

Themed Section: Opioids: New Pathways to Functional Selectivity

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EDITORIAL

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LINKED ARTICLES

This article is part of a themed section on Opioids: New Pathways to Functional Selectivity. To view the other articles in this section visit <http://dx.doi.org/10.1111/bph.2015.172.issue-2>

This is the first themed issue on new developments in opioid pharmacology published by British Journal of Pharmacology (BJP). It is a bumper issue, with 39 papers, including 17 topical reviews. The issue emerged from invited review submissions by speakers at the International Narcotics Research Conference (INRC) held in Cairns, Australia from 14–18 July 2013, along with open submissions from attendees, and articles freely submitted following a call for papers. The meeting was sponsored in part by BJP and the British Pharmacological Society. INRC has been the major international meeting on opioid research for more than 40 years (see <http://www.inrcworld.org/history.htm>). Invited presentations at the 2013 meeting were largely focused on novel mechanisms of opioid receptor function and systems that are developing novel therapeutic avenues that could improve the clinical profile of opioids. In their International Union of Basic and Clinical Pharmacology (IUPHAR) review, Cox *et al.* (2015) discuss nomenclature recommendations for opioid receptors. Most papers in the themed issue conform to these recommendations.

It is very difficult to separate therapeutic actions of opioids such as analgesia from serious adverse effects including (potentially lethal) respiratory depression, constipation, somnolence, tolerance and addiction because most are mediated by the opioid μ -receptor (MOPr). The developments discussed in the themed issue explore current knowledge of new pharmacological understanding of MOPr and its interactions other opioid receptors that could be exploited in future drug development to reduce these adverse effects. In its current state, the opioid therapeutic armamentarium has only just begun to exploit novel pharmacological mechanisms such as hetero-oligomer formation, ligand bias, allostery and synergy with other receptor systems, including other opioid receptors.

The INRC meeting was opened with the traditional Founders Lecture delivered by Graeme Henderson (Henderson, 2015). The Founders Lecture honours the contributions of individuals who have made a sustained and substantial contribution to the science upon which the conference is based. Graeme is certainly one of those. Graeme

was the first to show in 1980 that opioids directly inhibit CNS neurons via hyperpolarization (Pepper and Henderson, 1980) which was later shown to be due to potassium channel activation. At the time of his seminal work, the predominant thinking was that morphine acted much like a local anaesthetic, simply blocking nerve conduction. His review reflects the progress made since then and the unanswered questions from an electrophysiologist's perspective.

A potential opportunity to exploit functional selectivity is development of heteromer selective opioids. Since the ground-breaking work of Lakshmi Devi suggesting that different opioid receptor types can form heteromers in heterologous expression systems there has been an extensive search for their presence and function in the central nervous system. The review by Massotte (2015) critically evaluates the evidence required to establish existence of heteromers *in vivo*. One of the crucial pieces of evidence is co-expression of the potential partner GPCRs in the same neuron. Massotte (2015) appraises the evidence for this and introduces her own studies of co-localization of MOPr and the opioid δ -receptor (DOPr) using knock-in mice that express both MOPr fused with a red fluorescent protein (mCherry) and DOPr fused with eGFP. The restricted colocalization in the CNS suggests potential for opioid drugs that selectively target MOPr-DOPr heteromers, moreover the general expression in lower brain regions involved in nociception indicates the potential for heteromer selective analgesics. Of course co-localization does not establish the existence of functional heteromers. Massotte discusses this and the review by Gendron *et al.* (2015) also touches on the question. The review by Fujita *et al.* (2015) further discusses the evidence for potential heteromer formation among opioid receptors or between opioid receptors and other GPCRs, revealing extensive potential for heteromer formation.

Multiple opioid receptors expressed in a single cell may interact as heterodimers or, alternatively, modulate the surface expression and function of the other partner. Zhang *et al.* (2015) review the evidence that MOPr and DOPr interact in small dorsal root ganglion neurons and that the interaction is modulated by neuronal activity and morphine

tolerance. This may begin to explain the widely published findings that DOPr antagonists can suppress morphine antinociceptive tolerance. Other reviews (e.g. Gendron *et al.*, 2015) and research papers, e.g. Ong *et al.* (2015) also address this theme.

