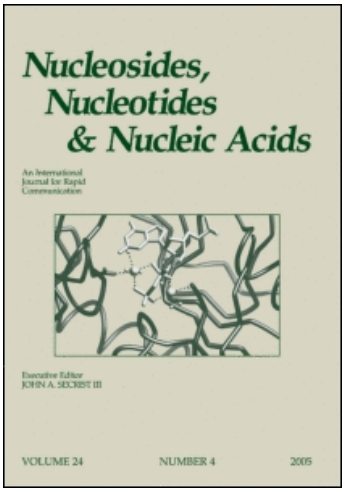

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Distribution and Roles of Purinoceptor Subtypes

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DISTRIBUTION AND ROLES OF PURINOCEPTOR SUBTYPES

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Abstract. The basis of the established subdivision of receptors for purines into P_1-purinoceptors for adenosine and P_2-purinoceptors for ATP and ADP is considered, as well as the proposals for subdivision of P_1-purinoceptors into A_1 and A_2 subtypes and of ATP receptors into P_{2X}-, P_{2Y}-, P_{2Z}- and P_{2T}-purinoceptor subtypes. The distribution and roles of these receptor subtypes in muscles, nerves and other tissues, including endothelial and epithelial cells, hepatocytes, blood cells, fibroblasts and astrocytes, are discussed.

It has been known since the seminal studies of Drury and Szent-Györgi [1] that purine nucleotides and nucleosides have widespread and potent extracellular actions on excitable membranes. Later, it was proposed that ATP was released as the principal neurotransmitter from some non-adrenergic, non-cholinergic ('purinergic') nerves [2] or as a cotransmitter with noradrenaline, acetylcholine and other substances [3,4]. In 1978, Burnstock [5] recognized separate receptors for adenosine and ATP which he termed P_1- and P_2-purinoceptor subtypes, respectively. Subsequently, biochemical, pharmacological and receptor-binding studies have led to a proposed subdivision of the P_1-purinoceptor into A_1- and A_2-receptors and P_2-purinoceptors into P_{2X}, P_{2Y}, P_{2Z} and P_{2T} subtypes [6-9].

SUBTYPES OF PURINOCEPTORS

P_1 and P_2-purinoceptors

A basis for distinguishing two types of purinergic receptor was proposed following an analysis of the voluminous literature about the actions of purine nucleotides and nucleosides on a wide variety of tissues [5]. Since that time, many experiments have been carried out that support and extend this proposal [9,10]. Classification into P_1- and P_2-purinoceptors was based on four criteria: the relative potencies of ATP, ADP, AMP and adenosine; the selective actions of antagonists, particularly methylxanthines; the activation of adenylate cyclase by adenosine, but not by ATP; the induction of prostaglandin synthesis by ATP, but not by adenosine. Thus the following classification was proposed: *P_1-purinoceptors*, which are more responsive to adenosine and AMP than to ATP and ADP, methylxanthines such as theophylline and caffeine are selective competitive antagonists and occupation of P_1-purinoceptors leads to inhibition or activation of an adenylate cyclase system with resultant changes in levels of intracellular cyclic AMP (cAMP); *P_2-purinoceptors*, which are more responsive to ATP and ADP than to AMP and adenosine, are not antagonized by methylxanthines, do not act via an adenylate cyclase system, and their occupation may lead to prostglandin synthesis.

Evaluation and expansion of this purinoceptor subclassification has taken several directions, including studies of the stereoselectivity of P_1- and P_2-purinoceptors, the structural requirements for the actions of purines on these subclasses of purinoceptors, analysis of the influence of ectoenzymatic breakdown of nucleotides and uptake of adenosine on measurements of relative agonist potencies, and development of more potent and selective P_1- and P_2-purinoceptor antagonists [11-14]. Since extracellular breakdown of ATP is rapid, some of the actions of ATP and ADP are mediated via P_1-purinoceptors following breakdown to adenosine [15].

