 29.5 nM), [ $^3$ H]-D-aspartate, [ $^3$ H]-L-aspartate          |
| Stoichiometry                 | Probably 3 Na $^+$ : 1 H $^+$ : 1 glutamate (in): 1 K $^+$ (out)                             | Probably 3 Na $^+$ : 1 H $^+$ : 1 glutamate (in): 1 K $^+$ (out)                             |

The  $K_B$  (or  $K_i$ ) values reported, unless indicated otherwise, are derived from transporter currents mediated by EAATs expressed in voltage-clamped *Xenopus laevis* oocytes (Vandenberg *et al.*, 1997; Shimamoto *et al.*, 1998; Eliasof *et al.* 2001; Shigeri *et al.* 2001).  $K_B$  (or  $K_i$ ) values derived in uptake assays are generally higher (*e.g.* Shimamoto *et al.*, 1998). In addition to acting as a poorly transportable inhibitor of EAAT2, (2*S*,4*R*)-4-methylglutamate, also known as SYM2081, is a competitive substrate for EAAT1 ( $K_M$  = 54  $\mu$ M; Vandenberg *et al.*, 1997; Huang *et al.*, 2009) and additionally is a potent kainate receptor agonist (Zhou *et al.*, 1997) which renders the compound unsuitable for autoradiographic localisation of EAATs (Apricò *et al.*, 2007). Similarly, at concentrations that inhibit EAAT2, dihydrokainate binds to kainate receptors (Shimamoto *et al.* 1998). WAY-855 and WAY-213613 are both non-substrate inhibitors with a preference for EAAT2 over EAAT3 and EAAT1 (Dunlop *et al.*, 2003; Dunlop *et al.*, 2005). NBI-59159 is a non-substrate inhibitor with modest selectivity for EAAT3 over EAAT1 (>10-fold) and EAAT2 (5-fold) (Coon *et al.*, 2004; Dunlop, 2006). Analogously, L- $\beta$ -*threo*-benzyl-aspartate (L- $\beta$ -BA) is a competitive non-substrate inhibitor that preferentially blocks EAAT3 versus EAAT1, or EAAT2 (Esslinger *et al.*, 2005b). [ $^3$ H]-[(2*S*,4*R*)-4-methylglutamate demonstrates low affinity binding ( $K_D$   $\approx$  6.0  $\mu$ M) to EAAT1 and EAAT2 in rat brain homogenates (Apricò *et al.*, 2001) and EAAT1 in murine astrocyte membranes (Apricò *et al.*, 2004), whereas [ $^3$ H]-ETB-TBOA binds with high affinity to all EAATs other than EAAT3 (Shimamoto *et al.*, 2007). The novel isoxazole derivative (-)-HIP-A may interact at the same site as TBOA and preferentially inhibit reverse transport of glutamate (Colleoni *et al.*, 2008). *Threo*-3-methylglutamate induces substrate-like currents at EAAT4, but does not elicit heteroexchange of [ $^3$ H]-aspartate in synaptosome preparations, inconsistent with the behaviour of a substrate inhibitor (Eliasof *et al.*, 2001). Parawixin1, a compound isolated from the venom from the spider *Parawixia bistriata* is a selective enhancer of the glutamate uptake through EAAT2 but not through EAAT1 or EAAT3 (Fontana *et al.*, 2003, 2007). In addition to the agents listed in the table, DL-*threo*- $\beta$ -hydroxyaspartate and L-*trans*-2,4-pyrrolidine dicarboxylate act as non-selective competitive substrate inhibitors of all EAATs. Zn $^{2+}$  and arachidonic acid are putative endogenous modulators of EAATs with actions that differ across transporter subtypes (reviewed by Vandenberg *et al.*, 2004).

### Alanine/serine/cysteine transporter subfamily

ASC transporters mediate Na $^+$ -dependent exchange of small neutral amino acids such as Ala, Ser, Cys and Thr and their structure is predicted to be similar to that of the glutamate transporters (Arizza *et al.*, 1993; Utsunomiya-Tate *et al.*, 1996). ASCT1 and ASCT2 also exhibit thermodynamically uncoupled chloride channel activity associated with substrate transport (Zerangue and Kavanaugh, 1996c; Bröer *et al.*, 2000). Whereas EAATs counter-transport K $^+$  (see above) ASCTs do not and their function is independent of the intracellular concentration of K $^+$  (Zerangue and Kavanaugh, 1996c).

|                     |                                       |                                       |
|---------------------|---------------------------------------|---------------------------------------|
| Common abbreviation | ASCT1                                 | ASCT2                                 |
| Systematic name     | SLC1A4                                | SLC1A5                                |
| Nomenclature        | Alanine/serine/cysteine transporter 1 | Alanine/serine/cysteine transporter 2 |

|                         |                                                                                                                                                    |                                                                                                                                                                                                                  |
|-------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Common abbreviation     | ASCT1                                                                                                                                              | ASCT2                                                                                                                                                                                                            |
| Other names             | Neutral amino acid transporter A,<br>SATT                                                                                                          | Neutral amino acid transporter B(0),<br>hATB <sup>o</sup> , AAAT                                                                                                                                                 |
| Ensembl ID              | ENSG00000115902                                                                                                                                    | ENSG00000105281                                                                                                                                                                                                  |
| Endogenous substrates   | L-cysteine > L-alanine = L-serine ><br>L-threonine                                                                                                 | L-alanine = L-serine = L-cysteine<br>(low $V_{max}$ ) = L-threonine =<br>L-glutamine = L-asparagine >><br>L-methionine $\equiv$ L-glycine $\equiv$ L-leucine<br>> L-valine > L-glutamate (enhanced<br>at low pH) |
| Inhibitors              | –                                                                                                                                                  | <i>p</i> -nitrophenyl glutamyl anilide<br>(Esslinger <i>et al.</i> , 2005a),<br>benzylserine, benzylcysteine<br>(Grewer and Grabsch, 2004)                                                                       |
| Predicted stoichiometry | 1 Na <sup>+</sup> : 1 amino acid (in): 1 Na <sup>+</sup> : 1<br>amino acid (out); (homo-, or<br>hetero-exchange; Zerangue and<br>Kavanaugh, 1996b) | 1 Na <sup>+</sup> : 1 amino acid (in): 1 Na <sup>+</sup> : 1<br>amino acid (out); (homo-, or<br>hetero-exchange; Bröer <i>et al.</i> , 1999)                                                                     |

The substrate specificity of ASCT1 may extend to proline and hydroxyproline (Pinilla-Tenas *et al.*, 2003). At low pH (~5.5) both ASCT1 and ASCT2 are able to exchange acidic amino acids such as cysteate and glutamate (Tamarappoo *et al.*, 1996; Utsunomiya-Tate *et al.*, 1996). In addition to the inhibitors tabulated above, HgCl<sub>2</sub>, methylmercury, mersalyl, at low micromolar concentrations, non-competitively inhibit ASCT2 by covalent modification of cysteine residues (Oppedisano *et al.*, 2010).

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## SLC2 family of hexose and sugar alcohol transporters

**Overview:** the SLC2 family transports glucose, fructose, inositol and related hexoses. Three classes of glucose transporter can be identified, separating GLUT1–4 and 14; GLUT6, 8, 10 and 12; and GLUT5, 7, 9 and 11. Modelling suggests a 12 TM membrane topology, with intracellular termini, with functional transporters acting as homodimers or homotetramers.

Class I transporters are able to transport glucose, but not fructose, in the direction of the concentration gradient and may be inhibited non-selectively by phloretin and cytochalasin B. GLUT1 is the major glucose transporter in brain, placenta and erythrocytes, GLUT2 is found in the pancreas, liver and kidneys, GLUT3 is neuronal and placental, while GLUT4 is the insulin-responsive transporter found in skeletal muscle, heart and adipose tissue. GLUT14 appears to result from gene duplication of GLUT3 and is expressed in the testes (Wu and Freeze, 2002).

| Systematic name        | SLC2A1                                                                                            | SLC2A2                                             | SLC2A3                                          | SLC2A4                                             | SLC2A14                |
|------------------------|---------------------------------------------------------------------------------------------------|----------------------------------------------------|-------------------------------------------------|----------------------------------------------------|------------------------|
| Preferred abbreviation | GLUT1                                                                                             | GLUT2                                              | GLUT3                                           | GLUT4                                              | GLUT14                 |
| Nomenclature           | Glucose transporter 1                                                                             | Glucose transporter 2                              | Glucose transporter 3                           | Glucose transporter 4                              | Glucose transporter 14 |
| Other names            | HepG2 glucose transporter, erythrocyte/brain glucose transporter                                  | Liver glucose transporter                          | Fructose transporter, brain glucose transporter | Insulin-responsive glucose transporter             | –                      |
| Ensembl ID             | ENSG00000117394                                                                                   | ENSG00000163581                                    | ENSG00000059804                                 | ENSG00000181856                                    | ENSG00000173262        |
| Substrates             | Glucose = glucosamine (Uldry <i>et al.</i> , 2002), dehydroascorbic acid (Bianchi and Rose, 1986) | Glucosamine > glucose (Uldry <i>et al.</i> , 2002) | Glucose                                         | Glucosamine ≥ glucose (Uldry <i>et al.</i> , 2002) | –                      |
| Probes                 | [ <sup>3</sup> H]-2-Deoxyglucose                                                                  | [ <sup>3</sup> H]-2-Deoxyglucose                   | [ <sup>3</sup> H]-2-Deoxyglucose                | [ <sup>3</sup> H]-2-Deoxyglucose                   | –                      |

Class II transporters transport fructose and appear to be insensitive to cytochalasin B.

|                        |                                                  |                                     |                                                      |                                                                                  |
|------------------------|--------------------------------------------------|-------------------------------------|------------------------------------------------------|----------------------------------------------------------------------------------|
| Systematic name        | SLC2A5                                           | SLC2A7                              | SLC2A9                                               | SLC2A11                                                                          |
| Preferred abbreviation | GLUT5                                            | GLUT7                               | GLUT9                                                | GLUT11                                                                           |
| Nomenclature           | Glucose transporter 5                            | Glucose transporter 7               | Glucose transporter 9                                | Glucose transporter 11                                                           |
| Other names            | Small intestine glucose transporter              | –                                   | –                                                    | –                                                                                |
| Ensembl ID             | ENSG00000142583                                  | ENSG00000197241                     | ENSG00000109667                                      | ENSG00000133460                                                                  |
| Substrates             | Fructose > glucose (Burant <i>et al.</i> , 1992) | Fructose, glucose (Cheeseman, 2008) | Fructose, uric acid (Caulfield <i>et al.</i> , 2008) | Glucose (Doerge <i>et al.</i> , 2001), fructose (Manolescu <i>et al.</i> , 2007) |

Class II transporters appear to be predominantly intracellularly located.

|                        |                       |                                         |                                                          |                                       |
|------------------------|-----------------------|-----------------------------------------|----------------------------------------------------------|---------------------------------------|
| Systematic name        | SLC2A6                | SLC2A8                                  | SLC2A10                                                  | SLC2A12                               |
| Preferred abbreviation | GLUT6                 | GLUT8                                   | GLUT10                                                   | GLUT12                                |
| Nomenclature           | Glucose transporter 6 | Glucose transporter 8                   | Glucose transporter 10                                   | Glucose transporter 12                |
| Ensembl ID             | ENSG00000160326       | ENSG00000136856                         | ENSG00000197496                                          | ENSG00000146411                       |
| Substrates             | –                     | Glucose (Ibberson <i>et al.</i> , 2000) | Glucose, dehydroascorbic acid (Lee <i>et al.</i> , 2010) | Glucose (Rogers <i>et al.</i> , 2003) |

Proton-coupled inositol transporters are expressed predominantly in the brain and can be inhibited by phloretin and cytochalasin B (Uldry *et al.*, 2002).

|                        |                                                                                                                           |
|------------------------|---------------------------------------------------------------------------------------------------------------------------|
| Systematic name        | SLC2A13                                                                                                                   |
| Preferred abbreviation | HMIT                                                                                                                      |
| Nomenclature           | Proton <i>myo</i> -inositol cotransporter                                                                                 |
| Ensembl ID             | ENSG00000151229                                                                                                           |
| Other names            | H <sup>+</sup> - <i>myo</i> -inositol symporter                                                                           |
| Substrates             | <i>myo</i> -Inositol, <i>scyllo</i> -inositol, <i>chiro</i> -inositol, <i>muco</i> -inositol (Uldry <i>et al.</i> , 2002) |
| Stoichiometry          | 1 H <sup>+</sup> : 1 inositol (in) (Di Daniel <i>et al.</i> , 2009)                                                       |

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# SLC3 and SLC7 families of heteromeric amino acid transporters (HATs)

**Overview:** these families combine to generate functional transporters, where the subunit composition is a disulphide-linked combination of a heavy chain (SLC3 family) with a light chain (SLC7 family).

**SLC3 family** members are single TM proteins with extensive glycosylation of the exterior C-terminus, which heterodimerize with SLC7 family members in the endoplasmic reticulum and assist in the plasma membrane localization of the transporter.

|                     |                                                                |                                                              |
|---------------------|----------------------------------------------------------------|--------------------------------------------------------------|
| Systematic name     | SLC3A1                                                         | SLC3A2                                                       |
| Common abbreviation | RBAT                                                           | 4F2hc                                                        |
| Nomenclature        | Cystine, dibasic, and neutral amino acid transporter           | 4F2 cell-surface antigen heavy chain                         |
| Ensembl ID          | ENSG00000138079                                                | ENSG00000168003                                              |
| Other names         | B <sup>0,+</sup> -type amino acid transport protein; D2H, ATR1 | CD98 antigen Lymphocyte activation antigen 4F2 large subunit |

**SLC7 family** members may be divided into two major groups: cationic amino acid transporters (CATs) and glycoprotein-associated amino acid transporters (gpaATs).

Cationic amino acid transporters are 14 TM proteins, which mediate pH- and sodium-independent transport of cationic amino acids (system y<sup>+</sup>), apparently as an exchange mechanism. These transporters are sensitive to inhibition by N-ethylmaleimide.

|                        |                                                                                                                |                                                |                                                |                                   |                |
|------------------------|----------------------------------------------------------------------------------------------------------------|------------------------------------------------|------------------------------------------------|-----------------------------------|----------------|
| Systematic name        | SLC7A1                                                                                                         | SLC7A2                                         | SLC7A3                                         | SLC7A4                            | SLC7A14        |
| Preferred abbreviation | CAT1                                                                                                           | CAT2                                           | CAT3                                           | CAT4                              | –              |
| Nomenclature           | High affinity cationic amino acid transporter 1                                                                | Low affinity cationic amino acid transporter 2 | Cationic amino acid transporter 3              | Cationic amino acid transporter 4 | –              |
| Ensembl ID             | ENSG00000139514                                                                                                | ENSG00000003989                                | ENSG00000165349                                | ENSG00000099960                   | ENSG0000013293 |
| Other names            | System Y <sup>+</sup> basic amino acid transporter, ecotropic retroviral leukemia receptor homolog, ERR, ATRC1 | ATRC2                                          | Cationic amino acid transporter y <sup>+</sup> | –                                 | –              |
| Substrates             | L-Arginine, L-lysine, L-ornithine, L-histidine                                                                 | L-Arginine, L-lysine, L-ornithine, L-histidine | L-Arginine, L-lysine, L-ornithine              | –                                 | –              |

CAT4 appears to be non-functional in heterologous expression (Wolf *et al.*, 2002), while SLC7A14 has yet to be characterized.

Glycoprotein-associated amino acid transporters are 12 TM proteins, which heterodimerize with members of the SLC3 family to act as cell-surface amino acid exchangers.

Heterodimers between 4F2hc and hLAT1 or hLAT2 generate sodium-independent system L transporters. These transport large neutral amino acids (L-leucine, L-isoleucine and L-methionine).

Heterodimers between 4F2hc and y+LAT1 or y+LAT2 generate sodium-dependent transporters, similar to the system y<sup>+</sup>L transporters. These transporters are N-ethylmaleimide-insensitive and transport neutral (L-leucine) as well as cationic (L-arginine, L-lysine and L-ornithine) amino acids. Heterodimers between RBAT and B<sup>0,+</sup>AT appear to mediate sodium-independent system b<sup>0,+</sup> transport of neutral and cationic amino acids (L-leucine, L-arginine, L-lysine and L-ornithine).

|                        |                                 |                                 |                              |                              |                                                 |
|------------------------|---------------------------------|---------------------------------|------------------------------|------------------------------|-------------------------------------------------|
| Systematic name        | SLC7A5                          | SLC7A8                          | SLC7A7                       | SLC7A6                       | SLC7A9                                          |
| Preferred abbreviation | hLAT1                           | hLAT2                           | y+LAT1                       | y+LAT2                       | B <sup>0,+</sup> AT                             |
| Nomenclature           | L-type amino acid transporter 1 | L-type amino acid transporter 2 | y+L amino acid transporter 1 | y+L amino acid transporter 2 | B <sup>0,+</sup> -type amino acid transporter 1 |
| Ensembl ID             | ENSG00000103257                 | ENSG00000092068                 | ENSG00000155465              | ENSG00000103064              | ENSG00000021488                                 |

|                 |                                                                                                                                                                                       |                                                       |                                       |                                                        |                                                |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|---------------------------------------|--------------------------------------------------------|------------------------------------------------|
| Systematic name | SLC7A5                                                                                                                                                                                | SLC7A8                                                | SLC7A7                                | SLC7A6                                                 | SLC7A9                                         |
| Other names     | Large neutral amino acids transporter small subunit 1, y <sup>+</sup> system cationic amino acid transporter, 4F2 light chain, 4F2LC, CD98 light chain, integral membrane protein E16 | Large neutral amino acids transporter small subunit 2 | Monocyte amino acid permease 2, MOP-2 | Cationic amino acid transporter, y <sup>+</sup> system | Glycoprotein-associated amino acid transporter |

Asc-1 appears to heterodimerize with 4F2hc to allow the transport of small neutral amino acids (such as L-alanine, L-serine and glycine), as well as D-serine, in a sodium-independent manner.

xCT generates a heterodimer with 4F2hc for a system x<sub>c</sub><sup>-</sup> transporter that accumulates cystine in a sodium-independent manner.

AGT has been conjugated with SLC3 members as fusion proteins to generate functional transporters, but the identity of a native heterodimer has yet to be ascertained.

|                        |                                   |                 |                 |
|------------------------|-----------------------------------|-----------------|-----------------|
| Systematic name        | SLC7A10                           | SLC7A11         | SLC7A13         |
| Preferred abbreviation | Asc-1                             | xCT             | XAT2            |
| Nomenclature           | Asc-type amino acid transporter 1 | –               | AGT1            |
| Ensembl ID             | ENSG00000130876                   | ENSG00000151012 | ENSG00000164893 |

**Abbreviations:** CAT, cationic amino acid transporter, **gpaAT**, glycoprotein-associated amino acid transporter

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## SLC4 family of bicarbonate transporters

**Overview:** together with the SLC26 family, the SLC4 family of transporters subserve anion exchange, principally of chloride and bicarbonate, but also carbonate and hydrogen sulphate (HSO<sub>4</sub><sup>-</sup>). SLC4 family members regulate bicarbonate fluxes as part of carbon dioxide movement, chyme neutralization and reabsorption in the kidney.

Within the family, subgroups of transporters are identifiable: the electroneutral sodium-independent Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> transporters (AE1, AE2 and AE3), the electrogenic sodium-dependent HCO<sub>3</sub><sup>-</sup> transporters (NBCe1 and NBCe2) and the electroneutral HCO<sub>3</sub><sup>-</sup> transporters (NBCn1 and NBCn2). Topographical information derives mainly from study of AE1, abundant in erythrocytes, which suggests a dimeric or tetrameric arrangement, with subunits made up of 13 TM domains and re-entrant loops at TM9/10 and TM11/12. The N terminus exhibits sites for interaction with multiple proteins, including glycolytic enzymes, haemoglobin and cytoskeletal elements.

Anion exchangers

|                       |                                                                |                                                                |                                                                            |                                    |
|-----------------------|----------------------------------------------------------------|----------------------------------------------------------------|----------------------------------------------------------------------------|------------------------------------|
| Systematic name       | SLC4A1                                                         | SLC4A2                                                         | SLC4A3                                                                     | SLC4A9                             |
| Common abbreviation   | AE1                                                            | AE2                                                            | AE3                                                                        | AE4                                |
| Nomenclature          | Anion exchange protein 1                                       | Anion exchange protein 2                                       | Anion exchange protein 3                                                   | Anion exchange protein 4           |
| Ensembl ID            | ENSG00000004939                                                | ENSG00000164889                                                | ENSG00000114923                                                            | ENSG00000113073                    |
| Other names           | Band 3, CD233                                                  | Non-erythroid band 3-like protein, BND3L                       | Neuronal band 3-like protein, cardiac/brain band 3-like protein, CAE3/BAE3 | Sodium bicarbonate cotransporter 5 |
| Endogenous substrates | Chloride, bicarbonate                                          | Chloride, bicarbonate                                          | Chloride, bicarbonate                                                      | –                                  |
| Stoichiometry         | 1 Cl <sup>–</sup> (in) : 1 HCO <sub>3</sub> <sup>–</sup> (out) | 1 Cl <sup>–</sup> (in) : 1 HCO <sub>3</sub> <sup>–</sup> (out) | 1 Cl <sup>–</sup> (in) : 1 HCO <sub>3</sub> <sup>–</sup> (out)             | –                                  |

Sodium-dependent HCO<sub>3</sub><sup>–</sup> transporters

|                       |                                                                                                                                                                        |                                                                                                                                                                        |                                                                                                                                                                      |                                                                                                                                                                      |
|-----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Systematic name       | SLC4A4                                                                                                                                                                 | SLC4A5                                                                                                                                                                 | SLC4A7                                                                                                                                                               | SLC4A10                                                                                                                                                              |
| Common abbreviation   | NBCE1                                                                                                                                                                  | NBCE2                                                                                                                                                                  | NBCn1                                                                                                                                                                | NBCn2                                                                                                                                                                |
| Nomenclature          | Electrogenic sodium bicarbonate cotransporter 1                                                                                                                        | Electrogenic sodium bicarbonate cotransporter 4                                                                                                                        | Electroneutral sodium bicarbonate cotransporter 1                                                                                                                    | Electroneutral sodium bicarbonate cotransporter 2                                                                                                                    |
| Ensembl ID            | ENSG00000080493                                                                                                                                                        | ENSG00000188687                                                                                                                                                        | ENSG00000033867                                                                                                                                                      | ENSG00000144290                                                                                                                                                      |
| Other names           | Sodium bicarbonate cotransporter, kNBC1, NBC2, pNBC                                                                                                                    | NBC4                                                                                                                                                                   | Sodium bicarbonate cotransporter 3, NBC3                                                                                                                             | Sodium-driven chloride bicarbonate exchanger, NCBE                                                                                                                   |
| Endogenous substrates | Sodium bicarbonate                                                                                                                                                     | Sodium bicarbonate                                                                                                                                                     | Sodium bicarbonate                                                                                                                                                   | Sodium bicarbonate                                                                                                                                                   |
| Stoichiometry         | 1 Na <sup>+</sup> : 2/3 HCO <sub>3</sub> <sup>–</sup> (out) or<br>1 Na <sup>+</sup> : CO <sub>3</sub> <sup>2–</sup> (out) or<br>1 NaCO <sub>3</sub> <sup>–</sup> (out) | 1 Na <sup>+</sup> : 2/3 HCO <sub>3</sub> <sup>–</sup> (out) or<br>1 Na <sup>+</sup> : CO <sub>3</sub> <sup>2–</sup> (out) or<br>1 NaCO <sub>3</sub> <sup>–</sup> (out) | 1 Na <sup>+</sup> : 1 HCO <sub>3</sub> <sup>–</sup> (out) or<br>1 Na <sup>+</sup> : CO <sub>3</sub> <sup>2–</sup> (out) or<br>1 NaCO <sub>3</sub> <sup>–</sup> (out) | 1 Na <sup>+</sup> : 1 HCO <sub>3</sub> <sup>–</sup> (out) or<br>1 Na <sup>+</sup> : CO <sub>3</sub> <sup>2–</sup> (out) or<br>1 NaCO <sub>3</sub> <sup>–</sup> (out) |

|                       |                                                                                   |                                                  |
|-----------------------|-----------------------------------------------------------------------------------|--------------------------------------------------|
| Systematic name       | SLC4A8                                                                            | SLC4A11                                          |
| Common abbreviation   | NDCBE                                                                             | BTR1                                             |
| Ensembl ID            | ENSG00000050438                                                                   | ENSG00000088836                                  |
| Other names           | Electroneutral Na <sup>+</sup> -driven Cl-HCO <sub>3</sub> exchanger, k-NBC3      | NaBC1, bicarbonate transporter-related protein 1 |
| Endogenous substrates | Chloride, sodium bicarbonate                                                      | –                                                |
| Stoichiometry         | 1 Na <sup>+</sup> : 2HCO <sub>3</sub> <sup>–</sup> (in) : 1 Cl <sup>–</sup> (out) | –                                                |

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## SLC5 family of sodium-dependent transporters

**Overview:** The SLC5 family of sodium-dependent transporters includes, in mammals, the Na<sup>+</sup>/substrate co-transporters for choline, glucose, monocarboxylates, *myo*-inositol and iodide (Ferguson and Blakely, 2004; Wright and Turk, 2004; Ganapathy *et al.*, 2008; Wright *et al.*, 2011). Members of the SLC5 and SLC6 families, along with other unrelated Na<sup>+</sup> cotransporters (*i.e.* Mhp1 and BetP), share a common structural core that contains an inverted repeat of 5TM  $\alpha$ -helical domains (Abramson and Wright, 2009).

### Choline transporter

The high affinity, hemicholinium-3-sensitive, choline transporter (CHT) is expressed mainly in cholinergic neurones on nerve cell terminals and synaptic vesicles (keratinocytes being an additional location). In autonomic neurones, expression of CHT requires an activity-dependent retrograde signal from postsynaptic neurones (Krishnaswamy and Cooper 2009). Through recapture of choline generated by the hydrolysis of ACh by acetylcholinesterase, CHT serves to maintain ACh synthesis within the presynaptic terminal (Ferguson and Blakely, 2004). Homozygous mice engineered to lack CHT die within one hour of birth as a result of hypoxia arising from failure of transmission at the neuromuscular junction of the skeletal muscles that support respiration (Ferguson *et al.*, 2004). A low affinity choline uptake mechanism that remains to be identified at the molecular level may involve multiple transporters. In addition, a family of choline transporter-like (CTL) proteins, (which are members of the SLC44 family) with weak Na<sup>+</sup>dependence have been described (Traiffort *et al.*, 2005).

|                                |                                                                                                               |
|--------------------------------|---------------------------------------------------------------------------------------------------------------|
| Common abbreviation            | CHT                                                                                                           |
| Systematic name                | SLC5A7                                                                                                        |
| Other names                    | CHT1, choline transporter 1                                                                                   |
| Ensembl ID                     | ENSG00000115665                                                                                               |
| Endogenous substrates          | Choline                                                                                                       |
| Synthetic substrates           | Triethylcholine                                                                                               |
| Selective inhibitors ( $K_i$ ) | HC-3 (1-5 nM)                                                                                                 |
| Probes ( $K_D$ )               | [ $^3$ H]-HC-3 (4-6 nM)                                                                                       |
| Stoichiometry                  | Na $^+$ : choline (variable stoichiometry); modulated by extracellular Cl $^-$ (Iwamoto <i>et al.</i> , 2006) |

$K_i$  and  $K_D$  values for hemicholinium-3 listed in the table are for human CHT expressed in *Xenopus laevis* oocytes (Okuda and Haga, 2000), or COS-7 cells (Apparsundaram *et al.*, 2000). Hemicholinium mustard is a substrate for CHT that causes covalent modification and irreversible inactivation of the transporter. Several exogenous substances (*e.g.* triethylcholine) that are substrates for CHT act as precursors to cholinergic false transmitters.

### Hexose transporter family

Detailed characterisation of members of the hexose transporter family is limited to SGLT1, 2 and 3, which are all inhibited in a competitive manner by phlorizin, a natural dihydrocholine glucoside, that exhibits modest selectivity towards SGLT2 (see Wright *et al.*, 2011 for an extensive review). SGLT1 is predominantly expressed in the small intestine, mediating the absorption of glucose, but also occurs in the brain, heart and in the late proximal straight tubule of the kidney. The expression of SGLT2 is almost exclusively restricted to the early proximal convoluted tubule of the kidney, where it is largely responsible for the renal reabsorption of glucose. SGLT3 is not a transporter but instead acts as a glucosensor generating an inwardly directed flux of Na $^+$  that causes membrane depolarization (Diez-Sampedro *et al.*, 2003).

| Common abbreviation              | SGLT1                                                                                                                                    | SGLT2                                                                                                                                    | SGLT3                                                                                                                                              | SGLT4                          | SGLT5                          |
|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|--------------------------------|
| Systematic name                  | SLC5A1                                                                                                                                   | SLC5A2                                                                                                                                   | SLC5A4                                                                                                                                             | SLC5A9                         | SLC5A10                        |
| Other names                      | Sodium/glucose cotransporter 1, high affinity sodium-glucose cotransporter                                                               | Sodium/glucose cotransporter 2, low affinity sodium-glucose cotransporter                                                                | Low affinity sodium-glucose cotransporter, sodium/glucose cotransporter 3 (note, these previous names are a misnomer since SGLT3 is a glucosensor) | Sodium/glucose cotransporter 4 | Sodium/glucose cotransporter 5 |
| Ensembl ID                       | ENSG00000100170                                                                                                                          | ENSG00000140675                                                                                                                          | ENSG00000100191                                                                                                                                    | ENSG00000117834                | ENSG00000154025                |
| Substrates                       | D-glucose, D-galactose                                                                                                                   | D-glucose                                                                                                                                | Ligands include D-glucose, 1-deoxynojirimycin, miglitol, miglustat, N-ethyl-1-deoxynojirimycin, and 1-deoxynojirimycin-1-sulfonic acid             | D-glucose, D-mannose           | D-glucose, D-galactose         |
| Synthetic substrates             | $\alpha$ MDG                                                                                                                             | $\alpha$ MDG                                                                                                                             | –                                                                                                                                                  | $\alpha$ MDG                   | –                              |
| Inhibitors ( $\text{pIC}_{50}$ ) | Dapagliflozin (5.9), canagliflozin (6.4), empagliflozin (5.1), remogliflozin ( $\text{p}K_i$ = 5.4), sergliflozin ( $\text{p}K_i$ = 5.1) | Dapagliflozin (9.0), canagliflozin (8.7), empagliflozin (8.5), remogliflozin ( $\text{p}K_i$ = 7.9), sergliflozin ( $\text{p}K_i$ = 6.8) | –                                                                                                                                                  | –                              | –                              |
| Stoichiometry                    | 2 Na $^+$ : 1 glucose (Kanai <i>et al.</i> , 1994)                                                                                       | 1 Na $^+$ : 1 glucose (Hummel <i>et al.</i> , 2011)                                                                                      | –                                                                                                                                                  | –                              | –                              |

Recognition and transport of substrate by SGLTs requires that the sugar is a pyranose. De-oxyglucose derivatives have reduced affinity for SGLT1, but the replacement of the sugar equatorial hydroxyl group by fluorine at some positions, excepting C2 and C3, is tolerated (see Wright *et al.*, 2011 for a detailed quantification). Although SGLT1 and SGLT2 have been described as high- and low-affinity sodium glucose co-transporters, respectively, recent work suggests that they have a similar affinity for glucose under physiological conditions (Hummel *et al.*, 2011). Selective blockers of SGLT2, and thus blocking ~50% of renal glucose reabsorption, are in development for the treatment of diabetes (*e.g.* Chao and Henry, 2010).

#### Sodium iodide symporter, sodium-dependent multivitamin transporter and sodium-coupled monocarboxylate transporters

The sodium-iodide symporter (NIS) is an iodide transporter found principally in the thyroid gland where it mediates the accumulation of iodide within thyrocytes. Transport of iodide by NIS from the blood across the basolateral membrane followed by apical efflux into the colloidal lumen, mediated at least in part by pendrin (SLC22A4), and most likely not SMCT1 (SLC5A8) as once thought, provides the iodide required for the synthesis of the thyroid hormones triiodothyronine (T<sub>3</sub>) and thyroxine (T<sub>4</sub>) (Bizhanova and Kopp, 2009). NIS is also expressed in the salivary glands, gastric mucosa, intestinal enterocytes and lactating breast. NIS mediates I<sup>-</sup> absorption in the intestine and I<sup>-</sup> secretion into the milk. SMVT is expressed on the apical membrane of intestinal enterocytes and colonocytes and is the main system responsible for biotin (vitamin H) and pantothenic acid (vitamin B<sub>5</sub>) uptake in humans (Said, 2009). SMVT located in kidney proximal tubule epithelial cells mediates the reabsorption of biotin and pantothenic acid. SMCT1 (SLC5A8), which transports a wide range of monocarboxylates, is expressed in the apical membrane of epithelia of the small intestine, colon, kidney, brain neurones and the retinal pigment epithelium (Ganapathy *et al.*, 2008). SMCT2 (SLC5A12) also localises to the apical membrane of kidney, intestine, and colon, but in the brain and retina is restricted to astrocytes and Müller cells, respectively (Ganapathy *et al.*, 2008). SMCT1 is a high-affinity transporter whereas SMCT2 is a low-affinity transporter. The physiological substrates for SMCT1 and SMCT2 are lactate, pyruvate, propionate, and nicotinate in non-colonic tissues such as the kidney. SMCT1 is also likely to be the principal transporter for the absorption of nicotinate (vitamin B<sub>3</sub>) in the intestine and kidney (Gopal *et al.*, 2005). In the small intestine and colon, the physiological substrates for these transporters are nicotinate and the short-chain fatty acids acetate, propionate, and butyrate that are produced by bacterial fermentation of dietary fiber (Miyauchi *et al.*, 2004). In the kidney, SMCT2 is responsible for the bulk absorption of lactate because of its low-affinity/high-capacity nature. Absence of both transporters in the kidney leads to massive excretion of lactate in urine and consequently drastic decrease in the circulating levels of lactate in blood (Thangaraju *et al.*, 2006a). SMCT1 also functions as a tumour suppressor in the colon as well as in various other non-colonic tissues (Ganapathy *et al.*, 2009). The tumour-suppressive function of SMCT1 is based on its ability to transport pyruvate, an inhibitor of histone deacetylases, into cells in non-colonic tissues (Thangaraju *et al.*, 2006b); in the colon, the ability of SMCT1 to transport butyrate and propionate, also inhibitors of histone deacetylases, underlies the tumour-suppressive function of this transporter (Gupta *et al.*, 2006; Ganapathy *et al.*, 2008; Ganapathy *et al.*, 2009). The ability of SMCT1 to promote histone acetylase inhibition through accumulation of butyrate and propionate in immune cells is also responsible for suppression of dendritic cell development in the colon (Singh *et al.*, 2010).

| Common abbreviation             | NIS                                                                                                                                                     | SMVT                                                                                | SMCT1                                                                                                                                                                                  | SMCT2                                                                                                                                        |
|---------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| Systematic name                 | SLC5A5                                                                                                                                                  | SLC5A6                                                                              | SLC5A8                                                                                                                                                                                 | SLC5A12                                                                                                                                      |
| Other names                     | Sodium/iodide cotransporter, sodium-iodide symporter                                                                                                    | Sodium-dependent multivitamin transporter                                           | Sodium-coupled monocarboxylate transporter 1, electrogenic sodium monocarboxylate cotransporter, sodium iodide-related cotransporter, apical iodide transporter (AIT)                  | Sodium-coupled monocarboxylate transporter 2, electroneutral sodium monocarboxylate cotransporter, low-affinity sodium-lactate cotransporter |
| Ensembl ID                      | ENSG00000105641                                                                                                                                         | ENSG00000138074                                                                     | ENSG00000139357                                                                                                                                                                        | ENSG00000148942                                                                                                                              |
| Substrates                      | I <sup>-</sup> , thiocyanate, nitrate                                                                                                                   | Pantothenic acid, biotin, lipoic acid, I <sup>-</sup> (de Carvalho and Quick, 2011) | Butyrate, L-lactate, propionate, acetoacetate, α-ketoisocaproate, nicotinate, pyroglutamate, pyruvate, D-lactate, β-D-hydroxybutyrate, γ-hydroxybutyrate, β-L-hydroxybutyrate, acetate | Lactate, pyruvate, nicotinate                                                                                                                |
| Synthetic substrates            | Perchlorate, pertectnetate                                                                                                                              | –                                                                                   | Benzoate, salicylate, 5-aminosalicylate, 2-oxothiazolidine-4-carboxylate, dichloroacetate, 8-bromopyruvate                                                                             | –                                                                                                                                            |
| Inhibitors (pIC <sub>50</sub> ) | –                                                                                                                                                       | –                                                                                   | Ibuprofen (4.2), ketoprofen, fenoprofen                                                                                                                                                | –                                                                                                                                            |
| Stoichiometry                   | 2 Na <sup>+</sup> : 1 I <sup>-</sup> (Eskandari <i>et al.</i> , 1997); 1 Na <sup>+</sup> : 1 ClO <sub>4</sub> <sup>-</sup> (Dohan <i>et al.</i> , 2007) | 2 Na <sup>+</sup> : 1 biotin (or pantothenic acid) (Prasad <i>et al.</i> , 2000)    | 2 Na <sup>+</sup> : 1 monocarboxylate (Coady <i>et al.</i> , 2007)                                                                                                                     | –                                                                                                                                            |

I<sup>-</sup>, perchlorate, thiocyanate and nitrate are competitive substrate inhibitors of NIS (Dohan *et al.*, 2007).  $\alpha$ -Lipoic acid appears to act as a competitive substrate inhibitor of SMVT (Wang *et al.*, 1999) and the anticonvulsant drugs primidone and carbamazepine competitively block the transport of biotin by brush border vesicles prepared from human intestine (Said *et al.*, 1998).

### Sodium myo-inositol cotransporter transporters

Three different mammalian myo-inositol cotransporters are currently known; two are the Na<sup>+</sup>-coupled SMIT1 and SMIT2 tabulated below and the third is proton-coupled HMIT (SLC2A13). SMIT1 and SMIT2 have a widespread and overlapping tissue location but in polarized cells, such as the Madin-Darby canine kidney cell line, they segregate to the basolateral and apical membranes, respectively (Bissonnette *et al.*, 2004). In the nephron, SMIT1 mediates myo-inositol uptake as a 'compatible osmolyte' when inner medullary tubules are exposed to increases in extracellular osmolality, whilst SMIT2 mediates the reabsorption of myo-inositol from the filtrate. In some species (e.g. rat, but not rabbit) apically located SMIT2 is responsible for the uptake of myo-inositol from the intestinal lumen (Aouameur *et al.*, 2007).

|                     |                                                                                                                                                                            |                                                                                                |
|---------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| Common abbreviation | SMIT1                                                                                                                                                                      | SMIT2                                                                                          |
| Systematic name     | SLC5A3                                                                                                                                                                     | SLC5A11                                                                                        |
| Other names         | Sodium/myo-inositol cotransporter (SMIT)                                                                                                                                   | Sodium/myo-inositol cotransporter 2, sodium/glucose cotransporter6, kST1                       |
| Ensembl ID          | ENSG00000198743                                                                                                                                                            | ENSG00000158865                                                                                |
| Substrates          | Myo-inositol, scyllo-inositol > L-fucose > L-xylose > L-glucose, D-glucose, alpha-methyl-D-glucopyranoside > D-galactose, D-fucose > D-xylose (Hager <i>et al.</i> , 1995) | Myo-inositol = D-chiro-inositol > D-glucose > D-xylose > L-xylose (Coady <i>et al.</i> , 2002) |
| Inhibitors          | Phlorizin                                                                                                                                                                  | Phlorizin                                                                                      |
| Stoichiometry       | 2 Na <sup>+</sup> :1 myo-inositol (Hager <i>et al.</i> , 1995)                                                                                                             | 2 Na <sup>+</sup> :1 myo-inositol (Bourgeois <i>et al.</i> , 2005)                             |

The data tabulated are those for dog SMIT1 and rabbit SMIT2. SMIT2 transports D-chiro-inositol, but SMIT1 does not. In addition, whereas SMIT1 transports both D- and L-xylose and D- and L-fucose, SMIT2 transports only the D-isomers of these sugars (Hager *et al.*, 1995; Coady *et al.*, 2002). Thus the substrate specificities of SMIT1 (for L-fucose) and SMIT2 (for D-chiro-inositol) allow discrimination between the two SMITs. Human SMIT2 appears not to transport glucose (Lin *et al.*, 2009).

**Abbreviations:** HC-3, hemicholinium-3;  $\alpha$ MDG,  $\alpha$ -methyl-D-glucose pyranoside

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## SLC6 neurotransmitter transporter family

**Overview:** Members of the solute carrier family 6 (SLC6) of sodium- and (sometimes chloride-) dependent neurotransmitter transporters (see Chen *et al.*, 2004; Bröer, 2006; Kristensen *et al.*, 2011) are primarily plasma membrane located and may be divided into four subfamilies that transport monoamines, GABA, glycine and neutral amino acids, plus the related bacterial NSS transporters (see Saier *et al.*, 2009). The members of this superfamily share a structural motif of 10 TM segments that has been observed in crystal structures of the NSS bacterial homolog LeuT<sub>AA</sub>, a Na<sup>+</sup>-dependent amino acid transporter from *Aquiflex aeolicus* (Yamashita *et al.*, 2005) and in several other transporter families structurally related to LeuT (Forrest and Rudnick, 2009).

### Monoamine transporter subfamily

Monoamine neurotransmission is limited by perisynaptic transporters. Presynaptic monoamine transporters allow recycling of synaptically released noradrenaline, dopamine and 5-hydroxytryptamine.

| Common abbreviation                     | NET                                                                                              | DAT                                                                                                                                 | SERT                                                                                                             |
|-----------------------------------------|--------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|
| Systematic name                         | SLC6A2                                                                                           | SLC6A3                                                                                                                              | SLC6A4                                                                                                           |
| Other names                             | NAT1                                                                                             | DAT1                                                                                                                                | 5-HTT, SERT1                                                                                                     |
| Ensembl ID                              | ENSG00000103546                                                                                  | ENSG00000142319                                                                                                                     | ENSG00000108576                                                                                                  |
| Endogenous substrates                   | Noradrenaline, adrenaline, dopamine                                                              | Dopamine, adrenaline, noradrenaline                                                                                                 | 5-HT                                                                                                             |
| Synthetic substrates                    | Amphetamine, methamphetamine, MPP <sup>+</sup>                                                   | Amphetamine, methamphetamine, MPP <sup>+</sup>                                                                                      | <i>p</i> -Chloroamphetamine, MDMA                                                                                |
| Selective inhibitors (pK <sub>i</sub> ) | Mazindol (8.9), nisoxetine (8.4), nomifensine (8.1), reboxetine (8.0, Wong <i>et al.</i> , 2000) | Mazindol (8.0), WIN35428 (7.9), GBR12935 (7.6)                                                                                      | Paroxetine (9.6, Tatsumi <i>et al.</i> , 1997), sertraline (9.1), fluoxetine (8.5, Tatsumi <i>et al.</i> , 1997) |
| Probes                                  | [ <sup>3</sup> H]-Mazindol (0.5 nM), [ <sup>3</sup> H]-nisoxetine (4 nM)                         | [ <sup>3</sup> H]-GBR12935 (3 nM, Pristupa <i>et al.</i> , 1994), [ <sup>3</sup> H]-WIN35428 (10 nM, Pristupa <i>et al.</i> , 1994) | [ <sup>3</sup> H]-Paroxetine (0.2 nM), [ <sup>3</sup> H]-citalopram (5 nM)                                       |
| Predicted stoichiometry                 | 1 Noradrenaline: 1 Na <sup>+</sup> :1 Cl <sup>-</sup> (Gu <i>et al.</i> , 1996)                  | 1 Dopamine:1–2 Na <sup>+</sup> :1 Cl <sup>-</sup> (Gu <i>et al.</i> , 1994)                                                         | 1 5-HT:1 Na <sup>+</sup> :1 Cl <sup>-</sup> (in), + 1 K <sup>+</sup> (out) (Talvenheimo <i>et al.</i> , 1983)    |

[<sup>125</sup>I]-RTI55 labels all three monoamine transporters (NET, DAT and SERT) with affinities between 0.5 and 5 nM. Cocaine is an inhibitor of all three transporters with pK<sub>i</sub> values between 6.5 and 7.2. Potential alternative splicing sites in non-coding regions of SERT and NET have been identified. A bacterial homologue of SERT shows allosteric modulation by selected anti-depressants (Singh *et al.*, 2007).

