

Review

Impact of GPCRs in clinical medicine: Monogenic diseases, genetic variants and drug targets

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Abstract

By virtue of their large number, widespread distribution and important roles in cell physiology and biochemistry, G-protein-coupled receptors (GPCR) play multiple important roles in clinical medicine. Here, we focus on 3 areas that subsume much of the recent work in this aspect of GPCR biology: (1) monogenic diseases of GPCR; (2) genetic variants of GPCR; and (3) clinically useful pharmacological agonists and antagonists of GPCR. Diseases involving mutations of GPCR are rare, occurring in <1/1000 people, but disorders in which antibodies are directed against GPCR are more common. Genetic variants, especially single nucleotide polymorphisms (SNPs), show substantial heterogeneity in frequency among different GPCRs but have not been evaluated for some GPCR. Many therapeutic agonists and antagonists target GPCR and show inter-subject variability in terms of efficacy and toxicity. For most of those agents, it remains an open question whether genetic variation in primary sequence of the GPCR is an important contributor to such inter-subject variability, although this is an active area of investigation.

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1. Introduction

In addition to their large number, widespread expression and important mechanistic and regulatory properties, as reviewed by others in this volume, G-protein-coupled receptors (GPCR) have well-recognized roles in clinical medicine. Their

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expression on the plasma membrane makes GPCR readily accessible, especially by hydrophilic hormones and drugs, including both agonists and antagonists, and their non-uniformity of expression in different tissues and cell types provides selectivity (in some cases, specificity) in the targeting of these receptors for the activation or blockade of physiological events. Studies in recent years have provided a number of new insights, many of them gleaned from application of the tools of the “genetic revolution”. In this article, we will review aspects of GPCR in clinical medicine with an emphasis on recent developments and insights in 3 areas: (1) monogenic diseases of GPCR; (2) genetic variants of GPCR; and (3) clinically useful pharmacological agonists and antagonists of GPCR. Each of these are large topics that have been the subject of reviews in recent years (e.g., [1–8]). We refer interested readers to such reviews for additional information that length restrictions prevent us from presenting in detail. Other sources of useful information related to these topics include a variety of web-based tools [9], including www.hapmap.org and sites accessible therefrom.

2. Monogenic diseases of GPCR

Monogenic diseases and genetic variants associated with those diseases are generally quite rare, occurring in <1% of the population and often variably among subjects of different ethnicities. Since GPCR comprise ~3% of the human genome

[10], it is perhaps not surprising that non-lethal mutations can occur in GPCR, especially those that are expressed in sensory and hormonal systems, where they serve as mediators of information transfer from the extracellular environment to the cell interior. One such critical action is in the visual system where rhodopsin in photoreceptor-expressing neurons, retinal rods and color (red, blue and green) opsins in retinal cones, transduce the input from photons of light into electrical impulses that then travel to the brain and are decoded. A second major class of physiologically important GPCR are those that mediate the action of hormones, especially polypeptide hormones but also including the action of hormones, such as the calcium-sensing receptor (CaSR) or receptors for other chemical entities (e.g., lipids, amines, fatty acids). A third class is receptors for physiologically important neurotransmitters, such as norepinephrine (and to a lesser extent, epinephrine), acetylcholine (at muscarinic cholinergic receptors), dopamine, serotonin (at certain receptors), glutamate (at metabotropic receptors) as well as numerous peptides and lipids that function as neuromodulators. To date, mutations that lead to human disease have been identified in a relatively limited number of GPCR. We will briefly discuss 3: rhodopsin, V_2 vasopressin and the calcium-sensing receptor.

A large number of monogenic mutations have been identified in rhodopsin, in particular in patients that have the disease retinitis pigmentosa; in addition, a number of hormonally responsive GPCR have been identified as pathologic

Table 1
Examples of rare mutants of GPCR that cause human diseases

Receptor/Gene name	Mutation	Disease	Ref
Calcium-Sensing (CaS)/ CaSR	Multiple (e.g. Arg185Gln)	Autosomal Dominant Hypocalcemia (ADH) Sporadic Hypoparathyroidism Familial Hypoparathyroidism	[15,90]
CXCR4	Multiple (e.g. Ser338X)	WHIM syndrome	[91,92]
Endothelin receptor B (ET _B)/EDNRB	Multiple (e.g. Trp276Cys)	Hirschsprung's disease	[93]
Follicle-stimulating hormone (FSH)/FSHR	Multiple (e.g. Ala189Val)	Female infertility	[94]
N-formyl-peptide (FPR)/FPR1	Phe110Ser, Cys126Trp	Juvenile periodontitis	[95]
Frizzled (FZD ₄)/FZD4	Multiple (e.g. Arg417Gln)	Familial exudative vitreoretinopathy (FEVR)	[96,97]
Gonadotropin-releasing hormone (GnRH)/GNRHR	Multiple (e.g. Arg262Gln)	Hypogonadotropic hypogonadism (HH)	[98, 99]
GPR54	Multiple (e.g. Cys223Arg)	Hypogonadotropic hypogonadism (HH)	[98,99]
GPR56	Multiple (e.g. Cys223Arg)	Bilateral frontoparietal polymicrogyria (BFPP)	[100,101]
vGPCR/KSHV-GPCR	(constitutively active)	Kaposi's sarcoma (KS)	[102,103]
Relaxin family peptide receptor 2 (RXFP2)/LGR8	Multiple (e.g. Thr222Pro)	Cryptorchidism	[104–106]
MASS1 (also called VLGR1, USH2C)	Multiple (e.g. Ser2652X)	Usher syndrome, Febrile seizures (FS)	[107–110]
Melanocortin (MC ₄)/MC4R	Multiple (e.g. Pro78Leu)	Dominant and recessive obesity	[111,112]
Rhodopsin/RHO	Multiple (e.g. Pro23His)	Retinitis pigmentosa (RP)	[113–115]
Vasopressin receptor (V ₂)/AVPR2	Multiple (e.g. Arg113Trp)	Nephrogenic diabetes insipidus (NDI)	[116,117]

