Editorial:

Pleiotropic GPCR Signaling in Health and Disease

Aylin C. Hanyaloglu[1]* and Dimitris K. Grammatopoulos[2]*

1. Institute of Reproductive and Developmental Biology, Dept. Surgery and Cancer, Imperial College London, UK
2. Translational Medicine, Warwick Medical School & Clinical Biochemistry, Coventry and Warwickshire Pathology Service, UK

*Corresponding authors: Dr. Aylin Hanyaloglu
Address: Institute of Reproductive and Developmental Biology, Dept. Surgery and Cancer, Hammersmith Campus, Imperial College London, Du Cane Road, London, W12 0NN, UK
Email: a.hanyaloglu@imperial.ac.uk
Tel: +44(0)20 759 42128

Prof. Dimitris Grammatopoulos
Address: Translational Medicine, Warwick Medical School & Clinical Biochemistry, Coventry and Warwickshire Pathology Service, Coventry, CV4 7AL, UK
Email: d.grammatopoulos@warwick.ac.uk
Tel: +44(0) 24 7696 8661

This Special Issue of Molecular and Cellular Endocrinology on 'Pleiotropic G protein-coupled receptor (GPCR) signaling in health and disease' illustrates the exquisite complexity of GPCR signal systems, current approaches to decode this complexity and progress in understanding the impact of these pleotropic systems to physiology, specifically endocrine functions, and in human disease. There are more than 800 different GPCRs in humans, playing central roles in almost all physiological systems. Furthermore, with >30% current drugs targeting these receptors, they represent a family of signaling molecules with paramount importance in understanding endocrine functions, from the molecular to clinical level.

Over the past two decades our view of GPCR signaling has evolved from a simple linear system where an individual receptor at the plasma membrane activates specific heterotrimeric G protein pathways, to one that is pluridimensional in its responses. Our molecular understanding of this superfamily of signaling receptors has been rapidly advanced by the generation of high resolution crystal structures of distinct active receptor states, including complexes with key protein partners, G proteins and the GPCR adaptor proteins the arrestins. These seminal studies led to the 2012 Nobel prize in Chemistry to Brian Kobilka and Robert Lefkowitz. The intricate details in ligand-receptor interactions and receptor activation states from these crystal structures has revolutionized drug targeting strategies to this highly desirable and successful super-group of therapeutic targets. The article by Woolley and Conner (Woolley and Conner, 2016) discuss advancements in our understanding of a key ligand-binding/activation domain of GPCRs emerged from recent structural information, that highlight the critical role for the second extracellular loop across many receptors as a direct binding site, a regulator for ligand entry in to the receptor transmembrane core and its impact on receptor function.

Diversity in GPCR signaling can be achieved via a number of mechanisms and in this special issue 3 distinct articles highlight primary mechanisms employed by GPCR interacting partners to achieve this. Routledge and colleagues (Routledge, 2017) discuss novel functions of the receptor activity modifying proteins (RAMPs), classically known for their role in regulating trafficking and activity of the Class B calcitonin and calcitonin-like receptors, they discuss their broader function in modulating the activity of other endocrine-relevant GPCRs across subfamilies, including the calcium-sensing receptor and the estrogen responsive GPCR GPR30/GPER. GPCRs can also associate with themselves and completely distinct GPCRs to form heteromers, which can form distinct functional units with unique properties from the GPCR homomer. The existence of such complexes has historically been met with much controversy in the field, but development of novel tools and

techniques to study the role of heteromers in vivo, and the potential to pharmacologically target these receptors in endocrine relevant disease, has been demonstrated. These are reviewed in (Jonas and Hanyaloglu, 2017). A critical interacting protein for many GPCRs are the arrestins. These proteins play multiple roles in regulation and activation of GPCR signaling; rapid desensitization of G protein signaling, receptor internalization, a scaffold for G protein-independent signal pathways and more recently in endosomal G protein signaling. To pharmacologically probe for these distinct properties of arrestin-dependent signaling versus G protein signaling has been of current high interest in the drug discovery industry for their potential to target beneficial physiological properties of the arrestin-dependent pathway or, for blocking unwanted side effects of full agonists/antagonists. The significance and potential of pharmacological bias of arrestin-dependent signaling for hormone activated GPCRs is discussed by Reiter and colleagues (Reiter, Ayoub, Pellissier et al., 2017).

The above articles clearly illustrate that GPCR signaling models are highly complex. A key question now is how to decode this complexity and understand how cells translate these signals in to downstream specific responses. This is particularly pertinent for endocrine systems where cells in a given tissue are exposed to a highly dynamic extracellular environment. A classic example of this is the pulsatile hypothalamic GnRH and its anterior pituitary GPCR, the GnRH receptor. The pulsatile nature of GnRH is altered during the cycle and to properly understand how GnRH receptor signal pathways are programmed under such conditions, Pratap and colleagues discuss their approaches to employ mathematical modeling (Pratap, Garner, Voliotis et al., 2016) that offers a theoretical approach to unpick complex, dynamic signal networks.

Translating the molecular and cell biological mechanisms described above to human physiology and disease is a an essential but challenging step. Kim et. al. (Kim, Bennett and Terzidou, 2017) review their latest findings in understanding pluridimensional signaling of the oxytocin receptor in human parturition and labor. Furthermore, that this mechanistically underlies the function of this receptor in both uterine contraction and inflammation during labor, and its significance to therapeutically targeting this receptor in both pre-term labor and post-dates pregnancy management. The impact of receptor signal crosstalk/synergy to energy homeostasis is elegantly demonstrated in the study by Hauge et. al. (Hauge, Ekberg, Engelstoft et al., 2016). Many GPCR types are expressed in the gut to control secretion of anorectic gut hormones to regulate appetite. In this Special Issue the authors present novel findings that in the colon distinct G protein pathways, $G\alpha q$ and $G\alpha s$, activated by distinct receptors, free fatty acid receptor 1/GPR40, the bile acid receptor TGR5 and GPR119 (that is activated by 2-monoacyl glycerol) act synergistically to regulate GLP-1 secretion and

provides novel information on how the gastrointestinal system senses and responds to fat in our diet.

It is perhaps not surprising that a growing number of human diseases have perturbed activity in specific GPCRs, particularly as our understanding of how these receptors function have evolved. Two articles in this issue highlight how such acquired understanding are being applied in platelet bleeding disorders (Cunningham, Aungraheeta and Mundell, 2017) and in human mood disorders and depression (Grammatopoulos, 2017). Cunningham and colleagues (Cunningham et al., 2017) discuss how GPCRs key to platelet function such as the purinergic, proteinase and thromboxane receptors exhibit altered spatial regulation, through the identification of function-disrupting variants of platelet GPCRs, highlighting the increasing importance of receptor localization and trafficking to cellular function, and particularly pertinent with the growing interest in GPCR signaling from intracellular compartments. In complex conditions such as depression, a number of GPCRs and GPCR mechanisms that are the focus of other reviews in this Issue, such as GPCR oligomerization, arrestin-dependent signaling and receptor trafficking have been demonstrated to be perturbed in mood disorders such as mania and depression. These conditions also provide a unique example of gender-specific defects in GPCR function with potential implications for disorders such as unipolar depression and post-traumatic stress disorder that occur more frequently in women than in men (Grammatopoulos, 2017).

In conclusion this Special Issue provides an exciting compilation of articles that demonstrates the pervasive nature of this superfamily of signaling receptors broadly across disciplines, and distinct physiological systems in both health and disease. They indicate both the areas in need of further research and the challenges to overcome in order to address them.

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