### GABA transporter subfamily

The activity of GABA-transporters located predominantly upon neurones (GAT1), glia (GAT3) or both (GAT2, BGT1) serves to terminate phasic GABA-ergic transmission, maintain low ambient extracellular concentrations of GABA, and recycle GABA for reuse by neurones. Nonetheless, ambient concentrations of GABA are sufficient to sustain tonic inhibition mediated by high affinity GABA<sub>A</sub> receptors in certain neuronal populations (Semyanov *et al.*, 2004). GAT1 is the predominant GABA transporter in the brain and occurs primarily upon the terminals of presynaptic neurones and to a much lesser extent upon distal astrocytic processes that are in proximity to axons terminals. GAT3 resides predominantly on distal astrocytic terminals that are close to the GABAergic synapse. By contrast, BGT1 occupies an extrasynaptic location possibly along with GAT2 which has limited expression in the brain (Madsen *et al.*, 2010). TauT is a high affinity taurine transporter involved in osmotic balance that occurs in the brain and non-neuronal tissues, such as the kidney, brush border membrane of the intestine and blood

brain barrier (Chen *et al.*, 2004; Han *et al.*, 2006). CT1, which transports creatine, has a ubiquitous expression pattern, often co-localizing with creatine kinase (Chen *et al.*, 2004).

|                                          |                                                                                                                                                                                                                                                                               |                                             |                                                      |
|------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|------------------------------------------------------|
| Common abbreviation                      | GAT1                                                                                                                                                                                                                                                                          | GAT2                                        | GAT3                                                 |
| Systematic name                          | SLC6A1                                                                                                                                                                                                                                                                        | SLC6A13                                     | SLC6A11                                              |
| Other names                              | mGAT1, GAT-A                                                                                                                                                                                                                                                                  | mGAT3                                       | mGAT4, GAT-B                                         |
| Ensembl ID                               | ENSG00000157103                                                                                                                                                                                                                                                               | ENSG00000010379                             | ENSG00000132164                                      |
| Endogenous substrates                    | GABA                                                                                                                                                                                                                                                                          | GABA, $\beta$ -alanine                      | GABA, $\beta$ -alanine                               |
| Synthetic substrates                     | Nipecotic acid, guvacine                                                                                                                                                                                                                                                      | Nipecotic acid, guvacine                    | Nipecotic acid, guvacine                             |
| Selective inhibitors (IC <sub>50</sub> ) | NNC-711 (0.14–1.4 $\mu$ M), SKF89976A (0.13 $\mu$ M), CI-966 (0.26 $\mu$ M), tiagabine (0.11 – 2.4 $\mu$ M), ( <i>R/S</i> ) EF-1500 (2 – 13 $\mu$ M) ( <i>R</i> )-EF1502 (4 $\mu$ M – 8.9 $\mu$ M), LU32-176B (4 $\mu$ M), ( <i>S</i> )-EF-1502 (120 $\mu$ M – > 250 $\mu$ M) | SNAP-5114 (20 $\mu$ M)                      | SNAP-5114 (6.6 $\mu$ M)                              |
| Probes                                   | [ <sup>3</sup> H]Tiagabine                                                                                                                                                                                                                                                    | –                                           | –                                                    |
| Predicted stoichiometry                  | 2 Na <sup>+</sup> : 1Cl <sup>–</sup> : 1GABA                                                                                                                                                                                                                                  | 2 Na <sup>+</sup> : 1Cl <sup>–</sup> :1GABA | $\geq 2$ Na <sup>+</sup> : 2 Cl <sup>–</sup> : 1GABA |

|                                          |                                                                                                                                                                                         |                                                                 |                                                                           |
|------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|---------------------------------------------------------------------------|
| Common abbreviation                      | BGT1                                                                                                                                                                                    | TauT                                                            | CT1                                                                       |
| Systematic name                          | SLC6A12                                                                                                                                                                                 | SLC6A6                                                          | SLC6A8                                                                    |
| Other names                              | mGAT2                                                                                                                                                                                   | Sodium- and chloride-dependent taurine transporter              | Sodium- and chloride-dependent creatine transporter 1, CRT, CRTR, SLC6A10 |
| Ensembl ID                               | ENSG00000111181                                                                                                                                                                         | ENSG00000131389                                                 | ENSG00000130821                                                           |
| Endogenous substrates                    | GABA, betaine                                                                                                                                                                           | Taurine, $\beta$ -alanine, GABA (Anderson <i>et al.</i> , 2009) | Creatine                                                                  |
| Synthetic substrates                     | –                                                                                                                                                                                       | –                                                               | –                                                                         |
| Selective inhibitors (IC <sub>50</sub> ) | NNC052090 (1.4 $\mu$ M), ( <i>R</i> )-EF-1502 (22 $\mu$ M–180 $\mu$ M), ( <i>R/S</i> ) EF-1500 (26 $\mu$ M) ( <i>S</i> )-EF-1502 (34 $\mu$ M – > 250 $\mu$ M), LU32-176B (>100 $\mu$ M) | –                                                               | –                                                                         |
| Predicted stoichiometry                  | 3 Na <sup>+</sup> : 1 (or 2) Cl <sup>–</sup> : 1 GABA                                                                                                                                   | 2 Na <sup>+</sup> : 1Cl <sup>–</sup> : 1 taurine                | Probably 2 Na <sup>+</sup> : 1Cl <sup>–</sup> : 1 creatine                |

The IC<sub>50</sub> values for GAT1-3 reported in the table reflect the range reported in the literature from studies of both human and mouse transporters. There is a tendency towards lower IC<sub>50</sub> values for the human orthologue (Kvist *et al.* 2009). SNAP-5114 is only weakly selective for GAT2 and GAT3, with IC<sub>50</sub> values in the range 22 to >30  $\mu$ M at GAT1 and BGT1, whereas NNC052090 has at least an order of magnitude selectivity for BGT1 [see Schousboe *et al.* (2004b) and Clausen *et al.* (2006) for reviews]. (*R*)-(1-[2-[tris(4-methoxyphenyl)methoxy]ethyl]pyrrolidin-2-yl)acetic acid is a compound that displays 20-fold selectivity for GAT3 over GAT1 (Fülep *et al.*, 2006). In addition to the inhibitors listed, EGYT3886 is a moderately potent, though non-selective, inhibitor of all cloned GABA transporters (IC<sub>50</sub> = 26–46  $\mu$ M; Dhar *et al.*, 1994). Diaryloxime and diarylvinyl ether derivatives of nipecotic acid and guvacine that potently inhibit the uptake of [<sup>3</sup>H]GABA into rat synaptosomes have been described (Knutsen *et al.*, 1999). Several derivatives of *exo*-THPO (e.g. *N*-methyl-*exo*-THPO and *N*-acetyloxyethyl-*exo*-THPO) demonstrate selectivity as blockers of astroglial, *versus* neuronal, uptake of GABA [see Schousboe *et al.* (2004a) and Clausen *et al.* (2006) for reviews]. GAT3 is inhibited by physiologically relevant concentrations of Zn<sup>2+</sup> (Cohen-Kfir *et al.*, 2005). TauT transports GABA, but with low affinity, but CT1 does not, although it can be engineered to do so by mutagenesis guided by LeuT as a structural template (Dodd and Christie, 2007). Although inhibitors of creatine transport by CT1 (e.g.  $\beta$ -guanidinopropionic acid, cyclocreatine,  $\gamma$ -guanidino sulphonic acid) are known (e.g. Dai *et al.*, 1999) they are insufficiently characterized to be included in the table.

### Glycine transporter subfamily

Two gene products, GlyT1 and GlyT2, are known that give rise to transporters that are predominantly located on glia and neurones, respectively. Five variants of GlyT1 (a,b,c,d & e) differing in their N- and C-termini are generated by alternative promoter usage and splicing, and three splice variants of GlyT2 (a,b & c) have also been identified (see Supplisson and Roux, 2002; Eulenburg *et al.*, 2005; Betz *et al.*, 2006; Gomeza *et al.*, 2006 for reviews). GlyT1 transporter isoforms expressed in glia surrounding glutamatergic synapses regulate synaptic glycine concentrations influencing NMDA receptor-mediated neurotransmission (Bergeron *et al.*, 1998; Gabernet *et al.*, 2005), but also are important, in early neonatal life, for regulating glycine concentrations at inhibitory glycinergic synapses (Gomeza *et al.*, 2003a). Homozygous mice engineered to totally lack GlyT1 exhibit severe respiratory and motor deficiencies due to hyperactive glycinergic signalling and die within the first postnatal day (Gomeza *et al.*, 2003a, Tsai *et al.*, 2004). Disruption of GlyT1 restricted to forebrain neurones is associated with enhancement of EPSCs mediated by NMDA receptors and behaviours that are suggestive of a promnesic action (Yee *et al.*, 2006). GlyT2 transporters localised on the axons and boutons of glycinergic neurones appear crucial for efficient transmitter loading of synaptic vesicles but may not be essential for the termination of inhibitory neurotransmission (Gomeza *et al.*, 2003b; Rousseau *et al.*, 2008). Mice in which GlyT2 has been deleted develop a fatal hyperekplexia phenotype during the second postnatal week (Gomeza *et al.*, 2003b) and mutations in the human gene encoding GlyT2 (SLC6A5) have been identified in patients with hyperekplexia (reviewed by Harvey *et al.*, 2008). ATB<sup>or</sup> (SLC6A14) is a transporter for numerous dipolar and cationic amino acids and thus has a much broader substrate specificity than the glycine transporters alongside which it is grouped on the basis of structural similarity (Chen *et al.*, 2004). ATB<sup>or</sup> is expressed in various peripheral tissues (Chen *et al.*, 2004). By contrast PROT (SLC6A7), which is expressed only in brain in association with a subset of excitatory nerve terminals, shows specificity for the transport of L-proline.

|                                          |                                                                                                                                                                                                                                              |                                                   |                                                                                                                                                                                     |                                                              |
|------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|
| Common abbreviation                      | GlyT1                                                                                                                                                                                                                                        | GlyT2                                             | ATB <sup>0,+</sup>                                                                                                                                                                  | PROT                                                         |
| Systematic name                          | SLC6A9                                                                                                                                                                                                                                       | SLC6A5                                            | SLC6A14                                                                                                                                                                             | SLC6A7                                                       |
| Other names                              | Glycine transporter 1                                                                                                                                                                                                                        | Glycine transporter 2                             | Sodium- and chloride-dependent neutral and basic amino acid transporter B <sup>0,+</sup>                                                                                            | Sodium-dependent proline transporter                         |
| Ensembl ID                               | ENSG00000196517                                                                                                                                                                                                                              | ENSG00000165970                                   | ENSG00000087916                                                                                                                                                                     | ENSG00000011083                                              |
| Endogenous substrates                    | Glycine, sarcosine                                                                                                                                                                                                                           | Glycine                                           | Iso > leu, met > phe > trp > val > ser (Sloan and Mager, 1999), $\beta$ -alanine (Anderson <i>et al.</i> , 2008, 2009)                                                              | L-Proline                                                    |
| Synthetic substrates                     | –                                                                                                                                                                                                                                            | –                                                 | BCH, 1-methyltryptophan (Karunakaran <i>et al.</i> , 2008), valganciclovir (Umapathy <i>et al.</i> , 2004), zwitterionic or cationic NOS inhibitors (Hatanaka <i>et al.</i> , 2001) | –                                                            |
| Selective inhibitors (IC <sub>50</sub> ) | (R)-NFPS (ALX 5407) (0.8 – 3 nM), SSR-103800 (2 nM), N-methyl-SSR-504734 (2.5 nM), NFPS (3 – 100 nM), LY2365109 (16 nM), SSR504734 (18 – 314 nM), GSK931145 (26 nM); RG1678 (30 nM); SB-733993 (31 nM); NPTS (37 nM), Org 24598              | ALX 1393, ALX 1405, Org 25543 (20 nM)             | $\alpha$ -methyltryptophan (250 $\mu$ M, Karunakaran <i>et al.</i> , 2008)                                                                                                          | LP-403812 (0.11 $\mu$ M, Yu <i>et al.</i> , 2009)            |
| Probes ( <i>K<sub>d</sub></i> )          | [ <sup>3</sup> H]-( <i>R</i> )-NPTS (1 nM), [ <sup>3</sup> H]-GSK931145 (1.7 nM), [ <sup>35</sup> S]-ACPPB (2 nM), [ <sup>3</sup> H]-SB-733993 (2.2 nM), [ <sup>3</sup> H]-N-methyl-SSR504734 (3.3–8.1 nM), [ <sup>3</sup> H]-NFPS (7–21 nM) | –                                                 | –                                                                                                                                                                                   | –                                                            |
| Predicted stoichiometry                  | 2 Na <sup>+</sup> : 1 Cl <sup>–</sup> : 1 glycine                                                                                                                                                                                            | 3 Na <sup>+</sup> : 1 Cl <sup>–</sup> : 1 glycine | 2–3 Na <sup>+</sup> : 1 Cl <sup>–</sup> : 1 amino acid (Sloan and Mager, 1999)                                                                                                      | Probably 2 Na <sup>+</sup> : 1 Cl <sup>–</sup> : 1 L-proline |

Sarcosine is a selective transportable inhibitor of GlyT1 and also a weak agonist at the glycine binding site of the NMDA receptor (Zhang *et al.*, 2009), but has no effect on GlyT2. This difference has been attributed to a single glycine residue in TM6 (serine residue in GlyT2) (Vandenberg *et al.*, 2007). Inhibition of GLYT1 by the sarcosine derivatives NFPS, NPTS and Org24598 is non-competitive (Mallorga *et al.*, 2003; Mezler *et al.*, 2008). IC<sub>50</sub> values for Org 24598 reported in the literature vary, most likely due to differences in assay conditions (Brown *et al.*, 2001; Mallorga *et al.*, 2003). The tricyclic antidepressant amoxapine weakly inhibits GlyT2 (IC<sub>50</sub> 92  $\mu$ M) with approximately 10-fold selectivity over GlyT1 (Nunez *et al.*, 2000). The endogenous lipids arachidonic acid and anandamide exert opposing effects upon GlyT1a, inhibiting (IC<sub>50</sub> ~ 2  $\mu$ M) and potentiating (EC<sub>50</sub> ~ 13  $\mu$ M) transport currents, respectively (Pearlman *et al.*, 2003). *N*-arachidonyl-glycine, *N*-arachidonyl- $\gamma$ -aminobutyric acid and *N*-arachidonyl-D-alanine have been described as endogenous non-competitive inhibitors of GlyT2a, but not GlyT1b (Wiles *et al.*, 2006; Edington *et al.*, 2009; Jeong *et al.*, 2010). Protons (Aubrey *et al.*, 2000) and Zn<sup>2+</sup> (Ju *et al.*, 2004) act as non-competitive inhibitors of GlyT1b, with IC<sub>50</sub> values of ~100 nM and ~10  $\mu$ M respectively, but neither ion affects GlyT2 (reviewed by Vandenberg *et al.*, 2004). Glycine transport by GLYT1 is inhibited by lithium, whereas GLYT2 transport is stimulated (both in the presence of Na<sup>+</sup>) (Pérez-Siles *et al.* 2011).

#### Neutral amino acid transporter subfamily

Certain members of neutral amino acid transport family are expressed upon the apical surface of epithelial cells and are important for the absorption of amino acids from the duodenum, jejunum and ileum and their reabsorption within the proximal tubule of the nephron (*i.e.* B<sup>0</sup>AT1 (SLC6A19), SLC6A17, SLC6A18, SLC6A20). Others may function as transporters for neurotransmitters or their precursors (*i.e.* B<sup>0</sup>AT2, SLC6A17) (Bröer, 2008).

|                         |                                                                                      |                                                                                       |                                                                                          |
|-------------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| Common abbreviation     | B <sup>0</sup> AT1                                                                   | B <sup>0</sup> AT2                                                                    | B <sup>0</sup> AT3                                                                       |
| Systematic name         | SLC6A19                                                                              | SLC6A15                                                                               | SLC6A18                                                                                  |
| Other names             | B <sup>0</sup> neutral amino acid transporter                                        | NTT73, v7-3, SBAT1                                                                    | XT2, XTRP2                                                                               |
| Ensembl ID              | ENSG00000174358                                                                      | ENSG00000072041                                                                       | ENSG00000164363                                                                          |
| Endogenous substrates   | Leu, met, iso, val > asn, phe, ala, ser > thr, gly, pro (Bröer <i>et al.</i> , 2006) | Pro > ala, val, met, leu > iso, thr, asn, ser, phe > gly (Bröer <i>et al.</i> , 2006) | Ala, gly > met, phe, leu, his, gln (Vanslambrouck <i>et al.</i> 2010)                    |
| Predicted stoichiometry | 1 Na: 1 amino acid (Böhmer <i>et al.</i> , 2005)                                     | 1 Na: 1 amino acid (Bröer <i>et al.</i> , 2006)                                       | Na <sup>+</sup> - and Cl <sup>-</sup> -dependent transport (Singer <i>et al.</i> , 2009) |

|                         |                 |                                                                                            |                                                                                   |
|-------------------------|-----------------|--------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Systematic name         | SLC6A16         | SLC6A17                                                                                    | SLC6A20                                                                           |
| Common abbreviation     | –               | –                                                                                          | SIT1                                                                              |
| Other names             | NTT5            | NTT4, XT1, XTRP1                                                                           | XTRP3, rB21A, IMINO, XT3, sodium/imino-acid transporter 1                         |
| Ensembl ID              | ENSG00000063127 | ENSG00000197106                                                                            | ENSG00000163817                                                                   |
| Endogenous substrates   | Unknown         | Leu, met, pro > cyst, ala, gln, ser > his, gly (Zaia and Reimer, 2009)                     | Proline                                                                           |
| Predicted stoichiometry | –               | Na <sup>+</sup> -dependent, Cl <sup>-</sup> -independent transport (Zaia and Reimer, 2009) | 2 Na <sup>+</sup> : 1 Cl <sup>-</sup> : 1 imino acid (Bröer <i>et al.</i> , 2009) |

Mutations in B<sup>0</sup>AT1 are associated with Hartnup disorder.

**Abbreviations:** ACPPB, (S)-2-amino-4-chloro-N-(1-(4-phenyl-1-(propylsulfonyl)piperidin-4-yl)ethyl)benzamide; ALX 1393, O-[2-benzyloxyphenyl-3-fluorophenyl]methyl-L-serine; ALX 1405, structure not available; BCH, 2-aminobicyclo[2.2.1]-heptane-2-carboxylic acid; CI966, [1-[2-[bis(4-(trifluoromethyl)phenyl)methoxy]ethyl]-1,2,5,6-tetrahydro-3-pyridinecarboxylic acid; EF1500, N-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-3-hydroxy-4-amino-4,5,6,7-tetrahydrobenzo[d]isoxazol-3-ol; EF1502, N-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-3-hydroxy-4-(methylamino)-4,5,6,7-tetrahydrobenzo[d]isoxazol-3-ol; EGYT3886, (-)-2-phenyl-2-[(dimethylamino)ethoxy]-(1R)-1,7,7-trimethylbicyclo[2.2.1]heptane; *exo*-THPO, 3-hydroxy-4-amino-4,5,6,7-tetrahydro-1,2-benzisoxazol; GBR12935, 1-(2-[diphenylmethoxy]ethyl)-4-(3-phenylpropyl)piperazine; GSK931145, N-[[1-(dimethylamino)cyclopentyl](phenyl)methyl]-2,6-dimethylbenzamide; LP-403812, see Yu *et al.* (2009) for structure; LU32-176B, N-[4,4-bis(4-fluorophenyl)-butyl]-3-hydroxy-4-amino-4,5,6,7-tetrahydrobenzo[d]isoxazol-3-ol; LY2365109, [[2-(4-benzo[1,3]dioxol-5-yl-2-tert-butylphenoxy)ethyl]-methylamino]-acetic acid; MDMA, 3,4-methylenedioxymethamphetamine; MPP<sup>+</sup>, 1-methyl-4-phenylpyridinium; NFPS, N-[3-(4'-fluorophenyl)-3-(4'-phenylphenoxy)propyl]sarcosine; NNC052090, 1-(3-(9H-carbazol-9-yl)-1-propyl)-4-(2-methoxyphenyl)-4-piperidinol; NNC711, 1-2-(((diphenylmethylene)amino)oxy)ethyl)-1,2,5,6-tetrahydro-3-pyridinecarboxylic acid hydrochloride; NPTS, (N-[3-phenyl-3-(4'-(4-toluoxy) phenoxy)propyl]sarcosine; Org 24598, R-(-)-N-[3-[(4-trifluoromethyl)phenoxy]-3-phenylpropyl]glycine; Org 25543, 4-benzyloxy-3,5-dimethoxy-N-[1-(dimethylaminocyclopentyl) methyl] benzamide; RG1678, [4-(3-fluoro-5-trifluoromethylpyridin-2-yl)piperazin-1-yl][5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methylethoxy)phenyl]methanone; RT155, 2β-carbomethoxy-3β-(4-iodophenyl) tropane (also known as β-CIT); SB-733993, (2R)-3-[(2R,6S)-2,6-dimethylpiperidin-1-yl]-2-hydroxy-S-(naphthalen-1-yl)propane-1-sulfonamide; SKF89976A, 1-(4,4-diphenyl-3-butenyl)-3-piperidinecarboxylic acid; SSR103800, structure not available; SSR504734, 2-chloro-N-(S)-phenyl[(2S)-piperidin-2-yl]methyl]-3-trifluoromethyl benzamide; WIN35428, 2β-carboxymethyl-3β-(4-fluorophenyl)tropane (also known as β-CFT).

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## SLC8 family of sodium/calcium exchangers

**Overview:** the sodium/calcium exchangers (NCX) use the extracellular sodium concentration to facilitate the extrusion of calcium out of the cell. Alongside the plasma membrane  $\text{Ca}^{2+}$ -ATPase (PMCA, see Page S219) and sarcoplasmic/endoplasmic reticulum  $\text{Ca}^{2+}$ -ATPase (SERCA, see Page S219), as well as the sodium/potassium/calcium exchangers (NKCCX, SLC24 family, see Page S255), NCX allow recovery of intracellular calcium back to basal levels after cellular stimulation. When intracellular sodium ion levels rise, for example, following depolarisation, these transporters can operate in the reverse direction to allow calcium influx and sodium efflux, as an electrogenic mechanism. Structural modelling suggests the presence of 9 TM segments, with a large intracellular loop between the fifth and sixth TM segments.

| Nomenclature           | Sodium/calcium exchanger 1                                                                                                                                                                       | Sodium/calcium exchanger 2 | Sodium/calcium exchanger 3 |
|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|----------------------------|
| Systematic name        | SLC8A1                                                                                                                                                                                           | SLC8A2                     | SLC8A3                     |
| Preferred abbreviation | NCX1                                                                                                                                                                                             | NCX2                       | NCX3                       |
| Ensembl ID             | ENSG00000183023                                                                                                                                                                                  | ENSG00000118160            | ENSG00000100678            |
| Stoichiometry          | 3 $\text{Na}^+$ (in) : 1 $\text{Ca}^{2+}$ (out)<br>or 4 $\text{Na}^+$ (in) : 1 $\text{Ca}^{2+}$ (out) (Dong <i>et al.</i> , 2002)<br>Reverse mode 1 $\text{Ca}^{2+}$ (in): 1 $\text{Na}^+$ (out) | –                          | –                          |

Although subtype-selective inhibitors of NCX function are not widely available, 3,4-dichlorobenzamil and CBDMB act as non-selective NCX inhibitors, while SEA0400, KB-R7943 and SN6 act to inhibit NCX function selectively in the reverse mode.

**Abbreviations:** CBDMB, 3-amino-6-chloro-5-[(4-chlorophenyl)methylamino]-N-[[2-[(2,4-dimethylphenyl)methyl]hydrazinyl]methylidene]pyrazine-2-carboxamide; KB-R7943, methanesulfonic acid; 2-[4-[(4-nitrophenyl)methoxy]phenyl]ethylcarbamidodithioate; SEA0400, 2-[4-[(2,5-difluorophenyl)methoxy]phenoxy]-5-ethoxyaniline; SN6, N-[4-[(1-methylpyridin-1-ium-4-yl)amino]phenyl]-4-[(1-methylquinolin-1-ium-4-yl)amino]benzamide, also known as SN6999

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## SLC9 family of sodium/hydrogen exchangers

**Overview:** sodium/hydrogen exchangers or sodium/proton antiports are a family of transporters that maintain cellular pH by utilising the sodium gradient across the plasma membrane to extrude protons produced by metabolism, in a stoichiometry of 1  $\text{Na}^+$  (in) : 1  $\text{H}^+$  (out). Several isoforms, NHE6, NHE7, NHE8 and NHE9 appear to locate on intracellular membranes (Miyazaki *et al.*, 2001; Numata and Orlowski, 2001;

Nakamura *et al.*, 2005).  $\text{Li}^+$  and  $\text{NH}_4^+$ , but not  $\text{K}^+$ , ions may also be transported by some isoforms. Modelling of the topology of these transporters indicates 12 TM regions with an extended intracellular C-terminus containing multiple regulatory sites.

NHE1 is considered to be a ubiquitously-expressed 'housekeeping' transporter. NHE2 and NHE3 are highly expressed in the intestine and kidneys and regulate sodium movements in those tissues. NHE10 is present in sperm (Wang *et al.*, 2003) and osteoclasts (Lee *et al.*, 2008); gene disruption results in infertile male mice (Wang *et al.*, 2003).

| Nomenclature                 | Systematic name | Common abbreviation | Ensembl ID      | Other names                                                           |
|------------------------------|-----------------|---------------------|-----------------|-----------------------------------------------------------------------|
| Sodium/hydrogen exchanger 1  | SLC9A1          | NHE1                | ENSG00000090020 | Na <sup>+</sup> /H <sup>+</sup> antiporter, amiloride-sensitive, APNH |
| Sodium/hydrogen exchanger 2  | SLC9A2          | NHE2                | ENSG00000115616 |                                                                       |
| Sodium/hydrogen exchanger 3  | SLC9A3          | NHE3                | ENSG00000066230 |                                                                       |
| Sodium/hydrogen exchanger 4  | SLC9A4          | NHE4                | ENSG00000180251 |                                                                       |
| Sodium/hydrogen exchanger 5  | SLC9A5          | NHE5                | ENSG00000135740 |                                                                       |
| Sodium/hydrogen exchanger 6  | SLC9A6          | NHE6                | ENSG00000198689 |                                                                       |
| Sodium/hydrogen exchanger 7  | SLC9A7          | NHE7                | ENSG00000065923 |                                                                       |
| Sodium/hydrogen exchanger 8  | SLC9A8          | NHE8                | ENSG00000197818 |                                                                       |
| Sodium/hydrogen exchanger 9  | SLC9A9          | NHE9                | ENSG00000181804 |                                                                       |
| Sodium/hydrogen exchanger 10 | SLC9A10         | NHE10               | ENSG00000172139 | Sperm-specific Na <sup>+</sup> /H <sup>+</sup> exchanger, sNHE        |
| Sodium/hydrogen exchanger 11 | SLC9A11         | NHE11               | ENSG00000162753 |                                                                       |

Analogues of the non-selective cation transport inhibitor amiloride appear to inhibit NHE function through competitive inhibition of the extracellular Na<sup>+</sup> binding site. The more selective amiloride analogues MPA and EIPA exhibit a rank order of affinity of inhibition of NHE1 > NHE2 > NHE3 (Counillon *et al.*, 1993; Tse *et al.*, 1993a, 1993b).

**Abbreviations:** EIPA, 3-amino-6-chloro-N-(diaminomethylidene)-5-[ethyl(propan-2-yl)amino]pyrazine-2-carboxamide; MPA, 3-amino-6-chloro-N-(diaminomethylidene)-5-[methyl(propyl)amino]pyrazine-2-carboxamide

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## SLC10 family of sodium-bile acid co-transporters

**Overview:** the SLC10 family transport bile acids and their derivatives in a sodium-dependent manner. Along with members of the ABC transporter family (MDR1/ABCB1; BSEP/ABCB11; and MRP2/ABCC2) and the organic solute transporter obligate heterodimer OSTα:OSTβ, these transporters allow enterohepatic circulation of bile acids (see Dawson *et al.*, 2009; Klaassen and Aleksunes, 2010).

The SLC10 family appear to be monomeric with external N-termini and cytoplasmic C-termini and seven TM segments (Hallen *et al.*, 1999; Banerjee and Swaan, 2006).

|                     |                                                                                                                                          |                                                                                                 |                                                                                                  |
|---------------------|------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Systematic name     | SLC10A1                                                                                                                                  | SLC10A2                                                                                         | SLC10A6                                                                                          |
| Common abbreviation | NTCP                                                                                                                                     | ASBT                                                                                            | SOAT                                                                                             |
| Nomenclature        | Sodium/bile acid cotransporter 1                                                                                                         | Sodium/bile acid cotransporter 2                                                                | Sodium/bile acid cotransporter 6                                                                 |
| Ensembl ID          | ENSG00000100652                                                                                                                          | ENSG00000125255                                                                                 | ENSG00000145283                                                                                  |
| Other names         | Sodium/bile acid cotransporter, Na <sup>+</sup> /taurocholate transport protein, cell growth-inhibiting gene 29 protein                  | Apical sodium-dependent bile acid transporter, ileal sodium/bile acid cotransporter, ISBT, IBAT | Sodium-dependent organic anion transporter                                                       |
| Substrates          | TUDA, TCA, TCDCA > GCA > CA (Meier <i>et al.</i> , 1997)<br>Thyroid hormone (Friesema <i>et al.</i> , 1999; Visser <i>et al.</i> , 2010) | GDCA > GUDCA, GCDA > TCA > CA (Craddock <i>et al.</i> , 1998)                                   | Estrone-3-sulphate, DHEAS (Geyer <i>et al.</i> , 2004), TLCA, PREGS (Geyer <i>et al.</i> , 2007) |
| Inhibitors          | Cyclosporin, propranolol (Kim <i>et al.</i> , 1999)                                                                                      | –                                                                                               | –                                                                                                |
| Probes              | Chenodeoxycholy-N <sup>ε</sup> -nitrobenzoxadiazol-lysine (Weinman <i>et al.</i> , 1998)                                                 | [ <sup>3</sup> H]-Taurocholate (Craddock <i>et al.</i> , 1998)                                  | –                                                                                                |
| Stoichiometry       | 2 Na <sup>+</sup> : 1 bile acid (Hagenbuch and Meier, 1996; Weinman, 1997)                                                               | >1 Na <sup>+</sup> : 1 bile acid (Craddock <i>et al.</i> , 1998)                                | –                                                                                                |

|                     |                                  |                                  |                                  |                                  |
|---------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
| Systematic name     | SLC10A3                          | SLC10A4                          | SLC10A5                          | SLC10A7                          |
| Common abbreviation | P3                               | P4                               | P5                               | P7                               |
| Nomenclature        | Sodium/bile acid cotransporter 3 | Sodium/bile acid cotransporter 4 | Sodium/bile acid cotransporter 5 | Sodium/bile acid cotransporter 7 |
| Ensembl ID          | ENSG00000126903                  | ENSG00000145248                  | ENSG00000205184                  | ENSG00000120519                  |
| Other names         | P3 protein                       | –                                | –                                | C4orf13                          |

Heterologously expressed SLC10A4 (Geyer *et al.*, 2008) or SLC10A7 (Godoy *et al.*, 2007) failed to exhibit significant transport of TCA, PREGS, DHEAS or choline. SLC10A4 has recently been suggested to associate with neuronal vesicles (Burger *et al.*, 2011).

**Abbreviations:** CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; DHEAS, dehydroepiandrosterone sulphate; GCA, glychocholic acid; GCDA, glychenodeoxycholic acid; GDCA, glycodeoxycholic acid; GUDCA, glyoursodeoxycholate; PREGS, pregnenolone sulphate; TCA, taurocholic acid; TCDCA, taurochenodeoxycholate; TLCA, tauroolithocholic acid; TUDA, taoursodeoxycholic acid

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# SLC11 family of proton-coupled metal ion transporters

**Overview:** the family of proton-coupled metal ion transporters are responsible for movements of divalent cations, particularly ferrous and manganese ions, across the cell membrane (DMT1) and across endosomal (DMT1) or lysosomal/phagosomal membranes (NRAMP1), dependent on proton transport. Both proteins appear to have 12 TM regions and cytoplasmic N- and C- termini. NRAMP1 is involved in antimicrobial action in macrophages, although its precise mechanism is undefined. Facilitated diffusion of divalent cations into phagosomes may increase intravesicular free radicals to damage the pathogen. Alternatively, export of divalent cations from the phagosome may deprive the pathogen of essential enzyme cofactors. DMT1 is more widely expressed and appears to assist in divalent cation assimilation from the diet, as well as in phagocytotic cells.

|                        |                                                                                                   |                                                                                              |
|------------------------|---------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
| Systematic name        | SLC11A1                                                                                           | SLC11A2                                                                                      |
| Preferred abbreviation | NRAMP1                                                                                            | DMT1                                                                                         |
| Nomenclature           |                                                                                                   | Divalent metal transporter 1                                                                 |
| Ensembl ID             | ENSG00000018280                                                                                   | ENSG00000110911                                                                              |
| Other names            | Natural resistance-associated macrophage protein 1                                                | Natural resistance-associated macrophage protein 2, NRAMP2, DCT1                             |
| Endogenous substrates  | Mn <sup>2+</sup> , Fe <sup>2+</sup>                                                               | Fe <sup>2+</sup> , Cd <sup>2+</sup> , Co <sup>2+</sup> , Cu <sup>2+</sup> , Mn <sup>2+</sup> |
| Stoichiometry          | 1 H <sup>+</sup> : 1 Fe <sup>2+</sup> (out) or<br>1 Fe <sup>2+</sup> (in); 1 H <sup>+</sup> (out) | 1 H <sup>+</sup> : 1 Fe <sup>2+</sup> (out) (Gunshin <i>et al.</i> , 1997)                   |

Loss-of-function mutations in NRAMP1 are associated with increased susceptibility to microbial infection. Loss-of-function mutations in DMT1 are associated with microcytic anemia.

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# SLC12 family of cation-coupled chloride transporters

**Overview:** the SLC12 family of chloride transporters contribute to ion fluxes across a variety of tissues. Within this family, further subfamilies are identifiable: NKCC1, NKCC2 and NCC constitute a group of therapeutically-relevant transporters, targets for loop and thiazide diuretics. These 12 TM proteins exhibit cytoplasmic termini and an extended extracellular loop at TM7/8 and are kidney-specific (NKCC2 and NCC) or show a more widespread distribution (NKCC1). A second family, the K-Cl co-transporters are also 12 TM domain proteins with cytoplasmic termini, but with an extended extracellular loop at TM 5/6. CCC6 exhibits structural similarities with the K-Cl co-transporters, while CCC9 is divergent, with 11 TM domains and a cytoplasmic N-terminus and extracellular C-terminus.

|                        |                                                                        |                                                                        |                                                       |
|------------------------|------------------------------------------------------------------------|------------------------------------------------------------------------|-------------------------------------------------------|
| Systematic name        | SLC12A1                                                                | SLC12A2                                                                | SLC12A3                                               |
| Preferred abbreviation | NKCC2                                                                  | NKCC1                                                                  | NCC                                                   |
| Nomenclature           | Kidney-specific Na-K-Cl symporter                                      | Basolateral Na-K-Cl symporter                                          | Na-Cl symporter                                       |
| Ensembl ID             | ENSG00000074803                                                        | ENSG00000064651                                                        | ENSG00000070915                                       |
| Other names            | Bumetanide-sensitive sodium-(potassium)-chloride cotransporter 2, BSC2 | Bumetanide-sensitive sodium-(potassium)-chloride cotransporter 1, BSC1 | Thiazide-sensitive sodium-chloride cotransporter, TSC |
| Inhibitors             | Bumetanide, piretanide, frusemide (Hannaert <i>et al.</i> , 2002)      | Bumetanide, piretanide, frusemide (Hannaert <i>et al.</i> , 2002)      | Hydrochlorothiazide, chlorothiazide, metolazone       |
| Stoichiometry          | 1 Na <sup>+</sup> : 1 K <sup>+</sup> : 2 Cl <sup>-</sup> (in)          | 1 Na <sup>+</sup> : 1 K <sup>+</sup> : 2 Cl <sup>-</sup> (in)          | 1 Na <sup>+</sup> : 1 Cl <sup>-</sup> (in)            |

|                        |                                                                                   |                                                                                   |                                                   |                                                   |
|------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|---------------------------------------------------|---------------------------------------------------|
| Systematic name        | SLC12A4                                                                           | SLC12A5                                                                           | SLC12A6                                           | SLC12A7                                           |
| Preferred abbreviation | KCC1                                                                              | KCC2                                                                              | KCC3                                              | KCC4                                              |
| Nomenclature           | K-Cl cotransporter 1                                                              | K-Cl cotransporter 2                                                              | K-Cl cotransporter 3                              | K-Cl cotransporter 4                              |
| Ensembl ID             | ENSG00000124067                                                                   | ENSG00000124140                                                                   | ENSG00000140199                                   | ENSG00000113504                                   |
| Other names            | Electroneutral potassium-chloride cotransporter 1, erythroid K-Cl cotransporter 1 | Electroneutral potassium-chloride cotransporter 2, erythroid K-Cl cotransporter 2 | Electroneutral potassium-chloride cotransporter 3 | Electroneutral potassium-chloride cotransporter 4 |
| Inhibitors             | DIOA                                                                              | VU0240551 (Delpire <i>et al.</i> , 2009), DIOA                                    | DIOA                                              | DIOA                                              |
| Stoichiometry          | 1 K <sup>+</sup> : 1 Cl <sup>-</sup> (out)                                        | 1 K <sup>+</sup> : 1 Cl <sup>-</sup> (out)                                        | 1 K <sup>+</sup> : 1 Cl <sup>-</sup> (out)        | 1 K <sup>+</sup> : 1 Cl <sup>-</sup> (out)        |

|                        |                                                                          |                                                             |
|------------------------|--------------------------------------------------------------------------|-------------------------------------------------------------|
| Systematic name        | SLC12A8                                                                  | SLC12A9                                                     |
| Preferred abbreviation | CCC9                                                                     | CCC6                                                        |
| Nomenclature           | Cation-chloride cotransporter 9                                          | Cation-chloride cotransporter 6                             |
| Ensembl ID             | ENSG00000221955                                                          | ENSG00000146828                                             |
| Other names            | –                                                                        | Potassium-chloride transporter 9, CCC-interacting protein 1 |
| Substrates             | Spermine, spermidine, glutamate, aspartate (Daigle <i>et al.</i> , 2009) | –                                                           |
| Stoichiometry          | Unknown                                                                  | –                                                           |

CCC6 is regarded as an orphan transporter.

DIOA is able to differentiate KCC isoforms from NKCC and NCC transporters, but also inhibits CFTR (Ito *et al.*, 2001).

**Abbreviations:** DIOA, 2-[(2-butyl-6,7-dichloro-2-cyclopentyl-1-oxo-3H-inden-5-yl)oxy]acetic acid; VU0240551, N-(4-methyl-1,3-thiazol-2-yl)-2-(6-phenylpyridazin-3-yl)sulfanylamide

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## SLC13 family of sodium-dependent sulphate/carboxylate transporters

**Overview:** within the SLC13 family, two groups of transporters may be differentiated on the basis of the substrates transported: NaS1 and NaS2 convey sulphate, while NaC1-3 transport carboxylates. NaS1 and NaS2 transporters are made up of 13 TM domains, with an intracellular N terminus and are electrogenic with physiological roles in the intestine, kidney and placenta. NaC1, NaC2 and NaC3 are made up of 11 TM domains with an intracellular N terminus and are electrogenic, with physiological roles in the kidney and liver.

|                        |                                                          |                                                        |                                                                   |
|------------------------|----------------------------------------------------------|--------------------------------------------------------|-------------------------------------------------------------------|
| Systematic name        | SLC13A1                                                  | SLC13A2                                                | SLC13A3                                                           |
| Preferred abbreviation | NaS1                                                     | NaC1                                                   | NaC3                                                              |
| Nomenclature           | Na <sup>+</sup> /sulfate cotransporter                   | Na <sup>+</sup> /dicarboxylate cotransporter 1         | Na <sup>+</sup> /dicarboxylate cotransporter 3                    |
| Other names            | Renal sodium/sulfate cotransporter, NaSi-1               | Renal sodium/dicarboxylate cotransporter, NaDC1        | Sodium-dependent high-affinity dicarboxylate transporter 2, NaDC3 |
| Ensembl ID             | ENSG00000081800                                          | ENSG00000007216                                        | ENSG00000158296                                                   |
| Endogenous substrates  | Sulphate, thiosulphate, selenate                         | Succinate, citrate                                     | Succinate, citrate                                                |
| Stoichiometry          | 3 Na <sup>+</sup> : 1 SO <sub>4</sub> <sup>2-</sup> (in) | 3 Na <sup>+</sup> : 1 dicarboxylate <sup>2-</sup> (in) | Unknown                                                           |

|                        |                                                        |                                                                                |
|------------------------|--------------------------------------------------------|--------------------------------------------------------------------------------|
| Systematic name        | SLC13A4                                                | SLC13A5                                                                        |
| Preferred abbreviation | NaS2                                                   | NaC2                                                                           |
| Nomenclature           | Na <sup>+</sup> /sulfate cotransporter                 | Na <sup>+</sup> /citrate cotransporter                                         |
| Other names            | SUT1                                                   | Sodium-coupled citrate transporter, sodium-dependent citrate transporter, NaCT |
| Ensembl ID             | ENSG00000164707                                        | ENSG00000141485                                                                |
| Endogenous substrates  | Sulphate                                               | Citrate, pyruvate                                                              |
| Stoichiometry          | 3 Na <sup>+</sup> : SO <sub>4</sub> <sup>2-</sup> (in) | Unknown                                                                        |

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## SLC14 family of facilitative urea transporters

**Overview:** as a product of protein catabolism, urea is moved around the body and through the kidneys for excretion. Although there is experimental evidence for concentrative urea transporters, these have not been defined at the molecular level. The SLC14 family are facilitative transporters, allowing urea movement down its concentration gradient. Multiple splice variants of these transporters have been identified; for UT-A transporters, in particular, there is evidence for cell-specific expression of these variants with functional impact (see Stewart, 2011). Topographical modelling suggests that the majority of the variants of SLC14 transporters have 10 TM domains, with a glycosylated extracellular loop at TM5/6, and intracellular C- and N-termini. The UT-A1 splice variant, exceptionally, has 20 TM domains, equivalent to a combination of the UT-A2 and UT-A3 splice variants.

|                        |                                                                                |                                     |
|------------------------|--------------------------------------------------------------------------------|-------------------------------------|
| Systematic name        | SLC14A1                                                                        | SLC14A2                             |
| Preferred abbreviation | UT-B                                                                           | UT-A                                |
| Nomenclature           | Erythrocyte urea transporter                                                   | Kidney urea transporter             |
| Ensembl ID             | ENSG00000141469                                                                | ENSG00000132874                     |
| Other names            | UTB1                                                                           | UTA1                                |
| Endogenous substrates  | Urea, formamide, ammonium carbonate (Zhao <i>et al.</i> , 2007)                | Urea (Maciver <i>et al.</i> , 2008) |
| Synthetic substrates   | Acetamide, methylurea, methylformamide, acrylamide (Zhao <i>et al.</i> , 2007) | –                                   |
| Stoichiometry          | Equilibrative                                                                  | Equilibrative                       |

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# SLC15 family of peptide transporters

**Overview:** the SLC15 family of peptide transporters may be divided on the basis of structural and functional differences into two subfamilies: SLC15A1 (PepT1) and SLC15A2 (PepT2) transport di- and tripeptides, but not amino acids, whereas SLC15A3 (PHT2) and SLC15A4 (PHT1) transport histidine and some di- and tripeptides (see Daniel and Kottra, 2004). The transporters are 12 TM proteins with intracellular termini and an extended extracellular loop at TM 9/10. The crystal structure of PepT<sub>so</sub> (a prokaryote homologue of PepT1 and PepT2 from *Shewanella oneidensis*) confirms many of the predicted structural features of mammalian PepT1 and PepT2 (Newstead *et al.*, 2011).

PHT1 has been suggested to be intracellular (Romano *et al.*, 2010), while PHT2 protein is located on lysosomes in transfected cells (Botka *et al.*, 2000; Sakata *et al.*, 2001; Herrera-Ruiz and Knipp, 2003). PHT1 is hypothesised to mediate efflux of bacterial-derived peptides into the cytosol perhaps in the colon where SLC15A4 mRNA expression is increased in inflammatory bowel disease (Lee *et al.*, 2009). Transport via PHT1 may be important in immune responses as both Toll-like receptor- and NOD1-mediated responses are reduced in PHT1 knockout mice or mouse strains expressing mutations in PHT1 (Blasius *et al.*, 2010; Sasawatari *et al.*, 2011).

| Systematic name        | SLC15A1                                                                                                                                                                                       | SLC15A2                                                                                                                                   | SLC15A3                                                                                                        | SLC15A4                                                      |
|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|
| Preferred abbreviation | PepT1                                                                                                                                                                                         | PepT2                                                                                                                                     | PHT2                                                                                                           | PHT1                                                         |
| Nomenclature           | Peptide transporter 1                                                                                                                                                                         | Peptide transporter 2                                                                                                                     | Peptide transporter 3                                                                                          | Peptide transporter 4                                        |
| Ensembl ID             | ENSG00000088386                                                                                                                                                                               | ENSG00000163406                                                                                                                           | ENSG00000110446                                                                                                | ENSG00000139370                                              |
| Other names            | Intestinal H <sup>+</sup> /peptide cotransporter, low affinity peptide transporter                                                                                                            | Kidney H <sup>+</sup> /peptide cotransporter, high affinity peptide transporter                                                           | Peptide/histidine transporter 2, osteoclast transporter, peptide transporter 3, PTR3, cAMP-inducible 1 protein | Peptide/histidine transporter 1, peptide transporter 4, PTR4 |
| Endogenous substrates  | Dipeptides, tripeptides, 5-aminolevulinic acid (Doring <i>et al.</i> , 1998)                                                                                                                  | Dipeptides, tripeptides, 5-aminolevulinic acid                                                                                            | Dipeptides, tripeptides, histidine, carnosine                                                                  | Dipeptides, tripeptides, histidine, carnosine                |
| Synthetic substrates   | Cyclacillin, cefadroxil (Ganapathy <i>et al.</i> , 1995), enalapril, captopril (Temple and Boyd, 1998), muramyl dipeptide (Vavricka <i>et al.</i> , 2004), fMLP (Merlin <i>et al.</i> , 1998) | Cyclacillin, cefadroxil (Ganapathy <i>et al.</i> , 1995)                                                                                  | –                                                                                                              | Valacyclovir (Bhardwaj <i>et al.</i> , 2006)                 |
| Inhibitors             | Lys[Z(NO <sub>2</sub> )]-Pro (Knutter <i>et al.</i> , 2001), 4-AMBA (Darcel <i>et al.</i> , 2005)                                                                                             | Lys[Z(NO <sub>2</sub> )]-Pro, Lys[Z(NO <sub>2</sub> )]-Lys[Z(NO <sub>2</sub> )] (Theis <i>et al.</i> , 2002; Biegel <i>et al.</i> , 2006) |                                                                                                                |                                                              |
| Probes                 | [ <sup>3</sup> H]-, [ <sup>14</sup> C]- or [ <sup>14</sup> C]-GlySar                                                                                                                          | [ <sup>3</sup> H]-, [ <sup>14</sup> C]- or [ <sup>14</sup> C]-GlySar                                                                      | [ <sup>3</sup> H]- or [ <sup>14</sup> C]-Histidine                                                             | [ <sup>3</sup> H]- or [ <sup>14</sup> C]-Histidine           |
| Stoichiometry          | 2 H <sup>+</sup> : 1 zwitterionic peptide (in)                                                                                                                                                | 2 H <sup>+</sup> : 1 zwitterionic peptide (in)                                                                                            | Unknown                                                                                                        | Unknown                                                      |

The PepT1 and PepT2 transporters are particularly promiscuous in the transport of dipeptides and tripeptides of any sequence from the endogenous amino acids, as well as some D-amino acid containing peptides. PepT1 has also been exploited to allow delivery of therapeutic pro-drugs, such as those for zidovudine (Han *et al.*, 1998), sulpiride (Watanabe *et al.*, 2002) and cytarabine (Sun *et al.*, 2009).

