BJP BRITISH JOURNAL OF PHARMACOLOGY
BPS BRITISH PHARMACOLOGICAL SOCIETY

British Journal of Pharmacology (2010), 159, 983–985

0007-1188/10
www.brjpharmacol.org

THEMED SECTION: MOLECULAR PHARMACOLOGY OF G PROTEIN-COUPLED RECEPTORS

EDITORIAL

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G protein-coupled receptors are the largest group of membrane proteins and are the targets for approximately 30% of drugs currently used therapeutically. These 7-transmembrane-spanning proteins continue to provide new opportunities to develop therapeutics based on emerging knowledge of their structure, signalling properties and interactions with other proteins. This themed issue of the British Journal of Pharmacology contains a series of papers that cover these issues and identify approaches that may determine future directions. Many of these papers contain material that was presented at the 5th International Molecular Pharmacology of G Protein-Coupled Receptors meeting held in Sydney Australia in late 2008.
British Journal of Pharmacology (2010) **159,** 983–985; doi:10.1111/j.1476-5381.2010.00695.x

This article forms the foreword to a themed section on the Molecular Pharmacology of G Protein-Coupled Receptors. See the reference list for all papers appearing in this section.

Keywords: G protein-coupled receptor; GPCR structure; allosteric modulator, dualsteric ligand; ligand-directed signalling; biased signalling; signalling scaffold; receptor dimerization; receptor activity modifying protein

This themed issue on G protein-coupled receptors (GPCRs) largely arose from a suggestion by Ian McGrath that contributors at the Molecular Pharmacology of G Protein-Coupled Receptors (MPGPCR) held at the Victor Chang Cardiac Research Institute in Sydney, Australia in late 2008 be invited to submit short reviews to the British Journal of Pharmacology. The MPGPCR meetings focus on recent developments in the field, with key presentations from leading researchers from around the world emphasizing novel concepts in GPCR pharmacology and drug discovery. The major themes covered at the meeting included the impact of the recent elucidation of GPCR structures, the identification of novel sites for drug interaction and the importance of protein/protein interactions for GPCR function. Most of the reviews arise from topics covered at the meeting together with other commissioned papers relevant to the issue. The next MPGPCR meeting will be held in December, 2010 in Melbourne. For more information visit http://www.gpcrmeeting.com

While GPCRs are arguably the most exploited membrane proteins in terms of successful therapeutic applications, with some 30% of currently used drugs targeting this receptor superfamily, this has been based on knowledge of about 200 proteins. As there are at least 800 GPCRs together with new opportunities to target novel sites on individual receptors and also sites formed by protein/protein interactions, there is clearly a great deal of potential for the development of new therapeutic agents.

The main obstacle to progress has been a lack of fundamental understanding of key facets of GPCR biology, in particular, those governing the structural basis for ligand binding and activation, novel allosteric and other sites distinct from the natural ligand binding site, and ligand- and conformation-directed differential signalling and regulation of receptors. The paper by Congreve and Marshall (2010) emphasizes how important the elucidation of the X-ray crystal structures of the β_1- and β_2-adrenoceptors and the adenosine A_{2A}-receptor will be to increasing our understanding of the changes in receptor conformation that underpin signalling and in particular signalling that occurs in response to novel ligands that are responsible for allosteric and ligand-directed signalling (LDS). Knowledge of the crystal structures will enable structure-based drug design and virtual screening, approaches that have the potential to have a major impact on GPCR drug development.

Several reviews deal with the identification of novel sites for drug interaction. Mohr *et al*. (2010) discuss dualsteric (also termed bitopic) ligands that represent a novel mode of targeting GPCRs and attach simultaneously to both the orthosteric and an allosteric site of the receptor. Interaction with the

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Received 27 November 2009; accepted 2 February 2010

natural neurotransmitter or orthosteric site activates the receptor while the allosteric interaction promotes subtype selectivity and may modulate both efficacy and the signalling pathway. The muscarinic cholinoceptor has been used as an example of how the conservation of the orthosteric binding site for acetylcholine between receptor subtypes has hindered the development of subtype selective drugs that could have great therapeutic potential and how this limitation might be overcome using rational design of dualsteric ligands.

