G-Protein-Coupled Receptors: from Structural Insights to Functional Mechanisms

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Abstract
The papers resulting from the recent Biochemical Society Focused Meeting ‘G-Protein-Coupled Receptors: from Structural Insights to Functional Mechanisms’ held in Prato in September 2012 are introduced in the present overview. A number of future goals for GPCR (G-protein-coupled receptor) research are considered, including the need to develop biophysical and computational methods to explore the full range of GPCR conformations and their dynamics, the need to develop methods to take this into account for drug discovery and the importance of relating observations on isolated receptors or receptors expressed in model systems to receptor function in vivo.

The Biochemical Society/Monash University Focused Meeting ‘G-Protein–Coupled Receptors: from Structural Insights to Functional Mechanisms’ held in Prato in September 2012 has proved particularly timely. During the course of the meeting, preliminary data for two new GPCR (G-protein-coupled receptor) structures were revealed, including the very first family B GPCR crystal structure. During the preparation of this issue of Biochemical Society Transactions, it was announced that the 2012 Nobel Prize for Chemistry had been awarded to Dr Robert Lefkowitz and Dr Brian Kobilka for their outstanding contributions to the biology of GPCRs; many of their close collaborators were speakers at the meeting. Organizing a meeting at such a pivotal time was a real privilege, as was editing this collection of papers arising from the event.

Given the current ferment of excitement about GPCR structure, it is not surprising that a number of papers in this collection focus directly on crystallization. Fiona Marshall [1] presents an overview of crystallization strategies, and Tony Warne [2] summarizes what is currently known about how agonists binding to the β-receptor cause the changes necessary for G-protein activation. The dynamics of β-receptor activation have previously been probed by FRET (fluorescence resonance energy transfer) by Kobilka and co-workers [3]; Jean-Louis Banères [4] describes his recent study extending the technique to look at the conformational landscape of the ghrelin receptor. The information available from family A GPCRs is also being applied to family B GPCRs. Lawrence Miller [5] describes his studies to determine how secretin binds to its receptor and Barwell et al. [6] consider how the CGRP (calcitonin gene-related peptide) receptor may become activated upon agonist binding. Inna Hoyer’s paper [7] describes the mapping of an allosteric binding site at the TSH (thyroid-stimulating hormone) receptor.

Although structural studies have recently dominated the GPCR field, there are many other aspects to their role, and these were also explored at the meeting. GPCR...
oligomerization remains an area of keen interest, with still unresolved issues. Thierry Durroux [8] considers the use of fluorescent ligands to investigate the extent of dimerization in native cells and membranes, thus avoiding potential artefacts that can arise with modified receptors and exogenous expression systems [9]. Another hot topic has been the multiplicity of signalling pathways that can be activated by GPCRs and the development of biased agonists to exploit these [10]. Elena Borroni [11] describes a novel chemokine receptor which signals exclusively via β-arrestin and Nigel Bunnett [12] describes that targeting the internalized receptor in an endosome will alter the balance between G-protein and β-arrestin-mediated signalling. Bice Chini [13] and Patrick Sexton [14] review the development of biased agonists at the oxytocin receptor and GLP-1 (glucagon-like peptide 1) receptor respectively. Eamonn Kelly [15] describes how quantification of agonist bias can help our understanding of agents acting at the μ-opioid receptor. The interaction of the P2Y_{12} receptor with proteins involved in its down-regulation is described by Margaret Cunningham [16].

A number of papers consider new techniques for GPCR research. In silico approaches to map the ligand-binding site of the oxytocin receptor thorough evolution are described by Christian Gruber [17], and Hugo Gutiérrez-de-Terán [18] gives an account of a number of useful web-based servers for carrying out molecular dynamics simulations of GPCRs in membrane environments. Scarselli et al. [19] introduce PALM (photoactivated localization microscopy) as a new method for studying receptor localization.

What of the future? Arising from the meeting, we think that it is possible to see a number of important areas for future research in GPCR biology. The crystal structures are wonderfully revealing, but provide only a static picture of what are highly flexible proteins. We still have little understanding of the conformational states which GPCRs can adopt in response to different ligands (full, partial, inverse and biased agonists, and neutral antagonists), transducing and interacting proteins (G-proteins, kinases and β-arrestins) and on the dynamics of the interconversion among all these states. To improve on this will require collaborations between biophysicists and molecular modellers, as well as biochemists and pharmacologists, to use existing techniques and develop new tools to solve the problems. But the rewards will be vast. There is growing concern at the failure of the drug-discovery pipeline and the realization that there are limits to robotic screening of compound libraries on GPCRs expressed in one cell type. A knowledge of the conformations of a receptor that couple to a given signalling pathway and which have relevance to a particular pathophysiological state could at last bring rational drug discovery to the world of GPCR pharmacology. The challenges are immense, requiring not only advances in GPCR structure, but also knowledge of downstream signalling in physiologically relevant systems for individual receptors. However, the benefits for human welfare and also for scientific endeavour surely make the effort worthwhile.

References


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