D-Ala-Lys-AMCA has been used as a fluorescent probe to identify transport via both PepT1 and PepT2 (Rubio-Aliaga and Daniel, 2008).

**Abbreviations:** d-Ala-Lys-AMCA, d-Ala-Lys-N<sup>ε</sup>-7-amino-4-methyl-coumarin-3-acetic acid; 4-AMBA, 4-(aminomethyl)benzoic acid; fMLP, formyl-Met-Leu-Phe

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# SLC16 family of monocarboxylate transporters

**Overview:** members of the SLC16 family may be divided into subfamilies on the basis of substrate selectivities, particularly lactate, pyruvate and ketone bodies, as well as aromatic amino acids. Topology modelling suggests 12 TM domains, with intracellular termini and an extended loop at TM 6/7.

The proton-coupled monocarboxylate transporters allow transport of the products of cellular metabolism, principally lactate and pyruvate.

| Systematic name        | SLC16A1                                                 | SLC16A3                                                 | SLC16A7                                                 | SLC16A8                                                 |
|------------------------|---------------------------------------------------------|---------------------------------------------------------|---------------------------------------------------------|---------------------------------------------------------|
| Preferred abbreviation | MCT1                                                    | MCT4                                                    | MCT2                                                    | MCT3                                                    |
| Nomenclature           | Monocarboxylate transporter 1                           | Monocarboxylate transporter 4                           | Monocarboxylate transporter 2                           | Monocarboxylate transporter 3                           |
| Ensembl ID             | ENSG00000155380                                         | ENSG00000141526                                         | ENSG00000118596                                         | ENSG00000100156                                         |
| Other names            | –                                                       | Monocarboxylate transporter 3, MCT 3                    | –                                                       | REMP                                                    |
| Endogenous substrates  | Lactate, pyruvate, $\beta$ -hydroxybutyrate             | Lactate, pyruvate                                       | Lactate, pyruvate                                       | Lactate                                                 |
| Synthetic substrates   | GHB (Wang <i>et al.</i> , 2006)                         | –                                                       | –                                                       | –                                                       |
| Stoichiometry          | 1 H <sup>+</sup> : 1 monocarboxylate <sup>–</sup> (out) | 1 H <sup>+</sup> : 1 monocarboxylate <sup>–</sup> (out) | 1 H <sup>+</sup> : 1 monocarboxylate <sup>–</sup> (out) | 1 H <sup>+</sup> : 1 monocarboxylate <sup>–</sup> (out) |

MCT1 and MCT2, but not MCT3 and MCT4, are inhibited by CHC, which also inhibits members of the mitochondrial transporter family, SLC25 (see Page S256).

| Systematic name        | SLC16A2                                                                    | SLC16A10                                                                  |
|------------------------|----------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Preferred abbreviation | MCT8                                                                       | TAT1                                                                      |
| Nomenclature           | Monocarboxylate transporter 8                                              | Monocarboxylate transporter 10                                            |
| Ensembl ID             | ENSG00000147100                                                            | ENSG00000112394                                                           |
| Other names            | Monocarboxylate transporter 7, MCT 7, X-linked PEST-containing transporter | T-type amino acid transporter 1, aromatic amino acid transporter 1, MCT10 |
| Endogenous substrates  | T3, T4 (Friesema <i>et al.</i> , 2006)                                     | L-Tryptophan, L-phenylalanine, L-tyrosine, L-DOPA                         |
| Stoichiometry          | Unknown                                                                    | Unknown                                                                   |

|                        |                                      |                                      |                                      |                               |
|------------------------|--------------------------------------|--------------------------------------|--------------------------------------|-------------------------------|
| Systematic name        | SLC16A4                              | SLC16A5                              | SLC16A6                              | SLC16A9                       |
| Preferred abbreviation | MCT5                                 | MCT6                                 | MCT7                                 | MCT9                          |
| Nomenclature           | Monocarboxylate transporter 5        | Monocarboxylate transporter 6        | Monocarboxylate transporter 7        | Monocarboxylate transporter 9 |
| Ensembl ID             | ENSG00000168679                      | ENSG00000170190                      | ENSG00000108932                      | ENSG00000165449               |
| Other names            | Monocarboxylate transporter 4, MCT 4 | Monocarboxylate transporter 5, MCT 5 | Monocarboxylate transporter 6, MCT 6 | –                             |
| Stoichiometry          | Unknown                              | Unknown                              | Unknown                              | Unknown                       |

MCT6 has been reported to transport bumetamide, but not short chain fatty acids (Murakami *et al.*, 2005).

|                        |                                |                                |                                |                                |
|------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
| Systematic name        | SLC16A11                       | SLC16A12                       | SLC16A13                       | SLC16A14                       |
| Preferred abbreviation | MCT11                          | MCT12                          | MCT13                          | MCT14                          |
| Nomenclature           | Monocarboxylate transporter 11 | Monocarboxylate transporter 12 | Monocarboxylate transporter 13 | Monocarboxylate transporter 14 |
| Ensembl ID             | ENSG00000174326                | ENSG00000152779                | ENSG00000174327                | ENSG00000163053                |
| Stoichiometry          | Unknown                        | Unknown                        | Unknown                        | Unknown                        |

MCT5-MCT7, MCT9 and MCT11-14 are regarded as orphan transporters.

**Abbreviations:** CHC, (E)-2-cyano-3-(4-hydroxyphenyl)prop-2-enoic acid; GHB, gamma-hydroxybutyrate; T3, (2S)-2-amino-3-[4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]propanoic acid, also known as triiodothyronine; T4, thyroxine

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## SLC17 phosphate and organic anion transporter family

**Overview:** The SLC17 family are sometimes referred to as Type I sodium-phosphate co-transporters, alongside Type II (SLC34 family, see Page S265) and Type III (SLC20 family, see Page S251) transporters. Within the SLC17 family, however, further subgroups of organic anion transporters may be defined, allowing the accumulation of sialic acid in the endoplasmic reticulum and glutamate or nucleotides in synaptic and secretory vesicles. Topology modelling suggests 12 TM domains.

**Type I sodium-phosphate co-transporters** are expressed in the kidney and intestine

| Systematic name        | SLC17A1                                                                  | SLC17A2                          | SLC17A3                          | SLC17A4                                                               |
|------------------------|--------------------------------------------------------------------------|----------------------------------|----------------------------------|-----------------------------------------------------------------------|
| Preferred abbreviation | NPT1                                                                     | NPT3                             | NPT4                             | –                                                                     |
| Nomenclature           | Sodium/phosphate cotransporter 1                                         | Sodium/phosphate cotransporter 3 | Sodium/phosphate cotransporter 4 | –                                                                     |
| Ensembl ID             | ENSG00000124568                                                          | ENSG00000112337                  | ENSG00000124564                  | ENSG00000146039                                                       |
| Other names            | NaPi-1, renal sodium-dependent phosphate transport protein 1             | –                                | –                                | Putative small intestine sodium-dependent phosphate transport protein |
| Substrates             | Phosphate, organic acids, chloride, urate (Iharada <i>et al.</i> , 2010) | –                                | –                                | –                                                                     |
| Synthetic substrates   | Probenecid, penicillin (Busch <i>et al.</i> , 1996)                      | –                                | –                                | –                                                                     |
| Stoichiometry          | Unknown                                                                  | Unknown                          | Unknown                          | Unknown                                                               |

The **sialic acid transporter** is expressed on both lysosomes and synaptic vesicles, where it appears to allow export of sialic acid and accumulation of acidic amino acids, respectively (Miyaji *et al.*, 2011), driven by proton gradients. In lysosomes, degradation of glycoproteins generates amino acids and sugar residues, which are metabolized further following export from the lysosome.

|                        |                                                                                                                   |
|------------------------|-------------------------------------------------------------------------------------------------------------------|
| Systematic name        | SLC17A5                                                                                                           |
| Preferred abbreviation | AST                                                                                                               |
| Nomenclature           | Sialin                                                                                                            |
| Ensembl ID             | ENSG00000119899                                                                                                   |
| Other names            | Sodium/sialic acid cotransporter, membrane glycoprotein HP59                                                      |
| Endogenous substrates  | Sialic acid, lactate, glucuronic acid, gluconate (out)<br>Aspartate, glutamate (in) (Miyaji <i>et al.</i> , 2011) |
| Stoichiometry          | 1 H <sup>+</sup> : 1 sialic acid (out)                                                                            |

Loss-of-function mutations in sialin are associated with Salla disease, an autosomal recessive neurodegenerative disorder associated with sialic acid storage disease (Verheijen *et al.*, 1999).

**Vesicular glutamate transporters (VGLUTs)** allow accumulation of glutamate into synaptic vesicles, as well as secretory vesicles in endocrine tissues. The roles of VGLUTs in kidney and liver are unclear. These transporters appear to utilize the proton gradient and also express a chloride conductance (Bellocchio *et al.*, 2000).

| Systematic name        | SLC17A7                                                                           | SLC17A6                                                                                                                  | SLC17A8                           |
|------------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| Preferred abbreviation | VGLUT1                                                                            | VGLUT2                                                                                                                   | VGLUT3                            |
| Nomenclature           | Vesicular glutamate transporter 1                                                 | Vesicular glutamate transporter 2                                                                                        | Vesicular glutamate transporter 3 |
| Ensembl ID             | ENSG00000104888                                                                   | ENSG00000091664                                                                                                          | ENSG00000179520                   |
| Other names            | Brain-specific Na <sup>+</sup> -dependent inorganic phosphate cotransporter, BNPI | Differentiation-associated Na <sup>+</sup> -dependent inorganic phosphate cotransporter, differentiation-associated BNPI | –                                 |
| Endogenous substrates  | L-glutamate > D-glutamate                                                         | L-glutamate > D-glutamate                                                                                                | L-glutamate > D-glutamate         |
| Stoichiometry          | Unknown                                                                           | Unknown                                                                                                                  | Unknown                           |

Endogenous ketoacids produced during fasting have been proposed to regulate VGLUT function through blocking chloride ion-mediated allosteric enhancement of transporter function (Juge *et al.*, 2010).

The **vesicular nucleotide transporter** is the most recent member of the SLC17 family to have an assigned function. Uptake of ATP was independent of pH, but dependent on chloride ions and membrane potential (Sawada *et al.*, 2008).

|                        |                                               |
|------------------------|-----------------------------------------------|
| Systematic name        | SLC17A9                                       |
| Preferred abbreviation | VNUT                                          |
| Nomenclature           | Vesicular nucleotide transporter              |
| Ensembl ID             | ENSG00000101194                               |
| Other names            | Uncharacterized MFS-type transporter C20orf59 |
| Endogenous substrates  | ATP, GTP, GDP (Sawada <i>et al.</i> , 2008)   |
| Stoichiometry          | Unknown                                       |

VGLUTs and VNUT can be inhibited by DIDS and Evans blue dye.

**Abbreviations:** DIDS, 5-isothiocyano-2-[(E)-2-(4-isothiocyano-2-sulphophenyl)ethenyl]benzenesulfonic acid

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## SLC18 family of vesicular amine transporters

**Overview:** The vesicular amine transporters (VATs) are putative 12 TM domain proteins that function to transport singly positively charged amine neurotransmitters and hormones from the cytoplasm and concentrate them within secretory vesicles. They function as amine/proton antiporters driven by secondary active transport utilizing the proton gradient established by a multi-subunit vacuolar ATPase (see Page S218) that acidifies secretory vesicles (reviewed by Eiden *et al.*, 2004). The vesicular acetylcholine transporter (VACHT; Erickson *et al.*, 1994) localizes to cholinergic neurons, but non-neuronal expression has also been claimed (Schirmer *et al.*, 2011). Vesicular monoamine transporter 1 (VMAT1, Erickson and Eiden, 1993) is mainly expressed in peripheral neuroendocrine cells, but most likely not in the CNS, whereas VMAT2 (Erickson *et al.*, 1996) distributes between both central and peripheral sympathetic monoaminergic neurones (Eiden and Weihe, 2011).

|                                       |                                                                                                                                      |                                                                                                                                                                                                                                                |                                                                                                                                                    |
|---------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| Common abbreviation                   | VMAT1                                                                                                                                | VMAT2                                                                                                                                                                                                                                          | VACHT                                                                                                                                              |
| Systematic name                       | SLC18A1                                                                                                                              | SLC18A2                                                                                                                                                                                                                                        | SLC18A3                                                                                                                                            |
| Nomenclature                          | Vesicular monoamine transporter 1                                                                                                    | Vesicular monoamine transporter 2                                                                                                                                                                                                              | Vesicular acetylcholine transporter                                                                                                                |
| Other names                           | Chromaffin granule amine transporter (CGAT), VAT1, MAT                                                                               | Synaptic vesicular amine transporter (SVAT), SVMAT, VAT2                                                                                                                                                                                       | (VACHT)                                                                                                                                            |
| Ensembl ID                            | ENSG00000036565                                                                                                                      | ENSG00000165646                                                                                                                                                                                                                                | ENSG00000187714                                                                                                                                    |
| Endogenous substrates ( $pK_m/pK_i$ ) | 5-HT (5.8), dopamine (5.4), adrenaline (5.3), noradrenaline (4.9), histamine (2.3) (Erickson <i>et al.</i> , 1996)                   | 5-HT (6.0), dopamine (5.9), adrenaline (5.7), noradrenaline (5.5), histamine (3.8) (Erickson <i>et al.</i> , 1996)                                                                                                                             | Acetylcholine (3.1), choline (2.3) (Bravo <i>et al.</i> , 2004; Khare <i>et al.</i> , 2010)                                                        |
| Synthetic substrates ( $pK_m/pK_i$ )  | Fenfluramine (5.5), MDMA (4.7), D-amphetamine (4.3), MPP <sup>+</sup> (4.2), phenyl-ethylamine (4.5) (Erickson <i>et al.</i> , 1996) | D-amphetamine (5.7), phenylethylamine (5.4), fenfluramine (5.3), MDMA (5.2), MPP <sup>+</sup> (5.1) (Erickson <i>et al.</i> , 1996)                                                                                                            | TPP <sup>+</sup> , N-methyl-pyridinium-2-aldoxime, N-(4'-pentanonyl)-4-(4''-dimethylamino-styryl)pyridinium, ethidium (Bravo <i>et al.</i> , 2005) |
| Inhibitors ( $pK_i$ )                 | Reserpine (7.45), ketanserin (5.8), TBZ (>4.7) (Erickson <i>et al.</i> , 1996)                                                       | Reserpine (7.9), TBZ (7.0), ketanserin (6.3) (Erickson <i>et al.</i> , 1996)                                                                                                                                                                   | Vesamicol (8.7), aminobenzovesamicol (10.9), (Efang <i>et al.</i> , 1995)                                                                          |
| Probes ( $K_d$ )                      |                                                                                                                                      | [ <sup>3</sup> H]-TBZOH (6.6 nM, Varoqui and Erickson, 1996), [ <sup>125</sup> I]-iodovinyl-TBZ (8.2 nM, Kung <i>et al.</i> , 1994); [ <sup>125</sup> I]-8-azido-3-iodoketanserin (photoaffinity ligand), [ <sup>11</sup> C]-DTBZ (PET ligand) | [ <sup>3</sup> H]-vesamicol (4.1 nM, Varoqui and Erickson, 1996), [ <sup>123</sup> I]-iodobenzovesamicol (SPECT ligand)                            |
| Stoichiometry                         | 1 amine (in): 2H <sup>+</sup> (out)                                                                                                  | 1 amine (in): 2H <sup>+</sup> (out)                                                                                                                                                                                                            | 1 amine (in): 2H <sup>+</sup> (out)                                                                                                                |

$pK_i$  values for endogenous and synthetic substrate inhibitors of human VMAT1 and VMAT2 are for inhibition of [<sup>3</sup>H]-5-HT uptake in transfected and permeabilised CV-1 cells as detailed by Erickson *et al.* (1996). In addition to the monoamines listed in the table, the trace amines tyramine and phenylethylamine are probable substrates for VMAT2 (Eiden and Weihe, 2011). Probes listed in the table are those currently employed; additional agents have been synthesized (*e.g.* Zhu *et al.*, 2009).

**Abbreviations:** DTBZ, dihydrotetrabenazine; MDMA, 3,4-methylenedioxymethamphetamine; MPP<sup>+</sup>, 1-methyl-4-phenylpyridinium; TBZ, tetrabenazine; TBZOH,  $\alpha$ -[O-methyl-<sup>3</sup>H]dihydrotetrabenazine; TPP<sup>+</sup>, tetraphenylphosphonium

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## SLC19 family of vitamin transporters

**Overview:** the B vitamins folate and thiamine are transported across the cell membrane, particularly in the intestine, kidneys and placenta, using pH differences as driving forces. Topological modelling suggests the transporters have 12 TM domains.

| Systematic name       | SLC19A1                                                                                                                                  | SLC19A2                                                 | SLC19A3                                                    |
|-----------------------|------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|------------------------------------------------------------|
| Nomenclature          | Folate transporter 1                                                                                                                     | Thiamine transporter 1                                  | Thiamine transporter 2                                     |
| Common abbreviation   | FOLT                                                                                                                                     | ThTr1                                                   | ThTr2                                                      |
| Ensembl ID            | ENSG00000173638                                                                                                                          | ENSG00000117479                                         | ENSG00000135917                                            |
| Other names           | Reduced folate carrier protein, RFC1, intestinal folate carrier, IFC1, placental folate transporter                                      | Thiamine carrier 1, TC1                                 |                                                            |
| Endogenous substrates | Tetrahydrofolate, N <sup>5</sup> -methylfolate, folate (Prasad <i>et al.</i> , 1995), thiamine monophosphate (Zhao <i>et al.</i> , 2002) | Thiamine                                                | Thiamine                                                   |
| Synthetic substrates  | Methotrexate, folinic acid                                                                                                               | –                                                       | –                                                          |
| Probes                | [ <sup>3</sup> H]-Folate, [ <sup>3</sup> H]-methotrexate (Assaraf <i>et al.</i> , 1998)                                                  | [ <sup>3</sup> H]-Thiamine (Dutta <i>et al.</i> , 1999) | [ <sup>3</sup> H]-Thiamine (Rajgopal <i>et al.</i> , 2001) |
| Stoichiometry         | 1 Folate (in) : 1 OH <sup>–</sup> (out)                                                                                                  | 1 Thiamine (in) : 1 H <sup>+</sup> (out)                | 1 Thiamine (in) : 1 H <sup>+</sup> (out)                   |

Loss-of-function mutations in ThTr1 underlie thiamine-responsive megaloblastic anemia syndrome (Diaz *et al.*, 1999).

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## SLC20 family of sodium-dependent phosphate transporters

**Overview:** the SLC20 family is looked upon not only as ion transporters, but also as retroviral receptors. As ion transporters, they are sometimes referred to as Type III sodium-phosphate co-transporters, alongside Type I (SLC17 family, see Page S247) and Type II (SLC34 family, see Page S265). PiTs are cell-surface transporters, composed of ten TM domains with cytoplasmic C- and N-termini. PiT1 is a focus for dietary phosphate and vitamin D (see Page S188) regulation of parathyroid hormone secretion from the parathyroid gland. PiT2 appears to be involved in intestinal absorption of dietary phosphate.

|                        |                                                            |                                                            |
|------------------------|------------------------------------------------------------|------------------------------------------------------------|
| Systematic name        | SLC20A1                                                    | SLC20A2                                                    |
| Preferred abbreviation | PiT1                                                       | PiT2                                                       |
| Nomenclature           | Sodium-dependent phosphate transporter 1                   | Sodium-dependent phosphate transporter 2                   |
| Ensembl ID             | ENSG00000144136                                            | ENSG00000168575                                            |
| Other names            | Gibbon ape leukemia virus receptor 1, GLVR-1               | Gibbon ape leukemia virus receptor 2, GLVR-2               |
| Substrates             | Phosphate, arsenate (Ravera <i>et al.</i> , 2007)          | Phosphate (Ravera <i>et al.</i> , 2007)                    |
| Stoichiometry          | >1 Na <sup>+</sup> : 1 HPO <sub>4</sub> <sup>2-</sup> (in) | >1 Na <sup>+</sup> : 1 HPO <sub>4</sub> <sup>2-</sup> (in) |

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## SLC22 family of organic cation and anion transporters

**Overview:** the SLC22 family of transporters is mostly composed of non-selective transporters, which are expressed highly in liver, kidney and intestine, playing a major role in drug disposition. The family may be divided into three subfamilies based on the nature of the substrate transported: organic cations (OCTs), organic anions (OATs) and organic zwitterion/cations (OCTN). Membrane topology is predicted to contain 12 TM domains with intracellular termini, and an extended extracellular loop at TM 1/2.

Organic cation transporters (OCT) are electrogenic, Na<sup>+</sup>-independent and reversible.

|                        |                                                    |                                                                                                       |                                                         |
|------------------------|----------------------------------------------------|-------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| Systematic name        | SLC22A1                                            | SLC22A2                                                                                               | SLC22A3                                                 |
| Preferred abbreviation | OCT1                                               | OCT2                                                                                                  | OCT3                                                    |
| Nomenclature           | Organic cation transporter 1                       | Organic cation transporter 2                                                                          | Organic cation transporter 3                            |
| Ensembl ID             | ENSG00000175003                                    | ENSG00000112499                                                                                       | ENSG00000146477                                         |
| Other names            | –                                                  | –                                                                                                     | Extraneuronal monoamine transporter, EMT                |
| Endogenous substrates  | Choline, 5HT, PGE <sub>2</sub> , PGF <sub>2α</sub> | Dopamine, histamine (Grundemann <i>et al.</i> , 1999), PGE <sub>2</sub> (Kimura <i>et al.</i> , 2002) | 5HT, noradrenaline, dopamine (Zhu <i>et al.</i> , 2010) |
| Synthetic substrates   | TEA, MPP, desipramine, acyclovir, metformin        | MPP, TEA, d-tubocurarine, pancuronium (Gorboulev <i>et al.</i> , 1997)                                | MPP, TEA, quinidine                                     |
| Stoichiometry          | Unknown                                            | Unknown                                                                                               | Unknown                                                 |

Corticosterone and quinine are able to inhibit all three organic cation transporters.

Organic zwitterion/cation transporters (OCTN) function as organic cation uniporters, organic cation/proton exchangers or sodium/carnitine co-transporters.

|                        |                                        |                                                             |                                                                                                                         |
|------------------------|----------------------------------------|-------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|
| Systematic name        | SLC22A4                                | SLC22A5                                                     | SLC22A16                                                                                                                |
| Preferred abbreviation | OCTN1                                  | OCTN2                                                       | CT2                                                                                                                     |
| Nomenclature           | Organic cation/carnitine transporter 1 | Organic cation/carnitine transporter 2                      | Carnitine transporter 2                                                                                                 |
| Ensembl ID             | ENSG00000197208                        | ENSG00000197375                                             | ENSG00000004809                                                                                                         |
| Other names            | Ergothioneine transporter, ET          | High-affinity sodium-dependent carnitine cotransporter, CT1 | Organic cation/carnitine transporter 6, OCT6, organic cation transporter OKB1, Fly-like putative transporter 2, Flipt 2 |
| Endogenous substrates  | L-Carnitine                            | L-Carnitine, acetyl-L-carnitine                             | L-Carnitine                                                                                                             |
| Synthetic substrates   | TEA, MPP, mepyramine, verapamil        | TEA, MPP, mepyramine, verapamil                             | –                                                                                                                       |
| Stoichiometry          | Unknown                                | Unknown                                                     | Unknown                                                                                                                 |

Organic anion transporters (OATs) are non-selective transporters prominent in the kidney and intestine.

|                        |                                                                   |                                                               |                                                                                 |                             |                                            |                                                                                            |
|------------------------|-------------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------------------------|-----------------------------|--------------------------------------------|--------------------------------------------------------------------------------------------|
| Systematic name        | SLC22A6                                                           | SLC22A7                                                       | SLC22A8                                                                         | SLC22A9                     | SLC22A10                                   | SLC22A11                                                                                   |
| Preferred abbreviation | OAT1                                                              | OAT2                                                          | OAT3                                                                            | OAT4                        | OAT5                                       |                                                                                            |
| Nomenclature           | Organic anion transporter 1                                       | Organic anion transporter 2                                   | Organic anion transporter 3                                                     | Organic anion transporter 4 | Organic anion transporter 5                | Organic anion transporter 4                                                                |
| Ensembl ID             | ENSG00000197901                                                   | ENSG00000137204                                               | ENSG00000149452                                                                 | ENSG00000149742             | ENSG00000184999                            | ENSG00000168065                                                                            |
| Other names            | Renal organic anion transporter 1, hROAT1, PAH transporter, hPAHT | Novel liver transporter                                       | –                                                                               | UST3                        | –                                          | OAT4                                                                                       |
| Synthetic substrates   | PAH, non-steroidal anti-inflammatory drugs                        | PAH, PGE <sub>2</sub> , non-steroidal anti-inflammatory drugs | PAH, ochratoxin A, estrone sulphate, cimetidine (Kusuhara <i>et al.</i> , 1999) | –                           | Ochratoxin A (Youngblood and Sweet, 2004)) | Estrone sulphate, dehydroepiandrosterone sulphate, ochratoxin A (Cha <i>et al.</i> , 2000) |
| Stoichiometry          | Unknown                                                           | Unknown                                                       | Unknown                                                                         | Unknown                     | Unknown                                    | Unknown                                                                                    |

Urate transporter.

|                        |                                                                           |
|------------------------|---------------------------------------------------------------------------|
| Systematic name        | SLC22A12                                                                  |
| Preferred abbreviation | URAT1                                                                     |
| Nomenclature           | Urate anion exchanger 1                                                   |
| Ensembl ID             | ENSG00000197891                                                           |
| Other names            | Renal-specific transporter, RST, organic anion transporter 4-like protein |
| Endogenous substrates  | Urate, orotate (Enomoto <i>et al.</i> , 2002)                             |
| Stoichiometry          | Unknown                                                                   |

Orphan or poorly characterized family members.

| Systematic name | Preferred abbreviation | Nomenclature                          | Ensembl ID      | Other names                                                                                                                                                                                                                                                                                                     |
|-----------------|------------------------|---------------------------------------|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| SLC22A13        | ORCTL3                 | Organic cation transporter-like 3     | ENSG00000172940 |                                                                                                                                                                                                                                                                                                                 |
| SLC22A14        | ORCTL4                 | Organic cation transporter-like 4     | ENSG00000144671 |                                                                                                                                                                                                                                                                                                                 |
| SLC22A15        | FLIPT1                 | Fly-like putative transporter 1       | ENSG00000163393 |                                                                                                                                                                                                                                                                                                                 |
| SLC22A17        | BOIT                   | Brain-type organic cation transporter | ENSG00000092096 | BOCT                                                                                                                                                                                                                                                                                                            |
| SLC22A18        | ORCTL2                 | Organic cation transporter-like 2     | ENSG00000110628 | Imprinted multi-membrane spanning polyspecific transporter-related protein 1, efflux transporter-like protein, tumor-suppressing subchromosomal transferable fragment candidate gene 5 protein, tumor-suppressing STF cDNA 5 protein, Beckwith-Wiedemann syndrome chromosomal region 1 candidate gene A protein |
| SLC22A20        |                        |                                       | ENSG00000197847 | S22AK_HUMAN Isoform 2 of A6NK97                                                                                                                                                                                                                                                                                 |
| SLC22A23        |                        |                                       | ENSG00000137266 |                                                                                                                                                                                                                                                                                                                 |
| SLC22A24        |                        |                                       | ENSG00000197658 |                                                                                                                                                                                                                                                                                                                 |
| SLC22A25        |                        |                                       | ENSG00000196600 | Organic anion transporter UST6                                                                                                                                                                                                                                                                                  |

**Abbreviations:** MPP, 1-methyl-4-phenylpyridin-1-ium; PAH, p-aminohippurate; TEA, tetraethylammonium

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## SLC23 family of ascorbic acid transporters

**Overview:** predicted to be 12 TM segment proteins, members of this family transport the reduced form of ascorbic acid (while the oxidized form may be handled by members of the SLC2 family (GLUT1/SLC2A1, GLUT3/SLC2A3 and GLUT4/SLC2A4, see Page S226).

|                        |                                                                                                     |                                                                                                                          |                                          |                                                                                                       |
|------------------------|-----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Systematic name        | SLC23A1                                                                                             | SLC23A2                                                                                                                  | SLC23A3                                  | SLC23A4                                                                                               |
| Preferred abbreviation | SVCT1                                                                                               | SVCT2                                                                                                                    | SVCT3                                    | SNBT1                                                                                                 |
| Nomenclature           | Sodium-dependent vitamin C transporter 1                                                            | Sodium-dependent vitamin C transporter 2                                                                                 | Sodium-dependent vitamin C transporter 3 | Sodium-dependent nucleobase transporter                                                               |
| Other names            | Yolk sac permease-like molecule 3                                                                   | Na <sup>+</sup> /L-ascorbic acid transporter 2, yolk sac permease-like molecule 2, nucleobase transporter-like 1 protein | Yolk sac permease-like molecule 1        | –                                                                                                     |
| Ensembl ID             | ENSG00000170482                                                                                     | ENSG00000089057                                                                                                          | ENSG00000213901                          | ENSRNOG00000026919                                                                                    |
| Substrates             | L-Ascorbic acid ><br>D-ascorbic acid ><br>dehydroascorbic acid<br>(Tsukaguchi <i>et al.</i> , 1999) | L-Ascorbic acid ><br>D-ascorbic acid ><br>dehydroascorbic acid<br>(Tsukaguchi <i>et al.</i> , 1999)                      | –                                        | Uracil > thymine ><br>guanine, hypoxanthine<br>> xanthine, uridine<br>(Yamamoto <i>et al.</i> , 2010) |
| Synthetic substrates   | –                                                                                                   | –                                                                                                                        | –                                        | 5-Fluorouracil<br>(Yamamoto <i>et al.</i> , 2010)                                                     |
| Inhibitors             | Phloretin (Tsukaguchi <i>et al.</i> , 1999)                                                         | –                                                                                                                        | –                                        |                                                                                                       |
| Probes                 | [ <sup>14</sup> C]-Ascorbic acid                                                                    | [ <sup>14</sup> C]-Ascorbic acid                                                                                         | –                                        |                                                                                                       |
| Stoichiometry          | 2 Na <sup>+</sup> : 1 ascorbic acid<br>(in) (Tsukaguchi <i>et al.</i> , 1999)                       | 2 Na <sup>+</sup> : 1 ascorbic acid<br>(in) (Tsukaguchi <i>et al.</i> , 1999)                                            | –                                        | 1 Na <sup>+</sup> : 1 uracil (in)<br>(Yamamoto <i>et al.</i> , 2010)                                  |

SLC23A3 does not transport ascorbic acid and remains an orphan transporter. SLC23A4/SNBT1 is found in rodents and non-human primates, but the sequence is truncated in the human genome.

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## SLC24 family of sodium/potassium/calcium exchangers

**Overview:** The sodium/potassium/calcium exchange family of transporters utilize the extracellular sodium gradient to drive calcium and potassium co-transport out of the cell. As is the case for NCX transporters (SLC8A family, see page S239), NKCX transporters are thought to be bidirectional, with the possibility of calcium influx following depolarization of the plasma membrane. Topological modeling suggests the presence of 10 TM domains, with a large intracellular loop between the fifth and sixth TM regions.

|                        |                                                           |                                      |                                      |
|------------------------|-----------------------------------------------------------|--------------------------------------|--------------------------------------|
| Systematic name        | SLC24A1                                                   | SLC24A2                              | SLC24A3                              |
| Preferred abbreviation | NKCX1                                                     | NKCX2                                | NKCX3                                |
| Nomenclature           | Sodium/potassium/calcium exchanger 1                      | Sodium/potassium/calcium exchanger 2 | Sodium/potassium/calcium exchanger 3 |
| Ensembl ID             | ENSG00000074621                                           | ENSG00000155886                      | ENSG00000185052                      |
| Other names            | Retinal rod Na-Ca+K exchanger                             | Retinal cone Na-Ca+K exchanger       | –                                    |
| Stoichiometry          | 4 Na <sup>+</sup> :(1Ca <sup>2+</sup> + 1K <sup>+</sup> ) | –                                    | –                                    |

|                        |                                      |                                      |                                      |
|------------------------|--------------------------------------|--------------------------------------|--------------------------------------|
| Systematic name        | SLC24A4                              | SLC24A5                              | SLC24A6                              |
| Preferred abbreviation | NKCX4                                | NKCX5                                | NKCX6                                |
| Nomenclature           | Sodium/potassium/calcium exchanger 4 | Sodium/potassium/calcium exchanger 5 | Sodium/potassium/calcium exchanger 6 |
| Ensembl ID             | ENSG00000140090                      | ENSG00000188467                      | ENSG00000089060                      |

NKCX6 exhibits sufficient structural diversity for it's function as a NKCX to be questioned (see Altimimi and Schnetkamp, 2007).

To date, there are no agents selective for this family of transporters.

### Further Reading

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## SLC25 family of mitochondrial transporters

**Overview:** mitochondrial transporters are nuclear-encoded proteins, which convey solutes across the inner mitochondrial membrane. Topological modelling suggests homodimeric transporters, each with six TM segments and termini in the cytosol.

**Mitochondrial di- and tri-carboxylic acid transporters** are grouped on the basis of commonality of substrates and include the citrate transporter which facilitates citrate export from the mitochondria to allow the generation of oxaloacetate and acetylCoA through the action of ATP:citrate lyase.

|                     |                                                                                            |                                                                 |                                                              |
|---------------------|--------------------------------------------------------------------------------------------|-----------------------------------------------------------------|--------------------------------------------------------------|
| Systematic name     | SLC25A1                                                                                    | SLC25A10                                                        | SLC25A11                                                     |
| Common abbreviation | CIC                                                                                        | DIC                                                             | OGC                                                          |
| Nomenclature        | Mitochondrial citrate transporter                                                          | Mitochondrial dicarboxylate transporter                         | Mitochondrial oxoglutarate carrier                           |
| Ensembl ID          | ENSG00000100075                                                                            | ENSG00000183048                                                 | ENSG00000108528                                              |
| Other names         | Citrate transport protein, CTP, tricarboxylate carrier protein, citrate isocitrate carrier |                                                                 |                                                              |
| Substrates          | Citrate, malate, PEP                                                                       | Malate, phosphate, succinate, sulphate, thiosulphate            | Oxoglutarate, malate                                         |
| Inhibitors          | 1,2,3-Benzenetricarboxylate                                                                |                                                                 | –                                                            |
| Stoichiometry       | Malate <sup>2-</sup> (in) : H-citrate <sup>2-</sup> (out)                                  | PO <sub>3</sub> <sup>4-</sup> (in) : malate <sup>2-</sup> (out) | Malate <sup>2-</sup> (in) : oxoglutarate <sup>2-</sup> (out) |

|                     |                                                      |                                                      |                                            |                                        |                                            |
|---------------------|------------------------------------------------------|------------------------------------------------------|--------------------------------------------|----------------------------------------|--------------------------------------------|
| Systematic name     | SLC25A12                                             | SLC25A13                                             | SLC25A18                                   | SLC25A21                               | SLC25A22                                   |
| Common abbreviation | AGC1                                                 | AGC2                                                 | GC2                                        | OXC                                    | GC1                                        |
| Nomenclature        | Aralar                                               | Citrin                                               | Mitochondrial glutamate carrier 2          | Mitochondrial oxodicarboxylate carrier | Mitochondrial glutamate carrier 1          |
| Ensembl ID          | ENSG00000115840                                      | ENSG00000004864                                      | ENSG00000182902                            | ENSG00000183032                        | ENSG00000177542                            |
| Substrates          | Aspartate, glutamate, cysteinesulphinate             | Aspartate, glutamate, cysteinesulphinate             | Glutamate                                  | Oxoadipate, oxoglutarate               | Glutamate                                  |
| Stoichiometry       | Aspartate : glutamate H <sup>+</sup> (bidirectional) | Aspartate : glutamate H <sup>+</sup> (bidirectional) | Glutamate : H <sup>+</sup> (bidirectional) | Oxoadipate (in) : oxoglutarate (out)   | Glutamate : H <sup>+</sup> (bidirectional) |

**Mitochondrial ornithine transporters** play a role in the urea cycle by exchanging cytosolic ornithine for mitochondrial citrulline in equimolar amounts.

|                     |                                                                                     |                                                                                  |
|---------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Systematic name     | SLC25A2                                                                             | SLC25A15                                                                         |
| Common abbreviation | ORC2                                                                                | ORC1                                                                             |
| Nomenclature        | Mitochondrial ornithine transporter 2                                               | Mitochondrial ornithine transporter 1                                            |
| Ensembl ID          | ENSG00000120329                                                                     | ENSG00000102743                                                                  |
| Substrates          | Ornithine, citrulline, lysine, arginine, histidine (Fiermonte <i>et al.</i> , 2003) | L-Ornithine, L-citrulline, L-lysine, L-arginine (Fiermonte <i>et al.</i> , 2003) |
| Stoichiometry       | 1 Ornithine (in) : 1 citrulline : 1 H <sup>+</sup> (out)                            | 1 Ornithine (in) : 1 citrulline : 1 H <sup>+</sup> (out)                         |

Both transporters are inhibited by the polyamine spermine (Fiermonte *et al.*, 2003). Loss-of-function mutations in these genes are associated with hyperornithinemia-hyperammonemia-homocitrullinuria.

**Mitochondrial phosphate transporters** allow the import of inorganic phosphate for ATP production

|                     |                                                                                                                   |
|---------------------|-------------------------------------------------------------------------------------------------------------------|
| Systematic name     | SLC25A3                                                                                                           |
| Common abbreviation | PHC                                                                                                               |
| Nomenclature        | Mitochondrial phosphate carrier                                                                                   |
| Ensembl ID          | ENSG00000075415                                                                                                   |
| Other names         | Phosphate transport protein, PTP, PiC                                                                             |
| Stoichiometry       | PO <sub>3</sub> <sup>4-</sup> (in) : OH <sup>-</sup> (out) or PO <sub>3</sub> <sup>4-</sup> : H <sup>+</sup> (in) |

**Mitochondrial adenine nucleotide translocator family**, under conditions of aerobic metabolism, allow coupling between mitochondrial oxidative phosphorylation and cytosolic energy consumption by exchanging cytosolic ADP for mitochondrial ATP.

|                     |                                                                                                                         |                                                                                                           |                                                                                                   |                                                  |
|---------------------|-------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|--------------------------------------------------|
| Systematic name     | SLC25A4                                                                                                                 | SLC25A5                                                                                                   | SLC25A6                                                                                           | SLC25A31                                         |
| Common abbreviation | ANT1                                                                                                                    | ANT2                                                                                                      | ANT3                                                                                              | ANT4                                             |
| Nomenclature        | Mitochondrial adenine nucleotide translocator 1                                                                         | Mitochondrial adenine nucleotide translocator 2                                                           | Mitochondrial adenine nucleotide translocator 3                                                   | Mitochondrial adenine nucleotide translocator 4  |
| Ensembl ID          | ENSG00000151729                                                                                                         | ENSG00000005022                                                                                           | ENSG00000169100                                                                                   | ENSG00000151475                                  |
| Other names         | Adenine nucleotide translocator 1, ADP,ATP carrier protein 1, ADP,ATP carrier protein, heart/skeletal muscle isoform T1 | Adenine nucleotide translocator 2, ADP,ATP carrier protein 2, ADP,ATP carrier protein, fibroblast isoform | Adenine nucleotide translocator 2, ADP,ATP carrier protein 3, ADP,ATP carrier protein, isoform T2 | Sperm flagellar energy carrier protein           |
| Inhibitors          | CATR, BKA                                                                                                               | –                                                                                                         | –                                                                                                 | –                                                |
| Stoichiometry       | ADP <sup>3-</sup> (in) : ATP <sup>4-</sup> (out)                                                                        | ADP <sup>3-</sup> (in) : ATP <sup>4-</sup> (out)                                                          | ADP <sup>3-</sup> (in) : ATP <sup>4-</sup> (out)                                                  | ADP <sup>3-</sup> (in) : ATP <sup>4-</sup> (out) |

**Mitochondrial uncoupling proteins** allow dissipation of the mitochondrial proton gradient associated with thermogenesis and regulation of radical formation.

|                     |                      |                      |                      |                     |                             |
|---------------------|----------------------|----------------------|----------------------|---------------------|-----------------------------|
| Systematic name     | SLC25A7              | SLC25A8              | SLC25A9              | SLC25A27            | SLC25A14                    |
| Common abbreviation | UCP1                 | UCP2                 | UCP3                 | UCP4                | UCP5                        |
| Nomenclature        | Uncoupling protein 1 | Uncoupling protein 2 | Uncoupling protein 3 |                     |                             |
| Ensembl ID          | ENSG00000109424      | ENSG00000175567      | ENSG00000175564      | ENSG00000153291     | ENSG00000102078             |
| Other names         | Thermogenin          | –                    | –                    | –                   | Brain mitochondrial carrier |
| Stoichiometry       | H <sup>+</sup> (in)  | H <sup>+</sup> (in)  | H <sup>+</sup> (in)  | H <sup>+</sup> (in) | H <sup>+</sup> (in)         |

**Mitochondrial nucleotide transporters** convey nucleotides and their derivatives

|                     |                            |                              |                                              |                              |                                            |
|---------------------|----------------------------|------------------------------|----------------------------------------------|------------------------------|--------------------------------------------|
| Systematic name     | SLC25A16                   | SLC25A17                     | SLC25A19                                     | SLC25A26                     | SLC25A42                                   |
| Common abbreviation | GDC                        | PMP34                        | DNC1                                         | SAMC                         |                                            |
| Nomenclature        | Graves disease carrier     | Peroxisomal membrane protein | Deoxynucleotide carrier 1                    | S-Adenosylmethionine carrier |                                            |
| Ensembl ID          | ENSG00000122912            | ENSG00000100372              | ENSG00000125454                              | ENSG00000144741              | ENSG00000181035                            |
| Other names         | Graves disease autoantigen | –                            | Mitochondrial thiamine pyrophosphate carrier | –                            | –                                          |
| Substrates          | CoA and congeners          | ATP, ADP, AMP                | dNDPs, dNTPs, NDPs, ddNTPs                   | S-Adenosylmethionine         | ADP, Co A (Fiermonte <i>et al.</i> , 2009) |
| Stoichiometry       | CoA (in)                   | ATP (in)                     | dNDP (in) : ATP (out)                        |                              |                                            |

**Miscellaneous:** many of the transporters identified below have yet to be assigned functions and are currently regarded as orphans.

| Systematic name | Common abbreviation | Nomenclature                      | Ensembl ID       | Comments                                                      |
|-----------------|---------------------|-----------------------------------|------------------|---------------------------------------------------------------|
| SLC25A20        | CAC                 | Carnitine/acylcarnitine carrier   | ENSG00000178537  | Exchanges cytosolic acylcarnitine for mitochondrial carnitine |
| SLC25A24        | APC1                | Mitochondrial phosphate carrier 1 | ENSG000000085491 |                                                               |
| SLC25A23        | APC2                | mitochondrial phosphate carrier 2 | ENSG00000125648  |                                                               |
| SLC25A25        | APC3                | mitochondrial phosphate carrier 3 | ENSG00000148339  |                                                               |
| SLC25A28        |                     | Mitoferrin2                       | ENSG00000155287  |                                                               |
| SLC25A29        | ORNT3               |                                   | ENSG00000197119  |                                                               |
| SLC25A30        |                     |                                   | ENSG00000174032  |                                                               |
| SLC25A32        | MFTC                |                                   | ENSG00000164933  |                                                               |
| SLC25A33        |                     |                                   | ENSG00000171612  |                                                               |
| SLC25A34        |                     |                                   | ENSG00000162461  |                                                               |
| SLC25A35        |                     |                                   | ENSG00000125434  |                                                               |
| SLC25A36        |                     |                                   | ENSG00000114120  |                                                               |
| SLC25A37        |                     | Mitoferrin1                       | ENSG00000147454  |                                                               |
| SLC25A38        |                     |                                   | ENSG00000144659  |                                                               |
| SLC25A39        |                     |                                   | ENSG00000013306  |                                                               |
| SLC25A40        |                     |                                   | ENSG00000181240  |                                                               |
| SLC25A41        |                     |                                   | ENSG00000181240  |                                                               |
| SLC25A43        |                     |                                   | ENSG00000077713  |                                                               |
| SLC25A44        |                     |                                   | ENSG00000160785  |                                                               |
| SLC25A45        |                     |                                   | ENSG00000162241  |                                                               |
| SLC25A46        |                     |                                   | ENSG00000164209  |                                                               |

Further relevant information on tabular data. For example, whether agent selectivity is less than 100-fold, whether evidence exists for further subtypes lacking molecular correlates or overlap with other transporter families; relationship with a common genetic disorder.