entities in a variety of endocrine disorders (Table 1). The latter disorders include those with either activating mutations or mutations that block hormonal response. Studies that documented hormone resistance in patients with particular disorders were often critical in focusing attention on GPCR or their signaling pathways as the sites of lesions in such disorders, whereas in other situations excessive response in the absence of increased levels of the activating hormones provided a similar impetus to infer a role for components and events that mediate hormonal response.

The location of clinically (i.e., pathophysiologically) significant mutations are not always sites that have been suspected from mutational analyses with cloned receptors. As shown in Fig. 1, which highlights the sites that are mutated in rhodopsin, a wide variety of residues have been identified in patients with retinitis pigmentosa, a leading cause of blindness and visual disability in younger people that occurs with an overall frequency of one in 4000. Retinitis pigmentosa is a disorder that leads to the progressive death of the rod photoreceptors; recent work suggests that such cell death may be a consequence of a high, constant rate of signal transduction that causes the rods to die, perhaps secondary to prolonged lowering of Ca^{2+} concentration [11].

Nephrogenic diabetes insipidus (NDI), which results from failure of vasopressin (antidiuretic hormone, ADH) to act on the renal collecting duct to facilitate water reabsorption, is another well-studied monogenic disorder of a GPCR, the arginine vasopressin receptor 2 (AVPR2, V_2), in which mutations cause congenital nephrogenic diabetes insipidus in ~90% of patients

via an X-linked recessive mode of inheritance [12]. To date, >280 families with a history of NDI have been shown to have >180 putative disease-causing mutations in AVPR2 (Fig. 2 and [12]). In most cases, these mutations lead to the intracellular trapping of the V_2 receptors, such that few receptors reach the plasma membrane to trigger the activation of G_s and adenylyl cyclase and thereby, the generation of cAMP. Therapeutic approaches are under investigation that involve the use of nonpeptide V_2 receptor antagonists to bind intracellular receptors as what have been termed “pharmacochaperones” that will facilitate their folding, insertion and function in the plasma membrane [13].

Rhodopsin belongs to Family A, which contains the largest group of GPCR superfamily members; receptors in this Family generally contain a relatively short extracellular N-terminus and highly conserved amino acids within each transmembrane domain. Family A members are activated by small ligands such as biogenic amines and nucleotides, although rhodopsin itself is stimulated by photons of light that activate a retinal bound in a transmembrane pocket. In contrast, the V_2 receptor belongs to Family B, whose receptors recognize large peptides and are generally characterized by longer N-termini, in the case of V_2 receptors one that has six conserved cysteine residues. Comparison of rhodopsin and the V_2 receptor (Cf. Figs. 1 and 2) reveals that disease-causing mutations occur in all portions of the two receptors with a greater number in transmembrane domains relative to mutants in non-transmembrane domains of V_2 receptors in NDI than of rhodopsin in retinitis pigmentosa.

