BJP British Journal of Pharmacology

DOI:10.1111/bph.12339
www.brjpharmacol.org

INTERNATIONAL UNION OF BASIC AND CLINICAL PHARMACOLOGY COMMENTARY

Evolving pharmacology of orphan GPCRs: IUPHAR Commentary

Anthony P Davenport[1] and Anthony J Harmar[2]

[1]*Clinical Pharmacology Unit, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK, and* [2]*University/BHF Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK*

Correspondence
Anthony P Davenport, Clinical Pharmacology Unit, University of Cambridge, Level 6, Centre for Clinical Investigation, Box 110, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK.
E-mail:apd10@medschl.cam.ac.uk

Keywords
chemerin receptor; chemokine receptors; free fatty acid receptors; hydroxycarboxylic acid receptors; lysophosphatidic acid receptors; oxoglutarate receptor; succinate receptor

Received
25 July 2013
Revised
9 August 2013
Accepted
13 August 2013

The award of the 2012 Nobel Prize in Chemistry to Robert Lefkowitz and Brian Kobilka for their work on the structure and function of GPCRs, spanning a period of more than 20 years from the cloning of the human β_2-adrenoceptor to determining the crystal structure of the same protein, has earned both researchers a much deserved place in the pantheon of major scientific discoveries. GPCRs comprise one of the largest families of proteins, controlling many major physiological processes and have been a major focus of the International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR) since its inception in 1987. We report here recent efforts by the British Pharmacological Society and NC-IUPHAR to define the endogenous ligands of 'orphan' GPCRs and to place authoritative and accessible information about these crucial therapeutic targets online.

Abbreviation

NC-IUPHAR, International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification

The completion of the human genome sequence at 99% coverage (International Human Genome Sequencing Consortium, 2004) permitted the identification of all genes encoding a GPCR structure. However, the activating ligands and signalling mechanisms of these predicted receptors were not yet known and they were designated as 'orphans'. The Evolving Pharmacology Group of the International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR) published, in 2005, a catalogue of all the human gene sequences known or predicted to encode GPCRs, excluding sensory receptors (Foord *et al.*, 2005). More detailed information that could be encompassed in the review is provided in the IUPHAR database (IUPHAR-DB; Harmar *et al.*, 2009; Sharman *et al.*, 2011; 2013), which is continually updated to reflect the dynamic nature of the field, describing new pairings of orphan GPCRs with their endogenous ligands at http://www.iuphar-db.org/latestPairings.jsp.

NC-IUPHAR, in collaboration with the British Pharmacological Society (BPS), has a major initiative to advance the nomenclature of GPCRs and the classification of remaining orphans. NC-IUPHAR has recently published a review which updates the 2005 paper to reflect new pairings and describes the criteria used to recommend the pairing of an orphan receptor with its cognate ligand(s) (Davenport *et al.*, 2013). In the review, recommendations are made for new receptor names based on 11 pairings for class A GPCRs: hydroxycarboxylic acid receptors [HCA_1 (*GPR81*) with lactate, HCA_2 (*GPR109A*) with 3-hydroxybutyric acid, HCA_3 (*GPR109B*) with 3-hydroxyoctanoic acid]; lysophosphatidic acid receptors [LPA_4 (GPR23), LPA_5 (*GPR92*), LPA_6 (*P2Y5*)]; free fatty acid receptors [FFA4 (*GPR120*) with omega-3 fatty acids]; chemerin receptor (*CMKLR1*; ChemR23) with chemerin; *CXCR7* (*CMKOR1*) with chemokines CXCL12 (SDF-1) and CXCL11 (ITAC); succinate receptor (*SUCNR1*) with succinate; and oxoglutarate receptor, *OXGR1* with 2-oxoglutarate. A