Cawston and Miller (2010) examine the therapeutic potential for drugs targeting the CCK_1 receptor with particular emphasis on small molecule ligands, partial agonists and allosteric modulators. They describe in detail studies with non-peptide CCK_1 agonists that have potential for the treatment of obesity but are limited by side-effects. They suggest ways in which these undesirable properties might be overcome by allosteric modulators, partial agonists or biased agonists. Allosteric modulators would be useful as their action would be dependent on the presence of the endogenous agonist and would be self-limiting as well as less likely to cause desensitization and tolerance. Partial agonists may activate only a subset of the actions of CCK_1 full agonists and may also antagonize the endogenous agonist at some sites by competing for binding. Some compounds are already available to test this hypothesis. Biased agonism (or LDS) may provide another approach that has yet to be explored for the CCK_1 receptor.

Evans *et al*. (2010) analyse the expanding body of data that strongly suggests that LDS occurs at β-adrenoceptors. The wealth of information available on the signalling properties of all three β-adrenoceptor subtypes together with the availability of a wide variety of agonist and antagonist ligands has promoted the development of the concept of LDS in this field. Such biased signalling has been detected not only by examining the relative efficacy of a variety of drugs across multiple signalling pathways, but also by using direct methods such as labelling receptors with an environmentally sensitive fluorophore to detect conformational changes via BRET or FRET approaches. While the evidence that LDS occurs is strong, the connection with therapeutic efficacy for many of these drugs has yet to be established. The determination of activity profiles that are optimized for clinical efficacy and the systems that are used to establish these profiles are major requirements for the future.

Khan and Conigrave (2010) describe the fascinating pharmacology of the calcium sensing receptor (CaR), a Family C GPCR characterized by a large extracellular Venus FlyTrap (VFT) domain and large cytoplasmic C-terminus. CaR are widely distributed, respond to a wide variety of nutrient and other signals in addition to Ca^{2+} and can couple to a number of G proteins providing several signalling options. CaR respond to not only Ca^{2+} but also ionic strength, pH and temperature, other inorganic cations, peptides, aminoglycoside antibiotics and amyloid peptides. L-amino-acids are physiological modulators of CaR function and both positive and negative allosteric modulators are described. The positive allosteric modulator, cinicalcet, used to treat secondary hyperparathyroidism is the first example of a therapeutic targeted to an allosteric site on a GPCR. Other reviews in this issue deal with the importance of protein/protein interaction for GPCR action. The homodimerization and heterodimerization of the CaR is also covered in the Khan and Conigrave paper and discussed in terms of receptor translocation and signalling whereas heterodimerization may provide a mechanism for tissue-specific nutrient sensing.

Schulte *et al*. (2010) examine the role of β-arrestins for scaffolding and signalling in the enigmatic WNT/Frizzled (FZD) signalling pathways. The β-arrestins were originally identified as negative regulators of GPCR signalling, but more recently it has been recognized that they have a broader role as scaffolding proteins that not only mediate receptor desensitization and internalization but also trigger many other G protein-independent signalling events. WNTs are glycolipoproteins that act through FZD family GPCRs to activate either β-catenin-dependent or β-catenin-independent pathways, both of which involve β-arrestins that promote internalization and signalling. β-Arrestins clearly play a crucial but not exclusive role in WNT/FZD signalling and a better understanding of their actions may be a key factor in determining the function of these unconventional GPCRs.

Qi and Hay (2010) reflect on the roles of receptor-activity modifying proteins (RAMPs) in GPCR function. As their discovery as partners of the calcitonin peptide family receptors, they have been shown to influence pharmacology, trafficking and recycling of particular GPCRs. Although RAMPs have never been shown to respond to ligands in the absence of a GPCR partner, they clearly participate in ligand binding either directly or by allosteric modulation for at least a subset of GPCR partners. The paper summarizes a great deal of the mutagenesis data that has attempted to identify the exact residues on RAMPs responsible for high affinity ligand binding. The authors suggest that combination of mutational analysis and insights provided by structural information on RAMP-receptor complexes is likely to be the best approach to understanding the pharmacology of these challenging receptors.

Recent years have seen remarkable progress in GPCR research. There have been major strides in the understanding of GPCR structure, the pleiotropic nature of signalling and how this is influenced by ligands acting at orthosteric and allosteric binding sites. The importance of scaffolding proteins in the regulation and signalling properties of receptors has also emerged. The stage is now set for the translation of these findings into novel therapeutics that will affect many of the major disease conditions throughout the world.

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