**Abbreviations:** BKA, bongkreic acid; CATR, carboxyatractyloside; PEP, phosphoenolpyruvate

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# SLC26 family of anion exchangers

**Overview:** along with the SLC4 family, the SLC26 family acts to allow movement of monovalent and divalent anions across cell membranes. The predicted topology is of 8–14 TM domains with intracellular C- and N-termini, probably existing as dimers. Within the family, subgroups may be identified on the basis of functional differences.

## Selective sulphate transporters

|                     |                                                       |                                                                |
|---------------------|-------------------------------------------------------|----------------------------------------------------------------|
| Systematic name     | SLC26A1                                               | SLC26A2                                                        |
| Common nomenclature | Sat-1                                                 | DTDST                                                          |
| Ensembl ID          | ENSG00000145217                                       | ENSG00000155850                                                |
| Other names         | –                                                     | –                                                              |
| Substrates          | SO <sub>4</sub> <sup>2-</sup> , oxalate <sup>2-</sup> | SO <sub>4</sub> <sup>2-</sup>                                  |
| Stoichiometry       | SO <sub>4</sub> <sup>2-</sup> (in) : anion (out)      | 1 SO <sub>4</sub> <sup>2-</sup> (in) : 2 Cl <sup>-</sup> (out) |

## Chloride/bicarbonate exchangers

|                     |                                                                                                                       |                                                                                                        |                                                                                                                                                                |
|---------------------|-----------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Systematic name     | SLC26A3                                                                                                               | SLC26A4                                                                                                | SLC26A6                                                                                                                                                        |
| Common nomenclature | DRA                                                                                                                   | Pendrin                                                                                                | PAT-1                                                                                                                                                          |
| Ensembl ID          | ENSG00000091138                                                                                                       | ENSG00000091137                                                                                        | ENSG00000225697                                                                                                                                                |
| Other names         | CLD                                                                                                                   | –                                                                                                      | CFEX                                                                                                                                                           |
| Substrates          | Cl <sup>-</sup>                                                                                                       | Cl <sup>-</sup> , I <sup>-</sup> , OH <sup>-</sup> , HCO <sub>3</sub> <sup>-</sup> , HCOO <sup>-</sup> | SO <sub>4</sub> <sup>2-</sup> , oxalate <sup>2-</sup> , Cl <sup>-</sup> , I <sup>-</sup> , OH <sup>-</sup> , HCO <sub>3</sub> <sup>-</sup> , HCOO <sup>-</sup> |
| Stoichiometry       | 2 Cl <sup>-</sup> (in) : 1 HCO <sub>3</sub> <sup>-</sup> (out) or<br>2 Cl <sup>-</sup> (in) : 1 OH <sup>-</sup> (out) | Unknown                                                                                                | 1 SO <sub>4</sub> <sup>2-</sup> (in) : 2 HCO <sub>3</sub> <sup>-</sup> (out) or<br>1 Cl <sup>-</sup> (in) : 2 HCO <sub>3</sub> <sup>-</sup> (out)              |

## Anion channels

|                            |                                                                                                                                       |                                                                                                      |
|----------------------------|---------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| Systematic name            | SLC26A7                                                                                                                               | SLC26A9                                                                                              |
| Ensembl ID                 | ENSG00000147606                                                                                                                       | ENSG00000174502                                                                                      |
| Ion selectivity            | NO <sub>3</sub> <sup>-</sup> >> Cl <sup>-</sup> = Br <sup>-</sup> = I <sup>-</sup> > SO <sub>4</sub> <sup>2-</sup> = Glu <sup>-</sup> | I <sup>-</sup> > Br <sup>-</sup> > NO <sub>3</sub> <sup>-</sup> > Cl <sup>-</sup> > Glu <sup>-</sup> |
| Functional characteristics | Voltage- and time-independent current, linear I-V relationship (Kim <i>et al.</i> , 2005)                                             | Voltage- and time-independent current, linear I-V relationship (Dorwart <i>et al.</i> , 2007)        |

SLC26A9 has been suggested to operate in two additional modes as a Cl<sup>-</sup>-HCO<sub>3</sub><sup>-</sup> exchanger and as a Na<sup>+</sup>-anion cotransporter (Chang *et al.*, 2009).

## Other

|                     |                                                 |                                                                         |                 |                               |
|---------------------|-------------------------------------------------|-------------------------------------------------------------------------|-----------------|-------------------------------|
| Systematic name     | SLC26A5                                         | SLC26A8                                                                 | SLC26A10        | SLC26A11                      |
| Common nomenclature | Prestin                                         | Tat1                                                                    | –               | –                             |
| Ensembl ID          | ENSG00000170615                                 | ENSG00000112053                                                         | ENSG00000135502 | ENSG00000181045               |
| Substrates          | Cl <sup>-</sup> , HCO <sub>3</sub> <sup>-</sup> | SO <sub>4</sub> <sup>2-</sup> , oxalate <sup>2-</sup> , Cl <sup>-</sup> | Unknown         | HSO <sub>4</sub> <sup>-</sup> |
| Stoichiometry       | Unknown                                         | Unknown                                                                 | Unknown         | Unknown                       |

SLC26A5 has been suggested to function as a molecular motor, rather than a transporter, while SLC26A10 is a possible pseudogene.

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# SLC27 family of fatty acid transporters

**Overview:** Fatty acid transporters are a family of at least one, and possibly six (Schaffer and Lodish, 1994), -TM segment proteins, predicted on the basis of structural similarities to form dimers. These transporters are unusual in that they appear to express intrinsic very long-chain acyl-CoA synthetase (EC 6.2.1.-, EC 6.2.1.7) enzyme activity as well as an intracellular AMP-binding domain. Within the cell, these transporters may associate with plasma and peroxisomal membranes.

| Nomenclature           | Fatty acid transport protein 1                                                                                 | Fatty acid transport protein 2                                                                                                               | Fatty acid transport protein 3                                                                   |
|------------------------|----------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Systematic name        | SLC27A1                                                                                                        | SLC27A2                                                                                                                                      | SLC27A3                                                                                          |
| Preferred abbreviation | FATP1                                                                                                          | FATP2                                                                                                                                        | FATP3                                                                                            |
| Ensembl ID             | ENSG00000130304                                                                                                | ENSG00000140284                                                                                                                              | ENSG00000143554                                                                                  |
| Other names            | Long-chain fatty acid transport protein 1                                                                      | Very-long-chain acyl-CoA synthetase, very-long-chain-fatty-acid-CoA ligase, THCA-CoA ligase, fatty-acid-coenzyme A ligase, very long-chain 1 | Long-chain fatty acid transport protein 3, very long-chain acyl-CoA synthetase homolog 3, VLCS-3 |
| Endogenous substrates  | C20:4 > C16 > C18:1 > C4 (Schaffer and Lodish, 1994); C16:0 > C18:1 > C18:3 > C8 (Gimeno <i>et al.</i> , 2003) | –                                                                                                                                            | –                                                                                                |

| Nomenclature           | Fatty acid transport protein 4                                                                                          | Fatty acid transport protein 5                                                                                                       | Fatty acid transport protein 6                                                                   |
|------------------------|-------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Systematic name        | SLC27A4                                                                                                                 | SLC27A5                                                                                                                              | SLC27A6                                                                                          |
| Preferred abbreviation | FATP4                                                                                                                   | FATP5                                                                                                                                | FATP6                                                                                            |
| Ensembl ID             | ENSG00000167114                                                                                                         | ENSG00000083807                                                                                                                      | ENSG00000113396                                                                                  |
| Other names            | ACSVL4                                                                                                                  | Bile acyl-CoA synthetase, BACS, bile acid CoA ligase, BAL, cholate-CoA ligase, very long-chain acyl-CoA synthetase homolog 2, VLCSH2 | Long-chain fatty acid transport protein 6, very long-chain acyl-CoA synthetase homolog 1, VLCSH1 |
| Endogenous substrates  | C16:0 > C18:1 > C4, C18:3 > C20:4 (Stahl <i>et al.</i> , 1999); C16:0, C18:1 > C18:3 > C8 (Gimeno <i>et al.</i> , 2003) |                                                                                                                                      | C16:0 > C18:1 > C18:3 > C8 (Gimeno <i>et al.</i> , 2003)                                         |

Although the stoichiometry of fatty acid transport is unclear, it has been proposed to be facilitated by the coupling of fatty acid transport to conjugation with CoA to form fatty acyl CoA esters. Small molecule inhibitors of FATP2 (Sandoval *et al.*, 2010) and FATP4 (Blackburn *et al.*, 2006) have been described; analysis of the mechanism of action of some of these inhibitors suggests that transport may be selectively inhibited without altering enzymatic activity of the FATP.

C1-BODIPY-C12 accumulation has been used as a non-selective index of fatty acid transporter activity.

**Abbreviations:** C12:, C16:0, palmitic acid; C18:0, stearic acid; C18:1, oleic acid; C18:2, linoleic acid; C18:3,n-6,  $\gamma$ -linolenic acid; C2, acetic acid; C20:4, arachidonic acid; C20:5,n-3, 5z,8z,11z,14z,17z-eicosapentaenoic acid, EPA; C22:6,n-3, 4z,7z,10z,13z,16z,19z-docosahexaenoic acid, DHA; C3, propionic acid; C4, butyric acid; C5, valeric acid; C8, octanoic acid

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## SLC28 and SLC29 families of nucleoside transporters

**Overview:** Nucleoside transporters are divided into two families, the sodium-dependent, solute carrier family 28 (SLC28) and the equilibrative, solute carrier family 29 (SLC29), where the endogenous substrates are nucleosides.

**SLC28 family** members have 13 TM segments with cytoplasmic N-termini and extracellular C-termini.

| Systematic name         | SLC28A1                                                 | SLC28A2                                                       | SLC28A3                                                                                                                               |
|-------------------------|---------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|
| Common abbreviation     | CNT1                                                    | CNT2                                                          | CNT3                                                                                                                                  |
| Ensembl ID              | ENSG00000156222                                         | ENSG00000137860                                               | ENSG00000099118                                                                                                                       |
| Other names             | N2/ <i>cit</i> , concentrative nucleoside transporter 1 | N1/ <i>cif</i> , SPNT, concentrative nucleoside transporter 2 | N3/ <i>cib</i> , concentrative nucleoside transporter 3                                                                               |
| Endogenous substrates   | Uridine, cytidine, thymidine, adenosine                 | Adenosine, guanosine, inosine, thymidine                      | Uridine, cytidine, thymidine, adenosine, guanosine, inosine                                                                           |
| Synthetic substrates    | AZT, zalcitabine, gemcitabine                           | Formycin B, cladribine, fludarabine, vidarabine, didanosine   | AZT, zalcitabine, didanosine, formycin B, 5-fluorouridine, 5-fluoro-2'-deoxyuridine, zebularine, gemcitabine, cladribine, fludarabine |
| Predicted stoichiometry | 1 Na <sup>+</sup> : 1 nucleoside (in)                   | 1 Na <sup>+</sup> : 1 nucleoside (in)                         | 2 Na <sup>+</sup> : 1 nucleoside (in)                                                                                                 |

A further two Na<sup>+</sup>-dependent (stoichiometry 1 Na<sup>+</sup> : 1 nucleoside (in)) nucleoside transporters have been defined on the basis of substrate and inhibitor selectivity: CNT4 (N4/*cit*, which transports uridine, thymidine and guanosine) and CNT5 (N5/*csg*, which transports guanosine and adenosine, and may be inhibited by NBTI).

**SLC29 family** members appear to be composed of 11 TM segments with cytoplasmic N-termini and extracellular C-termini. ENT1 and ENT2 are cell-surface transporters, while ENT3 is intracellular, possibly lysosomal (Baldwin *et al.*, 2005). ENT1–3 are described as broad-spectrum nucleoside transporters. Ahas been reported to be intracellular purine nucleoside transporters

| Systematic name         | SLC29A1                                                                                                                                                     | SLC29A2                                                                                         | SLC29A3                                                                                                                                                    | SLC29A4                                                                        |
|-------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Common abbreviation     | ENT1                                                                                                                                                        | ENT2                                                                                            | ENT3                                                                                                                                                       | PMAT                                                                           |
| Nomenclature            | Equilibrative nucleoside transporter 1                                                                                                                      | Equilibrative nucleoside transporter 2                                                          | Equilibrative nucleoside transporter 3                                                                                                                     | Plasma membrane monoamine transporter                                          |
| Ensembl ID              | ENSG00000112759                                                                                                                                             | ENSG00000174669                                                                                 | ENSG00000156604                                                                                                                                            | ENSG00000164638                                                                |
| Other names             | <i>es</i> , NBTI-sensitive                                                                                                                                  | <i>ei</i> , NBTI-insensitive                                                                    | -                                                                                                                                                          | Equilibrative nucleoside transporter 4                                         |
| Endogenous substrates   | Adenosine, guanosine, inosine, uridine, thymidine, cytidine, hypoxanthine, adenine, thymine (Yao <i>et al.</i> , 2011)                                      | Adenosine, guanosine, inosine, uridine, thymidine, hypoxanthine                                 | Adenosine, inosine, > guanosine, thymidine, uridine, adenine (Baldwin <i>et al.</i> , 2005)                                                                | 5HT, dopamine > tyramine, histamine (Engel and Wang, 2005)                     |
| Synthetic substrates    | 2-Chloroadenosine, dideoxyinosine, formycin B, tubercidin, vidarabine, cytarabine, cladribine, pentostatin, zalcitabine, didanosine, floxidine, gemcitabine | 2-Chloroadenosine, formycin B, tubercidin, cytarabine, cladribine, vidarabine, AZT, gemcitabine | Tubercidin, cordycepin, cladribine, fludarabine, 5-fluoro-2'-deoxyuridine, zebularine, dideoxyinosine, AZT, dideoxycytidine (Baldwin <i>et al.</i> , 2005) | MPP <sup>+</sup> > TEA (Engel and Wang, 2005)                                  |
| Selective inhibitors    | NBTI (9.7), drafazine (9.5), KF24345 (9.4, Hammond and Archer, 2004), NBTGR (9.3), dilazep (9), dipyrindamole (8.5)                                         | -                                                                                               | -                                                                                                                                                          | Cimetidine, quinidine, quinine, verapamil, rhodamine123 (Engel and Wang, 2005) |
| Probes                  | [ <sup>3</sup> H]-NBTI (0.5 nM), [ <sup>14</sup> C]-adenosine                                                                                               | [ <sup>14</sup> C]-Adenosine                                                                    | [ <sup>14</sup> C]-Adenosine                                                                                                                               | -                                                                              |
| Predicted stoichiometry | Equilibrative                                                                                                                                               | Equilibrative                                                                                   | Equilibrative                                                                                                                                              | Equilibrative                                                                  |

PMAT also transports adenosine at acidic pH (Barnes *et al.*, 2006; Zhou *et al.*, 2007).

The affinities of drafazine, dilazep, KF24345 and dipyrindamole at ENT1 transporters are species dependent, exhibiting lower affinity at rat transporters than at human transporters (Sundaram *et al.*, 1998; Hammond and Archer, 2004).

**Abbreviations:** 5HT, 5-hydroxytryptamine; AZT, 3'-azido-3'-deoxythymidine; MPP<sup>+</sup>, 1-methyl-4-phenylpyridin-1-ium; NBTI, nitrobenzylthioinosine (also known as NBMPR); NBTGR, nitrobenzylthioguanosine; KF24345, 3-(1-[6,7-diethoxy-2-morpholinoquinazolin-4-yl]piperidin-4-yl)-1,6-dimethyl-2,4(1H,3H)-quinazolinedione hydrochloride

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# SLC30 zinc transporter family

**Overview:** Along with the SLC39 family (see Page S270), SLC30 transporters regulate the movement of zinc ions around the cell. In particular, these transporters remove zinc ions from the cytosol, allowing accumulation into intracellular compartments or efflux through the plasma membrane. ZNT1 is thought to be placed on the plasma membrane extruding zinc, while ZNT3 is associated with synaptic vesicles and ZNT4 and ZNT5 are linked with secretory granules. Membrane topology predictions suggest a multimeric assembly with subunits having six TM domains, with both termini being cytoplasmic. Dityrosine covalent linking has been suggested as a mechanism for dimerisation, particularly for ZNT3 (Salazar *et al.*, 2009). The mechanism for zinc transport is unknown.

| Systematic name | Common abbreviation | Nomenclature        | Ensembl ID      | Other names                        |
|-----------------|---------------------|---------------------|-----------------|------------------------------------|
| SLC30A1         | ZNT1                | Zinc transporter 1  | ENSG00000170385 |                                    |
| SLC30A2         | ZNT2                | Zinc transporter 2  | ENSG00000158014 |                                    |
| SLC30A3         | ZNT3                | Zinc transporter 3  | ENSG00000115194 |                                    |
| SLC30A4         | ZNT4                | Zinc transporter 4  | ENSG00000104154 |                                    |
| SLC30A5         | ZNT5                | Zinc transporter 5  | ENSG00000145740 |                                    |
| SLC30A6         | ZNT6                | Zinc transporter 6  | ENSG00000152683 |                                    |
| SLC30A7         | ZNT7                | Zinc transporter 7  | ENSG00000162695 |                                    |
| SLC30A8         | ZNT8                | Zinc transporter 8  | ENSG00000164756 |                                    |
| SLC30A9         | ZNT9                | Zinc transporter 9  | ENSG00000014824 | Human embryonic lung protein, HUEL |
| SLC30A10        | ZNT10               | Zinc transporter 10 | ENSG00000196660 |                                    |

SLC30A8 is described as a type 2 diabetes susceptibility gene.

Zinc fluxes may be monitored through the use of radioisotopic Zn-65 or the fluorescent dye FluoZin 3.

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# SLC31 family of copper transporters

**Overview:** SLC31 family members, alongside the Cu-ATPases (see Page S219) are involved in the regulation of cellular copper levels. The CTR1 transporter is a cell-surface transporter to allow monovalent copper accumulation into cells, while CTR2 appears to be a vacuolar/vesicular transporter (Rees *et al.*, 2004). Functional copper transporters appear to be trimeric with each subunit having three TM regions and an extracellular N-terminus. CTR1 is considered to be a higher affinity copper transporter compared to CTR2. The stoichiometry of copper accumulation is unclear, but appears to be energy-independent (Lee *et al.*, 2002).

|                        |                      |                      |
|------------------------|----------------------|----------------------|
| Systematic name        | SLC31A1              | SLC31A2              |
| Preferred abbreviation | CTR1                 | CTR2                 |
| Nomenclature           | Copper transporter 1 | Copper transporter 2 |
| Ensembl ID             | ENSG00000136868      | ENSG00000136867      |
| Other names            | COPT1                | COPT2                |

Copper accumulation through CTR1 is sensitive to silver ions, but not divalent cations (Lee *et al.*, 2002). The CTR1 and CTR2 transporters regulate the cellular levels of the anticancer drug cisplatin (Ishida *et al.*, 2002, Blair *et al.*, 2009).

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# SLC32 vesicular inhibitory amino acid transporter

**Overview:** The vesicular inhibitory amino acid transporter, VIAAT (also termed the vesicular GABA transporter VGAT), which is the sole representative of the SLC32 family, transports GABA, or glycine, into synaptic vesicles (Gasnier, 2000, 2004). VIAAT was originally suggested to be composed of 10 TM segments with cytoplasmic N- and C-termini (McIntire *et al.*, 1997; Sagne *et al.*, 1997). However, an alternative 9TM structure with the N terminus facing the cytoplasm and the C terminus residing in the synaptic vesicle lumen has subsequently been reported (Martens *et al.*, 2008). VIAAT acts as an antiporter for inhibitory amino acids and protons. The accumulation of GABA and glycine within vesicles is driven by both the chemical ( $\Delta\text{pH}$ ) and electrical ( $\Delta\psi$ ) components of the proton electrochemical gradient ( $\Delta\mu_{\text{H}^+}$ ) established by a vacuolar  $\text{H}^+$ -ATPase (McIntire *et al.*, 1997). However, Juge *et al.* (2009) have presented evidence that VIAAT is instead a  $\text{Cl}^-$ /GABA co-transporter. VIAAT co-exists with VGLUT1 (SLC17A7), or VGLUT2 (SLC17A6), in the synaptic vesicles of selected nerve terminals (Fattorini *et al.*, 2009; Zander *et al.*, 2010). VIAAT knock out mice die between embryonic day 18.5 and birth (Wojcik *et al.*, 2006). In cultures of spinal cord neurones established from earlier embryos, the co-release of GABA and glycine from synaptic vesicles is drastically reduced, providing direct evidence for the role of VIAAT in the sequestration of both transmitters (Wojcik *et al.*, 2006; Saito *et al.*, 2010).

|                                 |                                                                                                                           |
|---------------------------------|---------------------------------------------------------------------------------------------------------------------------|
| Common abbreviation             | VIAAT                                                                                                                     |
| Systematic name                 | SLC32A1                                                                                                                   |
| Nomenclature                    | Vesicular inhibitory amino acid transporter                                                                               |
| Other names                     | VGAT (vesicular GABA transporter)                                                                                         |
| Ensembl ID                      | ENSG00000101438                                                                                                           |
| Endogenous substrates ( $K_m$ ) | GABA (5 mM; McIntire <i>et al.</i> , 1997), glycine, $\beta$ -alanine, $\gamma$ -hydroxybutyrate                          |
| Synthetic substrates            | –                                                                                                                         |
| Inhibitors ( $\text{IC}_{50}$ ) | Vigabatrin (7.5 mM; McIntire <i>et al.</i> , 1997)                                                                        |
| Probes                          | –                                                                                                                         |
| Stoichiometry                   | 1 amino acid (in): 1 $\text{H}^+$ (out) (Gasnier, 2004) or 1 amino acid: 2 $\text{Cl}^-$ (in) (Juge <i>et al.</i> , 2009) |

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# SLC33 acetylCoA transporter

**Overview:** acetylation of proteins is a post-translational modification mediated by specific acetyltransferases, using the donor acetylCoA. SLC33A1/AT1 is a putative 11 TM transporter present on the endoplasmic reticulum, expressed in all tissues, but particularly abundant in the pancreas (Kanamori *et al.*, 1997), which imports cytosolic acetylCoA into these intracellular organelles.

|                        |                              |
|------------------------|------------------------------|
| Systematic name        | SLC33A1                      |
| Preferred abbreviation | AT1                          |
| Nomenclature           | AcetylCoA transporter        |
| Ensembl ID             | ENSG00000169359              |
| Other names            | ACATN                        |
| Endogenous substrates  | AcetylCoA                    |
| Probes                 | [ <sup>14</sup> C]-AcetylCoA |
| Stoichiometry          | Unknown                      |

In heterologous expression studies, acetylCoA transport through AT1 was inhibited by CoA, but not acetate, ATP or UDP-galactose (Jonas *et al.*, 2010). A loss-of-function mutation in SLC33A1 has been associated with spastic paraplegia (SPG42, Lin *et al.*, 2008), although this observation could not be replicated in a subsequent study (Schlipf *et al.*, 2010).

**Abbreviations:** CoA, coenzyme A, [[(2R,3S,4R,5R)-5-(6-aminopurin-9-yl)-4-hydroxy-3-phosphonooxyoxolan-2-yl]methoxy-hydroxyphosphoryl][(3R)-3-hydroxy-2,2-dimethyl-4-oxo-4-[[3-oxo-3-(2-sulfanylethylamino)propyl]amino]butyl]hydrogen phosphate.

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## SLC34 family of sodium phosphate co-transporters

**Overview:** The SLC34 family are sometimes referred to as Type II sodium-phosphate co-transporters, alongside Type I (SLC17 family, see Page S247) and Type III (SLC20 family, see Page S251) transporters. Topological modelling suggests eight TM domains with C- and N- termini in the cytoplasm, and a re-entrant loop at TM5/6. SLC34 family members are expressed on the apical surfaces of epithelia in the intestine and kidneys to regulate body phosphate levels, principally NaPi-IIa and NaPi-IIb, respectively. NaPi-IIa and NaPi-IIb are electrogenic, while NaPi-IIc is electrogenic (Andrini *et al.*, 2008).

|                     |                                                                                          |                                                                                          |                                                                                          |
|---------------------|------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| Systematic name     | SLC34A1                                                                                  | SLC34A2                                                                                  | SLC34A3                                                                                  |
| Common abbreviation | NaPi-IIa                                                                                 | NaPi-IIb                                                                                 | NaPi-IIc                                                                                 |
| Nomenclature        | Sodium phosphate 1                                                                       | Sodium phosphate 2                                                                       | Sodium phosphate 3                                                                       |
| Ensembl ID          | ENSG00000131183                                                                          | ENSG00000157765                                                                          | ENSG00000198569                                                                          |
| Other names         | NAPI-3, NPT2, NPTIIa, SLC11, SLC17A2                                                     | NAPI-3B                                                                                  | NPTIIc                                                                                   |
| Stoichiometry       | 3 Na <sup>+</sup> : 1 HPO <sub>4</sub> <sup>2-</sup> (in) (Forster <i>et al.</i> , 1999) | 3 Na <sup>+</sup> : 1 HPO <sub>4</sub> <sup>2-</sup> (in) (Andrini <i>et al.</i> , 2008) | 2 Na <sup>+</sup> : 1 HPO <sub>4</sub> <sup>2-</sup> (in) (Andrini <i>et al.</i> , 2008) |

These transporters can be inhibited by PFA, in contrast to type III sodium-phosphate cotransporters, the SLC20 family (see Page S251).

**Abbreviations:** PFA, phosphonoformic acid

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# SLC35 family of nucleotide sugar transporters

**Overview:** glycoprotein formation in the Golgi and endoplasmic reticulum relies on the accumulation of nucleotide-conjugated sugars via the SLC35 family of transporters. These transporters have a predicted topology of 10 TM domains, with cytoplasmic termini, and function as exchangers, swapping nucleoside monophosphates for the corresponding nucleoside diphosphate conjugated sugar. Five subfamilies of transporters have been identified on the basis of sequence similarity.

| Systematic name | SLC35A1                                       | SLC35A2                                                                                          | SLC35A3                                               | SLC35A4         | SLC35A5         |
|-----------------|-----------------------------------------------|--------------------------------------------------------------------------------------------------|-------------------------------------------------------|-----------------|-----------------|
| Nomenclature    | CMP-sialic acid transporter                   | UDP-galactose transporter                                                                        | UDP-N-acetylglucosamine transporter                   | –               | –               |
| Ensembl ID      | ENSG00000164414                               | ENSG00000102100                                                                                  | ENSG00000117620                                       | ENSG00000176087 | ENSG00000138459 |
| Other names     | CMPST, hCST                                   | UGALT, UGAT, UGT, UGT1, UGT2, UGTL                                                               | –                                                     | –               | –               |
| Substrates      | CMP-sialic acid (Ishida <i>et al.</i> , 1998) | UDP-galactose, UDP-N-acetylglucosamine (Ishida <i>et al.</i> , 1996; Miura <i>et al.</i> , 1996) | UDP-N-acetylglucosamine (Ishida <i>et al.</i> , 1999) | –               | –               |

| Systematic name | SLC35B1         | SLC35B2                              | SLC35B3                              | SLC35B4                                                            |
|-----------------|-----------------|--------------------------------------|--------------------------------------|--------------------------------------------------------------------|
| Nomenclature    | –               | PAPS transporter 1                   | PAPS transporter 2                   | –                                                                  |
| Ensembl ID      | ENSG00000121073 | ENSG00000157593                      | ENSG00000124786                      | ENSG00000205060                                                    |
| Other names     | HUT-1           | PAPST1, SLL, UGTrel4                 | PAPST2, C6orf196, CGI-19, dj453H5.1  | YEA4                                                               |
| Substrates      | –               | PAPS (Kamiyama <i>et al.</i> , 2003) | PAPS (Kamiyama <i>et al.</i> , 2006) | UDP-xylose, UDP-N-acetylglucosamine (Ashikov <i>et al.</i> , 2005) |

| Systematic name | SLC35C1                                | SLC35C2         |
|-----------------|----------------------------------------|-----------------|
| Nomenclature    | GDP-Fucose transporter                 | –               |
| Ensembl ID      | ENSG00000181830                        | ENSG00000080189 |
| Other names     | FUCT1                                  | –               |
| Substrates      | GDP-fucose (Luhn <i>et al.</i> , 2001) | –               |

| Systematic name | SLC35D1                                                                       | SLC35D2                                                 | SLC35D3         |
|-----------------|-------------------------------------------------------------------------------|---------------------------------------------------------|-----------------|
| Nomenclature    | UDP-glucuronic acid/UDP-N-acetylgalactosamine dual transporter                | –                                                       | –               |
| Ensembl ID      | ENSG00000116704                                                               | ENSG00000130958                                         | ENSG00000182747 |
| Other names     | UDP-galactose transporter-related 7                                           | SQV7-like protein, UDP-galactose transporter-related 8  | FRCL1           |
| Substrates      | UDP-glucuronic acid, UDP-N-acetylgalactosamine (Muraoka <i>et al.</i> , 2001) | UDP-N-acetylgalactosamine (Ishida <i>et al.</i> , 2005) | –               |

## Orphan transporters

| Systematic name | SLC35E1         | SLC35E2         | SLC35E3         | SLC35E4         |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Ensembl ID      | ENSG00000127526 | ENSG00000175782 | ENSG00000215790 | ENSG00000100036 |

|                 |                 |                 |                 |                 |                 |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Systematic name | SLC35F1         | SLC35F2         | SLC35F3         | SLC35F4         | SLC35F5         |
| Ensembl ID      | ENSG00000196376 | ENSG00000110660 | ENSG00000183780 | ENSG00000151812 | ENSG00000115084 |

**Abbreviations:** PAPS, [(2R,3S,4R,5R)-5-(6-aminopurin-9-yl)-4-hydroxy-2-[[oxido(sulfonatooxy)phosphoryl]oxymethyl]oxolan-3-yl] phosphate

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## SLC36 family of proton-coupled amino acid transporters

**Overview:** the SLC36 family of proton-coupled amino acid transporters (or PAT) is highly expressed in the intestine and kidney, having roles in the disposition of amino acids (see Thwaites and Anderson, 2011). PAT1 is found predominantly in lysosomal membranes where it likely functions as an efflux mechanism for amino acids produced during intralysosomal proteolysis (Sagné *et al.*, 2001; Agulhon *et al.*, 2003). PAT2 is found mainly in the endoplasmic reticulum and, to a lesser extent, in other cellular compartments including the plasma membrane (Rubio-Aliaga *et al.*, 2004). PAT1 and PAT2 are predicted to have 11 TM domains with intracellular termini.

|                        |                                                                                                                                                                                                    |                                                                                |                                         |                                                 |
|------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-----------------------------------------|-------------------------------------------------|
| Systematic name        | SLC36A1                                                                                                                                                                                            | SLC36A2                                                                        | SLC36A3                                 | SLC36A4                                         |
| Preferred abbreviation | PAT1                                                                                                                                                                                               | PAT2                                                                           | PAT3                                    | PAT4                                            |
| Nomenclature           | Proton-coupled Amino acid Transporter 1                                                                                                                                                            | Proton-coupled Amino acid Transporter 2                                        | Proton-coupled Amino acid Transporter 3 | Proton-coupled Amino acid Transporter 4         |
| Ensembl ID             | ENSG00000123643                                                                                                                                                                                    | ENSG00000186335                                                                | ENSG00000186334                         | ENSG00000180773                                 |
| Other names            | LYAAT-1, LYsosomal Amino Acid Transporter 1, imino acid carrier, Tramdorin-3                                                                                                                       | Tramdorin-1                                                                    | Tramdorin-2                             | LYAAT-2                                         |
| Substrates             | GABA, L- and D-proline, glycine, L- and D-alanine, β-alanine, taurine, D-serine, D-cysteine, sarcosine, <i>trans</i> -4-hydroxy-proline, betaine, 5-aminolevulinic acid, β-guanidinopropionic acid | Glycine, proline, alanine, sarcosine, <i>trans</i> -4-hydroxy-proline          | –                                       | Proline, tryptophan (Pillai and Meredith, 2011) |
| Synthetic substrates   | MeAIB (Chen <i>et al.</i> , 2003a), vigabatrin, THPO, gaboxadol (Larsen <i>et al.</i> , 2009)                                                                                                      | MeAIB (Chen <i>et al.</i> , 2003b)                                             | –                                       | –                                               |
| Inhibitors             | L-Tryptophan, tryptamine, 5-hydroxy-L-tryptophan, serotonin, indole-3-propionic acid (Metzner <i>et al.</i> , 2005)                                                                                | 5-Hydroxy-L-tryptophan, α-methyl-D,L-tryptophan (Edwards <i>et al.</i> , 2011) | –                                       | –                                               |
| Probes                 | [ <sup>3</sup> H] or [ <sup>14</sup> C] substrates as listed above                                                                                                                                 | [ <sup>3</sup> H] or [ <sup>14</sup> C] substrates as listed above             | –                                       | –                                               |
| Stoichiometry          | 1 H <sup>+</sup> : 1 amino acid (in)                                                                                                                                                               | 1 H <sup>+</sup> : 1 amino acid (in)                                           | Unknown                                 | Unknown                                         |

Both PAT1 and PAT2 can also function as an electroneutral transport system for H<sup>+</sup> and fatty acids including acetate, propionate and butyrate (Foltz *et al.*, 2005).

Loss-of-function mutations in PAT2 lead to iminoglycinuria and hyperglycinuria in man (see Bröer, 2008b).

**Abbreviations:** MeAIB,  $\alpha$ - or 2-(methylamino)isobutyric acid; THPO, 4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridin-3-ol

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## SLC37 family of phosphosugar/phosphate exchangers

**Overview:** the family of sugar-phosphate exchangers pass particular phosphorylated sugars across intracellular membranes, exchanging for inorganic phosphate. Of the family of sugar phosphate transporters, most information is available on SPX4, the glucose-6-phosphate transporter. This is a 10 TM domain protein with cytoplasmic termini and is associated with the endoplasmic reticulum, with tissue-specific splice variation. The SPX1 glycerol 3-phosphate transporter is predicted to be expressed on mitochondria.

| Systematic name        | SLC37A1                          | SLC37A2                    | SLC37A3         | SLC37A4                         |
|------------------------|----------------------------------|----------------------------|-----------------|---------------------------------|
| Preferred abbreviation | SPX1                             | SPX2                       | SPX3            | SPX4                            |
| Nomenclature           | Glycerol-3-phosphate transporter |                            |                 | Glucose-6-phosphate transporter |
| Ensembl ID             | ENSG00000160190                  | ENSG00000134955            | ENSG00000157800 | ENSG00000137700                 |
| Other names            | G3PP                             | cAMP-inducible gene 2, cI2 | –               | G6PT1                           |
| Substrates             | Glycerol 3-phosphate             | –                          | –               | Glucose 6-phosphate             |
| Stoichiometry          | Unknown                          | Unknown                    | Unknown         | Unknown                         |

Multiple polymorphisms have been described for the SLC37A4 gene, some of which associate with a glycogen storage disease (Almqvist *et al.*, 2004).

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# SLC38 family of sodium-dependent neutral amino acid transporters

**Overview:** the SLC38 family of transporters appears to be responsible for the functionally-defined system A and system N mechanisms of amino acid transport and are mostly expressed in the CNS. Two distinct subfamilies are identifiable within the SLC38 transporters. SNAT1, SNAT2 and SNAT4 appear to resemble system A transporters in accumulating neutral amino acids under the influence of the sodium gradient. SNAT3 and SNAT5 appear to resemble system N transporters in utilizing proton co-transport to accumulate amino acids. The predicted membrane topology is of 11 TM domains with an extracellular N-terminus and intracellular C-terminus.

## System A-like transporters

|                        |                                                                                                                 |                                                                                    |                                                                                                            |
|------------------------|-----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|
| Systematic name        | SLC38A1                                                                                                         | SLC38A2                                                                            | SLC38A4                                                                                                    |
| Preferred abbreviation | SNAT1                                                                                                           | SNAT2                                                                              | SNAT4                                                                                                      |
| Ensembl ID             | ENSG00000111371                                                                                                 | ENSG00000134294                                                                    | ENSG00000139209                                                                                            |
| Other names            | Amino acid transporter system A, member 1, ATA1, N-system amino acid transporter 2, NAT2, glutamine transporter | Amino acid transporter system A, member 2, ATA2, SA1, SAT2                         | Amino acid transporter A3; ATA3, neutral amino acid transporter 3, NAT3, N-system amino acid transporter 3 |
| Substrates             | Ala > Ser, Gln, Asn, His, Cys, Met > Gly, Thr, Pro, Tyr, Val (Albers <i>et al.</i> , 2001)                      | Ala, Met > Asn, Gln, Ser, Pro, Gly > Thr, Leu, Phe (Hatanaka <i>et al.</i> , 2000) | His > Arg, Ala, Asn, Lys > Gly, Gln, Ser, Pro, Leu, Phe (Hatanaka <i>et al.</i> , 2001)                    |
| Synthetic substrates   | MeAIB                                                                                                           | MeAIB                                                                              | MeAIB                                                                                                      |
| Probes                 | [ <sup>3</sup> H] or [ <sup>14</sup> C]-Alanine                                                                 | [ <sup>3</sup> H] or [ <sup>14</sup> C]-Alanine                                    | [ <sup>3</sup> H] or [ <sup>14</sup> C]-Alanine, [ <sup>3</sup> H] or [ <sup>14</sup> C]-glycine           |
| Stoichiometry          | 1 Na <sup>+</sup> : 1 amino acid (in) (Albers <i>et al.</i> , 2001)                                             | 1 Na <sup>+</sup> : 1 amino acid (in) (Hatanaka <i>et al.</i> , 2000)              | 1 Na <sup>+</sup> : 1 neutral amino acid (in) (Hatanaka <i>et al.</i> , 2001)                              |

Transport of cationic amino acids by SNAT4 was sodium-independent (Hatanaka *et al.*, 2001).

## System N-like transporters

|                        |                                                                                           |                                                                                                 |
|------------------------|-------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Systematic name        | SLC38A3                                                                                   | SLC38A5                                                                                         |
| Preferred abbreviation | SNAT3                                                                                     | SNAT5                                                                                           |
| Ensembl ID             | ENSG00000188338                                                                           | ENSG00000017483                                                                                 |
| Other names            | Transport system N protein 1, SN1, G17, N-system amino acid transporter 1; NAT1           | Transport system N protein 2, SN2                                                               |
| Substrates             | His, Gln > Asn, Ala > Glu (Fei <i>et al.</i> , 2000)                                      | Asn, Ser, His, Gln > Gly, Ala (Nakanishi <i>et al.</i> , 2001)                                  |
| Synthetic substrates   | MeAIB                                                                                     | –                                                                                               |
| Probes                 | [ <sup>3</sup> H] or [ <sup>14</sup> C]-Glutamine                                         | [ <sup>3</sup> H] or [ <sup>14</sup> C]-Histidine                                               |
| Stoichiometry          | 1 Na <sup>+</sup> : 1 amino acid (in) : 1 H <sup>+</sup> (out) Broer <i>et al.</i> , 2002 | 1 Na <sup>+</sup> : 1 amino acid (in) : 1 H <sup>+</sup> (out) (Nakanishi <i>et al.</i> , 2001) |

## Orphan transporters

|                        |                 |                 |                 |                 |                 |                 |
|------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Systematic name        | SLC38A6         | SLC38A7         | SLC38A8         | SLC38A9         | SLC38A10        | SLC38A11        |
| Preferred abbreviation | SNAT6           | SNAT7           | –               | –               | –               | –               |
| Ensembl ID             | ENSG00000139974 | ENSG00000103042 | ENSG00000166558 | ENSG00000177058 | ENSG00000157637 | ENSG00000169507 |

SNAT7/SLC38A7 has recently been described to be a system N-like transporter allowing preferential accumulation of glutamine, histidine and asparagine (Hagglund *et al.*, 2011).

**Abbreviations:** MeAIB, 3-amino-2,2-dimethylpropanoic acid

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## SLC39 family of metal ion transporters

**Overview:** along with the SLC30 family (see Page S263), SLC39 family members regulate zinc movement in cells. SLC39 metal ion transporters accumulate zinc into the cytosol. Membrane topology modelling suggests the presence of eight TM regions with both termini extracellular. The mechanism for zinc transport for many members is unknown but appears to involve co-transport of bicarbonate ions (Girijashanker *et al.*, 2008, Liu *et al.*, 2008).

| Systematic name     | SLC39A1                                                                 | SLC39A2                     | SLC39A3                     | SLC39A4                     | SLC39A5                 |
|---------------------|-------------------------------------------------------------------------|-----------------------------|-----------------------------|-----------------------------|-------------------------|
| Common abbreviation | ZIP1                                                                    | ZIP2                        | ZIP3                        | ZIP4                        | ZIP5                    |
| Nomenclature        | Zinc transporter 1                                                      | Zinc transporter 2          | Zinc transporter 3          | Zinc transporter 4          | metal ion transporter 5 |
| Ensembl ID          | ENSG00000143570                                                         | ENSG00000165794             | ENSG00000141873             | ENSG00000206288             | ENSG00000139540         |
| Other names         | Zinc/iron-regulated transporter-like; ZIRT, ZRT- and IRT-like protein 1 | ZRT- and IRT-like protein 2 | ZRT- and IRT-like protein 3 | ZRT- and IRT-like protein 4 | Metal ion transporter 5 |

| Systematic name     | SLC39A6            | SLC39A7                                                                                         | SLC39A8                                                                                   | SLC39A9            | SLC39A10            |
|---------------------|--------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|--------------------|---------------------|
| Common abbreviation | ZIP6               | ZIP7                                                                                            | ZIP8                                                                                      | ZIP9               | ZIP10               |
| Nomenclature        | Zinc transporter 6 | Zinc transporter 7                                                                              | Zinc transporter 8                                                                        | Zinc transporter 9 | Zinc transporter 10 |
| Ensembl ID          | ENSG00000141424    | ENSG00000224399;<br>ENSG00000226614;<br>ENSG00000229802;<br>ENSG00000227402;<br>ENSG00000112473 | ENSG00000138821                                                                           | ENSG00000029364    | ENSG00000196950     |
| Other names         | LIV1               | HKE4                                                                                            | BIGM103                                                                                   | –                  | KIAA1265            |
| Other substrates    | –                  | –                                                                                               | Cadmium (Dalton <i>et al.</i> , 2005, Liu <i>et al.</i> , 2008)                           | –                  | –                   |
| Stoichiometry       | –                  | –                                                                                               | 1 Zn <sup>2+</sup> (in) : 2 HCO <sub>3</sub> <sup>–</sup> (in) (Liu <i>et al.</i> , 2008) | –                  | –                   |

|                     |                          |                     |                     |                                                                                             |
|---------------------|--------------------------|---------------------|---------------------|---------------------------------------------------------------------------------------------|
| Systematic name     | SLC39A11                 | SLC39A12            | SLC39A13            | SLC39A14                                                                                    |
| Common abbreviation | ZIP11                    | ZIP12               | ZIP13               | ZIP14                                                                                       |
| Nomenclature        | Zinc transporter 11      | Zinc transporter 12 | Zinc transporter 13 | Zinc transporter 14                                                                         |
| Ensembl ID          | ENSG00000133195          | ENSG00000148482     | ENSG00000165915     | ENSG00000104635                                                                             |
| Other names         | Metal ion transporter 11 | –                   | –                   | –                                                                                           |
| Other substrates    | –                        | –                   | –                   | Iron (Liuzzi <i>et al.</i> , 2006), cadmium, manganese (Girijashanker <i>et al.</i> , 2008) |

Zinc fluxes may be monitored through the use of radioisotopic Zn-65 or the fluorescent dye FluoZin 3.

The bicarbonate transport inhibitor DIDS has been reported to inhibit cation accumulation through ZIP14 (Girijashanker K *et al.*, 2008).

**Abbreviations:** DIDS, 5-isothiocyanato-2-[(E)-2-(4-isothiocyanato-2-sulfophenyl)ethenyl]benzenesulfonic acid

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## SLC40 iron transporter

**Overview:** alongside the SLC11 family (see Page S242) of proton-coupled metal transporters, IREG allows the accumulation of iron from the diet on the basolateral side of the enterocyte, as well as regulating macrophage and placental iron levels. The predicted topology is of nine TM domains, with an intracellular N-terminus and extracellular C-terminus, with the functional transporter is suggested to be a dimeric arrangement (Aguirre *et al.*, 2005; De Domenico *et al.*, 2007).

|                        |                                                                   |
|------------------------|-------------------------------------------------------------------|
| Systematic name        | SLC40A1                                                           |
| Preferred abbreviation | IREG1                                                             |
| Nomenclature           | Iron-regulated transporter                                        |
| Ensembl ID             | ENSG00000138449                                                   |
| Other names            | Ferroportin, metal transporter protein, MTP1, SLC11A3, FPN1, HFE4 |
| Endogenous substrates  | Fe <sup>2+</sup>                                                  |
| Stoichiometry          | Unknown                                                           |

Hepcidin (HAMP, ENSG00000105697), a small protein that increases upon inflammation, binds to ferroportin to regulate its cellular distribution and degradation. Gene disruption in mice results in embryonic lethality (Donovan *et al.*, 2005), while loss-of-function mutations in man are associated with haemochromatosis (De Domenico *et al.*, 2005).