further 30 receptors are highlighted where pairings have been reported but further input is needed from the scientific community – particularly from pharmacologists – to validate these findings. The review represents a snapshot of current classification: in some cases, such as GPR119, no recommendation has been made as the nomenclature is currently being actively considered (in this case, by the cannabinoid receptor subcommittee of NC-IUPHAR). Fifty-seven class A receptors are still considered orphans and information is given where a significant phenotype has been reported in genetically modified mice. In class B, six pairings have been described (each in a single publication, i.e. not yet replicated) with 28 still classified as orphans. Seven orphan receptors remain in class C, with one pairing described by a single paper. The review also discusses GPR33, TAAR2, TAAR9, GPR42, GPR79 and GnRH2, which may be pseudogenes in some, or all, humans. IUPHAR-DB contains further information, which has been updated this year to coincide with the review on the current state of orphan receptors in each of the three classes. It is comprehensively cross-linked with other public resources, including the human, rat and mouse genome databases, Entrez Gene, RefSeq, UniProt, Ensembl, DrugBank, OMIM and PubChem.

The technique of reverse pharmacology and high throughput screening continues to be used to pair orphan receptors with cognate ligands. A recent review incorporates information from a screen of 10 000 ligands against 82 GPCRs and also describes the identification of novel 'surrogate ligands' (Southern *et al.*, 2013). These are small molecule compounds that have been shown to act as agonists or inverse agonists on artificially expressed orphan receptors and can subsequently be used as pharmacological tools to explore the function and therapeutic potential of GPCRs, in the absence of an identified endogenous ligand.

The collaboration between NC-IUPHAR and the BPS has united and harmonized the information contained in IUPHAR-DB and the *British Journal of Pharmacology* (BJP) 'Guide to Receptors and Channels' (GRAC; Alexander *et al.*, 2011b) through the Guide to PHARMACOLOGY website (http://www.guidetopharmacology.org; Alexander *et al.*, 2011a; 2012; Pawson *et al.*, 2013), which houses the combined data on therapeutic targets, drugs and other ligands, and provides a single portal for accessing this information. The Wellcome Trust has recently awarded a major grant to support and develop this database. Over the next 4 years, it will expand as global resource designed to be accessible to all members of the scientific community, to maximize our increasing knowledge of how druggable gene targets affect health and disease. The ambition is for the database to become a key educational resource in pharmacology, as well as an accurate source of information for the wider scientific community and general public, on the basic science underlying drug action.

In a third initiative, BPS and IUPHAR have launched a series of 'IUPHAR Reviews' in BJP, particularly in the areas covered by the databases such as GPCRs, ion channels and nuclear receptors, as well as new areas being considered by NC-IUPHAR. Papers relating to nomenclature will continue to be published by *Pharmacological Reviews*. Eliot Ohlstein has responsibility for coordinating and editing these publications. Two reviews have been published to date as exemplars of the format. The inaugural paper reviews and updates the pharmacology of the GPCR family of vasoactive intestinal peptide and pituitary adenylate cyclase activating polypeptide-38 receptors where the nomenclature has been well established (Harmar *et al.*, 2012). The second explores an emerging key concept in pharmacology – biased signalling or biased agonism – which has the prospect to revolutionize drug discovery and the medicinal armamentarium (Kenakin, 2013).

In order to make these resources freely available to the scientific community and general public, the fifth edition of GRAC relied on the altruistic and enthusiastic expertise of over 100 international consultants. Nearly 800 international experts contribute to over 90 NC-IUPHAR sub-committees. For IUPHAR-DB, in 2013, their efforts were viewed on average each month by 8500 individual making 14 000 visits per month drawn from ~160 different countries. Experts are still needed to expand the online resources and to author NC-IUPHAR reviews. Volunteers can contact the curators at curators@iuphar-db.org.

The 10th anniversary of sequencing the human genome was notable for the lack of progress in translating the results of the considerable investment in genomics into clinical benefits. There are an unprecedented number of new targets emerging from the GPCRs and we hope that the joint NC-IUPHAR and BPS initiatives will stimulate more pharmacologists to take up the challenge (McGrath *et al.*, 2012). The award of the 2012 Nobel Prize in Chemistry to Robert Lefkowitz and Brian Kobilka for their work on the structure and function of GPCRs, spanning a period of more than 20 years from the cloning of the human Beta2 adrenoceptor (Dixon *et al.*, 1986) to determining the crystal structure of the same protein (Cherezov *et al.*, 2007; Rasmussen *et al.*, 2007), has earned both researchers a much deserved place in the pantheon of major scientific discoveries and is revolutionizing structure-based approaches to GPCR drug discovery.