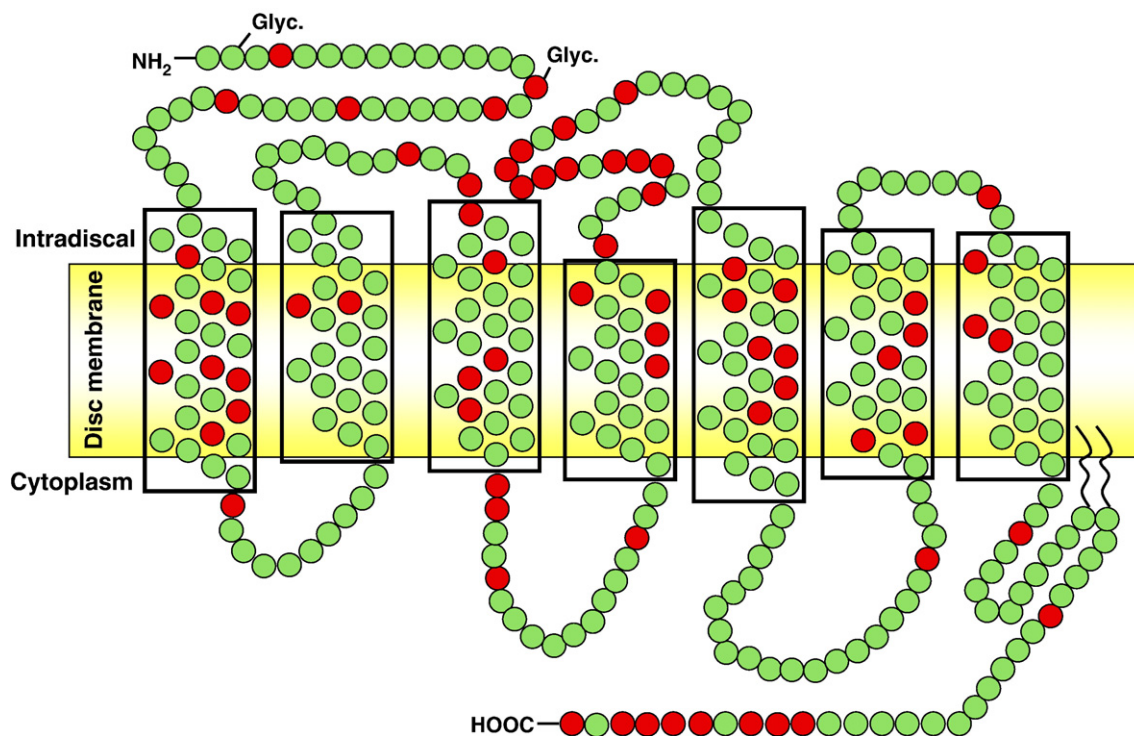


Fig. 1. Schematic structure of rhodopsin. Each amino acid residue is shown as a green dot; amino acid residues that are mutated in patients with retinitis pigmentosa are shown as red dots. Seven transmembrane domains are boxed. Mutations are collected from the Human Gene Mutation Database (www.hgmd.org), the Retinal Information Network (www.sph.uth.tmc.edu/RetNet/sys-dis.htm), and the Retina International Mutation Database (www.retina-international.com/sci-news/rhomut.htm) and references [88] and [89].

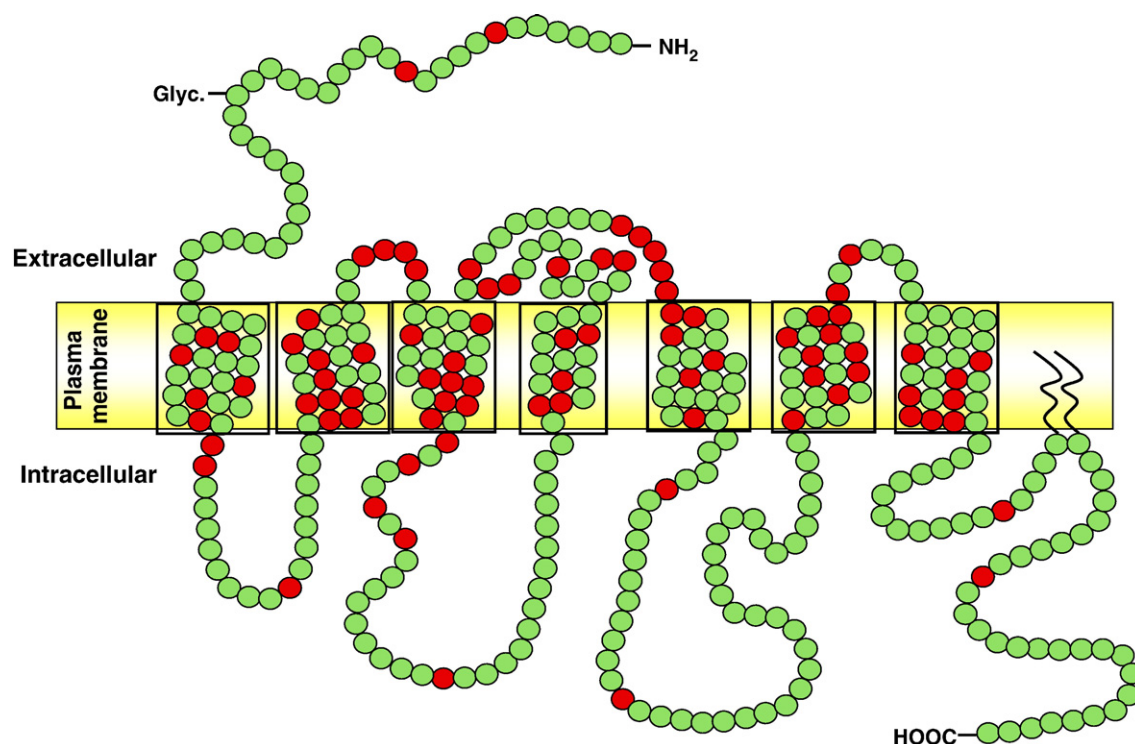


Fig. 2. Schematic structure of the vasopressin V_2 receptor (AVPR2). Each amino acid residue is shown as a green dot; amino acid residues that are mutated in patients with nephrogenic diabetes insipidus are shown as red dots. Seven transmembrane domains are boxed. Mutations found in the AVPR2 gene were collected from the Human Gene Mutation Database (www.hgmd.org) and the Diabetes Insipidus Mutation Database (www.medicine.mcgill.ca/nephros).