### Further Reading

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# SLC41 family of divalent cation transporters

**Overview:** by analogy with bacterial orthologues, this family is probably magnesium transporters. The prokaryote orthologue, MgtE, is responsible for uptake of divalent cations, while the heterologous expression studies of mammalian proteins suggest  $Mg^{2+}$  efflux. Topological modelling suggests 10 TM domains with cytoplasmic C- and N- termini.

|                 |                                                                                                                           |                                                                                                   |                 |
|-----------------|---------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|-----------------|
| Systematic name | SLC41A1                                                                                                                   | SLC41A2                                                                                           | SLC41A3         |
| Ensembl ID      | ENSG00000133065                                                                                                           | ENSG00000136052                                                                                   | ENSG00000114544 |
| Substrates      | $Mg^{2+}$ , $Sr^{2+}$ , $Zn^{2+}$ , $Cu^{2+}$ , $Fe^{2+}$ , $Co^{2+}$ , $Ba^{2+}$ , $Cd^{2+}$ (Goytain and Quamme, 2005a) | $Mg^{2+}$ , $Ba^{2+}$ , $Ni^{2+}$ , $Co^{2+}$ , $Fe^{2+}$ , $Mn^{2+}$ (Goytain and Quamme, 2005b) | –               |
| Stoichiometry   | Unknown                                                                                                                   | Unknown                                                                                           | Unknown         |

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# SLC42 family of non-erythroid Rhesus glycoprotein ammonium transporters

**Overview:** Rhesus is commonly defined as a ‘factor’ that determines, in part, blood type, and whether neonates suffer from haemolytic disease of the newborn. These glycoprotein antigens derive from two genes, RHCE (ENSG00000188672) and RHD (ENSG00000187010) expressed on the surface of erythrocytes. On erythrocytes, RhAG associates with these antigens and functions as an ammonium transporter. RhBG and RhCG are non-erythroid related sequences associated with epithelia. Topological modelling suggests the presence of 12TM with cytoplasmic N- and C-termini. The majority of information on these transporters derives from orthologues in yeast, plants and bacteria. More recent evidence points to family members being permeable to carbon dioxide, leading to the term gas channels.

|                        |                                                                                                                         |                 |                                             |
|------------------------|-------------------------------------------------------------------------------------------------------------------------|-----------------|---------------------------------------------|
| Systematic name        | SLC42A1                                                                                                                 | SLC42A2         | SLC42A3                                     |
| Preferred abbreviation | RhAG                                                                                                                    | RhBG            | RhCG                                        |
| Ensembl ID             | ENSG00000112077                                                                                                         | ENSG00000132677 | ENSG00000140519                             |
| Other names            | CD241, RH50A                                                                                                            | –               | C15orf6, PDRC2, RHGK                        |
| Substrates             | $NH_3$ (Ripoche <i>et al.</i> , 2004), $NH_4^+$ (Westhoff <i>et al.</i> , 2002), $CO_2$ (Endeward <i>et al.</i> , 2008) | –               | $NH_3$ (Zidi-Yahiaoui <i>et al.</i> , 2009) |
| Probes                 | [ $^{14}C$ ]-Methylamine                                                                                                | –               | [ $^{14}C$ ]-Methylamine                    |
| Stoichiometry          | Unknown                                                                                                                 | Unknown         | Unknown                                     |

RhBG is a possible pseudogene in man.

## Further Reading

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# SLC43 family of large neutral amino acid transporters

**Overview:** LAT3 (SLC43A1) and LAT4 (SLC43A2) are transporters with system L amino acid transporter activity, along with the structurally and functionally distinct transporters LAT1 and LAT2 that are members of the SLC7 family (see Page S227). LAT3 and LAT4 contain 12 putative TM domains with both N and C termini located intracellularly. They transport neutral amino acids in a manner independent of Na<sup>+</sup> and Cl<sup>-</sup> and with two kinetic components (Babu *et al.*, 2003; Bodoy *et al.*, 2005). LAT3/SLC43A1 is expressed in human tissues at high levels in the pancreas, liver, skeletal muscle and fetal liver (Babu *et al.*, 2003) whereas LAT4/SLC43A2 is primarily expressed in the placenta, kidney and peripheral blood leukocytes (Bodoy *et al.*, 2005). SLC43A3 is expressed in vascular endothelial cells (Wallgard *et al.*, 2008) but remains to be characterised.

| Systematic name        | SLC43A1                                                                             | SLC43A2                                                          | SLC43A3         |
|------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------|-----------------|
| Preferred abbreviation | LAT3                                                                                | LAT4                                                             | –               |
| Nomenclature           | L-type amino acid transporter 3                                                     | L-type amino acid transporter 4                                  | –               |
| Other names            | Large neutral amino acids transporter 1, prostate cancer overexpressed gene 1, POV1 | –                                                                | –               |
| Ensembl ID             | ENSG00000149150                                                                     | ENSG00000167703                                                  | ENSG00000134802 |
| Substrates             | L-leucine, L-isoleucine, L-valine, L-phenylalanine, L-methionine                    | L-leucine, L-isoleucine, L-valine, L-phenylalanine, L-methionine | –               |
| Synthetic substrates   | L-leucinol, L-valinol, L-phenylalaninol                                             | L-leucinol, L-valinol                                            | –               |
| Stoichiometry          | Operates by facilitative diffusion                                                  | Operates by facilitative diffusion                               | –               |

Covalent modification of LAT3 by *N*-ethylmaleimide inhibits its function (Babu *et al.*, 2003) and at LAT4 inhibits the low-, but not high-affinity component of transport (Bodoy *et al.*, 2005).

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# SLC44 family of choline transporters

**Overview:** Members of the choline transporter-like family are encoded by five genes (CTL1-CTL5) with further diversity occurring through alternative splicing of CTL1, 4 and 5 (Traiffort *et al.*, 2005). CTL family members are putative 10TM domain proteins that mediate Na<sup>+</sup>-independent transport of choline with an affinity that is intermediate to that of the high affinity choline transporter CHT1 (SLC5A7) and the low affinity organic-cation transporters [OCT1 (SLC22A1) and OCT2 (SLC22A2)] (Michel *et al.*, 2006). CLT1 is expressed almost ubiquitously in human tissues (Wille *et al.*, 2001) and mediates choline transport across the plasma and mitochondrial membranes (Michel and Bakovic, 2009). Transport of choline by CTL2, which in rodents is expressed as two isoforms (CTL2P1 and CLTP2; Kommareddi *et al.*, 2010) in lung, colon, inner ear and spleen and to a lesser extent in brain, tongue, liver, and kidney, has only recently been demonstrated (Kommareddi *et al.*, 2010; Nakamura *et al.*, 2010). CTL3-5 remain to be characterized functionally.

| Common name          | CTL1                                                                                                                                                                                                               | CTL2                       | CTL3                       | CTL4                       | CTL5                       |
|----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|----------------------------|----------------------------|----------------------------|
| Systematic name      | SLC44A1                                                                                                                                                                                                            | SLC44A2                    | SLC44A3                    | SLC44A4                    | SLC44A5                    |
| Nomenclature         | Choline transporter-like 1                                                                                                                                                                                         | Choline transporter-like 2 | Choline transporter-like 3 | Choline transporter-like 4 | Choline transporter-like 5 |
| Other names          | CHTL1, CDW92                                                                                                                                                                                                       | –                          | –                          | –                          | –                          |
| Ensembl ID           | ENSG00000070214                                                                                                                                                                                                    | ENSG00000129353            | ENSG00000143036            | ENSG00000204385            | ENSG00000137968            |
| Substrates           | Choline                                                                                                                                                                                                            | Choline                    | –                          | –                          | –                          |
| Synthetic substrates | –                                                                                                                                                                                                                  | –                          | –                          | –                          | –                          |
| Inhibitors (pK)      | HC-3 (4.5–5.3)                                                                                                                                                                                                     | –                          | –                          | –                          | –                          |
| Stoichiometry        | Unknown: uptake enhanced in the absence of extracellular Na <sup>+</sup> , reduced by membrane depolarization, extracellular acidification and collapse of plasma membrane H <sup>+</sup> electrochemical gradient | –                          | –                          | –                          | –                          |

Data tabulated are features observed for CLT1 endogenous to: rat astrocytes (Inazu *et al.*, 2005); rat renal tubule epithelial cells (Yabuki *et al.*, 2009); human colon carcinoma cells (Kouji *et al.*, 2009); human keratinocytes (Uchida *et al.*, 2009) and human neuroblastoma cells (Yamada *et al.*, 2011). Choline uptake by CLT1 is inhibited by numerous organic cations (*e.g.* Inazu *et al.*, 2005; Yabuki *et al.*, 2009; Yamada *et al.*, 2011). In the guinea-pig, CTL2 is a target for antibody-induced hearing loss (Nair *et al.*, 2004) and in man a polymorphism in CTL2 constitutes the human neutrophil alloantigen-3a (HNA-3a; Greinacher *et al.*, 2010).

**Abbreviations:** HC-3, hemicholinium 3

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## SLC45 orphans

**Overview:** Members of the SLC45 family remain to be functionally characterised. However, the *SLC45A2* gene is thought to encode a transporter protein that mediates melanin synthesis. Mutations in *SLC45A2* are a cause of oculocutaneous albinism type 4 (*e.g.* Newton *et al.*, 2001), and polymorphisms in this gene are associated with variations in skin and hair color (*e.g.* Graf *et al.*, 2005).

| Systematic name | SLC45A1         | SLC45A2                                             | SLC45A3                                                         | SLC45A4         |
|-----------------|-----------------|-----------------------------------------------------|-----------------------------------------------------------------|-----------------|
| Other names     | DNB5            | Melanin associated transporter protein (MATP), AIM1 | Prostate cancer associated protein 6 (PCANAP6), prostein (PRST) | –               |
| Ensembl ID      | ENSG00000162426 | ENSG00000164175                                     | ENSG00000158715                                                 | ENSG00000022567 |

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## SLC46 family of folate transporters

**Overview:** Based on the prototypical member of this family, PCFT, this family are proton-driven transporters with 11 TM segments. SLC46A1 has been described to act as an intestinal proton-coupled high-affinity folate transporter (Qiu *et al.*, 2006), with lower affinity for haem. Folate accumulation is independent of Na<sup>+</sup> or K<sup>+</sup> ion concentrations, but driven by extracellular protons with an as-yet undefined stoichiometry.

|                        |                                                                                                   |                               |                 |
|------------------------|---------------------------------------------------------------------------------------------------|-------------------------------|-----------------|
| Systematic name        | SLC46A1                                                                                           | SLC46A2                       | SLC46A3         |
| Preferred abbreviation | PCFT                                                                                              | TSCOT                         | –               |
| Nomenclature           | Proton-coupled folate transporter                                                                 | Thymic stromal co-transporter | –               |
| Ensembl ID             | ENSG00000076351                                                                                   | ENSG00000119457               | ENSG00000139508 |
| Other names            | Heme carrier protein-1, HCP-1                                                                     | –                             | –               |
| Substrates             | Folate (1.3 µM) > haem (>100 µM, Nakai <i>et al.</i> , 2007)                                      | –                             | –               |
| Synthetic substrates   | Methotrexate (Qiu <i>et al.</i> , 2006), folinic acid (Nakai <i>et al.</i> , 2007)                | –                             | –               |
| Inhibitors             | Sulfasalazine (60 µM, Qiu <i>et al.</i> , 2006), indomethacin (~200 µM, Qiu <i>et al.</i> , 2006) | –                             | –               |
| Probes                 | [ <sup>3</sup> H]-folate, [ <sup>3</sup> H]-methotrexate                                          | –                             | –               |

Loss-of-function mutations in PCFT (SLC46A1) are associated with hereditary folate malabsorption.

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 Qiu A *et al.* (2006). *Cell* **127**: 917–928.

## SLC47 family of multidrug and toxin extrusion transporters

**Overview:** these proton:organic cation exchangers are predicted to have 13 TM segments (Zhang and Wright, 2009) and are suggested to be responsible for excretion of many drugs in the liver and kidneys.

|                        |                                                                                                                                                 |                                                                                                                                                                                          |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Systematic name        | SLC47A1                                                                                                                                         | SLC47A2                                                                                                                                                                                  |
| Preferred abbreviation | MATE1                                                                                                                                           | MATE2-K                                                                                                                                                                                  |
| Nomenclature           | Multi antimicrobial extrusion protein                                                                                                           |                                                                                                                                                                                          |
| Other names            | Multidrug and toxin extrusion protein 1                                                                                                         |                                                                                                                                                                                          |
| Ensembl ID             | ENSG00000142494                                                                                                                                 | ENSG00000180638                                                                                                                                                                          |
| Synthetic substrates   | Cimetidine (Ohta <i>et al.</i> , 2006), cephalexin, cephradine, quinidine (Tanihara <i>et al.</i> , 2007), paraquat (Chen <i>et al.</i> , 2007) | Cimetidine, 1-methyl-4-phenylpyridinium, procainamide, metformin, N <sup>1</sup> -methylnicotinamide (Masuda <i>et al.</i> , 2006), guanidine, acyclovir (Tanihara <i>et al.</i> , 2007) |
| Inhibitors             | Pyrimethamine (0.15 µM, Ito <i>et al.</i> , 2010)                                                                                               |                                                                                                                                                                                          |
| Probes                 | [ <sup>14</sup> C]-TEA (Otsuka <i>et al.</i> , 2005), [ <sup>14</sup> C]-metformin (Tanihara <i>et al.</i> , 2007)                              | [ <sup>14</sup> C]-TEA (Tanihara <i>et al.</i> , 2007)                                                                                                                                   |

DAPI has been used to allow quantification of MATE1 and MATE2-mediated transport activity (Yasujima *et al.*, 2010).

**Abbreviations:** DAPI, 4',6-diamidino-2-phenylindole; MPP, 1-methyl-4-phenylpyridinium

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## SLC48 haem transporter

**Overview:** although identified as a heme transporter (Rajagopal *et al.*, 2008), subsequent evidence suggests this 4TM-containing protein associates with the V-type ATPase (see Page S218) in lysosomes for haem degradation (O'Callaghan *et al.*, 2010). As yet, this transporter awaits characterization.

|                        |                                |
|------------------------|--------------------------------|
| Systematic name        | SLC48A1                        |
| Preferred abbreviation | HRG1                           |
| Nomenclature           | Heme transporter               |
| Ensembl ID             | ENSG00000211584                |
| Other names            | Heme-responsive gene 1, hHRG-1 |

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## SLCO family of organic anion transporting polypeptides

**Overview:** The SLCO superfamily is comprised of the organic anion transporting polypeptides (OATPs). The 11 human OATPs are divided into 6 families and ten subfamilies based on amino acid identity. These proteins are located on the plasma membrane of cells throughout the body. They have 12 TM domains and intracellular termini, with multiple putative glycosylation sites. OATPs mediate the sodium-independent uptake of a wide range of amphiphilic substrates, including many drugs and toxins. Due to the multispecificity of these proteins, this guide lists classes of substrates and inhibitors for each family member. More comprehensive lists of substrates, inhibitors, and their relative affinities may be found in the review articles listed below.

|                       |                                                                                                                                                                     |                                                                                                                                                                                                                                 |                                                                                                                                                                                                            |                                                                                           |
|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Nomenclature          | OATP1A2                                                                                                                                                             | OATP1B1                                                                                                                                                                                                                         | OATP1B3                                                                                                                                                                                                    | OATP1C1                                                                                   |
| HGNC nomenclature     | SLCO1A2                                                                                                                                                             | SLCO1B1                                                                                                                                                                                                                         | SLCO1B3                                                                                                                                                                                                    | SLCO1C1                                                                                   |
| Ensembl ID            | ENSG00000084453                                                                                                                                                     | ENSG00000134538                                                                                                                                                                                                                 | ENSG00000111700                                                                                                                                                                                            | ENSG00000139155                                                                           |
| Other names           | OATP, OATP-A, SLC21A3                                                                                                                                               | OATP-C, OATP2, LST-1, SLC21A6                                                                                                                                                                                                   | OATP8, LST-2, SLC21A8                                                                                                                                                                                      | OATP-F, OATP1, SLC21A14, OATP14                                                           |
| Endogenous substrates | Bile acids, bilirubin, BSP, steroid conjugates, thyroid hormones                                                                                                    | Bile acids, bilirubin, BSP, leukotrienes, steroid conjugates, thyroid hormones                                                                                                                                                  | Bile acids, bilirubin, BSP, CCK-8, leukotriene C4, steroid conjugates, thyroid hormones                                                                                                                    | Thyroid hormones, steroid conjugates, BSP                                                 |
| Exogenous substrates  | Antibiotics, anticancer drugs, beta blockers, deltorphin II, fexofenadine, fluoroquinolones, HIV protease inhibitors, microcystin, ouabain, rosuvastatin, talinolol | ACE inhibitors, anticancer drugs, antifungals, $\beta$ -lactam antibiotics, bile acid derivatives and conjugates, endothelin receptor antagonists, fexofenadine, HIV protease inhibitors, opioids, rifampicin, sartans, statins | Amanitin, anticancer drugs, $\beta$ -lactam antibiotics, bile acid derivatives and conjugates, digoxin, erythromycin, fexofenadine, opioids, ouabain, phalloidin, rifampicin, saquinavir, sartans, statins | Statins                                                                                   |
| Inhibitors            | Naringin, rifampicin, rifamycin SV                                                                                                                                  | Cyclosporine A, fibrates, flavonoids, gemfibrozil, glitazones, glycyrrhizin, indocyanine green, macrolide antibiotics, rifampicin, rifamycin SV, sildenafil                                                                     | Cyclosporine A, gemfibrozil, glitazones, glycyrrhizin, HIV protease inhibitors, macrolide antibiotics, rifampicin, rifamycin SV, sildenafil                                                                | Probenicid, taurocholate, DPDPE                                                           |
| Common probes         | [ <sup>3</sup> H]-BSP, [ <sup>3</sup> H]-DPDPE, [ <sup>3</sup> H]-estrone-3-sulfate                                                                                 | [ <sup>3</sup> H]-estradiol-17 $\beta$ -glucuronide, [ <sup>3</sup> H]-estrone-3-sulfate, pravastatin                                                                                                                           | [ <sup>3</sup> H]-BSP, [ <sup>3</sup> H]-CCK-8, [ <sup>3</sup> H]-estradiol-17 $\beta$ -glucuronide                                                                                                        | [ <sup>125</sup> I]-thyroxine, [ <sup>3</sup> H]-BSP, [ <sup>3</sup> H]-estrone-3-sulfate |

|                       |                                                |                                                                                               |                                                                                     |
|-----------------------|------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Nomenclature          | OATP2A1                                        | OATP2B1                                                                                       | OATP3A1                                                                             |
| HGNC nomenclature     | SLCO2A1                                        | SLCO2B1                                                                                       | SLCO3A1                                                                             |
| Ensembl ID            | ENSG00000174640                                | ENSG00000137491                                                                               | ENSG00000176463                                                                     |
| Other names           | PGT, SLC21A2                                   | OATP-B, SLC21A9                                                                               | OATP-D, SLC21A11                                                                    |
| Endogenous substrates | Prostaglandins, eicosanoids                    | BSP, DHEAS, estrone-3-sulfate, thyroxine                                                      | Prostaglandins, thyroid hormones, BQ123, vasopressin                                |
| Exogenous substrates  | Synthetic prostaglandin derivatives            | Aliskiren, amiodarone, bosentan, fexofenadine, glibenclamide, statins, talinolol, telmisartan | –                                                                                   |
| Inhibitors            | Bromocresol green, BSP, NSAIDs                 | Citrus juices, gemfibrozil, glitazones, glyburide, rifamycin SV, rifampicin                   | –                                                                                   |
| Common probes         | [ <sup>3</sup> H]-prostaglandin E <sub>2</sub> | [ <sup>3</sup> H]-BSP, [ <sup>3</sup> H]-estrone-3-sulfate                                    | [ <sup>3</sup> H]-estrone-3-sulfate, [ <sup>3</sup> H]-prostaglandin E <sub>2</sub> |

|                       |                                                                  |                                                                         |                 |                                                     |
|-----------------------|------------------------------------------------------------------|-------------------------------------------------------------------------|-----------------|-----------------------------------------------------|
| Nomenclature          | OATP4A1                                                          | OATP4C1                                                                 | OATP5A1         | OATP6A1                                             |
| HGNC nomenclature     | SLCO4A1                                                          | SLCO4C1                                                                 | SLCO5A1         | SLCO6A1                                             |
| Ensembl ID            | ENSG00000101187                                                  | ENSG00000173930                                                         | ENSG00000137571 | ENSG00000205359                                     |
| Other names           | OATP-E, SLC21A12                                                 | SLC21A20, OATPX, OATP-H, OATP-M1                                        | OATPRP4, OATP-J | OATPY, MGC26949, OATP-I, gonad specific transporter |
| Endogenous substrates | Steroid conjugates, thyroid hormones, prostaglandins, bile acids | Thyroid hormones, steroid conjugates, cAMP                              | –               | –                                                   |
| Exogenous substrates  | Benzylpenicillin                                                 | Cardiac glycosides, anticancer drugs, dipeptidyl peptidase-4 inhibitors | –               | –                                                   |
| Common probes         | [ <sup>3</sup> H]-estrone-3-sulfate                              | [ <sup>3</sup> H]-digoxin                                               | –               | –                                                   |

**Abbreviations:** BSP, bromosulfophthalein; CCK-8, Cholecystokinin octapeptide; DHEAS, dehydroepiandrosterone-3-sulfate; DPDPE, [d-Pen2,d-Pen5]-Enkephalin; PGT, prostaglandin transporter

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# ENZYMES

Enzymes are protein catalysts facilitating the conversion of substrates into products. The Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (NC-IUBMB) classifies enzymes into families, using a four number code, on the basis of the reactions they catalyse. There are six main families: EC 1.-.-.- Oxidoreductases; EC 2.-.-.- Transferases; EC 3.-.-.- Hydrolases; EC 4.-.-.- Lyases; EC 5.-.-.- Isomerases; EC 6.-.-.- Ligases.

Many enzymes require additional entities for functional activity. Some of these are used in the catalytic steps, while others promote a particular conformational change. Co-factors are tightly bound to the enzyme and include metal ions and heme groups. Co-enzymes are typically small molecules which accept or donate functional groups to assist in the enzymatic reaction. Examples include ATP, NAD, NADP and S-adenosylmethionine, as well as a number of vitamins, such as riboflavin (vitamin B1) and thiamine (vitamin B2).

The majority of drugs which act on enzymes act as inhibitors; one exception is metformin, which appears to stimulate activity of AMP-activated protein kinase, albeit through an imprecisely-defined mechanism. Kinetic assays allow discrimination of competitive, non-competitive and un-competitive inhibitors. The majority of inhibitors are competitive (acting at the enzyme's ligand recognition site), non-competitive (acting at a distinct site; potentially interfering with co-factor or co-enzyme binding) or of mixed type. One rare example of an uncompetitive inhibitor is lithium ions, which are effective inhibitors at inositol monophosphatase only in the presence of high substrate concentrations. Some inhibitors are irreversible, including a group known as suicide substrates, which bind to the ligand recognition site and then couple covalently to the enzyme.

Although there are many more enzymes than receptors in biology, and many drugs that target prokaryotic enzymes are effective medicines, overall the number of enzyme drug targets is relatively small (Overington *et al.*, 2006), which is not to say that they are of modest importance.

## Further Reading

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# Adenosine turnover

**Overview:** Adenosine is a multifunctional, ubiquitous molecule that acts at cell-surface G protein-coupled receptors, as well as numerous enzymes, including protein kinases and adenylyl cyclase. Extracellular adenosine is thought to be produced either by export or by metabolism, predominantly through ecto-5'-nucleotidase activity (also producing inorganic phosphate). It is inactivated either by extracellular metabolism *via* adenosine deaminase (also producing ammonia) or, following uptake by nucleoside transporters, *via* adenosine deaminase or adenosine kinase (requiring ATP as co-substrate). Intracellular adenosine may be produced by cytosolic 5'-nucleotidases or through S-adenosylhomocysteine hydrolase (also producing homocysteine).

| Nomenclature                       | Adenosine deaminase                | Adenosine kinase                                                                           | Ecto-5'-Nucleotidase                              | S-Adenosylhomocysteine hydrolase                        |
|------------------------------------|------------------------------------|--------------------------------------------------------------------------------------------|---------------------------------------------------|---------------------------------------------------------|
| E.C.                               | 3.5.4.4                            | 2.7.1.20                                                                                   | 3.1.3.5                                           | 3.3.1.1                                                 |
| Preferred abbreviation             | ADA                                | ADK                                                                                        | NT5E                                              | SAHH                                                    |
| Ensembl ID                         | ENSG00000196839                    | ENSG00000156110                                                                            | ENSG00000135318                                   | ENSG00000101444                                         |
| Other names                        | Adenosine aminohydrolase, ADA1     | –                                                                                          | CD73, 5'-NT                                       | Adenosylhomocysteinase                                  |
| Rank order of affinity             | 2'-Deoxyadenosine $\geq$ adenosine | Adenosine                                                                                  | 5'-AMP, 5'-GMP, 5'-IMP, 5'-UMP > 5'-dAMP, 5'-dGMP | S-Adenosylhomocysteine                                  |
| Nucleoside products                | 2'-Deoxyinosine, inosine           | 5'-AMP                                                                                     | Adenosine, guanine, inosine, uridine              | Adenosine                                               |
| Selective inhibitors ( $IC_{50}$ ) | EHNA, 2'-deoxycoformycin           | A134974 (10.2, McGaraghty <i>et al.</i> , 2001), ABT702 (8.8, Jarvis <i>et al.</i> , 2000) | $\alpha\beta$ -methyleneADP                       | 3-Deazaadenosine (8.5, Guranowski <i>et al.</i> , 1981) |

An extracellular adenosine deaminase activity, termed ADA2 or adenosine deaminase growth factor (ADGF, CECR1, ENSG00000093072) has been identified (see Maier *et al.*, 2005), which is insensitive to EHNA (Zavialov *et al.*, 2010). Other forms of adenosine deaminase act on ribonucleic acids and may be divided into two families: ADAT1 (ENSG00000065457) deaminates transfer RNA; ADAR (EC 3.5.4.-, ENSG00000160710, also known as 136 kDa double-stranded RNA-binding protein, P136, K88DSRBP, Interferon-inducible protein 4); ADARB1 (EC 3.5.-.-, ENSG00000197381, also known as dsRNA adenosine deaminase) and ADARB2 (EC 3.5.-.-, ENSG00000185736, also known as dsRNA adenosine deaminase B2, RNA-dependent adenosine deaminase 3) act on double-stranded RNA. Particular polymorphisms of the ADA gene result in loss-of-function and severe combined immunodeficiency syndrome. Adenosine deaminase is able to complex with dipeptidyl peptidase IV (EC 3.4.14.5, ENSG00000197635, also known as T-cell activation antigen CD26, TP103, adenosine deaminase complexing protein 2) to form a cell-surface activity (Kameoka *et al.*, 1993).

## Other 5'-nucleotidases

| Nomenclature         | HGNC nomenclature | Ensembl ID      |
|----------------------|-------------------|-----------------|
| IA                   | NT5C1A            | ENSG00000116981 |
| IB                   | NT5C1B            | ENSG00000185013 |
| II                   | NT5C2             | ENSG00000076685 |
| III                  | NT5C3             | ENSG00000122643 |
| 5'(3')-nucleotidases | NT5C              | ENSG00000125458 |
| Mitochondrial        | NT5M              | ENSG00000205309 |

**Abbreviations:** 5'-AMP, adenosine 5'-monophosphate; 5'NT, 5'-nucleotidase; A134974,  $N^7$ -[(1'R,2'S,3' R,4'S)-2',3'-dihydroxy-4'-aminocyclopentyl]-4-amino-5-iodopyrrolopyrimidine; ABT702, 4-amino-5-(3-bromophenyl)-7-(6-morpholinopyridin-3-yl)pyrido[2,3-d]pyrimidine; ADA, adenosine deaminase; ADK, adenosine kinase, EHNA, *erythro*-9-(2-hydroxy-3-nonyl)adenine hydrochloride;

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# Amino acid hydroxylases (E.C.1.14.16.-)

**Overview:** The amino acid hydroxylases (monooxygenases) are iron-containing enzymes which utilise molecular oxygen and tetrahydrobiopterin as co-substrate and co-factor, respectively.

|                        |                                                                      |                                                                                                   |                                                                                          |
|------------------------|----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| Nomenclature           | L-Phenylalanine hydroxylase                                          | L-Tryptophan hydroxylase                                                                          | L-Tyrosine hydroxylase                                                                   |
| E.C.                   | 1.14.16.1                                                            | 1.14.16.4                                                                                         | 1.14.16.2                                                                                |
| Preferred abbreviation | PH                                                                   | TPH                                                                                               | TH                                                                                       |
| Ensembl ID             | ENSG00000171759                                                      | TPH1 ENSG00000129167;<br>TPH2 ENSG00000139287                                                     | ENSG00000180176                                                                          |
| Other names            | Phenylalanine 4-monooxygenase                                        | Tryptophan 5-monooxygenase                                                                        | Tyrosine 3-monooxygenase                                                                 |
| Product                | Tyrosine                                                             | 5-Hydroxytryptophan                                                                               | DOPA                                                                                     |
| Selective inhibitors   | $\alpha$ -Methylphenylalanine (Greengard <i>et al.</i> , 1976), PCPA | Fenfluramine, PCPA, $\alpha$ -propyldopacetamide, 6-fluorotryptophan (Nicholson and Wright, 1981) | 3-Chlorotyrosine, 3-iodotyrosine, $\alpha$ -methyltyrosine, $\alpha$ -propyldopacetamide |

**Abbreviations:** DOPA, 3,4-dihydroxyphenylalanine; PCPA, 4-chlorophenylalanine

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# L-Arginine turnover

**Overview:** L-arginine is a basic amino acid with a guanidino sidechain. As an amino acid, metabolism of L-arginine to form L-ornithine, catalysed by arginase, forms the last step of the urea production cycle. L-Ornithine may be utilised as a precursor of polyamines (see Carboxylases and Decarboxylases, Page S286) or recycled via L-arginosuccinate to L-arginine. L-Arginine may itself be decarboxylated (see Page S286) to form agmatine, although the prominence of this pathway in human tissues is uncertain. L-Arginine may be used as a precursor for guanidinoacetate formation in the creatine synthesis pathway under the influence of arginine:glycine amidinotransferase with L-ornithine as a byproduct. Nitric oxide synthase uses L-arginine to generate nitric oxide, with L-citrulline also as a byproduct.

L-Arginine in proteins may be subject to post-translational modification through methylation, catalysed by protein arginine methyltransferases. Subsequent proteolysis can liberate asymmetric  $N^G,N^G$ -dimethyl-L-arginine (ADMA), which is an endogenous inhibitor of nitric oxide synthase activities. ADMA is hydrolysed by dimethylarginine dimethylhydrolase activities to generate L-citrulline and dimethylamine.

**Arginase** (EC 3.5.3.1) are manganese-containing isoforms, which appear to show differential distribution, where the ARG1 isoform predominates in the liver and erythrocytes, while ARG2 is associated more with the kidney.

| Nomenclature           | Arginase I                         | Arginase II            |
|------------------------|------------------------------------|------------------------|
| Preferred abbreviation | ARG1                               | ARG2                   |
| Ensembl ID             | ENSG00000118520                    | ENSG00000081181        |
| Other names            | Liver arginase, cytosolic arginase | Mitochondrial arginase |

$N^w$ -Hydroxyarginine, an intermediate in NOS metabolism of L-arginine acts as a weak inhibitor and may function as a physiological regulator of arginase activity. Although isoform-selective inhibitors of arginase are not available, examples of inhibitors selective for arginase compared to NOS are  $N^w$ -hydroxy-nor-L-arginine (Tenu *et al.*, 1999), S-(2-boronoethyl)-L-cysteine (Colleluori and Ash, 2001; Kim *et al.*, 2001) and 2(S)-amino-6-boronoheptanoic acid (Baggio *et al.*, 1999; Colleluori and Ash, 2001).

**Arginine:glycine amidinotransferase** (AGAT, E.C. 2.1.4.1)

| Nomenclature           | Arginine:glycine amidinotransferase |
|------------------------|-------------------------------------|
| Preferred abbreviation | AGAT                                |
| Ensembl ID             | ENSG00000171766                     |
| Other names            | GATM, glycine amidinotransferase    |

**Dimethylarginine dimethylaminohydrolases** (DDAH, EC 3.5.3.18) are cytoplasmic enzymes which hydrolyse  $N^G,N^G$ -dimethyl-L-arginine to form dimethylamine and L-citrulline.

| Nomenclature           | $N^G,N^G$ -Dimethylarginine dimethylaminohydrolase 1                   | $N^G,N^G$ -Dimethylarginine dimethylaminohydrolase 2                                                  |
|------------------------|------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Preferred abbreviation | DDAH1                                                                  | DDAH2                                                                                                 |
| Ensembl ID             | ENSG00000153904                                                        | ENSG00000213722                                                                                       |
| Other names            | Dimethylarginine dimethylaminohydrolase 1, DDAH1, dimethylargininase-1 | Dimethylarginine dimethylaminohydrolase 2, DDAHII, dimethylargininase-2, S-phase protein, protein G6a |
| Cofactor               | $Zn^{2+}$                                                              | –                                                                                                     |

**Nitric oxide synthases** (NOS, E.C. 1.14.13.39) utilise L-arginine (not D-arginine) and molecular oxygen to generate nitric oxide and L-citrulline. The nomenclature suggested by NC-IUPHAR of NOS I, II and III (see Moncada *et al.*, 1997) has not gained wide acceptance. eNOS and nNOS isoforms are activated at concentrations of calcium greater than 100 nM, while iNOS shows higher affinity for  $Ca^{2+}$ /calmodulin and thus appears to be constitutively active. All the three isoforms are homodimers and require tetrahydrobiopterin, flavin adenine dinucleotide, flavin mononucleotide and NADPH for catalytic activity. L-NAME is an inhibitor of all three isoforms, with an  $IC_{50}$  value in the micromolar range.

| Nomenclature           | Endothelial NOS       | Inducible NOS                                                                                                                                                                                                                       | Neuronal NOS                                                                                |
|------------------------|-----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Preferred abbreviation | eNOS                  | iNOS                                                                                                                                                                                                                                | nNOS                                                                                        |
| Ensembl ID             | ENSG00000164867       | ENSG00000007171                                                                                                                                                                                                                     | ENSG00000089250                                                                             |
| Other names            | NOS III, NOS-3, ecNOS | NOS II, NOS-2                                                                                                                                                                                                                       | NOS I, NOS-1, brain NOS                                                                     |
| Selective inhibitors   | –                     | 1400W (8.2, Garvey <i>et al.</i> , 1997), 2-amino-4-methylpyridine (7.4, Faraci <i>et al.</i> , 1996), PIBTU (7.3, Garvey <i>et al.</i> , 1994), NIL (5.5, Moore <i>et al.</i> , 1994), aminoguanidine (Corbett and McDaniel, 1992) | 3-Bromo-7NI (6.1–6.5, Bland-Ward and Moore, 1995), 7NI (5.3, Babbedge <i>et al.</i> , 1993) |

The reductase domain of NOS catalyses the reduction of cytochrome *c* and other redox-active dyes (Mayer and Hemmens, 1997). NADPH:O<sub>2</sub> oxidoreductase catalyses the formation of superoxide anion/H<sub>2</sub>O<sub>2</sub> in the absence of arginine and tetrahydrobiopterin.

**Protein arginine N-methyltransferases** (PRMT, EC 2.1.1.-) encompass histone arginine N-methyltransferases (PRMT4, PRMT7, EC 2.1.1.125) and myelin basic protein N-methyltransferases (PRMT7, EC 2.1.1.126). They are dimeric or tetrameric enzymes which use S-adenosyl-L-methionine as a methyl donor, generating S-adenosyl-L-homocysteine as a by-product. They generate both mono-methylated and di-methylated products; these may be symmetric (SDMA) or asymmetric (ADMA) versions, where both guanidine nitrogens are monomethylated or one of the two is dimethylated, respectively.

| Nomenclature | Ensembl ID      | Other names                                                                                                                             |
|--------------|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| PRMT1        | ENSG00000126457 | Interferon receptor 1-bound protein 4, ANM1, HCP1, HRMT1L2                                                                              |
| PRMT2        | ENSG00000160310 | –                                                                                                                                       |
| PRMT3        | ENSG00000185238 | Heterogeneous nuclear ribonucleoprotein methyltransferase-like protein 3                                                                |
| PRMT4        | ENSG00000142453 | Histone-arginine methyltransferase CARM1, coactivator-associated arginine methyltransferase 1                                           |
| PRMT5        | ENSG00000100462 | Histone-arginine N-methyltransferase, Shk1 kinase-binding protein 1 homolog, SKB1Hs, Jak-binding protein 1, 72 kDa ICLN-binding protein |
| PRMT6        | ENSG00000198890 | Heterogeneous nuclear ribonucleoprotein methyltransferase-like protein 6                                                                |
| PRMT7        | ENSG00000132600 | Histone-arginine N-methyltransferase, myelin basic protein-arginine N-methyltransferase                                                 |
| PRMT8        | ENSG00000111218 | Heterogeneous nuclear ribonucleoprotein methyltransferase-like protein 4                                                                |
| PRMT9        | ENSG00000138081 | FBXO11, F-box only protein 11, vitiligo-associated protein 1, VIT-1                                                                     |
| PRMT10       | ENSG00000164169 | TPR repeat-containing protein LOC90826                                                                                                  |

A related gene has been described, CARMIL (Coactivator associated arginine methyltransferase 1-like fragment, ENSG00000227835).

**Abbreviations:** 1400W, N-(3-(aminomethyl) benzyl)acetamidine; ADMA, asymmetric dimethylarginine; DDAH, dimethylarginine dimethylaminohydrolase; NADPH, reduced nicotinamide adenosine dinucleotide phosphate; 7NI, 7-nitroindazole; NIL, L-N<sup>6</sup>-(1-iminoethyl)lysine; NOS, nitric oxide synthase; PIBTU, 13-phenylen-bis(1,2-ethanediy)bis-thiourea; PRMT, protein arginine methyltransferase; SDMA, symmetric dimethylarginine

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# Carboxylases and decarboxylases

**Carboxylases:** The carboxylases allow the production of new carbon-carbon bonds by introducing  $\text{HCO}_3^-$  or  $\text{CO}_2$  into target molecules. Two groups of carboxylase activities, some of which are bidirectional, can be defined on the basis of the cofactor requirement, making use of biotin (EC 6.4.1.-) or vitamin K (EC 4.1.1.-).

| Nomenclature           | Pyruvate carboxylase              | Acetyl-CoA carboxylase                      | Propionyl-CoA carboxylase              | $\gamma$ -Glutamyl carboxylase |
|------------------------|-----------------------------------|---------------------------------------------|----------------------------------------|--------------------------------|
| E.C.                   | 6.4.1.1                           | 6.4.1.2                                     | 6.4.1.3                                | 4.1.1.90                       |
| Preferred abbreviation | PC                                | ACC1, ACC2                                  | PCCA, PCCB                             | GGCX                           |
| Ensembl ID             | ENSG0000017359                    | ENSG00000132142,<br>ENSG00000076555         | ENSG00000175198<br>ENSG00000114054     | ENSG00000115486                |
| Other names            | PCB                               | ACACA, ACC $\alpha$ ;<br>ACACB, ACC $\beta$ | PCC $\alpha$ ,<br>PCC $\beta$          | –                              |
| Cofactors              | Biotin                            | Biotin                                      | Biotin                                 | Vitamin K, NADPH               |
| Substrate(s)           | Pyruvate, ATP                     | Acetyl-CoA, ATP                             | Propionyl-CoA, ATP                     | Glutamyl peptides              |
| Product(s)             | Oxaloacetate, ADP, P <sub>i</sub> | Malonyl-CoA, ADP, P <sub>i</sub>            | Methylmalonyl-CoA, ADP, P <sub>i</sub> | Carboxyglutamyl (Gla) peptides |
| Selective inhibitors   | –                                 | TOFA (Loftus <i>et al.</i> , 2000)          | –                                      | –                              |

Citrate and other dicarboxylic acids are able to activate ACC1/ACC2 activity allosterically. PCC is able to function in forward and reverse modes as a ligase (carboxylase) or lyase (decarboxylase) activity, respectively. Loss-of-function mutations in GGCX are associated with clotting disorders.

**Decarboxylases:** The decarboxylases generate  $\text{CO}_2$  and the indicated products from acidic substrates, requiring pyridoxal phosphate (ADC, AADC, GAD, HDC, ODC and PSDC) or pyruvate (SAMDC and PSDC) as a co-factor.

| Nomenclature           | S-Adenosylmethionine decarboxylase               | L-Arginine decarboxylase                                        | L-Aromatic amino-acid decarboxylase                         | Glutamic acid decarboxylase         |
|------------------------|--------------------------------------------------|-----------------------------------------------------------------|-------------------------------------------------------------|-------------------------------------|
| E.C.                   | 4.1.1.50                                         | 4.1.1.19                                                        | 4.1.1.28                                                    | 4.1.1.15                            |
| Preferred abbreviation | SAMDC                                            | ADC                                                             | AADC                                                        | GAD                                 |
| Ensembl ID             | ENSG00000123505                                  | ENSG00000142920                                                 | ENSG00000132437                                             | ENSG00000128683,<br>ENSG00000136750 |
| Other names            | –                                                | Ornithine decarboxylase-like protein (Zhu <i>et al.</i> , 2004) | DOPA decarboxylase (DDC), 5-hydroxytryptophan decarboxylase | GAD1 (GAD65), GAD2 (GAD67)          |
| Substrate(s)           | S-Adenosylmethionine                             | L-Arginine                                                      | DOPA, L-tryptophan, 5-hydroxy-L-tryptophan                  | L-Glutamate, L-aspartate            |
| Product(s)             | 5'-Deoxyadenosyl-(3-aminopropyl) methylsulfonium | Agmatine                                                        | 5-Hydroxytryptophan, dopamine                               | GABA                                |

The presence of a functional ADC activity in human tissues has been questioned (Coleman *et al.*, 2004). *s*-Allylglycine is also an inhibitor of SAMDC (Pajunen *et al.*, 1979).

| Nomenclature           | Histidine decarboxylase                         | Malonyl-CoA decarboxylase                                                       | Ornithine decarboxylase                                                   | Phosphatidylserine decarboxylase |
|------------------------|-------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------|----------------------------------|
| E.C.                   | 4.1.1.22                                        | 4.1.1.9                                                                         | 4.1.1.17                                                                  | 4.1.1.65                         |
| Preferred abbreviation | HDC                                             | MLYCD                                                                           | ODC                                                                       | PSDC                             |
| Ensembl ID             | ENSG00000140287                                 | ENSG00000103150                                                                 | ENSG00000115758                                                           | ENSG00000100141                  |
| Substrate(s)           | L-Histidine                                     | Malonyl-CoA                                                                     | L-Ornithine                                                               | Phosphatidylserine               |
| Product                | Histamine                                       | Acetyl-CoA                                                                      | Putrescine                                                                | Phosphatidylethanolamine         |
| Selective inhibitors   | FMH (Garbarg <i>et al.</i> , 1980)              | AMP-activated protein kinase-evoked phosphorylation (Saha <i>et al.</i> , 2000) | DFMO, APA                                                                 | –                                |
| Selective inhibitors   | SAM486A (8.0; Stanek <i>et al.</i> , 1993), AMA | –                                                                               | Benserazide, carbidopa, 3-hydroxybenzylhydrazine, L- $\alpha$ -methyldopa | S-Allylglycine                   |

The activity of ODC is regulated by the presence of an antizyme (ENSF00000002504) and an ODC antizyme inhibitor (ENSF00000002504).

**Abbreviations:** AMA, S-(5'-deoxy-5'-adenosyl)-methylthioethyl-hydroxylamine; APA, 1-aminooxy-3-aminopropane; DFMO,  $\alpha$ -difluoromethyl-L-ornithine, also known as eflornithine; FMH,  $\alpha$ -fluoromethylhistidine; SAM, S-adenosylmethionine; SAM486A, 1-guanidinoimino-2,3-dihydroindene-4-carboximidamide, also known as CGP48664; TOFA, 5-(tetradecyloxy)-2-furancarboxylic acid

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# Cyclic nucleotide turnover

**Overview:** cyclic nucleotides are second messengers generated by cyclase enzymes from precursor triphosphates and hydrolysed by phosphodiesterases. The cellular actions of these cyclic nucleotides are mediated through activation of protein kinases (cAMP- and cGMP-dependent protein kinases, see page S310), ion channels (cyclic nucleotide-gated, CNG, and hyperpolarization and cyclic nucleotide-gated, HCN, see Pages S153 & S156) and guanine nucleotide exchange factors (GEFs, Epac).

