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Themed Section: Secretin Family (Class B) G Protein-Coupled Receptors – from Molecular to Clinical Perspectives

EDITORIAL

Secretin family (Class B) G protein-coupled receptors – from molecular to clinical perspectives

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David R Poyner
David Poyner is a molecular pharmacologist with a long-term interest in GPCRs. While initially working on muscarinic receptors, for the last 20 years he has studied the molecular pharmacology of CGRP.

Debbie L Hay
Debbie Hay is a molecular pharmacologist, specialising in structure-function studies of family B GPCRs. In particular, her work focuses on the receptors for the CGRP/adrenomedullin/amylin/calcitonin family of peptides. These receptors are postulated to be good drug targets for a range of conditions including migraine, cardiovascular disease, cancer and diabetes.

Keywords
G protein-coupled receptor; GPCR; family B; secretin; CGRP

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Family B G protein-coupled receptors represent an important but under-researched group of receptors. This edition of the *British Journal of Pharmacology* considers the roles and pharmacology of a number of these receptors. Whilst common themes emerge, it is clear that more work is needed to understand the details of each receptor in order to properly exploit them therapeutically.

LINKED ARTICLES

This article is part of a themed section on Secretin Family (Class B) G Protein-Coupled Receptors. To view the other articles in this section visit http://dx.doi.org/10.1111/bph.2012.166.issue-1

GPCRs constitute a large family of cell surface proteins that respond to a diverse array of physiological stimuli to control cellular processes. GPCRs have been heavily exploited in the development of drugs but the therapeutic potential of these proteins is still relatively untapped. Most drugs that are active against GPCRs target the class/family A, or the rhodopsin family of GPCRs, which is the largest sub-grouping of these receptors. In recent years class/family B, or the secretin family of GPCRs, has attracted attention, particularly in the field of metabolic diseases. These GPCRs comprise 15 members and possess an extracellular amino terminal adaptation that accommodates the binding of peptides ranging from around 20 to 50 amino acids (Fredriksson *et al.*, 2003).

Historically the pharmaceutical industry has struggled to develop agents that act on family B GPCRs. This is partly because the cognate receptor ligands do not serve as useful templates for the development of lead compounds. With more acceptance of peptidic therapeutics and the identification of some high affinity small molecules, this is now changing. There are now marketed therapies targeting glucagon-like peptide 1 (GLP-1), amylin, calcitonin and glucagon receptors and other promising drugs are at different stages of clinical development (Archbold *et al.*, 2011).

There have been a series of very exciting advances in the field of family B GPCRs recently. Evidence for their involvement in pathological states continues to grow, affirming their

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importance as drug targets (Dunworth and Caron, 2009; Kadmiel *et al.*, 2011). Allied to this there have been important advances in structural biology including the publication of several crystal structures of their N-termini, with or without bound ligands (Grace *et al.*, 2004; Parthier *et al.*, 2007; Pioszak and Xu, 2008; Runge *et al.*, 2008; Grace *et al.*, 2010; ter Haar *et al.*, 2010; Pal *et al.*, 2010; Kusano *et al.*, 2011). This work increases our understanding of ligand binding and provides a useful platform for structure-based drug design.

Our knowledge of the structure of the transmembrane domains of family B GPCRs currently lags behind that of the family A, where we have an increasing repertoire of crystal structures of both ground-state and active receptors (Katritch *et al.*, 2011). However, the existing family A crystal structures help our understanding of how family B GPCRs recognise G proteins and, following the lessons learnt from the family A crystalisations, several groups are currently attempting to crystalise a family B GPCR. When successful, this will represent a major step forward. Even without this, real progress is being made at producing novel antagonists and agonists, either orthosteric or allosteric, which act at family B GPCRs (Axelsen *et al.*, 2012; de Graaf *et al.*, 2011). There is also is an increasing awareness of the complexities of signalling mediated by these receptors and how they can be exploited by the production of biased agonists or modulated by association with other proteins such as receptor activity-modifying proteins, and by splicing (Hay *et al.*, 2006; Karteris *et al.*, 2010; Gesty-Palmer and Luttrell, 2011).

This themed issue of the *British Journal of Pharmacology* draws together a series of 11 review and two original research articles from a number of the leading groups in the field of family B GPCRs. This issue contains the first International Union of Pharmacology receptor review in collaboration with the *British Journal of Pharmacology* (Harmar *et al.*, 2012). There are extensive discussions of the binding of peptides and non-peptide ligands to the secretin receptor (Miller *et al.*, 2012), the GLP-1 receptor (Donnelly, 2012), VPAC receptors (Couvineau and Laburthe, 2012) and the calcitonin and calcitonin receptor-like receptors (Barwell *et al.*, 2012). Two research papers explore the detailed pharmacology of peptide binding; the recognition of adrenomedullin by the adrenomedullin 1 receptor (Kuwasako *et al.*, 2012) and the significance of species differences in the pharmacology of amylin receptors (Bailey *et al.*, 2012). The way in which ligand binding can be modified by accessory proteins, and in particular the consequences of this for production of CGRP antagonists is reviewed by Moore and Salvatore (Moore and Salvatore, 2012). The unique way in which family B GPCRs may be activated is considered for the VPAC1 receptor (Langer, 2012). The diversity of signalling is explored by reference to the CRF1 receptor (Grammatopoulos, 2012) and the consequences of splicing on the function of family B GPCRs is considered by Furness and colleagues (Furness *et al.*, 2012). Finally, the pathophysiological role of agents that act on family B receptors are considered in two reviews; one on adrenomedullin 2 (Hong *et al.*, 2012) and the other on amylin and GLP-1 (Roth *et al.*, 2012).

What is becoming clear is that one size does not fit all for GPCRs in general or for family B GPCRs. Although there are commonalities in their general mode of binding and activation, each family B GPCR has its own unique properties that lend it to its role in physiology and disease. By exploring these in detail, it is hoped that this collection of articles will stimulate further research into this family of GPCRs.

Conflict of interest

None.

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