

MOLECULAR EVOLUTION OF GPCRS

What we know and what the future holds

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G protein-coupled receptors (GPCRs) are the largest family of cell membrane receptors in the human genome, comprising ~2% of human proteins. GPCRs are the target of a variety of signaling molecules such as peptide hormones, neuropeptides, chemokines, neurotransmitters, nucleotides, steroids, prostaglandins, cannabinoids, odorants, taste molecules, pheromones, and ions. A large number of clinically used drugs exert their biological effects via a GPCR, and orphan GPCRs provide valuable targets for the discovery of innovative drugs. Thus, it did not come as a surprise that the 2012 Nobel Prize in Chemistry was awarded to Robert J Lefkowitz and Brian K Kobilka for their pioneer work on GPCR structures and functions.

The presence of GPCRs in the genome of all living organisms including bacteria, yeast, plants, invertebrates, and vertebrates shows the early evolutionary origin of these ubiquitous and versatile receptors. As a result of two major whole-genome duplication rounds during vertebrate evolution (Van de Peer *et al.* 2010), GPCRs have had the opportunity to explore new functions (neofunctionalization) while maintaining the ancient ones. In particular, in the case of peptide hormones, neuropeptides, and their GPCRs, these genome duplication events have played a dual role in the diversification of both ligands and receptors. These (neuro)peptide/GPCR pairs thus represent exceptional models for studying the process of co-evolution of ligand–receptor systems. The aim of this special issue was to assemble a comprehensive series of review articles that illustrate the molecular and functional evolution of diverse families of neuropeptide GPCRs that are involved in the regulation of essential physiological functions, i.e. reproduction, growth, stress response, energy, and water homeostasis.

Secretin, the first peptide hormone to be discovered (Bayliss & Starling 1902), belongs to a large family of related peptides, which encompasses VIP, PACAP, GHRH, and glucagon (Vaudry *et al.* 2009). It is now established that secretin acts as a neuropeptide that regulates vasopressin release and water homeostasis (Chu *et al.* 2009). Herein, the evolutionary origin of secretin and its receptor is discussed by Tam *et al.* (2014). Glucagon-like peptide 1 (GLP1) is also a member of the VIP–PACAP–glucagon superfamily of peptides. The paper by Hwang *et al.* (2014) describes the phylogenetic history of GLP1 and its receptor, GLP1R, which is regarded as a promising target for the development of new drugs aimed at treating type 2 diabetes and obesity. POMC-derived peptides exert their corticotropic and melanotropic activities through specific interaction with melanocortin receptors (Cone 2006). The paper by Dores *et al.* (2014) focuses on ligand selectivity of the five melanocortin receptors and the role that reverse agonists (i.e. agouti and AgRP) and accessory proteins are playing in melanocortin receptor functions. The CRH family comprises several neuropeptides including urotensin I, urocortins, and sauvagine (Vaughan *et al.* 1995). Orthologs of these peptides and their receptors have now been identified in invertebrates, notably in arthropods. In their review, Lovejoy *et al.* (2014) examine the co-evolution process of these peptide–GPCR systems and the diversity of their functions from insects to human. Somatostatin and urotensin II are two cyclic neuropeptides that have recently been shown to derive from a single ancestral gene (Tostivint *et al.* 2006). In this review, the authors discuss the evolutionary dynamics of somatostatin/urotensin II peptides and their receptors that have led to the unexpected complexity of these

neuroendocrine systems (Tostivint *et al.* 2014). The identification of growth hormone secretagogue receptor (GHSR) and its natural ligand ghrelin is a striking example of the power of target base drug discovery, also termed 'reverse pharmacology', for the development of innovative therapeutic compounds (Kojima & Kangawa 2010). In their article, Kaiya *et al.* (2014) demonstrate that the remarkable simplicity of the ghrelin–GHSR system of tetrapods (i.e. one ligand and one receptor) markedly contrasts with the complexity of this system in teleosts. Kisspeptin, a member of the RFamide peptide superfamily, plays a critical role in sexual differentiation and reproduction (de Roux *et al.* 2003, Seminara *et al.* 2003). The paper by Pasquier *et al.* (2014) highlights the tumultuous history of kisspeptins and their receptors during vertebrate evolution. 26Rfa/QRFP is another RFamide peptide that was initially identified as an orexigenic neuropeptide (Chartrel *et al.* 2003). The article by Ukena *et al.* (2014) provides a complete overview of the molecular and functional evolution of 26Rfa and its receptor, called QRFP, from lamprey to mammals.

It is our hope that this issue will become a major reference for researchers working on the evolutionary aspects of GPCRs and their peptide ligands.

Declaration of interest

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