Genetic disorders of the CaSR are a third example of a monogenic disease in GPCR [14,15]. This receptor is found on numerous tissues involved in calcium homeostasis, including the parathyroid glands, kidney, and intestine. Binding of calcium to the CaSR is the mechanism by which parathyroid cells detect changes in ionized calcium concentration and in turn, modulate parathyroid hormone secretion so as to maintain serum calcium levels within a narrow physiologic range. CaSRs in renal tubules modulate calcium reabsorption in response to alterations in extracellular calcium concentrations. Several hypocalcemic and hypercalcemic disorders have been identified that derive from rarely occurring mutations of CaSR: loss-of-function CaSR mutations in the hypercalcemic disorders of familial benign (hypocalciuric) hypercalcaemia (FHH, FBH or FBHH) and neonatal severe primary hyperparathyroidism (NSHPT) (each of which occur $<1/10,000$) and gain-of-function CaSR mutations in autosomal dominant hypocalcaemia with hypercalciuria (ADHH) and Bartter's syndrome type V.

In addition to such "classical" monogenic diseases, another type of such disease can involve the generation of antibodies as monoclonal (or polyclonal) expansion of immune cells with the antibody products directed against GPCR or in some cases, their downstream targets. The most prevalent example is Graves disease, a form of hyperthyroidism with enhanced response to thyroid-stimulating hormone (TSH) that is most commonly secondary to autoimmune activation of TSH receptors [16,17]. Another example of activating (as well as inhibitory) antibodies directed at GPCR (e.g., β -adrenergic and muscarinic cholinergic) is Chagas' cardiomyopathy, which

is triggered by infection with the protozoan *Trypanosoma cruzi* [18,19].

In several other settings, antibodies directed at GPCR can blunt hormone action, preventing G-protein activation (e.g., [15,17,20–24]). Of note, such disorders are almost invariably ones that occur in adults rather than children whereas monogenic disorders of the receptors themselves often manifest clinical abnormalities much earlier in life.

3. Genetic variants of GPCR

Completion of the human genome has introduced a large amount of DNA sequence information that predicts 367 non-sensory GPCRs and an additional 380 or more chemosensory GPCRs [25]. Human genomic data also reveal that GPCR loci harbor a substantial number of genetic variants, including nucleotide insertion or deletion as well as the exchange of a single nucleotide, i.e. single nucleotide polymorphisms (SNPs). SNPs account for $\sim 80\%$ of all sequence variations and generally occur at a frequency ~ 1 in 1200 nucleotides. A polymorphism is defined as a genetic variant that occurs at a locus with an allelic frequency of greater than or equal to 1% whereas "mutations", such as those discussed in the prior section, designate rarer genetic variants that are germline-transmitted changes in a given individual or somatic variation identified in isolated tissues.

Genetic variants/polymorphisms identified in GPCRs can influence receptor expression, targeting, function, and receptor turnover; as well as the ability of receptors to recognize and

Table 2
Examples of polymorphisms of GPCR associated with human diseases

Receptor	Polymorphisms	Examples of disease associations	Ref
β_1 Adrenergic receptor	Arg389Gly	Heart failure	[64,71]
β_2 Adrenergic receptor	Multiple	Hypertension, Asthma	[118,119]
β_3 Adrenergic receptor	Trp64Arg	Obesity	[120]
CC chemokine receptor 2 (CCR2)	Val64Ile	Delayed progression of AIDS	[121]
CC chemokine receptor 5 (CCR5)	Multiple	Associated with progression of AIDS	[33,122]
Dopamine receptor 2 (D_2)	3'UTR52A/G	Associated with depression and anxiety	[123]
Dopamine receptor 3 (D_3)	Ser9Gly, Promoter SNPs	Haplotype associated with schizophrenia	[124]
Muscarinic receptor subtype 3 (M_3)	Promoter haplotype	Possible association with asthma and atopy	[125]
Neuropeptide S receptor (NPSR; also called GPR154, GPRA)	Haplotypes H1, H5, Asn107Ile, rs324981	Asthma susceptibility	[31,32,126]
P2Y ₁₂	CA deletion at Codon 240	Associated with bleeding diathesis	[127]

respond to pharmacologic agents. Below we describe selected GPCRs with polymorphisms involved in human diseases, in addition to elucidating their potential for serving as future therapeutic targets. Table 2 lists sequence variants identified in human GPCR genes that relate to human diseases.

