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Themed Section: Orexin Receptors

EDITORIAL

From orphans to orexins: an arousing fifteen years

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The inspiration for this Themed Issue came from a Reviews Editorial Board meeting for the British Journal of Pharmacology at a Winter BPS Meeting. I was actively engaged in orexin receptor drug discovery at the time and the dual orexin receptor antagonist, suvorexant (see below), was in Phase III clinical trials. It occurred to me that the orexin peptides and their receptors are truly one of the success stories of the 'age of de-orphanisation' that began in the 1990s. Compared to other neurotransmitters and neuropeptides, the orexin/hypocretin system represents the new kid on the block. First identified only in 1998, the past fifteen years has seen a steady growth in understanding of the roles that the orexin receptors and their cognate peptide ligands play in the CNS and beyond. Whilst NC-IUPHAR has endorsed the term orexin to designate the peptides' receptors (OX_1 and OX_2), the nomenclature of the peptides themselves is still the matter of much debate: they are variously referred to as orexins (from 'orexis', meaning 'appetite' in Latin) and hypocretins (as they are synthesised in the hypothalamus and display some similarity to the gut hormone secretin). In part this reflects the varied roles that the peptides have been shown to play; despite being produced by fewer than 20,000 cells in the hypothalamus, the orexin/hypocretin peptides are involved in a wide range of functions including energy homeostasis and feeding, sleep-wake regulation and control of reward. The common thread of these functions indicates that the orexinergic system is one primarily of arousal, indicating that both agonists and antagonists may be of therapeutic benefit in a range of conditions. In this issue, one of the pioneers of the field, Luis de Lecea and colleagues (Li *et al*., 2013) summarise the major physiological effects of the orexins/hypocretins, including not only arousal, but also sensory, locomotor and cognitive functions. In two sister reviews, Chris Leonard and Jyrki Kukkonen provide a comprehensive overview of orexin receptor signalling (Kukkonen & Leonard, 2013) and effects in native tissue systems, both central and peripheral (Leonard & Kukkonen, 2013). They show that orexin receptors display complex and pleiotropic signalling, engaging multiple G protein-dependent pathways, recruiting β-arrestins and regulating ion channel currents. In a research article, Jaeger *et al*. (2013) have used bioluminescence resonance energy transfer studies to investigate the ability of the OX_1 and OX_2 receptors to form stable complexes with β-arrestin and ubiquitin, identifying the importance of key serine/threonine residue clusters in the C-terminal tail. Chimeric receptor studies suggest that it is the intracellular face conformation, rather than just the secondary structure of the C-terminal tail, that dictate the stability of the complex.

For orexin receptor-targeted therapeutics, Chris Winrow and John Renger provide an excellent overview of the discovery and development of orexin receptor antagonists, showing how subtype selective antagonists have been used to delineate the roles of the OX_1 and OX_2 receptors and how dual orexin receptor antagonists (DORAs) that are in clinical development represent novel agents for the treatment of insomnia (Winrow & Renger, 2013). Data with suvorexant and other DORAs provides an alternative therapeutic strategy to the use of benzodiazepines and related drugs with a potentially increased therapeutic index. In a research article, Mould *et al*. (2013) have profiled a number of known orexin receptor antagonists in both equilibrium and non-equilibrium functional and radioligand binding assays at the OX_2 receptor. These studies demonstrate that the kinetics of antagonist binding, particularly association rate, is responsible for the functional antagonist profile observed, with the clinical candidate almorexant displaying pseudo-irreversible binding to the OX_2 receptor.

Given the important and varied roles played by the orexin/hypocretin peptides, it is surprising that they were only identified as recently as they were. The past fifteen years has yielded not only significant understanding of orexinergic physiology, but importantly progress in the discovery of newer and safer therapeutics – it is hoped that the next fifteen years continues to deliver in the same vein.

References

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