P_1-Purinoceptor subtypes

The P_1-purinoceptor was subdivided into A_1/R_i and A_2/R_a subtypes according to the relative potencies of a series of adenine analogues and also according to whether they increased or decreased adenylate cyclase activity [16,17]. In general, A_1-receptors are preferentially activated by N^6-substituted adenosine analogues, whereas A_2-receptors show

preference for 5'-substituted compounds. Thus for A_1-receptors: L-N^6-phenylisopropyladenosine (L-PIA), N^6-cyclohexyladenosine (CHA)>2-chloroadenosine (CAD)>5'-N-ethyl-carboxamidoadenosine (NECA), D-PIA and adenylate cyclase activity is decreased; while for A_2-receptors: NECA>CADO>L-PIA, CHA and adenylate cyclase activity is increased. There have been some problems with this subclassification on the basis largely of inconsistent potency series in different tissues, particularly between central and peripheral tissues, but the recent efforts to develop selective antagonists for A_1 and A_2 subclasses is giving more credibility to this classification [18].

An A_3 subclass of the P_1-purinoceptor has been claimed for an adenosine receptor present in the heart and nerve endings that is not coupled to adenylate cyclase [19]. Although A_1 and A_2 adenosine receptor agonists have been shown to alter the levels of cAMP, the involvement of such changes in the production of the final response is unclear. This underlines the view that a receptor is best conceived as being constructed of two units: a recognition component and a catalytic component. It is entirely possible that the same recognition component (e.g. A_1 or A_2) could be linked to a variety of catalytic components (e.g. stimulatory or inhibitory regulatory units of adenylate cyclase or Ca^{2+} channels) in the same or different cell types. Hence, it is preferable not to classify adenosine receptors according to their effect on adenylate cyclase, at least until the linkage between receptor occupation and cAMP levels is understood more thoroughly. Another type of recognition site modulating the activity of adenylate cyclase, but not susceptible to blockade by xanthines, the intracellular "P site", has also been described, although the physiological significance of this site is not known [20].

Subclassification of the P_2-purinoceptor

P_{2X}- and P_{2Y}-purinoceptor subclasses were proposed on the basis of relative potencies of ATP analogues and selective antagonism [7]. Thus for P_{2X}-purinoceptors: α,β-methylene ATP (α,β-meATP)>β,γ-meATP>ATP, 2-methylthio-ATP (2-Me.S.ATP), while arylazidoaminoproprionyl-ATP ($ANAPP_3$) is a selective antagonist and prolonged exposure to α,β-meATP selectively desensitizes this receptor [21]. For P_{2Y}-purinoceptors: 2-Me.S.ATP>>ATP>α,β-meATP, β,γ-meATP, while reactive blue 2, an anthraquinone sulphonic acid derivative, has been claimed to be a

selective antagonist, at least over a limited concentration range [22-24]. Studies of the pharmacological actions of isopolar phosphonate analogues of ATP on guinea-pig taenia coli and bladder have supported the P_{2X}, P_{2Y} subdivision of P_2-purinoceptors in smooth muscle and have also shown that L-adenosine 5'-(β,γ-methylene)triphosphonate and its analogues are selective agonists of the P_{2X}-purinoceptor [25], while adenosine 5'-(2-fluorodiphosphate) (ADP-β-F) is a specific agonist for the P_{2Y}-purinoceptor, mediating relaxation of smooth muscle [26]. Recently, suramin has been used as a competitive but non-selective P_{2X}- and P_{2Y}-purinoceptor antagonist in several preparations [27-29]. The receptors for ATP on platelets and mast cells (and other cells of the immune system) do not seem to fit this subclassification and have been termed P_{2T}- and P_{2Z}-purinoceptors, respectively [8]. A P_{2S}-purinoceptor was tentatively proposed for receptors to ATP in the guinea-pig ileum [30], but this needs confirmation. TABLE 1 summarizes the purinoceptor subclassification currently in use and lists some of the selective agonists and antagonists used for these receptors.