Funding

International Union of Basic and Clinical Pharmacology, British Pharmacological Society and The Wellcome Trust (Grant number 099156/Z/12/Z).

Conflicts of interest

None.

References

Alexander SPH, Harmar A, McGrath I (2011a). New updated GRAC Fifth Edition with searchable online version Launch of new portal Guide to Pharmacology in association with NC-IUPHAR Transporter-Themed Issue. Br J Pharmacol 164: 1749–1750.

Alexander SPH, Mathie A, Peters JA (2011b). Guide to receptors and channels (GRAC), 5th edn. Br J Pharmacol 164 (Suppl 1): S1–324.

Alexander SPH, Benson HE, Davenport A, Mathie A, McGrath IJ, Pawson AJ *et al*. (2012). GuideToPharmacology.org – an update. Br J Pharmacol 167: 697–698.

Cherezov V, Rosenbaum DM, Hanson MA, Rasmussen SG, Thian FS, Kobilka TS *et al*. (2007). High-resolution crystal structure of an engineered human beta2-adrenergic G protein-coupled receptor. Science 318: 1258–1265.

Davenport AP, Alexander SPH, Sharman JL, Pawson AJ, Benson HE, Monaghan AE *et al*. (2013). International Union of Basic and Clinical Pharmacology. LXXXVIII. G protein-coupled receptor list: recommendations for new pairings with cognate ligands. Pharmacol Rev 65: 967–986.

Dixon RA, Kobilka BK, Strader DJ, Benovic JL, Dohlman HG, Frielle T *et al*. (1986). Cloning of the gene and cDNA for mammalian beta-adrenergic receptor and homology with rhodopsin. Nature 321: 75–79.

Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP *et al*. (2005). International Union of Pharmacology. XLVI. G protein-coupled receptor list. Pharmacol Rev 57: 279–288.

Harmar AJ, Hills RA, Rosser EM, Jones M, Buneman OP, Dunbar DR *et al*. (2009). IUPHAR-DB: the IUPHAR database of G protein-coupled receptors and ion channels. Nucleic Acids Res 37: D680–D685.

Harmar AJ, Fahrenkrug J, Gozes I, Laburthe M, May V, Pisegna JR *et al*. (2012). Pharmacology and functions of receptors for vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide: IUPHAR review 1. Br J Pharmacol 166: 4–17.

International Human Genome Sequencing Consortium (2004). Finishing the euchromatic sequence of the human genome. Nature 431: 931–945.

Kenakin T (2013). New concepts in pharmacological efficacy at 7TM receptors: IUPHAR review 2. Br J Pharmacol 168: 554–575.

McGrath JC, Spedding M, Bruun J, Harmar A (2012). Calling all pharmacologists with time to spare! We need you! Build the drug discovery knowledge base, GuidetoPharmacology.org. Br J Pharmacol 167: 1393–1394.

Pawson AJ, Sharman JL, Benson HE, Faccenda E, Spedding M, Harmar AJ (2013). The Guide to PHARMACOLOGY portal – a one-stop pharmacology shop. Biochemist 35: 36–39.

Rasmussen SG, Choi HJ, Rosenbaum DM, Kobilka TS, Thian FS, Edwards PC *et al*. (2007). Crystal structure of the human beta2 adrenergic G-protein-coupled receptor. Nature 450: 383–387.

Sharman JL, Mpamhanga CP, Spedding M, Germain P, Staels B, Dacquet C *et al*. (2011). IUPHAR-DB: new receptors and tools for easy searching and visualization of pharmacological data. Nucleic Acids Res 39: D534–D538.

Sharman JL, Benson HE, Pawson AJ, Lukito V, Mpamhanga CP, Bombail V *et al*. (2013). IUPHAR-DB: updated database content and new features. Nucleic Acids Res 41: D1083–D1088.

Southern C, Cook JM, Neetoo-Isseljee Z, Taylor DL, Kettleborough CA, Merritt A *et al*. (2013). Screening beta-arrestin recruitment for the identification of natural ligands for orphan G-protein-coupled receptors. J Biomol Screen 18: 599–609.