## Adenylyl cyclases (E.C. 4.6.1.1)

**Overview:** Adenylyl cyclase (ENSG00000000188) converts 5'-ATP to 3',5'-adenosine monophosphate and pyrophosphate. Mammalian membrane-bound adenylyl cyclases are typically made up of two clusters of six TM domains separating two intracellular, overlapping catalytic domains that are the target for the nonselective activators forskolin, NKH477 (except AC9, Premont *et al.*, 1996) and  $G\alpha_s$  (the stimulatory G protein  $\alpha$  subunit, see Page S5). Adenosine and its derivatives (e.g. 2',5'-dideoxyadenosine), acting through the P-site, appear to be physiological inhibitors of adenylyl cyclase activity (Tesmer *et al.*, 2000). Three families of adenylyl cyclase are distinguishable:  $Ca^{2+}$ /CaM-stimulated (AC1, AC3 and AC8),  $Ca^{2+}$ -inhibitable (AC5 and AC6) and  $Ca^{2+}$ -insensitive (AC2, AC4 and AC7) forms.

| Nomenclature          | AC1                                                                                                                                   | AC2                                                                                                                             | AC3                                                                                                                                                    | AC4                                                       | AC5                                                                                                                                            |
|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| Ensembl ID            | ENSG00000164742                                                                                                                       | ENSG00000078295                                                                                                                 | ENSG00000138031                                                                                                                                        | ENSG00000129467                                           | ENSG00000173175                                                                                                                                |
| Other names           | AC I                                                                                                                                  | AC II, HBCA2                                                                                                                    | AC III, olfactory type                                                                                                                                 | AC IV                                                     | AC V                                                                                                                                           |
| Endogenous activators | $Ca^{2+}$ /CaM (Tang <i>et al.</i> , 1991), PKC-evoked phosphorylation (Jacobowitz <i>et al.</i> , 1993)                              | $G\beta\gamma$ (Taussig <i>et al.</i> , 1993), PKC-evoked phosphorylation (Chen and Iyengar, 1993; Lustig <i>et al.</i> , 1993) | $Ca^{2+}$ /CaM (Choi <i>et al.</i> , 1992), PKC-evoked phosphorylation (Jacobowitz <i>et al.</i> , 1993)                                               | $G\beta\gamma$ (Gao and Gilman, 1991)                     | PKC-evoked phosphorylation (Kawabe <i>et al.</i> , 1994)                                                                                       |
| Endogenous inhibitors | $G\alpha_i$ (Taussig <i>et al.</i> , 1994), $G\alpha_o$ (Taussig <i>et al.</i> , 1994), $G\beta\gamma$ (Taussig <i>et al.</i> , 1993) | –                                                                                                                               | $G\alpha_i$ (Taussig <i>et al.</i> , 1994), RGS2 (Sinnarajah <i>et al.</i> , 2001), CaM kinase II-evoked phosphorylation (Wayman <i>et al.</i> , 1995) | PKC-evoked phosphorylation (Zimmermann and Taussig, 1996) | $G\alpha_i$ (Taussig <i>et al.</i> , 1994), $Ca^{2+}$ (Ishikawa <i>et al.</i> , 1992), PKA-evoked phosphorylation (Iwami <i>et al.</i> , 1995) |
| Selective inhibitors  | –                                                                                                                                     | –                                                                                                                               | –                                                                                                                                                      | –                                                         | NKY80 (Onda <i>et al.</i> , 2001)                                                                                                              |

| Nomenclature          | AC6                                                                                                                                                                                               | AC7                                                      | AC8                                   | AC9                                                    |
|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|---------------------------------------|--------------------------------------------------------|
| Ensembl ID            | ENSG00000174233                                                                                                                                                                                   | ENSG00000121281                                          | ENSG00000155897                       | ENSG00000162104                                        |
| Other names           | AC VI, $Ca^{2+}$ -inhibitable cyclase                                                                                                                                                             | AC VII                                                   | AC VIII                               | AC IX                                                  |
| Endogenous activators | –                                                                                                                                                                                                 | PKC-evoked phosphorylation (Watson <i>et al.</i> , 1994) | $Ca^{2+}$ (Cali <i>et al.</i> , 1994) | –                                                      |
| Endogenous inhibitors | $G\alpha_i$ (Taussig <i>et al.</i> , 1994), $Ca^{2+}$ (Yoshimura and Cooper, 1992), PKA-evoked phosphorylation (Chen <i>et al.</i> , 1997), PKC-evoked phosphorylation (Lai <i>et al.</i> , 1999) | –                                                        | –                                     | $Ca^{2+}$ /calcineurin (Paterson <i>et al.</i> , 2000) |

Nitric oxide has been proposed to inhibit AC5 and AC6 selectively (Hill *et al.*, 2000), although it is unclear whether this phenomenon is of physiological significance. A soluble adenylyl cyclase has been described (ENSG00000143199, Buck *et al.*, 1999), unaffected by either  $G\alpha$  or  $G\beta\gamma$  subunits, which has been suggested to be a cytoplasmic bicarbonate (pH-insensitive) sensor (Chen *et al.*, 2000).

## Soluble guanylyl cyclase (E.C. 4.6.1.2)

**Overview:** Soluble guanylyl cyclase (GTP diphosphate-lyase (cyclising)) is a heterodimer comprising  $\alpha$  and  $\beta$  chains, both of which have two subtypes in man (predominantly  $\alpha 1\beta 1$ ; see Zabel *et al.*, 1998). A haem group is associated with the  $\beta$  chain and is the target for the endogenous ligand nitric oxide (NO•), and, potentially, carbon monoxide (Friebe *et al.*, 1996). The enzyme converts guanosine-5'-triphosphate (GTP) to the intracellular second messenger 3',5'-guanosine monophosphate (cGMP).

|                        |                                                                                                                                                                                                                |
|------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nomenclature           | Soluble guanylyl cyclase                                                                                                                                                                                       |
| Preferred abbreviation | sGC                                                                                                                                                                                                            |
| Ensembl ID             | $\alpha 1$ ENSG00000164116; $\alpha 2$ ENSG00000152402; $\beta 1$ ENSG00000061918; $\beta 2$ ENSG00000123201                                                                                                   |
| Selective activators   | NO•, YC1 (Friebe <i>et al.</i> , 1996), BAY412272 (Stasch <i>et al.</i> , 2001), cinaciguat (Stasch <i>et al.</i> , 2002), riociguat (Stasch <i>et al.</i> , 2002), ataciguat (Schindler <i>et al.</i> , 2006) |
| Selective inhibitors   | ODQ (7.5; Garthwaite <i>et al.</i> , 1995)                                                                                                                                                                     |

ODQ also shows activity at other haem-containing proteins (Feelisch *et al.*, 1999), while YC1 may also inhibit cGMP-hydrolysing phosphodiesterases (Friebe *et al.* 1998; Galle *et al.*, 1999).

### Exchange protein activated by cyclic AMP (Epac)

**Overview:** Epacs are members of a family of guanine nucleotide exchange factors (ENSM00250000000899), which also includes RapGEF5 (GFR, KIAA0277, MR-GEF, ENSG00000136237) and RapGEFL1 (Link-GEFI, ENSG00000108352). They are activated endogenously by cyclic AMP and with some pharmacological selectivity by 8-pCPT-2'-O-Me-cAMP (Enserink *et al.*, 2002). Once activated, Epacs induce an enhanced activity of the monomeric G proteins, Rap1 and Rap2 by facilitating binding of GTP in place of GDP, leading to activation of phospholipase C (Schmidt *et al.*, 2001) (see Page S302).

| Nomenclature | Ensembl ID      | Other names                |
|--------------|-----------------|----------------------------|
| Epac1        | ENSG00000079337 | RapGEF3, bcm910, cAMP-GEFI |
| Epac2        | ENSG00000091428 | RapGEF4, cAMP-GEFII, CGEF2 |

### Phosphodiesterases, 3',5'-cyclic nucleotide (E.C.3.1.4.17)

**Overview:** 3',5'-Cyclic nucleotide phosphodiesterases (PDEs, 3',5'-cyclic-nucleotide 5'-nucleotidohydrolase) catalyse the hydrolysis of a 3',5'-cyclic nucleotide (usually cyclic AMP or cyclic GMP). IBMX is a nonselective inhibitor with an  $IC_{50}$  value in the millimolar range for all isoforms except PDE 8A, 8B and 9A. A 2',3'-cyclic nucleotide 3'-phosphodiesterase (E.C. 3.1.4.37 CNPase) activity is associated with myelin formation in the development of the CNS.

| Nomenclature           | PDE1A                                                                                              | PDE1B                                            | PDE1C                                                                                              | PDE2A                                                                                    |
|------------------------|----------------------------------------------------------------------------------------------------|--------------------------------------------------|----------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| Ensembl ID             | ENSG00000115252                                                                                    | ENSG00000123360                                  | ENSG00000154678                                                                                    | SwissProt O00408                                                                         |
| Other names            | PDE I                                                                                              | PDE I                                            | PDE I                                                                                              | PDE II, cGMP-stimulated cAMP-PDE, CGS-PDE                                                |
| Rank order of affinity | cGMP > cAMP                                                                                        | cGMP > cAMP                                      | cGMP = cAMP                                                                                        | cAMP >> cGMP                                                                             |
| Activators             | Ca <sup>2+</sup> /CaM                                                                              | Ca <sup>2+</sup> /CaM                            | Ca <sup>2+</sup> /CaM                                                                              | cGMP                                                                                     |
| Selective inhibitors   | SCH51866 (7.2, Vemulapalli <i>et al.</i> , 1996), vinpocetine (5.1, Loughney <i>et al.</i> , 1996) | SCH51866 (7.2, Vemulapalli <i>et al.</i> , 1996) | SCH51866 (7.2, Vemulapalli <i>et al.</i> , 1996), vinpocetine (4.3, Loughney <i>et al.</i> , 1996) | BAY607550 (8.3–8.8, Boess <i>et al.</i> , 2004), EHNA (5.3, Michie <i>et al.</i> , 1996) |

PDE1A, 1B and 1C appear to act as soluble homodimers, while PDE2A is a membrane-bound homodimer. EHNA is also an inhibitor of adenosine deaminase (E.C. 3.5.4.4) (see Page S280).

| Nomenclature         | PDE3A                                                                                          | PDE3B                                                                                          |
|----------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| Ensembl ID           | ENSG00000172572                                                                                | ENSG00000152270                                                                                |
| Other names          | PDE III, cGMP-inhibited cAMP-PDE, CGI-PDE A                                                    | PDE III, cGMP-inhibited cAMP-PDE, CGI-PDE B                                                    |
| Selective inhibitors | Cilostamide (7.5, Sudo <i>et al.</i> , 2000), milrinone (6.3, Sudo <i>et al.</i> , 2000), cGMP | Cilostamide (7.3, Sudo <i>et al.</i> , 2000), milrinone (6.0, Sudo <i>et al.</i> , 2000), cGMP |

PDE3A and PDE3B are membrane-bound.

| Nomenclature           | PDE4A                                                                                                                        | PDE4B                                                                                | PDE4C                                                                                | PDE4D                                                                                |
|------------------------|------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| Ensembl ID             | ENSG00000065989                                                                                                              | ENSG00000184588                                                                      | ENSG00000105650                                                                      | ENSG00000113448                                                                      |
| Other names            | PDE IV                                                                                                                       | PDE IV                                                                               | PDE IV                                                                               | PDE IV                                                                               |
| Rank order of affinity | cAMP >> cGMP                                                                                                                 | cAMP >> cGMP                                                                         | cAMP >> cGMP                                                                         | cAMP >> cGMP                                                                         |
| Activators             | –                                                                                                                            | –                                                                                    | –                                                                                    | PKA-mediated phosphorylation (Houslay and Adams, 2003)                               |
| Selective inhibitors   | Rolipram (9.0, Wang <i>et al.</i> , 1997), YM976 (8.3, Aoki <i>et al.</i> , 2000), Ro201724 (6.5, Wang <i>et al.</i> , 1997) | Rolipram (9.0, Wang <i>et al.</i> , 1997), Ro201724 (6.4, Wang <i>et al.</i> , 1997) | Rolipram (6.5, Wang <i>et al.</i> , 1997), Ro201724 (5.4, Wang <i>et al.</i> , 1997) | Rolipram (7.2, Wang <i>et al.</i> , 1997), Ro201724 (6.2, Wang <i>et al.</i> , 1997) |

PDE4 isoforms are essentially cAMP specific. The potency of YM976 at other members of the PDE4 family has not been reported. PDE4B–D long forms are inhibited by extracellular signal-regulated kinase (ERK)-mediated phosphorylation (Hoffmann *et al.*, 1998; Hoffmann *et al.*, 1999). PDE4A–D splice variants can be membrane-bound or cytosolic (Houslay and Adams, 2003). PDE4 isoforms may be labelled with [<sup>3</sup>H]-rolipram.

| Nomenclature           | PDE5A                                                                                                                                                                                  | PDE7A                                        | PDE7B                                                                                                                          | PDE8A                                                | PDE8B                                            |
|------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|--------------------------------------------------|
| Ensembl ID             | ENSG00000138735                                                                                                                                                                        | ENSG00000104732                              | ENSG00000171408                                                                                                                | ENSG00000073417                                      | ENSG00000113231                                  |
| Other names            | PDE V, cGMP-specific PDE                                                                                                                                                               | HCP1                                         | –                                                                                                                              | High-affinity cAMP-specific and IBMX-insensitive PDE | –                                                |
| Rank order of affinity | cGMP > cAMP                                                                                                                                                                            | cAMP >> cGMP (Michaeli <i>et al.</i> , 1993) | cAMP >> cGMP (Gardner <i>et al.</i> , 2000)                                                                                    | cAMP >> cGMP (Fisher <i>et al.</i> , 1998a)          | cAMP >> cGMP (Hayashi <i>et al.</i> , 1998)      |
| Activators             | PKA (Corbin <i>et al.</i> , 2000), PKG (Corbin <i>et al.</i> , 2000)                                                                                                                   | –                                            | –                                                                                                                              | –                                                    | –                                                |
| Selective inhibitors   | T0156 (9.5, Mochida <i>et al.</i> , 2002), sildenafil (9.0, Turko <i>et al.</i> , 1999), SCH51866 (7.2, Vemulapalli <i>et al.</i> , 1996), zaprinast (6.8, Turko <i>et al.</i> , 1999) | BRL50481 (6.7, Smith <i>et al.</i> , 2004)   | Dipyridamole (5.7–6.0, Gardner <i>et al.</i> , 2000; Sasaki <i>et al.</i> , 2000), SCH51866 (5.8, Sasaki <i>et al.</i> , 2000) | Dipyridamole (5.1, Fisher <i>et al.</i> , 1998a)     | Dipyridamole (4.3, Hayashi <i>et al.</i> , 1998) |

PDE7A appears to be membrane-bound or soluble for PDE7A1 and 7A2 splice variants, respectively. BRL50481 appears not to have been examined as an inhibitor of PDE7B.

| Nomenclature          | PDE9A                                                                                       | PDE10A                                      | PDE11A                                    |
|-----------------------|---------------------------------------------------------------------------------------------|---------------------------------------------|-------------------------------------------|
| Ensembl ID            | ENSG00000160191                                                                             | ENSG00000112541                             | ENSG00000128655                           |
| Substrate specificity | cGMP >> cAMP (Fisher <i>et al.</i> , 1998b)                                                 | cAMP, cGMP (Fujishige <i>et al.</i> , 1999) | cAMP, cGMP (Fawcett <i>et al.</i> , 2000) |
| Selective inhibitors  | SCH51866 (5.8, Fisher <i>et al.</i> , 1998b), zaprinast (4.5, Fisher <i>et al.</i> , 1998b) | –                                           | –                                         |

| Nomenclature | PDE6A                        | PDE6B            | PDE6C                     | PDE6D             | PDE6G             | PDE6H             |
|--------------|------------------------------|------------------|---------------------------|-------------------|-------------------|-------------------|
| Ensembl ID   | ENSG00000132915              | ENSG00000133256  | ENSG00000095464           | ENSG00000156973   | ENSG00000185527   | ENSG00000139053   |
| Other names  | cGMP-PDE $\alpha$ , PDE V-b1 | cGMP-PDE $\beta$ | cGMP-PDE $\alpha$ , PDEA2 | cGMP-PDE $\delta$ | cGMP-PDE $\gamma$ | cGMP-PDE $\gamma$ |

PDE6 is a membrane-bound tetramer composed of two catalytic chains (PDE6A or PDE6C and PDE6B), an inhibitory chain (PDE6G or PDE6H) and the PDE6D chain. The enzyme is essentially cGMP specific and is activated by the  $\alpha$ -subunit of transducin ( $G\alpha_t$ , see Page S5) and inhibited by sildenafil, zaprinast and dipyridamole with potencies lower than those observed for PDE5A. Defects in PDE6B are a cause of retinitis pigmentosa and congenital stationary night blindness.

**Abbreviations:** BAY412272, 5-cyclopropyl-2-[1-(2-fluoro-benzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-pyrimidin-4-ylamine); BAY607550, 2-(3,4-dimethoxybenzyl)-7-[(1R)-1-[(1R)-1-hydroxyethyl]-4-phenylbutyl]-5-methylimidazo[5,1-f][1,2,4]triazin-4(3H)-one; BRL50481, 5-nitro-2,N-trimethylbenzenesulfonamide; CaM, calmodulin; EHNA, erythro-9-(2-hydroxy-3-nonyl)adenine; NKH477, 6-(3-dimethylaminopropionyl) forskolin hydrochloride; NKY80, 2-amino-7-(2-furanyl)-7,8-dihydro-5(6H)-quinazolinone; ODO, 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one;

PKA, protein kinase A or cyclic AMP-dependent protein kinase; PKC, protein kinase C; PKG, protein kinase G or cyclic GMP-dependent protein kinase; RGS2, Regulator of G-protein signalling 2 (ENSG00000116741); Ro201724, 4-(3-butoxy-4-methoxyphenyl)methyl-2-imidazolidone; SCH51866, *cis*-5,6a,7,8,9,9a-hexahydro-2-(4-[trifluoromethyl]phenylmethyl)-5-methyl-cyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)-one; YC1, 3-(5'-hydroxymethyl-2'-furyl)-1-benzylindazole; YM976, (4-[3-chlorophenyl]-1,7-diethylpyrido[2,3-*d*]pyrimidin-2(1*H*)-one);

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# Cytochrome P450 (E.C. 1.14.-.-)

**Overview:** the cytochrome P450 enzyme family (CYP450) were originally defined by their strong absorbance at 450 nm due to the reduced carbon monoxide-complexed haem component of the cytochromes. They are an extensive family of haem-containing monooxygenases with a huge range of both endogenous and exogenous substrates. Listed below are the human enzymes; their relationship with rodent CYP450 enzyme activities is obscure in that the species orthologue may not mediate metabolism of the same substrates. Although the majority of CYP450 enzyme activities are concentrated in the liver, the extrahepatic enzyme activities also contribute to patho/physiological processes. Genetic variation of CYP450 isoforms is widespread and likely underlies a significant proportion of the individual variation to drug administration.

## CYP1 family (ENSM0025000000349) (E.C. 1.14.1.1)

| Nomenclature | Ensembl ID      | Other names                                                      | Comments                                                                                       |
|--------------|-----------------|------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| CYP1A1       | ENSG00000140465 | Aryl hydrocarbon hydroxylase, CP11, CYP1, P1-450, P450-C, P450DX | –                                                                                              |
| CYP1A2       | ENSG00000140505 | Phenacetin O-deethylase, CP12, P3-450                            | –                                                                                              |
| CYP1B1       | ENSG00000138061 | CP1B, GLC3A                                                      | Mutations have been associated with primary congenital glaucoma (Stoilov <i>et al.</i> , 1997) |

## CYP2 family (ENSM00400000131704, ENSFM00400000131705, ENSFM00550000747662)

| Nomenclature | EC                                       | Ensembl ID      | Other names                                                                                                                                                       | Comments             |
|--------------|------------------------------------------|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| CYP2A6/2A7   | 1.14.14.1                                | ENSG00000198077 | Coumarin 7-hydroxylase, CPA6, CYP2A, CYP2A3, CYP2A, CYP1A7, P450-IIA4                                                                                             | Metabolises nicotine |
| CYP2A13      | 1.14.14.1                                | ENSG00000197838 | CYP1A13                                                                                                                                                           | –                    |
| CYP2B6       | 1.14.14.1                                | ENSG00000197408 | CYP1B6, P450 IIB1                                                                                                                                                 | –                    |
| CYP2C8       | 1.14.14.1                                | ENSG00000138115 | CYP1C8, P450 form 1, P450 MP-12/MP-20, P450 IIC2, S-mephenytoin 4-hydroxylase                                                                                     | –                    |
| CYP2C9       | 1.14.13.80,<br>1.14.13.48,<br>1.14.13.49 | ENSG00000138109 | (R)-Limonene 6-monooxygenase, (S)-limonene 6-monooxygenase, (S)-limonene 7-monooxygenase, CYP1C9, P450 PB-1, P450 MP-4/MP-8, S-mephenytoin 4-hydroxylase, P-450MP | –                    |
| CYP2C18      | 1.14.14.1                                | ENSG00000108242 | CYP1C18, P450-6B/29C                                                                                                                                              | –                    |
| CYP2C19      | 1.14.13.80,<br>1.14.13.48,<br>1.14.13.49 | ENSG00000165841 | (R)-limonene 6-monooxygenase, (S)-limonene 6-monooxygenase, (S)-limonene 7-monooxygenase, CYP1C19, P450-11A, mephenytoin 4-hydroxylase, CYP1C17, P450-254C        | –                    |
| CYP2D6       | 1.14.14.1                                | ENSG00000100197 | Debrisoquine 4-hydroxylase, CYP1D6, P450-DB1                                                                                                                      | –                    |
| CYP2E1       | 1.14.14.1                                | ENSG00000130649 | CYP1E1, P450-J                                                                                                                                                    | –                    |
| CYP2F1       | 1.14.14.1                                | ENSG00000197446 | CYP1F1                                                                                                                                                            | –                    |
| CYP2J2       | 1.14.14.1                                | ENSG00000134716 | Arachidonic acid epoxigenase, CYP1J2                                                                                                                              | –                    |
| CYP2R1       | 1.14.13.15                               | ENSG00000186104 | Vitamin D 25-hydroxylase                                                                                                                                          | –                    |
| CYP2S1       | 1.14.14.1                                | ENSG00000167600 | CYP1S1                                                                                                                                                            | –                    |
| CYP2U1       | 1.14.14.1                                | ENSG00000155016 |                                                                                                                                                                   | –                    |
| CYP2W1       | 1.14.14.-                                | ENSG00000073067 | CYP1W1                                                                                                                                                            | –                    |

CYP2A7P1 (ENSG00000213908), CYP2D7P1 (ENSG00000205702), CYP2G1P (ENSG00000130612) and AC008537.5-2 (ENSG00000198251, fragment) are uncharacterized potential pseudogenes from the same families.

## CYP3 family (ENSMF00310000088994)

| Nomenclature | EC                                       | Ensembl ID      | Other names                                                                                                                                                                                          | Comments                                                                                                                                   |
|--------------|------------------------------------------|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| CYP3A4       | 1.14.13.67,<br>1.14.13.97,<br>1.14.13.32 | ENSG00000160868 | Quinine 3-monooxygenase, CYP11A4, Nifedipine oxidase, CYP4503A3, CYP11A3, HLP, taurochenodeoxycholate 6- $\alpha$ -hydroxylase, NF-25, P450-PCN1, albendazole monooxygenase, albendazole sulfoxidase | Metabolises a vast range of xenobiotics, including antidepressants, benzodiazepines, calcium channel blockers, and chemotherapeutic agents |
| CYP3A5       | 1.14.14.1                                | ENSG00000106258 | CYP11A5, P450-PCN3, HLP2                                                                                                                                                                             | –                                                                                                                                          |
| CYP3A7       | 1.14.14.1                                | ENSG00000160870 | CYP11A7, P450-HFLA                                                                                                                                                                                   | –                                                                                                                                          |
| CYP3A43      | 1.14.14.1                                | ENSG00000021461 | Cytochrome P450 3A43                                                                                                                                                                                 | –                                                                                                                                          |

## CYP4 family (ENSMF00400000131716, ENSMF00400000131707)

| Nomenclature | EC         | Ensembl ID      | Other names                                                                                                                                                                               | Comments                                                                                                                                                                                                               |
|--------------|------------|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CYP4A11      | 1.14.15.3  | ENSG00000187048 | CYP1A11, lauric acid $\omega$ -hydroxylase, fatty acid $\omega$ -hydroxylase, P-450 HK $\omega$ , CYP4A11, P450-HL- $\omega$ , 20-hydroxyeicosatetraenoic acid synthase, 20-HETE synthase | –                                                                                                                                                                                                                      |
| CYP4A22      | 1.14.15.3  | ENSG00000162365 | CYP1A22, lauric acid $\omega$ -hydroxylase, fatty acid $\omega$ -hydroxylase                                                                                                              | –                                                                                                                                                                                                                      |
| CYP4B1       | 1.14.14.1  | ENSG00000142973 | CYP1B1, P450-HP                                                                                                                                                                           | –                                                                                                                                                                                                                      |
| CYP4F2       | 1.14.13.30 | ENSG00000186115 | Leukotriene B <sub>4</sub> 20-monooxygenase 1, leukotriene B <sub>4</sub> $\omega$ -hydroxylase 1, CYP1F2, cytochrome P450-LTB- $\omega$                                                  | Responsible for $\omega$ -hydroxylation of leukotriene B <sub>4</sub> , lipoxin B <sub>4</sub> (Mizukami <i>et al.</i> , 1993) and tocopherols, including vitamin E (Sontag and Parker, 2002)                          |
| CYP4F3       | 1.14.13.30 | ENSG00000186529 | Leukotriene B <sub>4</sub> 20-monooxygenase 2, leukotriene B <sub>4</sub> $\omega$ -hydroxylase 2, CYP1F3, cytochrome P450-LTB- $\omega$                                                  | Responsible for $\omega$ -hydroxylation of leukotriene B <sub>4</sub> , lipoxin B <sub>4</sub> (Mizukami <i>et al.</i> , 1993) and polyunsaturated fatty acids (Harmon <i>et al.</i> , 2006; Fer <i>et al.</i> , 2008) |
| CYP4F8       | 1.14.14.1  | ENSG00000186526 | CYP1F8                                                                                                                                                                                    | –                                                                                                                                                                                                                      |
| CYP4F11      | 1.14.14.1  | ENSG00000171903 | CYP1F11                                                                                                                                                                                   | –                                                                                                                                                                                                                      |
| CYP4F12      | 1.14.14.1  | ENSG00000186204 | CYP1F12                                                                                                                                                                                   | –                                                                                                                                                                                                                      |
| CYP4F22      | 1.14.14.-  | ENSG00000171954 |                                                                                                                                                                                           | –                                                                                                                                                                                                                      |
| CYP4V2       | 1.14.-.-   | ENSG00000145476 |                                                                                                                                                                                           | –                                                                                                                                                                                                                      |
| CYP4X1       | 1.14.14.1  | ENSG00000186377 | CYP1X1                                                                                                                                                                                    | –                                                                                                                                                                                                                      |
| CYP4Z1       | 1.14.14.1  | ENSG00000186160 | CYP1Z1                                                                                                                                                                                    | –                                                                                                                                                                                                                      |

AC004597.1 (ENSG00000225607) is described as being highly similar to CYP4F12.

## CYP5, CYP7 and CYP8 families (ENSMF00250000001362)

| Nomenclature | EC          | Ensembl ID      | Other names                                                                          | Comments                                                                                                                                                                     |
|--------------|-------------|-----------------|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CYP5A1       | 5.3.99.5    | ENSG00000059377 | Thromboxane synthase, TXA synthase, TBXA51, CYP5, THAS, TS, TXAS, TXS, TXS           | Converts prostaglandin H <sub>2</sub> to thromboxane A <sub>2</sub> . Inhibited by dazoxiben (Randall <i>et al.</i> , 1981) and camonagrel (Gryglewski <i>et al.</i> , 1995) |
| CYP7A1       | 1.14.13.17  | ENSG00000167910 | Cholesterol 7- $\alpha$ -monooxygenase, cholesterol 7- $\alpha$ -hydroxylase, CYPVII | –                                                                                                                                                                            |
| CYP7B1       | 1.14.13.100 | ENSG00000172817 | Oxysterol 7- $\alpha$ -hydroxylase, 25-hydroxycholesterol 7- $\alpha$ -hydroxylase   | –                                                                                                                                                                            |

| Nomenclature | EC         | Ensembl ID      | Other names                                                                                                                                                                                  | Comments                                                        |
|--------------|------------|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| CYP8A1       | 5.3.99.4   | ENSG00000124212 | Prostaglandin I <sub>2</sub> synthase, PTGIS                                                                                                                                                 | Inhibited by tranlylcypromine (Gryglewski <i>et al.</i> , 1976) |
| CYP8B1       | 1.14.13.95 | ENSG00000180432 | 7- $\alpha$ -Hydroxycholest-4-en-3-one<br>12- $\alpha$ -hydroxylase, CYPVIII B1,<br>7- $\alpha$ -hydroxy-4-cholesten-3-one<br>12- $\alpha$ -hydroxylase, sterol<br>12- $\alpha$ -hydroxylase | –                                                               |

## CYP11 (ENSM00500000269868), CYP17, CYP19, CYP20 and CYP21 families

| Nomenclature | EC                      | Ensembl ID      | Other names                                                                                                         | Comments                                                                                                                                                                                                                                                                                                       |
|--------------|-------------------------|-----------------|---------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CYP11A1      | 1.14.15.6               | ENSG00000140459 | Cholesterol side-chain cleavage enzyme, cholesterol desmolase, CYPXI A1, P450 <sub>sc</sub>                         | Converts cholesterol to pregnenolone                                                                                                                                                                                                                                                                           |
| CYP11B1      | 1.14.15.4               | ENSG00000160882 | Steroid 11 $\beta$ -hydroxylase, CYPXI B1, P450C11, P-450c11                                                        | Converts deoxycortisone and 11-deoxycortisol to cortisone and cortisol, respectively. Loss-of-function mutations are associated with familial adrenal hyperplasia and hypertension. Inhibited by metyrapone (Watanuki <i>et al.</i> , 1978)                                                                    |
| CYP11B2      | 1.14.15.4,<br>1.14.15.5 | ENSG00000179142 | Aldosterone synthase, ALDOS, CYPXI B2, P-450Aldo, aldosterone-synthesizing enzyme, steroid 18-hydroxylase, P-450C18 | Converts corticosterone to aldosterone                                                                                                                                                                                                                                                                         |
| CYP17A1      | 1.14.99.9               | ENSG00000148795 | Steroid 17- $\alpha$ -hydroxylase/17,20 lyase, CYPXVII, P450-C17, P450c17, steroid 17- $\alpha$ -monooxygenase      | Converts pregnenolone and progesterone to 17 $\alpha$ -hydroxypregnenolone and 17 $\alpha$ -hydroxyprogesterone, respectively. Converts 17 $\alpha$ -hydroxypregnenolone and 17 $\alpha$ -hydroxyprogesterone to dehydroepiandrosterone and androstenedione, respectively. Converts corticosterone to cortisol |
| CYP19A1      | 1.14.14.1               | ENSG00000137869 | Aromatase, estrogen synthetase, P-450AROM, CYPXIX                                                                   | Converts androstenedione and testosterone to estrone and estradiol, respectively. Inhibited by anastrozole (Plourde <i>et al.</i> , 1994) and letrozole (Bhatnagar <i>et al.</i> , 1990)                                                                                                                       |
| CYP20A1      | 1.14.-.-                | ENSG00000119004 | CYP-M                                                                                                               | –                                                                                                                                                                                                                                                                                                              |
| CYP21A2      | 1.14.99.10              | ENSG00000198457 | Steroid 21-hydroxylase, cytochrome P450 XXI, 21-OHase, P450-C21, P-450c21, P450-C21B                                | Converts progesterone and 17 $\alpha$ -hydroxyprogesterone to deoxycortisone and 11-deoxycortisone, respectively                                                                                                                                                                                               |

## CYP24, CYP26 and CYP27 families (ENSM00500000269772, ENSFM00250000002048)

| Nomenclature | EC         | Ensembl ID      | Other names                                                                                                                                                                                      | Comments               |
|--------------|------------|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| CYP24A1      | 1.14.13.n4 | ENSG00000019186 | 1,25-Dihydroxyvitamin D <sub>3</sub> 24-hydroxylase, vitamin D <sub>3</sub> 24-hydroxylase, 24-OHase, P450-CC24                                                                                  | –                      |
| CYP26A1      | 1.14.-.-   | ENSG00000095596 | Retinoic acid-metabolizing cytochrome, P450 retinoic acid-inactivating 1, P450RAI, retinoic acid 4-hydroxylase                                                                                   | Inhibited by liarozole |
| CYP26B1      | 1.14.-.-   | ENSG00000003137 | Retinoic acid-metabolizing cytochrome, P450 retinoic acid-inactivating 2, P450RAI-2, P450 26A2                                                                                                   | –                      |
| CYP26C1      | 1.14.-.-   | ENSG00000187553 | –                                                                                                                                                                                                | –                      |
| CYP27A1      | 1.14.13.15 | ENSG00000135929 | Sterol 26-hydroxylase, cytochrome P-450C27/25, sterol 27-hydroxylase, vitamin D <sub>3</sub> 25-hydroxylase, 5- $\beta$ -cholestane-3- $\alpha$ ,7- $\alpha$ ,12- $\alpha$ -triol 27-hydroxylase | –                      |

| Nomenclature | EC         | Ensembl ID      | Other names                                                                                                                                                                                                                                                                | Comments |
|--------------|------------|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| CYP27B1      | 1.14.13.13 | ENSG00000111012 | 25-hydroxyvitamin D-1 $\alpha$ hydroxylase, cytochrome P450 subfamily XXVIIIB polypeptide 1, calcidiol 1-monooxygenase, 25-OHD-1 $\alpha$ -hydroxylase, 25-hydroxyvitamin D <sub>3</sub> 1- $\alpha$ -hydroxylase, VD3 1A hydroxylase, P450C1 $\alpha$ , P450VD1- $\alpha$ | –        |
| CYP27C1      | 1.14.-.-   | ENSG00000186684 | –                                                                                                                                                                                                                                                                          | –        |

### CYP39, CYP46 and CYP51 families

| Nomenclature | EC         | Ensembl ID      | Other names                                                                                                                                          |
|--------------|------------|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| CYP39A1      | 1.14.13.99 | ENSG00000146233 | Oxysterol 7- $\alpha$ -hydroxylase, 24-hydroxycholesterol 7- $\alpha$ -hydroxylase                                                                   |
| CYP46A1      | 1.14.13.98 | ENSG00000036530 | Cholesterol 24-hydroxylase, CH24H                                                                                                                    |
| CYP51A1      |            | ENSG00000001630 | Lanosterol 14- $\alpha$ -demethylase, leucine-rich repeat and death domain-containing protein LOC401387, CP51, CYP51, CYPL1, LDM, P450-14 DM, P450L1 |

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# Eicosanoid turnover

Eicosanoids are 20-carbon fatty acids, where the usual focus is the polyunsaturated analogue arachidonic acid and its metabolites. Arachidonic acid is thought primarily to derive from phospholipase A<sub>2</sub> action on membrane phosphatidylcholine (see Page S302), and may be re-cycled to form phospholipid through conjugation with coenzyme A and subsequently glycerol derivatives. Oxidative metabolism of arachidonic acid is conducted through three major enzymatic routes: cyclooxygenases; lipoxygenases and cytochrome P450-like epoxigenases, particularly CYP2J2 (see Page S293). Isoprostanes are structural analogues of the prostanooids (hence the nomenclature D-, E-, F-isoprostanes and isothromboxanes), which are produced in the presence of elevated free radicals in a non-enzymatic manner, leading to suggestions for their use as biomarkers of oxidative stress. Molecular targets for their action have yet to be defined.

## Cyclooxygenase (E.C. 1.14.99.1)

**Overview:** Prostaglandin (PG) G/H synthase, most commonly referred to as cyclooxygenase (COX, (5Z,8Z,11Z,14Z)-icosa-5,8,11,14-tetraenoate,hydrogen-donor : oxygen oxidoreductase) activity, catalyses the formation of PG G<sub>2</sub> from arachidonic acid. Hydroperoxidase activity inherent in the enzyme catalyses the formation of PGH<sub>2</sub> from PGG<sub>2</sub>. COX-1 and -2 can be nonselectively inhibited by ibuprofen, ketoprofen, naproxen, indometacin and paracetamol (acetaminophen). PGH<sub>2</sub> may then be metabolised to prostaglandins and thromboxanes by various prostaglandin synthases in an apparently tissue-dependent manner.

| Nomenclature         | COX-1                                                                                              | COX-2                                                                                              |
|----------------------|----------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
| Ensembl ID           | ENSG00000095303                                                                                    | ENSG00000073756                                                                                    |
| Other names          | Prostaglandin G <sub>2</sub> /H <sub>2</sub> synthase-1                                            | Prostaglandin G <sub>2</sub> /H <sub>2</sub> synthase-2                                            |
| Substrates           | Arachidonic acid                                                                                   | Arachidonic acid, docosahexaenoic acid (see Smith, 2008)                                           |
| Selective inhibitors | FR122047 (7.5, Ochi <i>et al.</i> , 2000), valeroylsalicylate (Bhattacharyya <i>et al.</i> , 1995) | Diclofenac (6.7), celecoxib (5.1), rofecoxib (4.3), valdecoxib, parecoxib, etoricoxib, lumiracoxib |

## Prostaglandin synthases

Subsequent to the formation of PGH<sub>2</sub>, the cytochrome P450 activities (see Page S293) thromboxane synthase (CYP5A1, EC 5.3.99.5, ENSG00000059377) and prostacyclin synthase (CYP8A1, EC 5.3.99.4, ENSG00000124212) generate thromboxane A<sub>2</sub> and prostacyclin (PGI<sub>2</sub>), respectively. Additionally, multiple enzyme activities are able to generate prostaglandin E<sub>2</sub>, prostaglandin D<sub>2</sub> and prostaglandin F<sub>2α</sub> (see tables).

| Nomenclature | EC       | Ensembl ID      | Other names                                                                                                                                                                                    |
|--------------|----------|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| mPGES1       | 5.3.99.3 | ENSG00000148344 | Prostaglandin E synthase, microsomal glutathione S-transferase 1-like 1, MGST1-L1, p53-induced gene 12 protein, p53-induced gene 12; PIG12                                                     |
| mPGES2       | 5.3.99.3 | ENSG00000148334 | Prostaglandin E synthase 2, microsomal prostaglandin E synthase 2, mPGES-2                                                                                                                     |
| cPGES        | 5.3.99.3 | ENSG00000110958 | Cytosolic prostaglandin E <sub>2</sub> synthase, prostaglandin E synthase 3, telomerase-binding protein p23, hsp90 co-chaperone, progesterone receptor complex p23                             |
| L-PGDS       | 5.3.99.2 | ENSG00000107317 | Lipocalin-type prostaglandin-D synthase, prostaglandin D <sub>2</sub> synthase, prostaglandin H <sub>2</sub> D-isomerase, glutathione-independent PGD synthetase, β-trace protein, cerebrin-28 |
| H-PGDS       | 5.3.99.2 | ENSG00000163106 | Hematopoietic prostaglandin D synthase, glutathione-requiring prostaglandin D synthase, glutathione-dependent PGD synthetase, prostaglandin-H <sub>2</sub> D-isomerase                         |

YS121 has been reported to inhibit mPGES1 and 5-LOX with a pIC<sub>50</sub> value of 5.5 (Koeberle *et al.*, 2008).

Prostaglandin D<sub>2</sub> can be metabolised to 9α,11β-prostaglandin F<sub>2α</sub> through the multifunctional enzyme activity AKR1C3. Prostaglandin E<sub>2</sub> can be metabolised to 9α,11α-prostaglandin F<sub>2α</sub> through the 9-ketoreductase activity of CBR1. Conversion of the 15-hydroxyeicosanoids, including prostaglandins, lipoxins and leukotrienes to their keto derivatives by the NAD-dependent enzyme HPGD leads to a reduction in their biological activity.

| Nomenclature | AKR1C3                                             | CBR1                            | HPGD            |
|--------------|----------------------------------------------------|---------------------------------|-----------------|
| EC           | 1.1.1.188, 1.3.1.20, 1.1.1.213, 1.1.1.63, 1.1.1.64 | 1.1.1.197, 1.1.1.184, 1.1.1.189 | 1.1.1.141       |
| Ensembl ID   | ENSG00000196139                                    | ENSG00000159228                 | ENSG00000164120 |

|              |                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                            |                                             |
|--------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| Nomenclature | AKR1C3                                                                                                                                                                                                                                                                                                                                                                                                                             | CBR1                                                                                                                                                                                       | HPGD                                        |
| Other names  | Aldo-keto reductase family 1 member C3, prostaglandin F synthase, PGFS, <i>trans</i> -1,2-dihydrobenzene-1,2-diol dehydrogenase, 3 $\alpha$ -hydroxysteroid dehydrogenase type 2, 3 $\alpha$ -HSD type 2, testosterone 17 $\beta$ -dehydrogenase 5, 17 $\beta$ -hydroxysteroid dehydrogenase type 5, 17 $\beta$ -HSD 5, dihydrodiol dehydrogenase type I, dihydrodiol dehydrogenase 3, chlordecone reductase homolog HAKRb, HA1753 | Carbonyl reductase [NADPH] 1, prostaglandin E <sub>2</sub> 9-reductase, prostaglandin 9-ketoreductase, NADPH-dependent carbonyl reductase 1, 15-hydroxyprostaglandin dehydrogenase [NADP+] | 15-hydroxyprostaglandin dehydrogenase (NAD) |
| Inhibitors   | Flufenamic acid, indometacin (Matsuura <i>et al.</i> , 1998), flavonoids (Skarydova <i>et al.</i> , 2009)                                                                                                                                                                                                                                                                                                                          | –                                                                                                                                                                                          | –                                           |

### Lipoxygenases (E.C. 1.13.11.-)

**Overview:** The lipoxygenases (LOXs) are a structurally related family of non-haem iron dioxygenases that function in the production, and in some cases metabolism, of fatty acid hydroperoxides. For arachidonic acid as substrate, these products are hydroperoxyeicosatetraenoic acids (HPETEs). In humans there are five lipoxygenases, the 5S-(arachidonate : oxygen 5-oxidoreductase), 12R-(arachidonate 12-lipoxygenase, 12R-type), 12S-(arachidonate : oxygen 12-oxidoreductase), and two distinct 15S-(arachidonate : oxygen 15-oxidoreductase) LOXs that oxygenate arachidonic acid in different positions along the carbon chain and form the corresponding 5S-, 12S-, 12R-, or 15S-hydroperoxides, respectively. The sixth lipoxygenase member, epidermal lipoxygenase 3 (E-LOX), metabolises the product from the 12R-lipoxygenase (12R-HPETE) to a specific epoxyalcohol compound (Yu *et al.*, 2003).

|                      |                                                  |                     |                                       |
|----------------------|--------------------------------------------------|---------------------|---------------------------------------|
| Nomenclature         | 5-LOX                                            | 12R-LOX             | 12S-LOX                               |
| E.C.                 | 1.13.11.34                                       | 1.13.11.-           | 1.13.11.31                            |
| Ensembl ID           | ENSG00000012779                                  | ENSG00000179477     | ENSG00000108839                       |
| Other names          | ALOX5                                            | ALOX12B             | ALOX12, platelet-type 12-lipoxygenase |
| Substrates           | Arachidonic acid                                 | Methyl arachidonate | Arachidonic acid                      |
| Activators           | FLAP                                             | –                   | –                                     |
| Selective inhibitors | Zileuton, CJ13610 (Fischer <i>et al.</i> , 2004) | –                   | –                                     |

FLAP activity can be inhibited by MK886 (Dixon *et al.*, 1990) and BAY-X1005 (Hatzelmann *et al.*, 1993) leading to a selective inhibition of 5-LOX activity.

|              |                                               |                  |                      |
|--------------|-----------------------------------------------|------------------|----------------------|
| Nomenclature | 15-LOX-1                                      | 15-LOX-2         | E-LOX                |
| E.C.         | 1.13.11.33                                    | 1.13.11.33       | 1.13.11.-            |
| Ensembl ID   | ENSG00000161905                               | ENSG00000179593  | ENSG00000179148      |
| Other names  | ALOX15, arachidonate $\omega$ -6 lipoxygenase | ALOX15B          | Epidermis type LOX 3 |
| Substrates   | Linoleic acid, arachidonic acid               | Arachidonic acid | 12R-HPETE            |

An 8-LOX (EC 1.13.11.40, arachidonate:oxygen 8-oxidoreductase) may be the mouse orthologue of 15-LOX-2 (Furstenberger *et al.*, 2002). Some general LOX inhibitors are NDGA and esculetin. Zileuton and caffeic acid are used as 5-lipoxygenase inhibitors, while baicalein and CDC are 12-lipoxygenase inhibitors. The specificity of these inhibitors has not been rigorously assessed with all LOX forms: baicalein, along with other flavonoids, such as fisetin and luteolin, also inhibits 15-LOX-1 (Sadik *et al.*, 2003).