The transduction mechanisms associated with P_2-purinoceptor activation are beginning to be understood. The excitatory actions of ATP acting on P_{2X}-purinoceptors on vascular and visceral smooth muscle cells appear to be associated with the opening of non-selective cation channels, resulting in depolarization and subsequent opening of voltage-dependent Ca^{2+} channels [31-33]. In addition, in some arterial smooth muscles, it has been claimed that increased calcium influx is also the result of direct activation of ATP-gated cation channels without any requirement for depolarization [34]. In patch-clamp studies of developing chick skeletal muscle, external ATP has also been shown to activate cation-selective channels [35]. The effects of ATP in neuronal cells are complex, but one direct effect is a rapid depolarization caused by increased cation conductance [36].

Extracellular ATP acting on P_{2Y}-purinoceptors stimulates inositol 1,4,5-trisphosphate production and intracellular Ca^{2+} mobilization in hepatocytes [37], adrenal medullary and other vascular endothelial cells [38], aortic and ventricular myocytes [39], erythrocytes [40], Ehrlich ascites tumour cells [41] and chick myotubes [42]. P_{2Y}-purinoceptors coupled to phospholipase C activation and intracellular Ca^{2+} mobilization have also been demonstrated in primary cultures of sheep anterior pituitary cells

TABLE 1. SUBCLASSIFICATION OF PURINOCEPTORS

		Agonists	Antagonists	Main Actions
P_1 (Adenosine)	A_1	R-PIA CHA CCPA	XAC DPCPX CGS15943	Prejunctional inhibition Negative ino- and chronotropy of heart
	A_2	NECA CGS21680	CGS15943 PD 115,199	Relaxation of smooth muscle
	A_3?			
P_2 (ATP/ADP)	P_{2X}	α,β-MeATP L-AMP-PCP	$ANAPP_3$ α,β-MeATP Suramin	Contraction of visceral and vascular smooth muscle
	P_{2Y}	2-MeS ATP ADP-β-F	RB2 Suramin	Relaxation Endothelium-dependent vasodilatation Secretion
	P_{2Z}	ATP^{4-}	2MeS-L-ATP	Mast cell degranulation
	P_{2T}	ADP 2-MeS ADP	2-Cl-ATP	Platelet aggregation
	P_{2S}?			
"P" (Adenosine)	Intracellular binding site			

R-PIA, R-N^6-phenylisopropyladenosine; **XAC**, xanthine-amine congener; **CHA**, N^6-cyclohexyladenosine; **DPCPX** (PD 116,948), 1,3-dipropyl-8-cyclopentyl xanthine; **CCPA**, 2-chloro-N^6-cyclopentyladenosine; **CGS15943**, 4-amino-2-(2-furyl)[1,2,4]triazolo[1,5-*c*]quinazoline; **NECA**, *N*-5'ethylcarboxamido adenosine; **PD 115,199**, *N*-[2-(dimethylamino)ethyl]-*N*-methyl(-4-(2,3,6,7-tetrahydro-2,6-dioxo-1,3-dipropyl-1H-purin-8-yl)benzenesulphonamide; **CGS21680**, (2-*p*-carboxyethyl)phenethylamino-5'-*N*-carboxamidoadenosine; **α,β-MeATP**, α,β methylene ATP; **$ANAPP_3$**, arylazidoaminopropionyl-ATP; **L-AMP-PCP**, L-β,γ-methylene ATP; **2-MeS ATP**, 2-methylthio ATP; **RB2**, reactive blue 2; **ADP-β-F**, adenosine 5'-(2-fluorodiphosphate); **2-MeS-L-ATP**, 2-methylthio-L-ADP; **ADP**, adenosine diphosphate; **2-MeS ADP**, 2-methylthio ADP.

[43] and turkey erythrocyte membranes [40]. The inhibitory actions of ATP acting on P_{2Y}-purinoceptors that lead to hyperpolarization of smooth muscle cells of the intestine appear to be associated with selective opening of K^+ channels [44].

