British Pharmacological Society, 5th Focused Meeting on Cell Signalling: Matters arising………

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Running title: BPS Cell Signalling Meeting

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Since the work of pharmacology pioneers such as JN Langley and AJ Clark we have increasingly appreciated that chemical information is converted into cellular and systems responses by receptors that often exhibit exquisite chemical specificity (Maehle et al., 2002). Over the subsequent decades, receptors for a vast array of different ligands have been identified. It transpired that a large number of receptor-mediated effects involve changes in the levels of intracellular second messengers and occur via activation of heterotrimeric G proteins. The importance of these findings to our understanding of the way in which many hormones and neurotransmitters work has been recognised by the award of Nobel Prizes to Sutherland in 1971 for his work on cyclic AMP, to Gilman and Rodbell in 1994 for their work on G proteins and most recently to Brian Kobilka and Robert Lefkowitz for their work on the structure and function of G protein-coupled receptors (GPCRs).

Even before the isolation and sequencing of members of the GPCR superfamily, there was a rapid development of drugs that targeted these receptors, as either agonists or antagonists, allowing the treatment of conditions as diverse as pain, high blood pressure and schizophrenia. However, the purification of the β2-adrenoceptor by the Lefkowitz group in 1979 (Caron et al., 1979), its subsequent cloning and the recognition of the homology to rhodopsin (Dixon et al., 1986) underpinned an appreciation of the extent and importance of this family and opened up the possibility of detailed structure-function analysis for the first time. It was perhaps not until this cloning era and ultimately the sequencing of the human genome in 2001 (Venter et al., 2001) that the size of this family of receptors was fully appreciated. We now know that GPCRs (also known as seven-transmembrane domain (7TM) receptors) represent the largest receptor superfamily, comprising of more than 800 members in humans (Fredriksson et al., 2003). GPCRs are responsible for a vast array of cellular and systems responses underlying most physiological processes, being able to transduce signals initiated by first messengers as diverse as photons of light, ions, neurotransmitters, hormones and large glycoproteins that might be comparable in size to their cognate GPCRs.

The under-activity or over-activity of GPCRs (ligand-dependent or -independent) can cause or contribute to a range of diseases (Thompson et al., 2005). In addition to underlying disease processes, these receptors can provide levers to regulate cellular activity and have become, therefore, key therapeutic targets. Despite non-sensory receptors representing >50% of the GPCRome, only around 50 GPCR sub-types are established as therapeutic targets (Allen and Roth, 2011). Thus, although GPCRs are clearly highly druggable, there remain a large number of receptors that are as yet unexplored with respect to the treatment of disease. There is also considerable expectation that as our pharmacological understanding and capabilities in medicinal chemistry increases, we will be able to exploit more aspects of GPCR activation and signalling to develop more selective and effective therapeutics. Such novel approaches are already paying dividends, with drugs such as cinacalcet, a positive allosteric modulator of the calcium-sensing GPCR used to treat hyperparathyroidism (Nemeth, 2013), and maraviroc, a negative allosteric modulator of viral gp120 binding to chemokine receptor 5 (CCR5) used in the treatment of AIDS (Lagane et al., 2013), reaching patients. There is no doubt that other pharmacological aspects of GPCR structure and function, including inverse agonism, G protein-dependent and G protein-independent signalling, ligand bias, homo- and heterodimerization, bitopic or bivalent ligands, the GPCR interactome and receptor desensitization, internalization, trafficking and recycling, remain to be fully exploited therapeutically.

Such matters have been at the heart of the previous four biennial (almost) British Pharmacological Society Focused Meetings on Cell Signalling, held at the University of Leicester, and the fifth meeting, held for the first time in association with the Biochemical Society in April 2014, maintained this focus. These two-day meetings have provided the UK
and international GPCR community with an opportunity to see and hear the latest research in basic signalling mechanisms through systems physiology and pharmacology to the development of novel therapeutics. The 2014 meeting was centred around twelve lectures by world-leading researchers ranging across subjects, such as signalling mechanisms, structural dynamics, viral GPCRs, disease and drug development. These lectures were supported by seven short presentations selected from the submitted abstracts and more than sixty poster presentations. This year the lecture series also included both The Paton Memorial Lecture presented by Morley Hollenberg from the University of Calgary, and the EPHAR (Federation of European Pharmacological Societies) Lecture presented by Ralf Jockers from the Institut Cochin, Paris. Within this issue both Hollenberg and Jockers present their work along with that of Vsevolod Gurevich, Stuart Mundell and Graeme Milligan.

Morley Hollenberg provides an overview of proteinase-mediated signalling, specifically the role of the proteinase-activated receptors (PARs) in health and inflammatory conditions (Hollenberg, 2015). Hollenberg also provides an historical context to his work and in particular relates this to his time as a Canadian Rhodes Scholar working in the Oxford Department of Pharmacology in the mid-1960s when it was led by William Paton. The EPHAR lecture given by Ralf Jockers discussed a widening appreciation of roles for melatonin and melatonin receptors in physiology, focusing on the role of MT1 and MT2 heterodimers in the regulation of retinal light sensitivity. Within the accompanying article, Jockers and colleagues discuss ligand-independent actions of GPCRs, particularly the premise that some orphan receptors may not have traditional ligands and may operate through aspects such as constitutive activity and protein-protein interactions (Ahmad et al., 2015). They also consider pathophysiological roles for orphan GPCRs and means of determining function in the absence of ligands. Vsevolod Gurevich presents a paper discussing the shortcomings of small-molecule drugs and presents an overview of alternative treatment strategies, including biologics, gene therapy and genome editing (Gurevich and Gurevich, 2015). Stuart Mundell and his group present a paper outlining their strategy to understand more about the molecular basis of bleeding disorders and in particular the use of natural GPCR variants to explore such issues (Nisar et al., 2015). Graeme Milligan and colleagues present an overview of recent work on the free fatty acid GPCRs, FFA1 and FFA4, particularly their attempts to identify specific ligands to probe their functions (Milligan et al., 2015).

GPCRs will, no doubt, continue to provide a focus of drug development activity for many years to come, ensuring that there will be a continuing need to explore the molecular, cellular and systems basis of GPCR biology. We hope that these meetings will continue to provide an important meeting point for molecular pharmacologists in the coming years. The 6th Focused Meeting on Cell Signalling will be held at the University of Leicester 18-19th April, 2016. Make a note in your diary!

REFERENCES


Nisar SP, Jones ML, Cunningham MR, Mumford AD, Mundell SJ (2015). Rare platelet G protein-coupled receptor variants: what can we learn? Br J Pharmacol (this issue)