The β_2 -adrenergic receptor possesses multiple polymorphisms, including several in the coding region and 5' untranslated region, that generate 4 common haplotypes (collections of variants) in different ethnic groups (Caucasian, African-American, Hispanic-Latino and Asian) [26]. Two common (i.e., occur >20%) non-synonymous polymorphisms, Arg16Gly and the Gln27Glu, have been shown to influence regulation of receptors by agonists but not receptor binding or coupling to G_s/adenylyl cyclase. Individuals who are Arg16 homozygotes display slower/impaired bronchodilatory response upon agonist activation of the β_2 -adrenergic receptor than do people who are Gly16 homozygotes [27,28]. Such results suggest that Arg16Gly may predict β_2 -adrenergic receptor agonist response in the therapy of asthma, although additional studies are needed [29]. Other recent data obtained with patients from the UK indicate that such variants do not contribute in a major way to asthma incidence or prevalence [30].

Another candidate GPCR associated with asthma susceptibility was recently de-orphanized and named the neuropeptide S receptor (NPSR), formerly known as orphan receptor GPRA or GPR154 [31]. One non-synonymous SNP, Asn107Ile, has a strong association with asthma but with as-yet no clear evidence to explain the genetic association. Melen et al. studied 7 polymorphisms of NPSR and inferred 7 haplotypes (H1–H7) in a case-control study of childhood allergy and asthma and found that haplotypes H1 and H5 were significantly associated with asthma [32].

The best studied example of genetic variants in a GPCR functioning as disease modifier is the CC chemokine receptor-5 (CCR5) [33]. This receptor plays a crucial role in HIV-1 pathogenesis, serving as a co-receptor for viral entry and CCR5 polymorphisms, including promoter SNP (59029A/G) and a deletion of 32 base pairs (Δ 32), influence progression of HIV infection to AIDS. CCR5 Δ 32 causes a frame shift at amino acid 185 leading to a premature termination of the receptor between putative transmembrane domains IV and V [33]; whereas promoter SNP 59029G shows lesser activity than 59029A allele by *in-vitro* promoter reporter assay [34]. Thus both CCR5 Δ 32

and 59029G SNP seem to be protective in HIV infection due to lower expression of CCR5 receptors on the cell surface.

Significant progress has been achieved in recent years in identifying genetic polymorphisms of GPCR's and in providing suggestive evidence of their relevance in various human diseases, in addition to yielding information regarding mechanisms of GPCR signal transduction. Given the complexity of this receptor superfamily, including structural heterogeneity, receptor multiplicity, and redundancy in signaling pathways, further efforts will be required to identify and document definitively the contributing role of polymorphisms in disease and as disease modifiers. There is as-yet incomplete information regarding the full-range of genetic variants of most GPCRs, including orphan GPCRs, and thus this is likely to remain an area of active research with potential clinical importance. In addition, two aspects of such variants that have not yet been well explored include the possible role of synonymous SNPs that may change the binding and action of exon splicing enhancer (ESE) proteins and thus affect RNA splicing even though they do not produce amino acid substitutions [3,35] and the potential contribution of genetic variants in GPCR coding sequences that will alter the ability of receptors to oligomerize [36]. Studies of GPCR variants should be aided by the completion of the HapMap [37] and identification of tag SNPs for particular haplotypes in genes of interest [38].

4. Drug effects and the role of genetic variants of GPCR

As a class, GPCR have been the most successful molecular drug targets in clinical medicine. Agonists and antagonists of GPCR are used in the treatment of diseases of every major organ system including the CNS, cardiovascular, respiratory, metabolic and urogenital systems. Certain GPCRs have been particularly useful as drug targets. These include AT₁ angiotensin, adrenergic, dopamine and serotonin (5-hydroxy-tryptamine, 5-HT) receptor subtypes as well as GPCR for hormones whose activity is increased or decreased in particular endocrine disorders. For example, antagonists of AT₁ angiotensin II receptors are used to prevent diabetes mellitus-induced renal damage [39] and to treat essential hypertension and congestive heart failure. α_1 -Adrenergic receptor antagonists are employed for symptomatic treatment and to slow the clinical progression of benign prostatic hyperplasia [40]. β -adrenergic

receptor antagonists, acting on β_1 -and/or β_2 -adrenergic receptors, increase survival in patients with congestive heart failure [41] and are used to treat essential hypertension and coronary heart disease. β_2 -adrenergic receptor agonists are a cornerstone in the treatment of asthma and chronic obstructive pulmonary disease and are used to delay preterm labor [42]. Dopamine receptor antagonists, primarily via their actions on D_2 receptors, are standard therapeutic agents in the treatment of schizophrenia, although some representatives of this class may exert antipsychotic effects via other dopamine receptor subtypes and/or 5-HT receptors [43]. Dopamine receptor agonists (e.g., levodopa serving as a precursor for dopamine) are widely used to treat Parkinson's disease [43]. Inhibitors of 5-HT uptake act as indirect agonists at various subtypes of 5-HT receptors and are used to treat major depressive disorders; several of these subtypes may also be involved in the effects of atypical antipsychotic drugs.