DISTRIBUTION AND ROLES OF PURINOCEPTOR SUBTYPES

Purinoceptors of various kinds have been identified on a wide variety of cell types (see TABLE 2). In general, adenosine is inhibitory in its actions, whereas ATP is either excitatory or inhibitory.

ATP has been proposed as a transmitter or cotransmitter in autonomic nerves supplying visceral and vascular organs [4,45,46]. Postjunctional receptors for ATP are implicit in the purinergic transmission mechanism: thus it is not surprising that P_2-purinoceptors are present in many smooth muscles. In some muscles, for example those in the intestine and rabbit portal vein, ATP acting via P_{2Y}-purinoceptors is a potent relaxant, whereas in other muscles, for example those in the urinary bladder, vas deferens and most vascular smooth muscles, ATP acting via P_{2X}-purinoceptors has a potent contractile action [7]. P_1-purinoceptors (usually of the A_2 subtype) mediating relaxation are widespread in both vascular and visceral smooth muscle. Both P_1- and P_2-purinoceptors have been identified in the vertebrate heart [47,48]. It is proposed that the P_1-purinoceptor present in heart is of the A_3 subtype [19]. From a study of the effects of ATP on the papillary and right ventricles of the rat, it has been suggested that P_2-purinoceptor activation induces both a positive inotropy and an increase in inositol-lipid metabolism [49]. The P_2-purinoceptors have been identified in developing myotubes [35,42,50].

Adenosine, acting via prejunctional P_1-purinoceptors (usually of the A_1 subtype), is a potent modulator of transmitter release from terminal varicosities of peripheral adrenergic and cholinergic nerves [51]. The P_1-purinoceptors are particularly prominent in the brain where their main role appears to be neuromodulatory [13,52]. P_2-purinoceptors have been described on cell bodies of sensory neurones in nodose ganglion, spinal cord and brain [36,53,54] and also on intrinsic ganglionic neurones in heart and bladder [55-57]. There are P_2- as well as P_1-purinoceptors on astrocytes [58,59].

TABLE 2. DISTRIBUTION AND ROLES OF PURINOCEPTORS

Tissue	Purinoceptor	Principal Action
NERVES		
Sympathetic	P_1 (A_1)	Inhibition
Parasympathetic	P_1 (A_1)	Inhibition
Purinergic	P_1 (A_1)	Autoinhibition
Sensory	P_{2Y}	Excitation
NEUROBLASTOMA	P_1 (A_2)	Elevation of cAMP
ASTROCYTES (CNS)	P_1	Hyperpolarization
	P_2	Accumulation of IP_3
MUSCLES		
Smooth muscle (visceral and vascular)	P_{2X}	Contraction
	P_{2Y}	Relaxation
	P_1 (A_2)	Relaxation
Heart muscle	P_1 (A_3?)	Inhibition
	P_{2X}/P_{2Y}	Excitation/Inhibition
Developing myotube	P_2	Excitation
RETINAL PERICYTES	P_2	Contraction
ENDOTHELIAL CELLS	P_{2Y}	Increase in EDRF
FIBROBLASTS	P_{2X}	Contraction;Depolarization
HEPATOCYTES	P_1	Activates adenylate cyclase
	P_{2Y}	Glycogenolysis
ADIPOCYTES	P_1	
CAROTID CHEMORECEPTORS	P_1 (A_2)	Excitation
THYROID CELLS	P_1 (A_2)	
	P_2	Increased IP_3 turnover
HUMAN AMNION CELLS	P_{2Y}	Activates phospholipase-c
CHONDROCYTES	P_2	Increase in prostaglandins
BLOOD-BORNE CELLS		
Mast cells	P_{2Z}	Degranulation
Immune cells	P_1 (A_2)	
(lymphocytes, granulocytes, splenocytes, leucocytes, basophils, thymocytes, macrophages, neutrophils)	P_{2Z}	Depolarization; Membrane permeabilization
Platelets	P_{2T}	Aggregation
Erythrocytes	P_1	
	P_{2Y}	
	P_{2Z}	
MEGAKARYOCYTES	P_{2T}	Excitation
SECRETORY CELLS		
Alveolar type II cells	P_{2Y}	Surfactant secretion
Parotid acinar cells	P_{2Y}	Amylase secretion
Pancreatic B cells	P_{2Y}	Insulin secretion
Pancreatic A cells	P_1 (A_2)	Glucagon secretion
Intestinal epithelial cells	P_2	Ion fluxes
LLC-PK_1 cells	P_2 cells	Increases intracellular Ca^{2+}
EHRLICH ASCITES TUMOUR CELLS	P_{2Y}	Inhibits proliferation