### Leukotriene and lipoxin metabolism

Leukotriene A<sub>4</sub>, produced by 5-LOX activity, and lipoxins may be subject to further oxidative metabolism;  $\omega$ -hydroxylation is mediated by CYP4F2 and CYP4F3 (see Page S293), while  $\beta$ -oxidation in mitochondria and peroxisomes proceeds in a manner dependent on coenzyme A conjugation. Conjugation of LTA<sub>4</sub> at the 6 position with reduced glutathione to generate LTC<sub>4</sub> occurs under the influence of leukotriene C<sub>4</sub> synthase, with the subsequent formation of LTD<sub>4</sub> and LTE<sub>4</sub>, all three of which are agonists at CysLT receptors (see Page S74). LTD<sub>4</sub> formation is

catalysed by  $\gamma$ -glutamyltransferase, and subsequently dipeptidase 2 removes the terminal glycine from LTD<sub>4</sub> to generate LTE<sub>4</sub>. Leukotriene A<sub>4</sub> hydrolase converts the 5,6-epoxide LTA<sub>4</sub> to the 5-hydroxylated LTB<sub>4</sub>, an agonist for BLT receptors (see Page S74). LTA<sub>4</sub> is also acted upon by 12S-LOX to produce the trihydroxyeicosatetraenoic acids lipoxins LXA<sub>4</sub> and LXB<sub>4</sub>. Treatment with an LTA<sub>4</sub> hydrolase inhibitor in a murine model of allergic airway inflammation increased LXA<sub>4</sub> levels, in addition to reducing LTB<sub>4</sub>, in lung lavage fluid (Rao *et al.*, 2010)

LTA<sub>4</sub> hydrolase is also involved in biosynthesis of resolvin Es (see Page S74). Aspirin has been reported to increase endogenous formation of 18S-hydroxyeicosapentaenoate (18S-HEPE) compared with 18R-HEPE, a resolvin precursor. Both enantiomers may be metabolised by human recombinant 5-LOX; recombinant LTA<sub>4</sub> hydrolase converted chiral 5S(6)-epoxide-containing intermediates to resolvin E1 and 18S-resolvin E1 (Oh *et al.*, 2011).

| Nomenclature | Leukotriene C <sub>4</sub> synthase | $\gamma$ -Glutamyltransferase | Dipeptidase 1                            | Dipeptidase 2   | Leukotriene A <sub>4</sub> hydrolase   |
|--------------|-------------------------------------|-------------------------------|------------------------------------------|-----------------|----------------------------------------|
| E.C.         | 4.4.1.20                            | 2.3.2.2                       | 2.3.2._                                  | 2.3.2._         | 3.3.2.6                                |
| Ensembl ID   | ENSG000000213316                    | ENSG00000006625               | ENSG00000015413                          | ENSG00000167261 | ENSG00000111144                        |
| Other names  | LTC4S                               | GGT                           | DPEP1                                    | DPEP2           | LTA4H                                  |
| Inhibitors   | –                                   | –                             | Cilastatin (Koller <i>et al.</i> , 1985) | –               | Bestatin (Orning <i>et al.</i> , 1991) |

LTA4H is a member of a family of arginyl aminopeptidases (ENSM00250000001675), which also includes aminopeptidase B (RNPEP, ENSG00000176393) and aminopeptidase B-like 1 (RNPEPL1, ENSG00000142327). Dipeptidase 1 and 2 are members of a family of membrane dipeptidases (ENSM00250000001170), which also includes DPEP3 (ENSG00000141096) for which LTD<sub>4</sub> appears not to be a substrate.

**Abbreviations:** CDC, cinnamyl-3,4-dihydroxy- $\alpha$ -cyanocinnamate; **CJ13610**, 1-carboxamido-1-(3-*S*-[4-[2-methylimidazole]-thiophenyl])-4-cyclopentylether; **esculetin**, 6,7-dihydroxycoumarin; **FR122047**, 1-([4,5-bis(methoxyphenyl)-2-thiazoyl]carbonyl)-4-methylpiperazine hydrochloride; **12R-HPETE**, 12R-hydroperoxyeicosatetraenoic acid; **FLAP**, 5-lipoxygenase-activating protein, also known as MK-886-binding protein (ENSG00000132965); **NDGA**, nordihydroguaiaretic acid

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# Endocannabinoid turnover

**Overview:** the principle endocannabinoids are 2-arachidonoylglycerol (2AG) and anandamide (*N*-arachidonylethanolamine, AEA), thought to be generated on demand rather than stored. For 2AG, the key enzyme involved is diacylglycerol lipase (DGL), whilst several routes for AEA synthesis have been described, the best characterized of which involves *N*-acylphosphatidylethanolamine-phospholipase D (NAPE-PLD, see Simon and Cravatt, 2010). Inactivation of these endocannabinoids appears to occur predominantly through monoacylglycerol lipase (MGL) and fatty acid amide hydrolase (FAAH) for 2AG and AEA, respectively. *In vitro* experiments indicate that the endocannabinoids are also substrates for oxidative metabolism via cyclooxygenase, lipoxygenase and cytochrome P450 enzyme activities (see Alexander and Kendall, 2007; Fowler, 2007, Snider *et al.*, 2010).

| Nomenclature                        | Diacylglycerol lipase $\alpha$                                    | Diacylglycerol lipase $\beta$                                     | <i>N</i> -Acylphosphatidylethanolamine-phospholipase D |
|-------------------------------------|-------------------------------------------------------------------|-------------------------------------------------------------------|--------------------------------------------------------|
| Preferred abbreviation              | DGL $\alpha$                                                      | DGL $\beta$                                                       | NAPE-PLD                                               |
| E.C.                                | 3.1.1.-                                                           | 3.1.1.-                                                           | –                                                      |
| Ensembl ID                          | ENSG00000134780                                                   | ENSG00000164535                                                   | ENSG00000161048                                        |
| Other names                         | Neural stem cell-derived dendrite regulator                       | KCCR13L                                                           | –                                                      |
| Selective inhibitors ( $pIC_{50}$ ) | Tetrahydrolipstatin (7.2, Bisogno <i>et al.</i> , 2003), RHC80267 | Tetrahydrolipstatin (7.0, Bisogno <i>et al.</i> , 2003), RHC80267 | –                                                      |

NAPE-PLD activity appears to be enhanced by polyamines in the physiological range (Liu *et al.*, 2002), but fails to transphosphatidylate with alcohols (Petersen and Hansen, 1999) unlike phosphatidylcholine-specific phospholipase D.

| Nomenclature                        | Monoacylglycerol lipase                          | Fatty acid amide hydrolase-1                                                                                                                                                                                       | Fatty acid amide hydrolase-2                                                      | <i>N</i> -Acylethanolamine acid amidase                                                                                   |
|-------------------------------------|--------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|
| Preferred abbreviation              | MGL                                              | FAAH                                                                                                                                                                                                               | FAAH2                                                                             | NAAA                                                                                                                      |
| E.C.                                | 3.1.1.23                                         | 3.5.1._                                                                                                                                                                                                            | 3.5.1._                                                                           | 3.5.1._                                                                                                                   |
| Ensembl ID                          | ENSG00000074416                                  | ENSG00000117480                                                                                                                                                                                                    | ENSG00000165591                                                                   | ENSG00000138744                                                                                                           |
| Other names                         | HU-K5, lysophospholipase homolog                 | Oleamide hydrolase, anandamide hydrolase, FAAH1                                                                                                                                                                    | –                                                                                 | Acid ceramidase-like protein, <i>N</i> -acylsphingosine amidohydrolase-like, <i>N</i> -palmitoylethanolamine acid amidase |
| Substrate potency order             | 2OG = 2AG >> AEA (Ghafouri <i>et al.</i> , 2004) | AEA > ODA > OEA > PEA (Wei <i>et al.</i> , 2006)                                                                                                                                                                   | ODA > OEA > AEA > PEA (Wei <i>et al.</i> , 2006)                                  | PEA > MEA > SEA > OEA > AEA (Ueda <i>et al.</i> , 2001)                                                                   |
| Selective inhibitors ( $pIC_{50}$ ) | JZL184 (8.1, Long <i>et al.</i> , 2009)          | PF3845 (6.6, Ahn <i>et al.</i> , 2009), PF750 (6.3–7.8, Ahn <i>et al.</i> , 2007), JNJ1661010 (7.8, Keith <i>et al.</i> , 2008), URB597 (6.3–7.0, Wei <i>et al.</i> , 2006), OL135 (7.4, Wei <i>et al.</i> , 2006) | URB597 (7.5–8.3, Wei <i>et al.</i> , 2006), OL135 (7.9, Wei <i>et al.</i> , 2006) | CCP (5.3, Tsuboi <i>et al.</i> , 2004)                                                                                    |

Many of the compounds described as inhibitors are irreversible and so potency estimates will vary with incubation time. FAAH2 is not found in rodents (Wei *et al.*, 2006). 2AG has been reported to be hydrolysed by multiple enzyme activities from neural preparations, including ABHD6 (ENSG00000163686, Blankman *et al.*, 2007), ABHD12 (ENSG00000100997, Blankman *et al.*, 2007), neuropathy target esterase (PNPLA6, ENSG00000032444, Marrs *et al.*, 2010) and carboxylesterase 1 (CES1, ENSG00000198848, Xie *et al.*, 2010). Although these have been incompletely defined, WWL70 has been described to inhibit ABHD6 selectively with a  $pIC_{50}$  value of 7.2 (Li *et al.*, 2007).

**Abbreviations:** 2AG, 2-arachidonoylglycerol; 2OG, 2-oleoylglycerol; AEA, anandamide; CCP, *N*-cyclohexylcarbonylpentadecylamine; DGL, diacylglycerol lipase; FAAH, fatty acid amide hydrolase; JNJ1661010, 4-(3-phenyl-[1,2,4] thiadiazol-5-yl)-piperazine-1-carboxylic acid phenylamide; JZL184, 4-nitrophenyl 4-(dibenzod[1,3]dioxol-5-yl(hydroxy)methyl)piperidine-1-carboxylate; MGL, monoacylglycerol lipase; MEA, *N*-myristoylethanolamine; NAAA, *N*-acylethanolamine acid amidase; NAPE-PLD, *N*-acylphosphatidylethanolamine-phospholipase D; ODA, octadec(9,10z)enamide; OEA, *N*-oleoylethanolamine OL135, 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-phenylheptane; PEA, *N*-palmitoylethanolamine; PF3845, 4-(3-[5-(trifluoromethyl)pyridin-2-yloxy]benzyl)-*N*-(pyridin-3-yl)piperidine-1-carboxamide; PF750, *N*-phenyl-4-(quinolin-3-ylmethyl)piperidine-1-carboxamide; RHC80267, 1,6-bis(cyclohexyloximinocarbonylamino)hexane; SEA, *N*-stearoylethanolamine; URB597, cyclohexyl carbamic acid 3'-carbamoyl-biphenyl-3-yl ester; WWL70, 4'-carbamoylbiphenyl-4-yl methyl(3-(pyridin-4-yl)benzyl)carbamate

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# Glycerophospholipid turnover

**Overview:** phospholipids are the basic barrier components of membranes in eukaryotic cells divided into glycerophospholipids (phosphatidic acid, phosphatidylethanolamine, phosphatidylcholine, phosphatidylserine, phosphatidylinositol and its phosphorylated derivatives) and sphingolipids (ceramide phosphorylcholine and ceramide phosphorylethanolamine).

## Phosphoinositide-specific phospholipase C (E.C. 3.1.4.11)

**Overview:** Phosphoinositide-specific phospholipase C (PLC) catalyses the hydrolysis of phosphatidylinositol 4,5-bisphosphate to inositol 1,4,5-trisphosphate and 1,2-diacylglycerol, each of which have major second messenger functions. Two domains, X and Y, essential for catalytic activity, are conserved in the different forms of PLC. Isoforms of PLC- $\beta$  (ENSF00000000466) are activated primarily by G protein-coupled receptors through members of the  $G_{q/11}$  family of G proteins. The receptor-mediated activation of PLC- $\gamma$  involves their phosphorylation by receptor tyrosine kinases (RTK, see Page S203) in response to activation of a variety of growth factor receptors and immune system receptors. PLC- $\epsilon$ 1 may represent a point of convergence of signalling via both G protein-coupled and catalytic receptors.  $Ca^{2+}$  ions are required for catalytic activity of PLC isoforms and have been suggested to be the major physiological form of regulation of PLC- $\delta$  activity. PLC has been suggested to be activated non-selectively by the small molecule *m*-3M3FBS (Bae *et al.*, 2003), although this mechanism of action has been questioned (Krkukova *et al.*, 2004). The aminosteroid U73122 has been described as an inhibitor of phosphoinositide-specific PLC (Smith *et al.*, 1990), although its selectivity among the isoforms is untested and it has been reported to occupy the  $H_1$  histamine receptor (Hughes *et al.*, 2000).

| Nomenclature          | PLC $\beta$ 1                                                                                                                                                    | PLC $\beta$ 2                                                                                                                                                        | PLC $\beta$ 3                                                                                                    | PLC $\beta$ 4                           |
|-----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|-----------------------------------------|
| Ensembl ID            | ENSG00000182621                                                                                                                                                  | ENSG00000137841                                                                                                                                                      | ENSG00000149782                                                                                                  | ENSG00000101333                         |
| Other names           | PLC-I, PLC-154, KIAA0581                                                                                                                                         | –                                                                                                                                                                    | –                                                                                                                | –                                       |
| Endogenous activators | $G\alpha_q$ (Smrcka <i>et al.</i> , 1991; Hepler <i>et al.</i> , 1993), $G\alpha_{11}$ (Hepler <i>et al.</i> , 1993), $G\beta\gamma$ (Park <i>et al.</i> , 1993) | $G\alpha_{16}$ (Lee <i>et al.</i> , 1992), $G\beta\gamma$ (Camps <i>et al.</i> , 1992; Park <i>et al.</i> , 1993), <i>rac2</i> (Illenberger <i>et al.</i> , 2003a,b) | $G\alpha_q$ (Lee <i>et al.</i> , 1992), $G\beta\gamma$ (Carozzi <i>et al.</i> , 1993; Park <i>et al.</i> , 1993) | $G\alpha_q$ (Jhon <i>et al.</i> , 1993) |

| Nomenclature          | PLC $\gamma$ 1                              | PLC $\gamma$ 2                                                                                  | PLC $\delta$ 1                                                                                                                                                            | PLC $\delta$ 3  | PLC $\delta$ 4  |
|-----------------------|---------------------------------------------|-------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|-----------------|
| Ensembl ID            | ENSG00000124181                             | ENSG00000197943                                                                                 | ENSG00000187091                                                                                                                                                           | ENSG00000161714 | ENSG00000115556 |
| Other names           | PLC-II, PLC-148                             | PLC-IV                                                                                          | PLC-III                                                                                                                                                                   | –               | –               |
| Endogenous activators | PIP <sub>3</sub> (Bae <i>et al.</i> , 1998) | PIP <sub>3</sub> (Bae <i>et al.</i> , 1998)                                                     | Transglutaminase II (Murthy <i>et al.</i> , 1999), p122-RhoGAP (Homma and Emori, 1995), spermine (Haber <i>et al.</i> , 1991), $G\beta\gamma$ (Park <i>et al.</i> , 1993) | –               | –               |
| Inhibitors            | –                                           | Rac1, <i>rac2</i> , <i>rac3</i> (Piechulek <i>et al.</i> , 2005; Walliser <i>et al.</i> , 2008) | Sphingomyelin (Pawelczyk and Lowenstein, 1992)                                                                                                                            | –               | –               |

PLC- $\delta$ 2 has been cloned from bovine sources (Meldrum *et al.*, 1991).

| Nomenclature          | PLC $\epsilon$ 1                                                 | PLC $\zeta$ 1                       | PLC $\eta$ 1    | PLC $\eta$ 2                               |
|-----------------------|------------------------------------------------------------------|-------------------------------------|-----------------|--------------------------------------------|
| Ensembl ID            | ENSG00000138193                                                  | ENSG00000139151                     | ENSG00000114805 | ENSG00000149527                            |
| Other names           | Pancreas-enriched PLC                                            | Testis-development protein NYD-SP27 | –               | –                                          |
| Endogenous activators | Ras (Song <i>et al.</i> , 2001), Rho (Wing <i>et al.</i> , 2003) | –                                   | –               | $G\beta\gamma$ (Zhou <i>et al.</i> , 2005) |

A series of PLC-like proteins (PLCL1 ENSG00000115896; PLCL2 ENSG00000154822 and PLCL3 ENSG00000114805) form a family (ENSF00000000386) with PLC $\delta$  and PLC $\zeta$ 1 isoforms, but appear to lack catalytic activity.

**Phospholipase A<sub>2</sub> (E.C. 3.1.1.4)**

**Overview:** Phospholipase A<sub>2</sub> (PLA<sub>2</sub>) cleaves the *sn*-2 fatty acid of glycerophospholipids, primarily phosphatidylcholine, to generate lysophosphatidylcholine and arachidonic acid. Most commonly-used inhibitors (e.g. BEL, ATFMK or MAFP) are either non-selective within the family of phospholipase A<sub>2</sub> enzymes or have activity against other eicosanoid-metabolising enzymes.

**Secreted or extracellular forms**

| Nomenclature           | Ensembl ID      | Other names                                                                                                                             |
|------------------------|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| sPLA <sub>2</sub> -1B  | ENSG00000170890 | GIB, pancreatic PLA <sub>2</sub>                                                                                                        |
| sPLA <sub>2</sub> -2A  | ENSG00000188257 | GIIA, GIIC sPLA <sub>2</sub> , non-pancreatic secretory phospholipase A <sub>2</sub> , NPS-PLA <sub>2</sub> , synovial PLA <sub>2</sub> |
| sPLA <sub>2</sub> -2D  | ENSG00000117215 | GIID, GIID sPLA <sub>2</sub> , secretory-type PLA <sub>2</sub> , stroma-associated homolog                                              |
| sPLA <sub>2</sub> -2E  | ENSG00000188784 | GIIE, GIIE sPLA <sub>2</sub>                                                                                                            |
| sPLA <sub>2</sub> -2F  | ENSG00000158786 | GIIF, GIIF sPLA <sub>2</sub>                                                                                                            |
| sPLA <sub>2</sub> -3   | ENSG00000100078 | GIII, GIII sPLA <sub>2</sub>                                                                                                            |
| sPLA <sub>2</sub> -10  | ENSG00000069764 | GX, GX sPLA <sub>2</sub>                                                                                                                |
| sPLA <sub>2</sub> -12A | ENSG00000123739 | GXIIA, GXII sPLA <sub>2</sub>                                                                                                           |

PLA<sub>2</sub>-2C (ENSG00000187980) may be a pseudogene, while PLA<sub>2</sub>-12B (GXIIIB, GXIII sPLA<sub>2</sub>-like, ENSG00000138308) appears to be catalytically inactive (Rouault *et al.*, 2003). A further fragment has been identified with sequence similarities to Group II PLA<sub>2</sub> members (ENSG00000187980).

A binding protein for secretory phospholipase A<sub>2</sub> has been identified (ENSG00000153246) which shows modest selectivity for sPLA<sub>2</sub>-1B over sPLA<sub>2</sub>-2A, and also binds snake toxin phospholipase A<sub>2</sub> (Ancian *et al.*, 1995). The binding protein appears to have clearance function for circulating secretory phospholipase A<sub>2</sub>, as well as signalling functions, and is a candidate antigen for idiopathic membranous nephropathy (Beck *et al.*, 2009).

**Cytosolic, calcium-dependent forms**

| Nomenclature          | Ensembl ID      | Other names                                                                         |
|-----------------------|-----------------|-------------------------------------------------------------------------------------|
| cPLA <sub>2</sub> -4A | ENSG00000116711 | GIVA, Calcium-dependent PLA <sub>2</sub> , cytosolic phospholipase A <sub>2</sub> α |
| cPLA <sub>2</sub> -4B | ENSG00000168970 | GIVB, cytosolic phospholipase A <sub>2</sub> β                                      |
| cPLA <sub>2</sub> -4C | ENSG00000105499 | GIVC, cytosolic phospholipase A <sub>2</sub> γ                                      |
| cPLA <sub>2</sub> -4D | ENSG00000159337 | GIVD, cytosolic phospholipase A <sub>2</sub> δ                                      |
| cPLA <sub>2</sub> -4E | ENSG00000188089 | GIVE, cytosolic phospholipase A <sub>2</sub> ε                                      |
| cPLA <sub>2</sub> -4F | ENSG00000168907 | GIVF, cytosolic phospholipase A <sub>2</sub> ζ                                      |

cPLA<sub>2</sub>-4A also expresses lysophospholipase (EC 3.1.1.5) activity (Sharp *et al.*, 1994).

**Other forms**

| Nomenclature          | Ensembl ID      | Other names                                                           |
|-----------------------|-----------------|-----------------------------------------------------------------------|
| PLA <sub>2</sub> -G5  | ENSG00000127472 | GV, PLA <sub>2</sub> -10                                              |
| iPLA <sub>2</sub> -G6 | ENSG00000184381 | GVI, 85 kDa Ca <sup>2+</sup> -independent, iPLA <sub>2</sub> , PNPLA9 |
| PLA <sub>2</sub> -G7  | ENSG00000146070 | GVII, LDL-associated phospholipase A <sub>2</sub>                     |

PLA<sub>2</sub>-G7 and a close homologue (HSD-PLA<sub>2</sub>, also known as serine-dependent phospholipase A<sub>2</sub>, PAFAH2, ENSG00000158006) also express platelet-activating factor acetylhydrolase activity (EC 3.1.1.47). Otoconin 90 (OC90, ENSG00000132297) shows sequence homology to PLA<sub>2</sub>-G10.

**Phosphatidylcholine-specific phospholipase D (E.C. 3.1.4.4)**

**Overview:** Phosphatidylcholine-specific phospholipase D (PLD, ENSF0000001451) catalyses the formation of phosphatidic acid from phosphatidylcholine. In addition, the enzyme can make use of alcohols, such as butanol in a transphosphatidylation reaction (Randall *et al.*, 1990).

|                       |                                                                                                                          |                                                                                             |
|-----------------------|--------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Nomenclature          | PLD1                                                                                                                     | PLD2                                                                                        |
| Ensembl ID            | ENSG00000075651                                                                                                          | ENSG00000129219                                                                             |
| Other names           | Choline phosphatase 1                                                                                                    | Choline phosphatase 2                                                                       |
| Endogenous activators | ARF, PIP <sub>2</sub> , RhoA, PKC-evoked phosphorylation (Hammond <i>et al.</i> , 1997), RalA (Luo <i>et al.</i> , 1997) | ARF, PIP <sub>2</sub> (Lopez <i>et al.</i> , 1998), oleic acid (Sarri <i>et al.</i> , 2003) |
| Endogenous inhibitors | Gβγ (Preininger <i>et al.</i> , 2006)                                                                                    | Gβγ (Preininger <i>et al.</i> , 2006)                                                       |
| Selective inhibitors  | –                                                                                                                        | VU0364739 (pIC <sub>50</sub> 7.7, Lavieri <i>et al.</i> , 2010)                             |

A lysophospholipase D activity (ENPP2, ENSG00000136960, also known as ectonucleotide pyrophosphatase/phosphodiesterase 2, phosphodiesterase I, nucleotide pyrophosphatase 2, autotaxin) has been described, which not only catalyses the production of lysophosphatidic acid from lysophosphatidylcholine, but also cleaves ATP (see Goding *et al.*, 2003). Additionally, an *N*-acylethanolamine-specific phospholipase D (NAPE-PLD, ENSG00000161048) has been characterized, which appears to have a role in the generation of endocannabinoids/endovanilloids (see Page S300), including anandamide (Okamoto *et al.*, 2004). This enzyme activity appears to be enhanced by polyamines in the physiological range (Liu *et al.*, 2002) and fails to transphosphatidylate with alcohols (Petersen and Hansen, 1999).

**Lipid phosphate phosphatases (E.C. 3.1.3.4)**

**Overview:** Lipid phosphate phosphatases, divided into phosphatidic acid phosphatases (ENSM00260000050433) or lipins (ENSM00250000001227), catalyse the dephosphorylation of phosphatidic acid to generate inorganic phosphate and diacylglycerol.

| Nomenclature | Ensembl ID      | Other names |
|--------------|-----------------|-------------|
| Lipin1       | ENSG00000134324 | –           |
| Lipin2       | ENSG00000101577 | –           |
| Lipin3       | ENSG00000132793 | SMP2        |
| PPA2A        | ENSG00000067113 | LPP1        |
| PPA2B        | ENSG00000162407 | LPP3        |
| PPA3A        | ENSG00000141934 | LPP2        |

**Abbreviations:** *m*-3M3FBS, 2,4,6-trimethyl-*N*-(*meta*-3-trifluoromethylphenyl)-benzenesulphonamide; ARF, ADP-ribosylation factor; ATFMK, arachidonoyltrifluoromethylketone; BEL, bromoenolactone; MAFP, methylarachidonoylfluorophosphonate; NAPE-PLD, *N*-acylethanolamine-specific phospholipase D; PIP<sub>2</sub>, phosphatidylinositol 4,5-bisphosphate; PIP<sub>3</sub>, phosphatidylinositol 3,4,5-trisphosphate; PKC, protein kinase C; U73122, 1-(6-[[[(17β)-3-methoxyestra-1,3,5[10]-trien-17-yl]amino]hexyl]-1*H*-pyrrole-2,5-dione; VU0364739, *N*-[2-[4-(3-fluorophenyl)-1-oxo-2,4,8-triazaspiro[4.5]decan-8-yl]ethyl]naphthalene-2-carboxamide;

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# Haem oxygenase (EC 1.14.99.3)

**Overview:** Haem oxygenase (heme,hydrogen-donor:oxygen oxidoreductase ( $\alpha$ -methene-oxidizing, hydroxylating)) converts haem into biliverdin and carbon monoxide, utilizing NADPH as cofactor.

|                        |                              |                          |
|------------------------|------------------------------|--------------------------|
| Nomenclature           | Haem oxygenase 1             | Haem oxygenase 2         |
| Preferred abbreviation | HO1                          | HO2                      |
| Ensembl ID             | ENSG00000100292              | ENSG00000103415          |
| Other names            | Inducible form, HMOX1, hsp32 | Constitutive form, HMOX2 |

The existence of a third non-catalytic version of haem oxygenase, HO3, has been proposed, although this has been suggested to be a pseudogene (Hayashi *et al.*, 2004).

Tin protoporphyrin IX acts as a haem oxygenase inhibitor in rat liver with an  $IC_{50}$  value of 11 nM (Drummond and Kappas, 1981).

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# Hydrogen sulphide synthesis

**Overview:** Hydrogen sulfide is a putative gasotransmitter, with similarities to nitric oxide and carbon monoxide. Although the enzymes indicated have multiple enzymatic activities, the focus of this table is the generation of hydrogen sulfide and the enzymatic characteristics are described accordingly.

| Nomenclature           | Cystathionine $\beta$ -synthase                          | Cystathionine $\gamma$ -lyase       | L-Cysteine:2-oxoglutarate aminotransferase                                                                                                                 | 3-Mercaptopyruvate sulfurtransferase                       |
|------------------------|----------------------------------------------------------|-------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|
| Preferred abbreviation | CBS                                                      | CSE                                 | CAT                                                                                                                                                        | MPST                                                       |
| EC number              | 4.2.1.22                                                 | 4.4.1.1                             | 4.4.1.13                                                                                                                                                   | 2.8.1.2                                                    |
| Ensembl ID             | ENSG00000160200                                          | ENSG00000116761                     | ENSG00000171097                                                                                                                                            | ENSG00000128309                                            |
| Other names            | Serine sulfhydrylase, $\beta$ -thionase                  | CGL, $\gamma$ -cystathioninase, CTH | Kynurenine:2-oxoglutarate transaminase (EC 2.6.1.7), glutamine-phenylpyruvate transaminase (EC 2.6.1.64), cysteine transaminase, cysteine aminotransferase | –                                                          |
| Cofactor/s             | Pyridoxal phosphate                                      | Pyridoxal phosphate                 | Pyridoxal phosphate                                                                                                                                        | Zinc                                                       |
| Substrates ( $K_m$ )   | Cysteine (6 mM, Chen <i>et al.</i> , 2004), homocysteine | Cysteine                            | Cysteine                                                                                                                                                   | 3-Mercaptopyruvate (1.2 mM, Nagahara <i>et al.</i> , 1995) |
| Products               | Cystathionine                                            | Pyruvate, ammonia                   | Pyruvate, ammonia                                                                                                                                          | Pyruvate                                                   |
| Inhibitors             | Aminooxyacetic acid                                      | Propargylglycine                    |                                                                                                                                                            |                                                            |

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# Inositol phosphate turnover

**Overview:** the sugar alcohol D-*myo*-inositol is a component of the phosphatidylinositol signalling cycle (see Page S302), where the principal second messenger is inositol 1,4,5-trisphosphate, IP<sub>3</sub>, which acts at intracellular ligand-gated ion channels, IP<sub>3</sub> receptors (see Page S157) to elevate intracellular calcium. IP<sub>3</sub> is recycled to inositol by phosphatases or phosphorylated to form other active inositol polyphosphates. Inositol produced from dephosphorylation of IP<sub>3</sub> is recycled into membrane phospholipid under the influence of phosphatidylinositol synthase activity (CDP-diacylglycerol-inositol 3-phosphatidyltransferase [EC 2.7.8.11]).

**Inositol 1,4,5-trisphosphate 3-kinases** (E.C. 2.7.1.127, ENSFM0025000001260) catalyse the generation of inositol 1,3,4,5-tetrakisphosphate (IP<sub>4</sub>) from IP<sub>3</sub>. IP<sub>3</sub> kinase activity is enhanced in the presence of calcium/calmodulin (Conigrave and Roufogalis, 1989).

| Nomenclature      | IP <sub>3</sub> kinase A | IP <sub>3</sub> kinase B | IP <sub>3</sub> kinase C |
|-------------------|--------------------------|--------------------------|--------------------------|
| HGNC nomenclature | ITPKA                    | ITPKB                    | ITPKC                    |
| Ensembl ID        | ENSG00000137825          | ENSG00000143772          | ENSG00000086544          |
| Other names       | IP3-3KC, IP3KA           | IP3-3KB, IP3KB           | IP3-3KC, IP3KC           |

**Inositol polyphosphate phosphatases:** members of this family exhibit phosphatase activity towards IP<sub>3</sub>, as well as towards other inositol derivatives, including the phospholipids PIP<sub>2</sub> and PIP<sub>3</sub>. With 1,4,5-IP<sub>3</sub> as substrate, 1-phosphatase (EC 3.1.3.57) generates 4,5-IP<sub>2</sub>, 4-phosphatases (EC 3.1.3.66, ENSFM0025000001432) generate 1,5-IP<sub>2</sub> and 5-phosphatases (E.C. 3.1.3.36 or 3.1.3.56) generate 1,4-IP<sub>2</sub>.

| Nomenclature                          | HGNC nomenclature                                                                                    | Ensembl ID                                                                                                                                                                                         | Other names                                                                                                                                                                                                                                        |
|---------------------------------------|------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Inositol polyphosphate 1-phosphatase  | INPP1                                                                                                | ENSG00000151689                                                                                                                                                                                    | –                                                                                                                                                                                                                                                  |
| Inositol polyphosphate 4-phosphatases | INPP4A;<br>INPP4B                                                                                    | ENSG00000040933;<br>ENSG00000109452                                                                                                                                                                | Type I, 107 kDa INPP4;<br>Type II, 105 kDa INPP4                                                                                                                                                                                                   |
| Inositol polyphosphate 5-phosphatases | INPP5A;<br>INPP5B;<br>INPP5D;<br>INPP5E;<br>INPP5J;<br>INPP5K;<br>INPPL1<br>OCRL;<br>SYNJ1;<br>SYNJ2 | ENSG00000068383;<br>ENSG00000204084;<br>ENSG00000168918;<br>ENSG00000148384;<br>ENSG00000185133;<br>ENSG00000132376;<br>ENSG00000165458<br>ENSG00000122126;<br>ENSG00000159082;<br>ENSG00000078269 | SPTASE;<br>75 kDa inositol polyphosphate-5-phosphatase;<br>hp51CN, SHIP;<br>COR1, JBTS1, PPI5PIV;<br>–<br>SKIP;<br>SHIP2, SH2-containing inositol phosphatase 2;<br>Oculocerebrorenal syndrome of Lowe, OCSL;<br>Synaptojanin 1;<br>Synaptojanin 2 |

*In vitro* analysis suggested IP<sub>3</sub> and IP<sub>4</sub> were poor substrates for SKIP, synaptojanin 1 and synaptojanin 2, but suggested that PIP<sub>2</sub> and PIP<sub>3</sub> were more efficiently hydrolysed (Schmid *et al.*, 2004).

**Inositol monophosphatase** (E.C.3.1.3.25, IMPase, *myo*-inositol-1(or 4)-phosphate phosphohydrolase) is a magnesium-dependent homodimer which hydrolyses *myo*-inositol monophosphate to generate *myo*-inositol and phosphate. Glycerol may be a physiological phosphate acceptor. Lithium is a nonselective un-competitive inhibitor more potent at IMPase 1 (pK<sub>i</sub> ca. 3.5, McAllister *et al.*, 1992; pIC<sub>50</sub> 3.2, Ohnishi *et al.*, 2007) than IMPase 2 (pIC<sub>50</sub> 1.8–2.1, Ohnishi *et al.*, 2007). IMPase activity may be inhibited competitively by L690330 (pK<sub>i</sub> 5.5, McAllister *et al.*, 1992), although the enzyme selectivity is not yet established.

| Nomenclature | Ensembl ID      | Other names | Substrate rank order                                                                             |
|--------------|-----------------|-------------|--------------------------------------------------------------------------------------------------|
| IMPase 1     | ENSG00000133731 | IMPA1       | Inositol 4-phosphate>inositol 3-phosphate>inositol 1-phosphate (McAllister <i>et al.</i> , 1992) |
| IMPase 2     | ENSG00000141401 | IMPA2       | –                                                                                                |

Polymorphisms in either of the genes encoding these enzymes have been linked with bipolar disorder (Sjoholt *et al.*, 1997; 2000; Yoshikawa *et al.*, 1997). Disruption of the gene encoding IMPase 1, but not IMPase 2, appears to mimic the effects of lithium in mice (Cryns *et al.*, 2007; 2008).

**Abbreviations:** IP<sub>3</sub>, inositol 1,4,5-trisphosphate; L690330, 1-(4-hydroxyphenoxy)ethane-1,1-bisphosphonate; PIP<sub>2</sub>, phosphatidylinositol-4,5-bisphosphate; PIP<sub>3</sub>, phosphatidylinositol-3,4,5-trisphosphate

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# Protein serine/threonine kinases (E.C. 2.7.1.-)

**Overview:** Protein serine/threonine kinases use the co-substrate ATP to phosphorylate serine and/or threonine residues on target proteins. Analysis of the human genome suggests the presence of 518 protein kinases in man, with over 100 protein kinase-like pseudogenes (see Manning *et al.*, 2002). It is beyond the scope of the Guide to list all these protein kinase activities; this summary focusses on AGC protein kinases associated with GPCR signalling, which may be divided into 15 subfamilies in man.

Most inhibitors of these enzymes have been assessed in cell-free investigations and so may appear to 'lose' potency and selectivity in intact cell assays. In particular, ambient ATP concentrations may be influential in responses to inhibitors, since the majority are directed at the ATP binding site (Davies *et al.*, 2000).

## G protein coupled receptor kinases

G protein-coupled receptor kinases, epitomized by  $\beta$ ARK, are involved in the rapid phosphorylation and desensitization of GPCR. Classically, high concentrations of  $\beta_2$ -adrenoceptor agonists (see Page S26) binding to the receptor lead to the consequent activation and dissociation of the heterotrimeric G protein  $G_s$ .  $G\alpha_s$  activates adenylyl cyclase activity (see Page S288), while  $G\beta\gamma$  subunits perform other functions, one of which is to recruit  $\beta$ ARK to phosphorylate serine/threonine residues in the cytoplasmic tail of the  $\beta_2$ -adrenoceptor. The phosphorylated receptor binds, with high affinity, a member of the arrestin family (ENSM0025000000572), which prevents further signalling through the G protein (uncoupling) and may allow interaction with scaffolding proteins, such as clathrin, with the possible consequence of internalization and/or degradation.

| Systematic nomenclature | Preferred abbreviation | Ensembl ID      | Other names                                                      | Comment                                                                                                                              |
|-------------------------|------------------------|-----------------|------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| GRK1                    | RHOK                   | ENSG00000185974 | Rhodopsin kinase, G protein-coupled receptor kinase 1, GPRK1, RK | –                                                                                                                                    |
| GRK2                    | $\beta$ ARK            | ENSG00000173020 | $\beta$ -Adrenergic receptor kinase, ADRBK1                      | Protein kinase C-mediated phosphorylation increases membrane association (Chuang <i>et al.</i> , 1995; Winstel <i>et al.</i> , 1996) |
| GRK3                    | $\beta$ ARK2           | ENSG00000100077 | $\beta$ -Adrenergic receptor kinase 2, ADRBK2                    | –                                                                                                                                    |
| GRK4                    | –                      | ENSG00000125388 | G protein-coupled receptor kinase 4, GPRK2L                      | Inhibited by $Ca^{2+}$ /calmodulin (Sallese <i>et al.</i> , 1997)                                                                    |
| GRK5                    | –                      | ENSG00000198873 | G protein-coupled receptor kinase 5                              | Phosphorylated and inhibited by protein kinase C (Pronin and Benovic, 1997)                                                          |
| GRK6                    | –                      | ENSG00000198055 | G protein-coupled receptor kinase 6                              | –                                                                                                                                    |
| GRK7                    | –                      | ENSG00000114124 | G protein-coupled receptor kinase 7                              | –                                                                                                                                    |

Loss-of-function mutations in RHOK or retinal and pineal gland arrestin (ENSG00000130561) are associated with Oguchi disease, a form of congenital stationary night blindness.

## Protein kinase A (PKA)

Cyclic AMP-mediated signalling involves regulation of ion channels (see Page S153 and S156), members of the Rap guanine nucleotide exchange family (Epac, ENSM00250000000899, see Page S288) and activation of protein kinase A (PKA, also known as cyclic AMP-dependent protein kinase). PKA is a heterotetrameric enzyme composed of two regulatory and two catalytic subunits, which can be distinguished from Epac (exchange protein directly activated by cAMP, de Rooij *et al.*, 1998) by differential activation by  $N^6$ -benzyl-cAMP (see Table) and CPT-2'-OMe-cAMP, respectively (Kang *et al.*, 2005).

| Nomenclature        | Regulatory subunits                                                                                                  | Catalytic subunits:                                                                |
|---------------------|----------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| Ensembl ID          | PRKAR1A (ENSG00000108946);<br>PRKAR1B (ENSG00000188191);<br>PRKAR2A (ENSG00000114302);<br>PRKAR2B (ENSG00000005249); | PRKACA (ENSG00000072062);<br>PRKACB (ENSG00000142875);<br>PRKACG (ENSG00000165059) |
| Selective activator | $N^6$ -Benzyl-cAMP (Christensen <i>et al.</i> , 2003)                                                                | –                                                                                  |
| Selective inhibitor | Rp-cAMPS                                                                                                             | –                                                                                  |
| Probe               | [ $^3H$ ]-cAMP                                                                                                       | –                                                                                  |

Other members of the PKA family are PRKX (X-linked protein kinase, PKX1, ENSG00000183943) and PRKY (Y-linked protein kinase, ENSG00000099725). PRKX and PRKY are expressed on X and Y chromosomes, respectively, and appear to interchange in some XX males and XY females (Schiebel *et al.*, 1997).

**Protein kinase B (PKB)**

The action of phosphatidylinositol 3-kinase (PI3K), a downstream kinase activated by receptor tyrosine kinases (see Page S203), produces a series of phosphorylated phosphoinositides, which recruit 3-phosphoinositide-dependent kinase (PDK1, see below) activity to the plasma membrane, leading to activation of PKB (also known as Akt, Rac serine/threonine protein kinase, v-akt murine thymoma viral oncogene). PKB may be activated by PIP<sub>3</sub>, PDK1-mediated phosphorylation (Alessi *et al.*, 1997) and mTORC2-mediated phosphorylation (Hresko and Mueckler, 2005, Sarbassov *et al.*, 2005).

|                     |                                           |                 |                 |
|---------------------|-------------------------------------------|-----------------|-----------------|
| Nomenclature        | PKB1                                      | PKB2            | PKB2            |
| HGNC nomenclature   | AKT1                                      | AKT2            | AKT3            |
| Ensembl ID          | ENSG00000142208                           | ENSG00000105221 | ENSG00000117020 |
| Other names         | PKB $\alpha$                              | PKB $\beta$     | PKB $\gamma$    |
| Selective inhibitor | GSK690693 (Heerding <i>et al.</i> , 2008) |                 |                 |

**Protein kinase C**

Protein kinase C is the target for the tumour-promoting phorbol esters, such as tetradecanoyl- $\beta$ -phorbol acetate (TPA, also known as PMA).

*Classical protein kinase C isoforms:* Members of the classical protein kinase C family are activated by Ca<sup>2+</sup> and diacylglycerol, and may be inhibited by GF109203X, calphostin C, Gö6983, chelerythrine and Ro318220.

|                      |                 |                                                                                                   |                 |
|----------------------|-----------------|---------------------------------------------------------------------------------------------------|-----------------|
| Nomenclature         | PKC $\alpha$    | PKC $\beta$                                                                                       | PKC $\gamma$    |
| HGNC nomenclature    | PRKCA           | PRKCB                                                                                             | PRKCG           |
| Ensembl ID           | ENSG00000154229 | ENSG00000166501                                                                                   | ENSG00000126583 |
| Selective inhibitors | –               | Ruboxistaurin (8.3, Jirousek <i>et al.</i> , 1996), CGP53353 (6.4, Chalfant <i>et al.</i> , 1996) | –               |

*Novel protein kinase C isoforms:* Members of the classical protein kinase C family are activated by diacylglycerol and may be inhibited by calphostin C, Gö6983 and chelerythrine.

|                   |                 |                 |                 |                 |                                    |
|-------------------|-----------------|-----------------|-----------------|-----------------|------------------------------------|
| Nomenclature      | PKC $\delta$    | PKC $\epsilon$  | PKC $\eta$      | PKC $\theta$    | PKC $\mu$                          |
| HGNC nomenclature | PRKCD           | PRKCE           | PRKCH           | PRKCQ           | PRKD1                              |
| Ensembl ID        | ENSG00000163932 | ENSG00000171132 | ENSG00000027075 | ENSG00000065675 | ENSG00000184304                    |
| Other names       | –               | –               | –               | –               | PKCM, PRKCM, protein kinase D, PKD |

**Atypical protein kinase C isoforms**

|                       |                          |                  |
|-----------------------|--------------------------|------------------|
| Nomenclature          | PKC $\iota$              | PKC $\zeta$      |
| HGNC nomenclature     | PRKCI                    | PRKCZ            |
| Ensembl ID            | ENSG00000163558          | ENSG00000067606  |
| Other names           | PKC $\lambda$ in rodents | –                |
| Endogenous activators | –                        | Arachidonic acid |

**Protein kinase G (PKG)**

Cyclic GMP-dependent protein kinase is a dimeric enzyme activated by cGMP generated by particulate guanylyl cyclases (see Page S195) or soluble guanylyl cyclases (see Page S288).

|                        |                                            |                 |
|------------------------|--------------------------------------------|-----------------|
| Preferred abbreviation | PKG1                                       | PKG2            |
| HGNC nomenclature      | PRKG1                                      | PRKG2           |
| Ensembl ID             | ENSG00000185532                            | ENSG00000138669 |
| Selective inhibitors   | Rp-8-CPT-cGMPS (Butt <i>et al.</i> , 1994) |                 |

**Mitogen-activated protein kinases (MAP kinases)**

MAP kinases (CMGC kinases, ENSF00000000137) may be divided into three major families: ERK, JNK and p38 MAP kinases.

**ERK** may be activated by phosphorylation by the dual specificity mitogen-activated kinase kinases, MAP2K1 (also known as MEK1, ENSG00000169032) and MAP2K2 (also known as MEK2, ENSG00000126934). The inhibitors PD98059 (Alessi *et al.*, 1995; Dudley *et al.*, 1995) and U0126 (Duncia *et al.*, 1998; Favata *et al.*, 1998) act to inhibit these enzymes (Davies *et al.*, 2000), and are used to inhibit ERK1 and ERK2.

| Nomenclature | HGNC nomenclature | Ensembl ID      | Other names                                                                             |
|--------------|-------------------|-----------------|-----------------------------------------------------------------------------------------|
| ERK1         | MAPK3             | ENSG00000102882 | Insulin-stimulated MAP2 kinase, ERT2, p44-MAPK, microtubule-associated protein-2 kinase |
| ERK2         | MAPK1             | ENSG00000100030 | Mitogen-activated protein kinase 2, p42-MAPK, ERT1                                      |

**JNK** may be activated by phosphorylation by the dual specificity mitogen-activated kinase kinases, MAP2K4 (also known as JNKK1, ENSG00000065559) and MAP2K7 (also known as JNKK2, ENSG00000076984).

| Nomenclature | HGNC nomenclature | Ensembl ID      | Other names                                    |
|--------------|-------------------|-----------------|------------------------------------------------|
| JNK1         | MAPK8             | ENSG00000107643 | SAPK1, c-Jun N-terminal kinase 1, JNK-46       |
| JNK2         | MAPK9             | ENSG00000050748 | c-Jun N-terminal kinase 2, JNK-55              |
| JNK3         | MAPK10            | ENSG00000109339 | c-Jun N-terminal kinase 3, MAP kinase p49 3F12 |

SP600125 is able to inhibit all three isoforms of JNK with  $pIC_{50}$  values of 6.7 (Bennett *et al.*, 2001).