While most GPCR are expressed in a tissue-selective manner, it remains a key challenge for the safe use of drugs to identify compounds that will selectively act on a particular receptor in a target tissue and largely spare those receptors in other tissues, thereby potentially minimizing side effects. Such tissue selectivity may result from pharmacokinetic phenomena (e.g. distribution and metabolism) [44] but may also involve tissue-specific expression of GPCR splice variants and/or receptor oligomers [45,46].

Responses to drugs target to GPCRs can show substantial inter-subject variability. Attempts to use clinical factors as a means to predict individual drug responses have had limited success. Therefore, much recent attention has involved assessment of genetic features that potentially influence variability in drug responses. Genetic variations of enzymes or transporters involved in the pharmacokinetics of drugs [47,48] and polymorphisms of GPCR genes have been investigated as possible determinants of heterogeneous drug responses.

GPCR polymorphisms may have tissue-, cell type- or ligand-specific effects on drug responses. Apart from the possibility of response-specific physiological counter-regulatory mechanisms, factors intrinsic to the biochemical properties of polymorphic receptors may contribute to such heterogeneity. Tissue-selective factors may relate to the differential expression of specific biochemical properties in different cell types. For example, the human α_{1A} -adrenergic receptor can couple to the activation of extracellular signal-regulated kinases in Chinese hamster ovary cells [49] but to its inhibition in rat-1 fibroblasts [50]. Such differences are not yet well documented for a large number of GPCR polymorphisms but may have specific consequences in different cell types and tissues. Although such differences in tissue selectivity are primarily expected from genetic variants that affect the coding region of a gene and/or its splicing, polymorphisms in the promoter region of GPCR genes may affect transcription in a tissue-selective manner [51].

GPCR polymorphisms not only may demonstrate tissue-specificity but also may act in a ligand-specific manner, termed "ligand-directed signaling", whereby activation of a given GPCR by two chemically distinct ligands leads to differential

signaling responses [52]. Indeed, some GPCR polymorphisms can affect functional responses to some but not other ligands, e.g. with β_3 -adrenergic receptors [53–55]. Such concepts may apply not only to acutely measured GPCR responses but also to receptor regulation, especially because certain GPCR polymorphisms alter such regulation [56]. In the following we illustrate these principles based upon examples from several drug classes acting on GPCR that are frequently used in clinical medicine (Table 3).

4.1. Angiotensin II receptors

Administration of AT_1 antagonists to patients with high blood pressure can lower blood pressure, increase glomerular filtration rate and decrease cardiac hypertrophy. The most widely investigated AT_1 receptor polymorphism, A1166C SNP, is located in an untranslated part of exon 5; its functional relevance for the biology of AT_1 receptors is unclear. This SNP has been associated with enhanced responses to antagonists of AT_1 receptors or inhibition of angiotensin converting enzyme (and hence a reduction of endogenous agonist) [57–59]. However, whenever more than one study has been reported for a given response parameter, studies without significant differences [60–62] or even with a significant difference in favor of the opposite allele have been reported [63].

Thus, currently available data do not allow definitive conclusions regarding the role of the A1166C SNP of the AT_1 receptor but do point to some general notions. Firstly, all of the above studies included relatively small numbers of patients (<100 in most cases) and hence probably are statistically underpowered. Second, searches for the role of a SNP for which functional correlates are not known at the molecular and cellular level are difficult to interpret, as such SNPs may only be indicative of other genetic variants, including SNPs or extended haplotypes, with which they are in linkage disequilibrium. Thirdly, efforts that emphasize a single SNP outside the coding region may not readily allow inferences that link gene structure to function.

4.2. Adrenergic receptors

α_1 -Adrenergic receptor antagonists are the most frequently used for the medical treatment of lower urinary tract symptoms related to benign prostatic enlargement. Various SNPs have been detected in the genes encoding the three α_1 -adrenergic receptor subtypes [1,3,64]. However, the SNPs reported thus far have only limited effects on protein function [65] and have not been found to associate with clinical responses to α_1 -adrenergic receptor antagonists [66].

β -Adrenergic receptor antagonists are widely used in several disorders, including the treatment of hypertension, congestive heart failure, angina pectoris and myocardial infarction. Studies on a role of β_1 -adrenergic receptor polymorphisms in the response to such drugs have focused on the non-synonymous SNPs Ser49Gly and Arg389Gly. Multiple studies have reported increased β_1 -antagonist effects associated with Arg389 [67–71], an allele exhibiting an increased function *in vitro* [72],

Table 3
GPCR as drug targets: some examples of the impact of receptor polymorphisms