cAMP, cyclic AMP; CNS, central nervous system; EDRF, endothelium-derived relaxing factor; IP_3, inositol 1,4,5-trisphosphate.

Potent actions of ATP on vascular endothelial cells via P_{2Y}-purinoceptors leading to release of endothelium-derived relaxing factor and vasodilatation have been described now in many vessels [38,60-64]. P_2-purinoceptors have been shown to regulate ion transport in epithelial cells from a variety of different sources, including intestinal epithelial cells and kidney epithelium, where ATP stimulates Cl^- transport and alters Ca^{2+} distribution. ATP also regulates gastric acid secretion and surfactant secretion from type II alveolar epithelial cells [65,66] and parotid acinar cells [67].

ATP has glycogenolytic and hyperpolarizing actions on hepatocytes that are mediated by P_{2Y}-purinoceptors [37,68,69]. Pancreatic B cells respond to ATP via P_{2X}-purinoceptors to increase insulin secretion, whereas adenosine acts via the A_2 subtype of a P_1-purinoceptor in pancreatic A cells to increase glucagon secretion [70].

ATP induces calcium-dependent histamine secretion from mast cells [71]. The agonist form is the tetrabasic acid ATP^{4-} [72] and this receptor has therefore been given the separate subclassification of P_{2Z}. P_1-purinoceptors of the A_2 subtype have been described on various cells of the immune system, including macrophages, lymphocytes and granulocytes [73]. ATP modifies cation fluxes and could thereby deliver the calcium signal for lymphocyte activation [74] and extracellular ATP has also been shown to stimulate transmembrane ion fluxes in macrophages, possibly via a P_{2Z}-purinoceptor [75].

ADP causes platelets to change shape rapidly, which leads to platelet aggregation, while P_1-purinoceptors mediate inhibition of ADP-induced platelet aggregation [76]. Since the platelet receptor is unique in being activated by ADP rather than by ATP, it has been classified as a P_{2T}-purinoceptor. P_{2Y}-purinoceptors have been demonstrated in turkey erythrocytes [40].

ATP receptors mediating membrane potential changes and contraction of fibroblasts have been described [77,78] and the possibility has been raised that ATP released as a cotransmitter with noradrenaline from sympathetic nerves exerts some control of fibroblast function [79]. Purinoceptors have also been identified on spermatozoa, osteoblasts, chemoreceptor cells in the carotid body, neuroblastoma, chromaffin adipose, thyroid, salivary acinar and tumour cells [4].

FUTURE DEVELOPMENTS

A strategy to clone a gene encoding P_1- and P_2-purinoceptors analogous to the methods successfully used in recent years for muscarinic receptors and adrenoceptors [80,81] could lead to clear identification of purinoceptor subtypes and to information that will allow the rational design of better selective agonists and antagonists. Adenosine 5'-O-2-thio[^{35}S]diphosphate has been proposed as a radioligand for the P_{2Y}-purinoceptor in purified turkey erythrocyte membranes [82]. My own laboratory has recently identified [^{3}H]-α,β-methylene ATP as a strongly binding ligand for the P_2-purinoceptor [83,84] and we are currently collaborating with molecular biologists to clone this receptor and hopefully to use the Xenopus oocyte to examine the expression of its nucleic acid. Cloning and expression of a DNA coding for rat liver ecto-ATPase has recently been claimed [85].

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