**p38** may be activated by phosphorylation by the dual specificity mitogen-activated kinase kinases, MAP2K3 (also known as MEK3, ENSG00000034152) and MAP2K6 (also known as SAPKK3, ENSG00000108984).

| Nomenclature | HGNC nomenclature | Ensembl ID      | Other names                                                                            |
|--------------|-------------------|-----------------|----------------------------------------------------------------------------------------|
| p38 $\alpha$ | MAPK14            | ENSG00000112062 | Cytokine suppressive anti-inflammatory drug binding protein, MAX-interacting protein 2 |
| p38 $\beta$  | MAPK11            | ENSG00000185386 | p38-2, SAPK2                                                                           |
| p38 $\gamma$ | MAPK12            | ENSG00000188130 | ERK-6, ERK5, SAPK3                                                                     |
| p38 $\delta$ | MAPK13            | ENSG00000156711 | SAPK4                                                                                  |

SB203580 has been reported to inhibit p38 $\alpha$  and p38 $\beta$  with  $pIC_{50}$  values of 8.0 and 7.0, respectively (Eyers *et al.*, 1998). SB202190 inhibits p38 $\beta$  (Lee *et al.*, 1994).

**Rho kinase**

Rho kinase (also known as P160ROCK, Rho-activated kinase) is activated by members of the Rho small G protein family (ENSM00500000269651), which are activated by GTP exchange factors, such as ARHGEF1 (p115-RhoGEF, ENSG00000076928), which in turn may be activated by  $G\alpha_{12/13}$  subunits (Kozasa *et al.*, 1998).

| Nomenclature | HGNC nomenclature | Ensembl ID      | Other names |
|--------------|-------------------|-----------------|-------------|
| Rho kinase 1 | ROCK1             | ENSG00000067900 | p160ROCK    |
| Rho kinase 2 | ROCK2             | ENSG00000134318 | –           |

Rho kinase may be inhibited selectively by Y27362 (Uehata *et al.*, 1997) or fasudil (Asano *et al.*, 1989).

**Other AGC kinases**

For many of these remaining protein kinases, there is less information about the regulation and substrate specificity, as well as a paucity of pharmacological data.

| Subfamily | Nomenclature  | HGNC nomenclature | Ensembl ID      | Other names                                                                                                  | Comment                                                                                                                                                                                                       |
|-----------|---------------|-------------------|-----------------|--------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| DMPK      | DMPK          | DMPK              | ENSG00000104936 | Dystrophia myotonica-protein kinase, myotonin-protein kinase                                                 | Reduced expression of DMPK is associated with myotonic dystrophy 1 (see Kaliman and Lagostera 2008)                                                                                                           |
|           | DMPK2         | CDC42BPG          | ENSG00000171219 | Myotonic dystrophy kinase-related CDC42 binding protein kinase $\gamma$ , HSMDPKIN, kappa-200, MRCK $\gamma$ |                                                                                                                                                                                                               |
|           | MRCK $\alpha$ | CDC42BPA          | ENSG00000143776 | MRCKA, myotonic dystrophy kinase-related CDC42-binding protein kinase $\alpha$                               | Reported to have a role in cellular iron regulation (Cmejla <i>et al.</i> , 2010)                                                                                                                             |
|           | MRCK $\beta$  | CDC42BPB          | ENSG00000198752 | MRCKB, myotonic dystrophy kinase-related CDC42-binding protein kinase $\beta$                                | Reported to be involved in cell migration (Huo <i>et al.</i> , 2011)                                                                                                                                          |
|           | CRIK          | CIT               | ENSG00000122966 | Citron Rho-interacting kinase, serine/threonine-protein kinase 21                                            | Shares structural homology with the Rho kinases                                                                                                                                                               |
| MAST      | MAST1         | MAST1             | ENSG00000105613 | Syntrophin-associated protein kinase                                                                         | Members of the microtubule-associated serine/threonine kinase family appear to have a role in platelet production (Johnson <i>et al.</i> , 2009) and inflammatory bowel disease (Labbe <i>et al.</i> , 2008). |
|           | MAST2         | MAST2             | ENSG00000086015 | –                                                                                                            |                                                                                                                                                                                                               |
|           | MAST3         | MAST3             | ENSG00000099308 | –                                                                                                            |                                                                                                                                                                                                               |
|           | MAST4         | MAST4             | ENSG00000069020 | –                                                                                                            |                                                                                                                                                                                                               |
|           | MASTL         | MASTL             | ENSG00000120539 | Microtubule associated serine/threonine kinase-like, greatwall, GWL                                          |                                                                                                                                                                                                               |
| NDR       | LATS1         | LATS1             | ENSG00000131023 | Large tumor suppressor homologue 1, WARTS                                                                    | The large tumour suppressor protein kinases are phosphorylated and activated by MST2 kinase (serine/threonine kinase 3, ENSG00000104375, Chan <i>et al.</i> , 2005)                                           |
|           | LATS2         | LATS2             | ENSG00000150457 | Large tumor suppressor homologue 2, KPM                                                                      |                                                                                                                                                                                                               |
|           | NDR1          | STK38             | ENSG00000112079 | Serine/threonine kinase 38, nuclear Dbf2-related kinase 1                                                    |                                                                                                                                                                                                               |
|           | NDR2          | STK38L            | ENSG00000211455 | Serine/threonine kinase 38 like, nuclear Dbf2-related kinase 2                                               |                                                                                                                                                                                                               |
| PKB       | PDK1          | PDPK1             | ENSG00000140992 | 3-Phosphoinositide-dependent protein kinase 1                                                                |                                                                                                                                                                                                               |

| Subfamily | Nomenclature | HGNC nomenclature | Ensembl ID      | Other names                                                                                                                | Comment                                                                                                                                                                                                                              |
|-----------|--------------|-------------------|-----------------|----------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PKN       | PKN1         | PKN1              | ENSG00000123143 | Protein kinase N1, protein kinase C-related kinase 1, PAK1, PKN, PRK1, PRKCL1                                              | PKN family members are activated by Rho, PIP <sub>3</sub> and PDK1 (Dong <i>et al.</i> , 2000)                                                                                                                                       |
|           | PKN2         | PKN2              | ENSG00000065243 | Protein kinase N2, pak-2, PRK2, PRKCL2                                                                                     |                                                                                                                                                                                                                                      |
|           | PKN3         | PKN3              | ENSG00000160447 | Protein kinase N3, PKN $\beta$                                                                                             |                                                                                                                                                                                                                                      |
| RSK       | MSK1         | RPS6KA5           | ENSG00000100784 | Ribosomal protein S6 kinase $\alpha$ 5, nuclear mitogen- and stress-activated protein kinase 1, RSK-like protein kinase    | The mitogen- and stress-acted protein kinases are activated by phosphorylation evoked by MAP kinases and appear to be central to that pathway of cAMP response element-binding protein phosphorylation (Wiggin <i>et al.</i> , 2002) |
|           | MSK2         | RPS6KA4           | ENSG00000162302 | Ribosomal protein S6 kinase $\alpha$ 4, nuclear mitogen- and stress-activated protein kinase 2, ribosomal protein kinase B |                                                                                                                                                                                                                                      |
|           | S6K1         | RPS6KB1           | ENSG00000108443 | S6K $\beta$ 1                                                                                                              |                                                                                                                                                                                                                                      |
|           | S6K2         | RPS6KB2           | ENSG00000175634 | S6K $\beta$ , S6K $\beta$ 2                                                                                                |                                                                                                                                                                                                                                      |
|           | RSK1         | RPS6KA1           | ENSG00000117676 | MAPKAPK1A, RSK $\alpha$ 1                                                                                                  |                                                                                                                                                                                                                                      |
|           | RSK2         | RPS6KA3           | ENSG00000177189 | MAPKAPK1B, RSK $\alpha$ 3, ISPK1                                                                                           |                                                                                                                                                                                                                                      |
|           | RSK3         | RPS6KA2           | ENSG00000071242 | MAPKAPK1C, RSK $\alpha$ 2                                                                                                  |                                                                                                                                                                                                                                      |
|           | RSK4         | RPS6KA6           | ENSG00000072133 | RSK $\alpha$ 6                                                                                                             |                                                                                                                                                                                                                                      |
|           | SGK494       | –                 | ENSG00000167524 | AC005726.6                                                                                                                 |                                                                                                                                                                                                                                      |
|           |              |                   |                 |                                                                                                                            |                                                                                                                                                                                                                                      |
| RSKL      |              | RPS6KC1           | ENSG00000136643 | 52 kDa ribosomal protein S6 kinase, RPK118, humS6PKh1                                                                      | Serum- and glucocorticoid-inducible kinases are regulated at the transcriptional level by serum and glucocorticoids. SGK1 has been reported to be phosphorylated and activated by mTORC2 (Garcia-Martinez and Alessi, 2008)          |
|           |              | RPS6KL1           | ENSG00000198208 | ribosomal protein S6 kinase-like 1                                                                                         |                                                                                                                                                                                                                                      |
| SGK       | SGK1         | SGK1              | ENSG00000118515 | SGK                                                                                                                        |                                                                                                                                                                                                                                      |
|           | SGK2         | SGK2              | ENSG00000101049 | –                                                                                                                          |                                                                                                                                                                                                                                      |
|           | SGK3         | SGK3              | ENSG00000104205 | SGK2, SGK1                                                                                                                 |                                                                                                                                                                                                                                      |
| YANK      | YANK1        | STK32A            | ENSG00000169302 |                                                                                                                            |                                                                                                                                                                                                                                      |
|           | YANK2        | STK32B            | ENSG00000152953 | STK32, STKG6                                                                                                               |                                                                                                                                                                                                                                      |
|           | YANK3        | STK32C            | ENSG00000165752 | PKE                                                                                                                        |                                                                                                                                                                                                                                      |

## Selected non-AGC protein kinase activities

| Nomenclature           | AMP kinase                                                                                                                                                                                                                       | Casein kinase 2                                                                    | Myosin light chain kinase                                                        | Calmodulin-dependent kinase II                                                                                         |
|------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|
| Preferred abbreviation | AMPK                                                                                                                                                                                                                             | CK2                                                                                | MLCK1 (smooth muscle and non-muscle isoform),<br>MLCK2 (skeletal muscle isoform) | CaMKII                                                                                                                 |
| Ensembl ID             | $\alpha$ 1 (ENSG00000132356);<br>$\alpha$ 2 (ENSG00000162409);<br>$\beta$ 1 (ENSG00000111725);<br>$\beta$ 2 (ENSG00000131791);<br>$\gamma$ 1 (ENSG00000181929);<br>$\gamma$ 2 (ENSG00000106617);<br>$\gamma$ 3 (ENSG00000115592) | $\alpha$ ENSG00000101266;<br>$\alpha'$ ENSG00000070770;<br>$\beta$ ENSG00000204435 | MLCK1 ENSG00000065534;<br>MLCK2 ENSG00000101306                                  | $\alpha$ (ENSG00000070808);<br>$\beta$ (ENSG00000058404);<br>$\gamma$ (ENSG00000148660);<br>$\delta$ (ENSG00000145349) |
| Other names            | –                                                                                                                                                                                                                                | –                                                                                  | MYLK                                                                             | –                                                                                                                      |
| Endogenous activator   | AMP                                                                                                                                                                                                                              | –                                                                                  | Ca <sup>2+</sup> -calmodulin                                                     | Ca <sup>2+</sup> -calmodulin                                                                                           |
| Selective activators   | AICA-riboside (Corton <i>et al.</i> , 1995)                                                                                                                                                                                      | –                                                                                  | –                                                                                | –                                                                                                                      |
| Selective inhibitors   | Dorsomorphin (Zhou <i>et al.</i> , 2001)                                                                                                                                                                                         | DRB (Zandomeni <i>et al.</i> , 1986)                                               | –                                                                                | K252a (Hashimoto <i>et al.</i> , 1991)                                                                                 |

AMP-activated protein kinase is a heterotrimeric protein kinase, made up of  $\alpha$ ,  $\beta$  and  $\gamma$  subunits, while casein kinase 2 is a heterotetrameric protein kinase, made up of 2  $\beta$  subunits with two other subunits of  $\alpha$  and/or  $\alpha'$  composition. STO609 is an inhibitor of calmodulin kinase kinase (ENSM0025000001201, Tokumitsu *et al.*, 2002), an upstream activator of calmodulin-dependent kinase.

**Abbreviations:** AICA-riboside, 5-aminoimidazole-4-carboxamide-1- $\beta$ -ribose, also known as acadesine; API2, 1,5-dihydro-5-methyl-1- $\beta$ -D-ribofuranosyl-1,4,5,6,8-pentaazaacennaphthyl-3-amine, also known as tricinibine; CGP53353, 5,6-bis([4-fluorophenyl]amino)-2H-isoindole-1,3-dione; CPT-2'-Ome-cAMP, 8-(4-chlorophenylthio)-2'-O-methyladenosine 3',5'-cyclic monophosphate monosodium hydrate; DRB, 5,6-dichloro-1- $\beta$ -D-ribofuranosylbenzimidazole; fasudil, 1-(5-isoquinolylsulfonyl)homopiperazine dihydrochloride, also known as HA1077; GSK690693, 4-[2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-7-[[[(3S)-piperidin-3-yl]methoxy]imidazo[4,5-c]pyridin-4-yl]-2-methylbut-3-yn-2-ol]; PD98059, 2-(2-amino-3-methoxy-phenyl)chromen-4-one; PDK1, phosphoinositide-dependent protein kinase 1 (ENSG00000140992); Rp-8-CPT-cGMPs, Rp-8-[(4-chlorophenyl)thio]-guanosine-cyclic 3',5'-hydrogen phosphorothioate; ruboxistaurin, (S)-13-[(dimethylamino)methyl]-10,11,14,15-tetrahydro-4,9:16,21-dimetheno-1H,13H-dibenzo[*e,k*]pyrrolo[3,4-*h*][1,4,13]oxadiazacyclohexadecene-1,3(2H)-dione, also known as LY333531; SB203580, 4-(5-[4-fluorophenyl]-2-[4-methylsulfinylphenyl]-3H-imidazol-4-yl)pyridine; SP600125, anthra[1,9-*cd*]pyrazol-6(2H)-one; STO609, trans-4-[(1R)-1-aminoethyl]-N-4-pyridinyl-cyclohexane carboxamide (Y-27632), and 7-oxo-7H-benzimidazo (2,1a) benz (de) isoquinoline-3-carboxy acid acetate

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# Protein turnover

**Overview:** peptidases and proteinases hydrolyse peptide bonds, and can be simply divided on the basis of whether terminal peptide bonds are cleaved (exopeptidases and exoproteinases) at the amino terminus (aminopeptidases) or carboxy terminus (carboxypeptidases). Non-terminal peptide bonds are cleaved by endopeptidases and endoproteinases, which are divided into serine endopeptidases (EC 3.4.21.-), cysteine endopeptidases (EC 3.4.22.-), aspartate endopeptidases (EC 3.4.23.-), metalloendopeptidases (EC 3.4.24.-) and threonine endopeptidases (EC 3.4.25.-).

It is beyond the scope of the Guide to list all peptidase and proteinase activities; this summary focusses on selected enzymes of significant pharmacological interest.

## Aminopeptidases (E.C. 3.4.11.-)

| Nomenclature                                     | HGNC nomenclature | Ensembl ID      | Other names                                                                                                                                                             | Comments                                                                                                                                                       |
|--------------------------------------------------|-------------------|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Aminopeptidase A                                 | DNPEP             | ENSG00000123992 | Aspartyl aminopeptidase, ASPEP, DAP                                                                                                                                     | Hydrolyses CCK-8 (Migaud <i>et al.</i> , 1996); angiotensin-II (Zini <i>et al.</i> , 1996), neurokinin B, chromogranin A, kallidin (Goto <i>et al.</i> , 2006) |
| Aminopeptidase N                                 | ANPEP             | ENSG00000166825 | Alanyl aminopeptidase, microsomal aminopeptidase, gp150, myeloid plasma membrane glycoprotein CD13                                                                      | –                                                                                                                                                              |
| Aminopeptidase O                                 | C9orf3            | ENSG00000148120 | AOPEP                                                                                                                                                                   | –                                                                                                                                                              |
| Aminopeptidase Q                                 | –                 | ENSG00000172901 | Laeverin, AC010282.1                                                                                                                                                    | –                                                                                                                                                              |
| Aminopeptidase-like 1                            | NPEPL1            | ENSG00000215440 | –                                                                                                                                                                       | –                                                                                                                                                              |
| Arginyl aminopeptidase                           | RNPEP             | ENSG00000176393 | Aminopeptidase B                                                                                                                                                        | –                                                                                                                                                              |
| Arginyl aminopeptidase-like 1                    | RNPEPL1           | ENSG00000142327 | Aminopeptidase B-like                                                                                                                                                   | –                                                                                                                                                              |
| Endoplasmic reticulum aminopeptidase 1           | ERAP1             | ENSG00000164307 | Adipocyte-derived leucine aminopeptidase, puromycin-insensitive leucyl-specific aminopeptidase, type 1 tumor necrosis factor receptor shedding aminopeptidase regulator | –                                                                                                                                                              |
| Endoplasmic reticulum aminopeptidase 2           | ERAP2             | ENSG00000164308 | Leukocyte-derived arginine aminopeptidase                                                                                                                               | –                                                                                                                                                              |
| Glutamyl aminopeptidase                          | ENPEP             | ENSG00000138792 | EAP, aminopeptidase A, differentiation antigen gp160, CD249 antigen                                                                                                     | –                                                                                                                                                              |
| Leucine aminopeptidase 3                         | LAP3              | ENSG00000002549 | LAP, LAPEP                                                                                                                                                              | –                                                                                                                                                              |
| Leucyl-cysteinyl aminopeptidase                  | LNPEP             | ENSG00000113441 | Oxytocinase, OTase, insulin-regulated membrane aminopeptidase, insulin-responsive aminopeptidase, IRAP, placental leucine aminopeptidase, P-LAP                         | Hydrolyses vasopressin, oxytocin, kallidin, met-enkephalin, dynorphin A                                                                                        |
| Leukotriene A <sub>4</sub> hydrolase             | LTA4H             | ENSG00000111144 | –                                                                                                                                                                       | Hydrolyses leukotriene A <sub>4</sub> (see Page S296)                                                                                                          |
| Methionyl aminopeptidase 1                       | METAP1            | ENSG00000164024 | MAP1A                                                                                                                                                                   | –                                                                                                                                                              |
| Methionyl aminopeptidase 2                       | METAP2            | ENSG00000111142 | –                                                                                                                                                                       | –                                                                                                                                                              |
| Methionyl aminopeptidase type 1D (mitochondrial) | METAP1D           | ENSG00000172878 | MAP1D                                                                                                                                                                   | –                                                                                                                                                              |
| Puromycin-sensitive aminopeptidase               | NPEPPS            | ENSG00000141279 | Aminopeptidase puromycin sensitive                                                                                                                                      | –                                                                                                                                                              |

| Nomenclature                                    | HGNC nomenclature | Ensembl ID      | Other names                                                                                            | Comments |
|-------------------------------------------------|-------------------|-----------------|--------------------------------------------------------------------------------------------------------|----------|
| Puromycin-sensitive aminopeptidase-like protein | –                 | ENSG00000174093 | RP11-1407O15.2                                                                                         | –        |
| TRH-specific aminopeptidase                     | TRHDE             | ENSG00000072657 | Thyrotropin-releasing hormone-degrading ectoenzyme, thyroliberinase, pyroglutamyl-peptidase II, PAP-II | –        |
| X-prolyl aminopeptidase 1                       | XPNPEP1           | ENSG00000108039 | Aminopeptidase P 1, soluble X-prolyl aminopeptidase                                                    | –        |
| X-prolyl aminopeptidase 2                       | XPNPEP2           | ENSG00000122121 | Aminopeptidase P 2, membrane-bound X-prolyl aminopeptidase                                             | –        |
| X-prolyl aminopeptidase 3                       | XPNPEP3           | ENSG00000196236 | Aminopeptidase P 3, APP3, NPHPL1                                                                       | –        |

### Serine-type carboxypeptidases (3.4.16.-)

| Nomenclature                               | HGNC nomenclature | Ensembl ID      | Other names                                                     |
|--------------------------------------------|-------------------|-----------------|-----------------------------------------------------------------|
| Cathepsin A                                | CTSA              | ENSG00000064601 | GSL, PPGB, carboxypeptidase C                                   |
| Carboxypeptidase D                         | CPD               | ENSG00000108582 | –                                                               |
| Vitellogenic carboxypeptidase-like protein | CPVL              | ENSG00000106066 | –                                                               |
| Prolylcarboxypeptidase                     | PRCP              | ENSG00000137509 | Angiotensinase C, HUMPCP, PCP, lysosomal Pro-X carboxypeptidase |
| Serine carboxypeptidase 1                  | SCPEP1            | ENSG00000121064 | RISC                                                            |

### Metallo-carboxypeptidases (3.4.17.-)

| Nomenclature                                          | HGNC nomenclature | Ensembl ID      | Other names                               |
|-------------------------------------------------------|-------------------|-----------------|-------------------------------------------|
| AE binding protein 1                                  | AEBP1             | ENSG00000106624 | Aortic carboxypeptidase-like protein ACLP |
| Carboxypeptidase A1 (pancreatic)                      | CPA1              | ENSG00000091704 | –                                         |
| Carboxypeptidase A2 (pancreatic)                      | CPA2              | ENSG00000158516 | –                                         |
| Carboxypeptidase A3 (mast cell)                       | CPA3              | ENSG00000163751 | –                                         |
| Carboxypeptidase A4                                   | CPA4              | ENSG00000128510 | –                                         |
| Carboxypeptidase A5                                   | CPA5              | ENSG00000158525 | –                                         |
| Carboxypeptidase A6                                   | CPA6              | ENSG00000165078 | CPAH                                      |
| Carboxypeptidase B1 (tissue)                          | CPB1              | ENSG00000153002 | –                                         |
| Carboxypeptidase B2 (plasma)                          | CPB2              | ENSG00000080618 | CPU, PCPB, TAFI                           |
| Carboxypeptidase E                                    | CPE               | ENSG00000109472 | –                                         |
| Carboxypeptidase M                                    | CPM               | ENSG00000135678 | –                                         |
| Carboxypeptidase N, polypeptide 1                     | CPN1              | ENSG00000120054 | Carboxypeptidase N, polypeptide 1         |
| Carboxypeptidase N, polypeptide 2                     | CPN2              | ENSG00000178772 | ACBP                                      |
| Carboxypeptidase O                                    | CPO               | ENSG00000144410 | –                                         |
| Carboxypeptidase X (M14 family), member 1             | CPXM1             | ENSG00000088882 | CPX-1, CPX1, CPXM                         |
| Carboxypeptidase X (M14 family), member 2             | CPXM2             | ENSG00000121898 | –                                         |
| Carboxypeptidase Z                                    | CPZ               | ENSG00000109625 | –                                         |
| Carnosine dipeptidase 1 (metallopeptidase M20 family) | CNDP1             | ENSG00000150656 | Glutamate carboxypeptidase-like protein 2 |
| Carnosine dipeptidase 2                               | CNDP2             | ENSG00000133313 | HsT2298, PEPA                             |
| Dipeptidyl-peptidase 7                                | DPP7              | ENSG00000176978 | DPPII                                     |

| Nomenclature                                            | HGNC nomenclature | Ensembl ID      | Other names                                |
|---------------------------------------------------------|-------------------|-----------------|--------------------------------------------|
| Folate hydrolase (prostate-specific membrane antigen) 1 | FOLH1             | ENSG00000086205 | GCP2, GCPII, NAALAD1, NAALAdase, PSM, PSMA |
| Folate hydrolase 1B                                     | FOLH1B            | ENSG00000134612 | FOLH2, FOLHP, GCPIII, PSMAL                |
| N-Acetylated $\alpha$ -linked acidic dipeptidase-like 1 | NAALADL1          | ENSG00000168060 | –                                          |
| N-Acetylated $\alpha$ -linked acidic dipeptidase 2      | NAALAD2           | ENSG00000077616 | –                                          |
| Plasma glutamate carboxypeptidase                       | –                 | ENSG00000104324 | AC010859.1                                 |

### Endopeptidases

| Nomenclature          | Neutral endopeptidase          | Dipeptidyl peptidase IV                        |
|-----------------------|--------------------------------|------------------------------------------------|
| E.C.                  | 3.4.24.11                      | 3.4.14.5                                       |
| HGNC nomenclature     | MME                            | DPP4                                           |
| Ensembl ID            | ENSG00000196549                | ENSG00000197635                                |
| Other names           | Enkephalinase, neprilysin, NEP | CD26, adenosine deaminase complexing protein-2 |
| Endogenous substrates | Enkephalins                    | GLP1                                           |
| Selective inhibitors  | Thiorphan                      | –                                              |

| Nomenclature          | Angiotensin-converting enzyme 1                   | Angiotensin-converting enzyme 2                                 | Endothelin-converting enzyme 1         | Endothelin-converting enzyme 2 |
|-----------------------|---------------------------------------------------|-----------------------------------------------------------------|----------------------------------------|--------------------------------|
| E.C.                  | 3.4.15.1                                          | 3.4.15.1                                                        | 3.4.24.71                              | 3.4.24.71                      |
| HGNC nomenclature     | ACE                                               | ACE2                                                            | ECE1                                   | ECE2                           |
| Ensembl ID            | ENSG00000159640                                   | ENSG00000130234                                                 | ENSG00000117298                        | ENSG00000145194                |
| Other names           | Dipeptidyl carboxypeptidase I, Kininase II, CD143 | –                                                               | –                                      | –                              |
| Endogenous substrates | Angiotensin I > angiotensin II                    | Angiotensin I > angiotensin I-9 (Donoghue <i>et al.</i> , 2000) | Endothelin-1, -2, -3                   | Endothelin-1, -2, -3           |
| Selective inhibitors  | Captopril                                         | Captopril                                                       | SM19712 (Umekawa <i>et al.</i> , 2000) | –                              |
| Probes                | Hip-His Leu                                       | Abz-Ser-Pro-Tyr(NO <sub>2</sub> )-OH                            | –                                      | –                              |

ACE1 appears to express a distinct GPI hydrolase activity (Kondoh *et al.* 2005).

### Caspases (E.C. 3.4.22.-)

**Overview:** Caspases, which derive their name from Cysteine ASpartate-specific proteASES, include at least two families; initiator caspases (caspases 2, 8, 9 and 10), which are able to hydrolyse and activate a second family of effector caspases (caspases 3, 6 and 7), which themselves are able to hydrolyse further cellular proteins to bring about programmed cell death. Caspases are heterotetrameric, being made up of two pairs of subunits, generated by a single gene product, which is proteolysed to form the mature protein. Members of the mammalian inhibitors of apoptosis proteins (IAP) are able to bind the procaspases, thereby preventing maturation to active proteinases.

| Nomenclature | Caspase 1                                                                                                                            | Caspase 2                                                                                               | Caspase 3                                                                               | Caspase 4                                        |
|--------------|--------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|--------------------------------------------------|
| EC           | 3.4.22.36                                                                                                                            | 3.4.22.55                                                                                               | 3.4.22.56                                                                               | 3.4.22.57                                        |
| Ensembl ID   | ENSG00000137752                                                                                                                      | ENSG00000106144                                                                                         | ENSG00000164305                                                                         | ENSG00000196954                                  |
| Other names  | CASP1, interleukin-1 $\beta$ convertase, IL-1BC, interleukin-1 $\beta$ -converting enzyme, IL-1 $\beta$ -converting enzyme, ICE, p45 | CASP2, ICH-1 protease, neural precursor cell expressed developmentally down-regulated protein 2, NEDD-2 | CASP3, apopain, cysteine protease CPP32, Yama protein, SREBP cleavage activity 1, SCA-1 | CASP4, ICH-2 protease, TX protease, ICE(rel)-II, |
| Subunits     | Caspase-1 subunit p20; caspase-1 subunit p10                                                                                         | Caspase-2 subunit p18; caspase-2 subunit p13; caspase-2 subunit p12                                     | Caspase-3 subunit p17; caspase-3 subunit p12                                            | Caspase-4 subunit 1; caspase-4 subunit 2         |

| Nomenclature          | Caspase 1                                                 | Caspase 2                                | Caspase 3                                                                                                                      | Caspase 4     |
|-----------------------|-----------------------------------------------------------|------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|---------------|
| Substrates            | Pro-caspase 4, pro-interleukin-1 $\beta$ , D4-GD1, parkin |                                          | Pro-caspase 7, caspase 3, PARP, ICAD, Rb, PKC $\delta$ , Huntingtin                                                            | Pro-caspase 1 |
| Endogenous activators | –                                                         | –                                        | Caspase 8, caspase 9, caspase 10, GrB                                                                                          | –             |
| Activators            | –                                                         | –                                        | PAC1 (Putt <i>et al.</i> , 2006), PETCM (Jiang <i>et al.</i> , 2003)                                                           | –             |
| Selective inhibitors  | Z-YVAD-FMK (Avivi-Green <i>et al.</i> , 2002)             | Z-VDVAD-FMK (Gamen <i>et al.</i> , 2000) | AZ10417808 (Scott <i>et al.</i> , 2003), Z-DEVD-FMK (Brockstedt <i>et al.</i> , 1998), Z-DQMD-FMK (Izban <i>et al.</i> , 2001) | –             |

CARD16 (Caspase recruitment domain-containing protein 16, caspase-1 inhibitor COP, CARD only domain-containing protein 1, pseudo interleukin-1 $\beta$  converting enzyme, pseudo-ICE, ENSG00000204397) shares sequence similarity with some of the caspases.

| Nomenclature          | Caspase 5                                        | Caspase 6                                    | Caspase 7                                                                       | Caspase 8                                                                                                                                                                                              |
|-----------------------|--------------------------------------------------|----------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| EC                    | 3.4.22.58                                        | 3.4.22.59                                    | 3.4.22.60                                                                       | 3.4.22.61                                                                                                                                                                                              |
| Ensembl ID            | ENSG00000137757                                  | ENSG00000138794                              | ENSG00000165806                                                                 | ENSG00000064012                                                                                                                                                                                        |
| Other names           | CASP5, ICH-3 protease, TY protease, ICE(rel)-III | CASP6, apoptotic protease Mch-2              | CASP7, ICE-like apoptotic protease 3, ICE-LAP3, apoptotic protease Mch-3, CMH-1 | CASP8, CE-like apoptotic protease 5, MORT1-associated CED-3 homolog, MACH, FADD-homologous ICE/ CED-3-like protease, FADD-like ICE, FLICE, apoptotic cysteine protease, apoptotic protease Mch-5, CAP4 |
| Subunits              | Caspase-5 subunit p20; caspase-5 subunit p10     | Caspase-6 subunit p18; caspase-6 subunit p11 | Caspase-7 subunit p20; caspase-7 subunit p11                                    | Caspase-8 subunit p18; caspase-8 subunit p10                                                                                                                                                           |
| Substrates            | –                                                | –                                            | Pro-caspase 7, caspase 3, PARP, ICAD, Rb, PKC $\delta$ , Huntingtin             | Pro-caspase 3, pro-caspase 7, caspase 8, Bid, FLIP, pro-caspase 6                                                                                                                                      |
| Endogenous activators |                                                  | –Caspase 8, caspase 9, caspase 10, GrB       | Caspase 8, caspase 9, caspase 10, GrB                                           | DISC                                                                                                                                                                                                   |
| Selective inhibitors  | Z-WEHD-FMK (Naito <i>et al.</i> , 2002)          | Z-VEID-FMK (Ruchaud <i>et al.</i> , 2002)    | –                                                                               | Z-IETD-FMK (Gregoli and Bondurant, 1999)                                                                                                                                                               |

| Nomenclature          | Caspase 9                                                                                                               | Caspase 10                                                                                                                                              | Caspase 14                                     |
|-----------------------|-------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| EC                    | 3.4.22.62                                                                                                               | 3.4.22.63                                                                                                                                               | 3.4.22.-                                       |
| Ensembl ID            | ENSG00000132906                                                                                                         | ENSG00000003400                                                                                                                                         | ENSG00000105141                                |
| Other names           | CASP, ICE-like apoptotic protease 6, ICE-LAP6, apoptotic protease Mch-6, apoptotic protease-activating factor 3, APAF-3 | CASP10, ICE-like apoptotic protease 4, apoptotic protease Mch-4, FAS-associated death domain protein interleukin-1 $\beta$ -converting enzyme 2, FLICE2 | CASP14                                         |
| Subunits              | Caspase-9 subunit p35; caspase-9 subunit p10                                                                            | Caspase-10 subunit p23/17; caspase-10 subunit p12                                                                                                       | Caspase-14 subunit p19; caspase-14 subunit p10 |
| Substrates            | Pro-caspase 3, pro-caspase 7, caspase 9, pro-caspase 6, PARP                                                            | Pro-caspase 3, pro-caspase 7, caspase 10, pro-caspase 6                                                                                                 | –                                              |
| Endogenous activators | –                                                                                                                       | DISC                                                                                                                                                    | –                                              |
| Selective inhibitors  | Z-LEHD-FMK (Mocanu <i>et al.</i> , 2000)                                                                                | –                                                                                                                                                       | –                                              |

**Cell-surface protein and extracellular matrix metalloproteinases (E.C. 3.4.24.-)**

**Matrix metalloproteinases (MMP)** are calcium- and zinc-dependent proteinases regulating the extracellular matrix and are often divided (e.g. Verma and Hansch, 2007) on functional and structural bases into gelatinases, collagenases, stromelysinases and matrilysins, as well as membrane type-MMP (MT-MMP).

| Nomenclature | Ensembl ID      | Other names                                                                                 | Selective inhibitors                           |
|--------------|-----------------|---------------------------------------------------------------------------------------------|------------------------------------------------|
| MMP1         | ENSG00000196611 | Collagenase-1, interstitial collagenase, fibroblast collagenase                             | ARP100 (Tuccinardi <i>et al.</i> , 2006)       |
| MMP2         | ENSG00000087245 | Gelatinase-A, 72 kDa type IV collagenase precursor, TBE- 1                                  |                                                |
| MMP3         | ENSG00000149968 | Stromelysin-1, transin-1                                                                    |                                                |
| MMP7         | ENSG00000137673 | Matrilysin, PUMP-1 protease, uterine metalloproteinase, matrin                              |                                                |
| MMP8         | ENSG00000118113 | Neutrophil collagenase, PMNL collagenase                                                    | CL82198, WAY170523 (Chen <i>et al.</i> , 2000) |
| MMP9         | ENSG00000100985 | Gelatinases-B, 92 kDa type IV collagenase, GELB                                             |                                                |
| MMP10        | ENSG00000166670 | Stromelysin-2, transin-2                                                                    |                                                |
| MMP11        | ENSG00000099953 | Stromelysin-3                                                                               |                                                |
| MMP12        | ENSG00000110347 | Macrophage metalloelastase, macrophage elastase, HME                                        |                                                |
| MMP13        | ENSG00000137745 | Collagenase-3                                                                               |                                                |
| MMP14        | ENSG00000157227 | MT1-MMP, MMP- X1                                                                            |                                                |
| MMP15        | ENSG00000102996 | MT2-MMP, SMCP- 2                                                                            |                                                |
| MMP16        | ENSG00000156103 | MT3-MMP, MMP- X2                                                                            |                                                |
| MMP17        | ENSG00000198598 | MT4-MMP                                                                                     |                                                |
| MMP19        | ENSG00000123342 | Matrix metalloproteinase RASI, MMP18                                                        |                                                |
| MMP20        | ENSG00000137674 | Enamelysin, enamel metalloproteinase                                                        |                                                |
| MMP21        | ENSG00000154485 | –                                                                                           |                                                |
| MMP23        | ENSG00000189409 | Matrix metalloproteinase 21, MMP-21, matrix metalloproteinase 22, MMP-22, Femalysin, MIFR-1 |                                                |
| MMP24        | ENSG00000125966 | MT5-MMP                                                                                     |                                                |
| MMP25        | ENSG00000008516 | MT6-MMP, leukolysin                                                                         |                                                |
| MMP26        | ENSG00000167346 | Matrilysin-2, endometase                                                                    |                                                |
| MMP27        | ENSG00000137675 | –                                                                                           |                                                |
| MMP28        | ENSG00000129270 | Epilysin                                                                                    |                                                |

A number of small molecule ‘broad spectrum’ inhibitors of MMP have been described, including marimastat and batimastat.

**Tissue inhibitors of metalloproteinase (TIMP)** proteins are endogenous inhibitors acting to chelate MMP proteins.

| Nomenclature | Ensembl ID      | Other names                                                                                                                                                            |
|--------------|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| TIMP1        | ENSG00000102265 | Tissue inhibitor of metalloproteinases 1, metalloproteinase inhibitor 1, erythroid-potentiating activity, EPA, fibroblast collagenase inhibitor, collagenase inhibitor |
| TIMP2        | ENSG00000035862 | CSC-21K                                                                                                                                                                |
| TIMP3        | ENSG00000100234 | Tissue inhibitor of metalloproteinases 3, metalloproteinase inhibitor 3 Precursor , MIG-5                                                                              |
| TIMP4        | ENSG00000157150 | Tissue inhibitor of metalloproteinases 4, metalloproteinase inhibitor 4                                                                                                |

**ADAM** (A Disintegrin And Metalloproteinase domain containing proteins) and **ADAMTS** (with thrombospondin motifs) metalloproteinases cleave cell-surface or transmembrane proteins to generate soluble and membrane-limited products.

| Nomenclature | Ensembl ID      | Other names                                                                                   |
|--------------|-----------------|-----------------------------------------------------------------------------------------------|
| ADAM2        | ENSG00000104755 | Fertilin subunit $\beta$ , PH30 $\beta$ , cancer/testis antigen 15, CT15                      |
| ADAM3        | ENSG00000197475 | ADAM3A, cyritestin 1, CYRN1, tMDCI                                                            |
| ADAM5        | ENSG00000196115 | Transmembrane metalloproteinase-like, disintegrin-like, and cysteine-rich protein II, tMDC II |
| ADAM6        | ENSG00000233988 | C14orf96, tMDCIV                                                                              |

| Nomenclature | Ensembl ID      | Other names                                                                                                                                                              |
|--------------|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ADAM7        | ENSG00000069206 | Sperm maturation-related glycoprotein GP-83                                                                                                                              |
| ADAM8        | ENSG00000151651 | Cell surface antigen MS2, CD156a antigen                                                                                                                                 |
| ADAM9        | ENSG00000168615 | Metalloprotease/disintegrin/cysteine-rich protein 9, myeloma cell metalloproteinase, meltrin $\gamma$ , cellular disintegrin-related protein                             |
| ADAM10       | ENSG00000137845 | Mammalian disintegrin-metalloprotease, Kuzbanian protein homolog, CDw156, CD156c antigen                                                                                 |
| ADAM11       | ENSG00000073670 | Metalloproteinase-like, disintegrin-like, and cysteine-rich protein, MDC                                                                                                 |
| ADAM12       | ENSG00000148848 | Meltrin $\alpha$                                                                                                                                                         |
| ADAM15       | ENSG00000143537 | Metalloproteinase-like, disintegrin-like, and cysteine-rich protein 15, MDC-15, Metalloprotease RGD disintegrin protein, metargidin                                      |
| ADAM17       | ENSG00000151694 | TNF $\alpha$ -converting enzyme, TNF $\alpha$ convertase, snake venom-like protease, CD156b antigen                                                                      |
| ADAM18       | ENSG00000168619 | Transmembrane metalloproteinase-like, disintegrin-like, and cysteine-rich protein III, tMDC III, ADAM27                                                                  |
| ADAM19       | ENSG00000135074 | Meltrin $\beta$ , metalloprotease and disintegrin dendritic antigen marker, MADDAM                                                                                       |
| ADAM20       | ENSG00000134007 | –                                                                                                                                                                        |
| ADAM21       | ENSG00000139985 | ADAM21P, ADAM31                                                                                                                                                          |
| ADAM22       | ENSG00000008277 | Metalloproteinase-like, disintegrin-like, and cysteine-rich protein 2, metalloproteinase-disintegrin ADAM22-3                                                            |
| ADAM23       | ENSG00000114948 | Metalloproteinase-like, disintegrin-like, and cysteine-rich protein 3, MDC-3                                                                                             |
| ADAM28       | ENSG00000042980 | Metalloproteinase-like, disintegrin-like, and cysteine-rich protein L, MDC-L, epididymal metalloproteinase-like, disintegrin-like, and cysteine-rich protein II, eMDC II |
| ADAM29       | ENSG00000168594 | Cancer/testis antigen 73, CT73                                                                                                                                           |
| ADAM30       | ENSG00000134249 | –                                                                                                                                                                        |
| ADAM32       | ENSG00000197140 | –                                                                                                                                                                        |
| ADAM33       | ENSG00000149451 | –                                                                                                                                                                        |

Additional family members include AC123767.2 (cDNA FLJ58962, moderately similar to mouse ADAM3, ENSG00000231168), AL160191.3 (ADAM21-like protein, ENSG00000235812), AC136428.3-2 (ENSG00000185520) and ADAMDEC1 (decysin 1, ENSG00000134028).

#### ADAMTS family

| Nomenclature | EC        | Ensembl ID      | Other names                                                                                                                 | Comment                                                                                                     |
|--------------|-----------|-----------------|-----------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| ADAMTS1      |           | ENSG00000154734 | METH-1                                                                                                                      |                                                                                                             |
| ADAMTS2      | 3.4.24.14 | ENSG00000087116 | Procollagen I/II amino propeptide-processing enzyme, procollagen I N-proteinase, PC I-NP, procollagen N-endopeptidase, pNPI |                                                                                                             |
| ADAMTS3      |           | ENSG00000156140 | Procollagen II amino propeptide-processing enzyme, procollagen II N-proteinase, PC II-NP                                    |                                                                                                             |
| ADAMTS4      | 3.4.24.82 | ENSG00000158859 | Aggrecanase-1, ADMP-1                                                                                                       |                                                                                                             |
| ADAMTS5      |           | ENSG00000154736 | Aggrecanase-2, ADMP-2, ADAMTS11                                                                                             |                                                                                                             |
| ADAMTS6      |           | ENSG00000049192 | –                                                                                                                           |                                                                                                             |
| ADAMTS7      |           | ENSG00000136378 | COMPase                                                                                                                     |                                                                                                             |
| ADAMTS8      |           | ENSG00000134917 | METH-2, METH-8                                                                                                              |                                                                                                             |
| ADAMTS9      |           | ENSG00000163638 | –                                                                                                                           |                                                                                                             |
| ADAMTS10     |           | ENSG00000142303 | –                                                                                                                           |                                                                                                             |
| ADAMTS12     |           | ENSG00000151388 | –                                                                                                                           |                                                                                                             |
| ADAMTS13     |           | ENSG00000160323 | von Willebrand factor-cleaving protease, vWF-CP                                                                             | Loss-of-function mutations of autoimmune antibodies are associated with thrombotic thrombocytopenic purpura |
| ADAMTS14     |           | ENSG00000138316 | –                                                                                                                           |                                                                                                             |
| ADAMTS15     |           | ENSG00000166106 | –                                                                                                                           |                                                                                                             |
| ADAMTS16     |           | ENSG00000145536 | –                                                                                                                           |                                                                                                             |
| ADAMTS17     |           | ENSG00000140470 | –                                                                                                                           |                                                                                                             |

| Nomenclature | EC | Ensembl ID      | Other names | Comment |
|--------------|----|-----------------|-------------|---------|
| ADAMTS18     |    | ENSG00000140873 | ADAMTS21    |         |
| ADAMTS19     |    | ENSG00000145808 | –           |         |
| ADAMTS20     |    | ENSG00000173157 | –           |         |
| PAPLN        |    | ENSG00000100767 | Papilin     |         |

Other family members include AC104758.12-5 (FLJ00317 protein Fragment ENSG00000231463), AC139425.3-1 (ENSG00000225577), and AC126339.6-1 (ENSG00000225734).

**Abbreviations:** **ARP100**, 2-([(1,1'-biphenyl)-4-ylsulfonyl]-[1-methylethoxy]amino)-N-hydroxyacetamide, **AZ10417808**, 2-([(3,4-dichlorophenyl)amino]-1,4-dihydro-6-nitro-4-oxo-N-2-propenyl-8-quinazolinecarboxamide; **CL82189**, N-(4-[4-morpholinyl]butyl)-2-benzofurancarboxamide hydrochloride; **PAC1**, 4-(phenylmethyl)-1-piperazineacetic acid ([2-hydroxy-3-(2-propenyl)phenyl]methylene)hydrazide; **PETCM**, 1-(trichloromethyl)-2-(4-pyridine)ethanol; **WAY170523**, N-(2-[4-([(2-[(hydroxyamino)carbonyl]-4,6-dimethylphenyl] (phenylmethyl) amino]sulfonyl] phenoxy)ethyl)-2-benzofurancarboxamide; **Z-DEVD-FMK**, benzyloxycarbonyl-Asp(OMe)-Glu(OMe)-Val-Asp(OMe)-fluoromethylketone; **Z-DQMD-FMK**, benzyloxycarbonyl-Asp(OMe)-Gln-Met-Asp(OMe)-fluoromethylketone; **Z-LEHD-FMK**, benzyloxycarbonyl-Leu-Glu(OMe)-His-Asp(OMe)-fluoromethylketone; **Z-VDVAD-FMK**, benzyloxycarbonyl-Val-Asp(OMe)-Val-Ala-Asp(OMe)-fluoromethylketone; **Z-VEID-FMK**, benzyloxycarbonyl-Val-Glu(OMe)-Ile-Asp(OMe)-fluoromethylketone; **Z-VYAD-FMK**, benzyloxycarbonyl-Tyr-Val-Ala-Asp(OMe)-fluoromethylketone; **Z-WEHD-FMK**, benzyloxycarbonyl-Trp-Glu(OMe)-His-Asp(OMe)-fluoromethylketone

### Further Reading

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