Receptor	Drugs and some key indications	Polymorphisms	Relevance	Ref
AT ₁ angiotensin II receptor	Antagonists (e.g. losartan) in the treatment of essential hypertension or congestive heart failure	A1166C SNP in untranslated part of exon 5	Inconclusive data for drug responses where multiple studies have been done	[57–63]
α_{1A} -adrenergic receptor	Antagonists (e.g. tamsulosin) to treat micturition (bladder emptying) disorders associated with enlarged prostate glands	C1475T	Short- and long-term antagonist effects apparently not affected	[66]
β_1 -adrenergic receptor	Antagonists (e.g. propranolol, atenolol, metoprolol, carvedilol) to treat essential hypertension or congestive heart failure	Ser49Gly, Arg389Gly	Arg389 linked to increased antagonist effect	[60,67–69, 73,128]
β_2 -adrenergic receptor	Agonists (e.g. terbutaline, salbutamol, formoterol, salmeterol) for treatment of obstructive airway disease or premature labor	Arg16Gly, Gln27Glu, Thr164Ile	Possibly reduced responses with Ile164 otherwise no consistent association with drug responsiveness	[56]
D ₂ dopamine receptor	Antagonists (e.g. haloperidol and clozapine) to treat schizophrenia Agonists (e.g. levodopa) for the treatment of Parkinson's disease	-141C Ins/Del, Taq1A	Reduced antagonist response with Del or homozygous A2 allele. No consistent associations with therapeutic response or side effects of agonists	[75–77]
D ₃ dopamine receptor	Antagonists (e.g. haloperidol) in the treatment of schizophrenia	Ser9Gly	Increased risk of tardive dyskinesia with Gly allele	[75,76]
5-HT _{2A} receptor	Antagonists (e.g. clozapine) to treat schizophrenia Indirect agonists (e.g. fluvoxamine) for the treatment of depression	T102C	Reduced response to clozapine with C allele Possibly reduced response to agonists with homozygous T allele	[76,82]
5-HT _{2C} receptor	Antagonists (e.g. clozapine) to treat schizophrenia	Multiple polymorphisms in promoter and coding region in linkage disequilibrium	Genotypes associate with therapeutic response and with side effects such as tardive dyskinesia and weight gain	[81,83]

although not all investigators have confirmed this [60,73]. By contrast, no association has been observed in most studies of β_1 -adrenergic receptor antagonist responses with the Ser49Gly SNP, which also alters function *in vitro* [60,67,70,73].

Selective β_2 -adrenergic receptor agonists are used as bronchodilators in patients with obstructive airway disease and as tocolytic agents in women with premature labor. Three β_2 -adrenergic receptor nonsynonymous SNPs have been studied: Arg16Gly, Gln27Glu, and Thr164Ile. Although the position 16 and 27 variants are expressed both heterozygously and homozygously, homozygous Ile164Ile subjects have not been identified, implying that this is a lethal variant. Many studies have tested the impact of these SNPs on agonist responses but have yielded inconsistent findings with the exception of a lower response of the rarer (found in <5% subjects) Ile164 genotype [56]. However, as noted above, recent data have indicated that asthmatic patients with the Arg16 variant shows less response to short- or long-acting β_2 -adrenergic receptor agonists than do patients with Gly16 β_2 -adrenergic receptors [27–29]. Numerous inconclusive studies have reported an association of these SNPs with arterial hypertension [51] but recent data with a large population sample document association of the Arg16 variant with higher diastolic blood pressure but only in males, implying an interaction of gender with this variant in regulation of blood pressure [74]. The relevance of such a finding for the overall population may be limited since the effect appears to be small and gender-specific.

In conclusion, the emerging picture from studies of adrenergic receptor SNPs is that most have little effect on

ligand recognition or receptor function *in vitro* and limited influence on drug responsiveness *in vivo*. SNPs that affect the sensitivity for receptor regulation by agonists, e.g. the Arg16Gly and Gln27Glu SNPs in the β_2 -adrenergic receptor, have yielded inconsistent results in terms of functional effects and disease associations *in vivo*. In contrast, altered drug responsiveness has been observed for certain SNPs that affect receptor function *in vitro*, e.g. the β_1 -adrenergic receptor Arg389Gly SNP and the infrequent Thr164Ile SNP in the β_2 -adrenergic receptor with thus far less definitive evidence for other β_2 -adrenergic receptor variants [29]. The findings highlight the need to carefully test the biochemical consequences of SNPs *in vitro* in order to enhance understanding of their potential role in clinical association studies.

4.3. Dopamine receptors

Dopamine receptor antagonists are used clinically as antipsychotic agents but frequently associated with side effects such as tardive dyskinesia and weight gain. It was initially believed that such agents act primarily via D₂ receptors but some atypical antipsychotics have also been shown to act via D₃ receptors or 5-HT receptors (see below). By contrast, Parkinson's disease, which involves brain region-specific depletion of dopamine neurons, is treated with dopamine receptor agonists and compounds such as levodopa that are metabolized to dopamine receptor agonists.

Various studies have investigated a possible role of polymorphisms in dopamine receptor genes in the treatment

of schizophrenia [75–77]. Such studies have found that both the Del allele of the -141C Ins/Del polymorphism and the homozygous A2 allele of the Taq1A polymorphism of the D₂ receptor gene are associated with reduced therapeutic responses to both typical antipsychotics (e.g., haloperidol) and atypical antipsychotics (e.g., clozapine). Recent studies confirm such findings [78,79]. Although side effects of typical antipsychotics, such as the motor disorder tardive dyskinesia, are classically linked to D₂ receptors, studies that have assessed for these polymorphisms have not yielded consistent associations. Tardive dyskinesia has instead been linked to the Ser9Gly polymorphism of D₃ receptors [75–77]. The same SNP has also been associated with therapeutic response to the atypical antipsychotic risperidone [80]. By contrast, few studies are available regarding polymorphisms of D₂ and D₃ receptors; therapeutic responses or side effects of agonists have not yielded consistent associations. In aggregate, studies of dopamine receptor polymorphisms have suggested that the presumed molecular target of a drug may not always be the best candidate for polymorphisms association studies, thus emphasizing anew that a drug may have molecular targets distinct from those generally assumed to mediate its effect.

4.4. 5-HT receptors

Classical antipsychotics (e.g., haloperidol) are thought to be dopamine receptor antagonists while atypical antipsychotics (e.g., clozapine) have similar or even higher affinity for 5-HT receptor subtypes. 5-HT receptors are also indirectly targeted by 5-HT uptake inhibitors such as fluoxetine, i.e. drugs that increase the availability of 5-HT in the synaptic cleft. Such uptake inhibitors are a cornerstone in the treatment of major depressive disorders. Therapeutic responses and/or side effects of both drug classes have been associated with polymorphisms in the genes for 5-HT receptor subtypes, with most attention focused on 5-HT_{2A} and 5-HT_{2C} receptors [76,77,81,82].

5-HT_{2A} receptors may be involved in the response to atypical antipsychotics and to 5-HT uptake inhibitors. The T102C SNP in the 5-HT_{2A} receptor gene has been associated with altered drug responses: the C allele associating with a reduced response to antagonists and the homozygous T allele with reduced response to agonists [76,82]. Multiple polymorphisms, including a-1027 (GT) repeat in the promoter and a Cys23Ser SNP in the coding region, exist in the gene for the 5-HT_{2C} receptor and are in linkage disequilibrium [81]. Although all studies are not consistent, some of these polymorphisms, and certain haplotypes thereof, appear to be associated with differences in the therapeutic response to atypical antipsychotics and in the production of side effects such as tardive dyskinesia and weight gain [81,83].

5. Conclusions and perspective

Given their large number, widespread expression and roles in the regulation of virtually every organ system throughout the body, GPCR are physiologically important in maintaining homeostasis, in particular via their ability to mediate responses

to circulating hormones and neurotransmitter input in the central, peripheral and autonomic nervous systems. The cloning and characterization of GPCR and of components involved in mediating receptor responses and in regulating receptor expression has provided a number of new insights, only some of which have been exploited in clinical medicine. For example, the physiologic agonists and functional role for a large number of orphan GPCR remain unknown, although such orphan receptors may prove to be as important—perhaps more so—than GPCR currently emphasized in physiologic and pharmacologic studies and in drug development [84–86]. Newly identified receptors (initially “orphans”) in the cloning era have already yielded pharmacologically useful drugs, for example CaSR agonists (calcimimetics) and antagonists (calcilytics) as therapies for a variety of disorders [87].

A number of monogenic diseases of GPCR have been defined, most thoroughly retinitis pigmentosa and NDI (Figs. 1 and 2), and these have provided useful insights regarding the roles of particular residues and in the disease-causing potential of GPCR mutations. Other disorders that involve antibodies to GPCR are more common and have had a larger overall impact on clinical medicine.

In spite of an ever-expanding identification of genetic variants of GPCR, in particular SNPs, many studies on associations of GPCR polymorphisms with disease or drug responses are difficult to interpret because the specific consequences of particular polymorphisms have not been unequivocally established at the molecular and cellular level and because most clinical studies are statistically underpowered to allow robust conclusions. Perhaps polymorphisms have stronger effects on therapeutic and adverse effects of their ligands than on disease because any given GPCR plays a larger role for specific drugs acting on a GPCR than for a complex disease with multiple genetic and non-genetic determinants.

GPCR polymorphisms have yielded numerous interesting mechanistic results, in particular by identifying residues not necessarily implicated as functionally important prior to their identification in sequencing studies of polymorphic receptors. To date, however, most associations are too weak to allow clinically meaningful predictions of GPCR variants and their relationship to disease onset or progression or in drug responses (the results with Arg389Gly SNP in the β_1 -adrenergic receptor being an exception [60–64]). Additional data are clearly needed.

GPCR will continue to be highly important in clinical medicine because of their large number, wide expression and role in physiologically important responses. We speculate that future discoveries will reveal new GPCR drugs, in part because it is relatively easy to screen for pharmacologic agents that access these receptors and stimulate or block receptor-mediated biochemical or physiological responses. In addition, further insights into GPCR biology may reveal novel, unexpected therapeutic targets that influence the GPCR life cycle or “ligand directed signaling”. The existence of a large number of orphan GPCRs provides a treasure trove of possibilities. Our bias is that the full flowering of genetic studies of GPCR variants and their clinical role has yet to be realized. Thus, we would argue, “let the future begin!”

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