Biased signaling and allostery have emerged as properties of many GPCRs that may provide opportunities to limit side effects. Biased opioid agonists that select for G-protein signaling in preference to β -arrestin pathways are in clinical development as analgesics with reduced side effects. Based on the plenary lecture from Arthur Christopoulos on bias and allostery, Thompson *et al.* (2015) provide an introduction to mechanisms of bias at opioid receptors focusing on MOPr with a detail review of the issues that must be considered in quantification of bias. The DOPr is also a potential target for pain management, particularly in neuropathic pain. Gendron *et al.* (2015) have comprehensively reviewed evidence for physiological functions of DOPr, including its potential for biased signaling, as well as the role of trafficking and surface expression of the receptor and potential interacting proteins involved in its regulation. Charfi *et al.* (2015) review different approaches to identify and quantify ligand-dependent bias at DOPr and review different types of experimental and analytical confounds in these analyses.

Allosteric modulators have been reported for a range of GPCRs but until very recently none were known for opioid receptors. Burford *et al.* (2015) review the principles of positive, negative and 'silent' (neutral antagonists at the allosteric site) allosteric modulation in the context of their exciting recent discovery of allosteric modulators of MOPr, particularly positive allosteric modulators (PAMs) that enhance the activity of orthosteric MOPr agonists. PAMs of MOPr have the potential to enhance the effects of endogenously released opioids or low doses of opioid orthosteric agonists. The authors speculate on the potential advantages that a PAM approach might bring to the design of novel therapeutics for pain that may avoid the side effects currently associated with opioid therapy. The further development of PAMs and biased PAMs has great potential to contribute to pain therapy, perhaps in ways that have not been considered previously.

Analgesics such as tramadol and more recently tapentadol exploit therapeutic interactions between opioid and other neurotransmitter systems. Synergistic interactions improve the therapeutic profile of opioids by limiting the degree of stimulus of the opioid system required to produce pain relief. Chabot-Doré *et al.* (2015) comprehensively review evidence for the best established interactions between α_2 -noradrenergic agonists and both MOPr, and DOPr to provide pain relief in animal models. Sadeghi *et al.* (2015) describe additive mechanisms underlying the action of tapentadol in brain neurons.

Development of tolerance is one of the major limitations of long-term opioid treatment. Understanding the mechanisms of MOPr regulation is thought to be crucial for understanding and potentially developing strategies to limit tolerance. Coordinated phosphorylation of C-terminal serine and threonine residues on MOPr plays a crucial role in the initial steps and perhaps sustained mechanisms of MOPr regulation, arrestin binding and endocytosis. Stefan Schulz's group review their pioneering work (Mann *et al.*, 2015) on

the development and use of phospho-site specific antibodies to study homologous and heterologous MOPr regulation, the latter mediated by protein kinase C phosphorylation of MOPr. This could provide an explanation for the protein kinase C (PKC)-mediated desensitization of MOPr by morphine, when PKC has been activated, as observed in a range of cells (Henderson, 2015). However, the research paper of Arttamangkul *et al.* (2015) suggests the effects of PKC-inhibitors on MOPr may be indirect. Understanding the relevance of different phosphorylation sites and regulation of MOPr is very important because many splice variants and some of the polymorphisms of human MOPr involve this region of the receptor with potential implications for sensitivity to opioid analgesics, tolerance and addiction. Knapman and Connor (2015) comprehensively review the evidence for functional implications of human MOPr polymorphisms and a research paper in the themed issue (Cooke *et al.*, 2015) examines the effects of one of these polymorphisms, L83I, on MOPr endocytosis in detail. Several of the submitted research papers in the themed issue further address mechanisms of MOPr regulation after chronic treatment with morphine (e.g. Connor *et al.*, 2015; Macey *et al.*, 2015). The research paper by Lowe and Bailey (2015) adds to the evidence that the mechanisms of MOPr desensitization in nerve terminals differ from those in the soma.

The important role of the DOPr in mechanisms of tolerance and dependence to MOPr agonists and addiction related mechanisms is discussed in a number of papers that highlight the as yet unrealised therapeutic potential of DOPr drugs for addiction management. Comprehensive review and research papers by Laurent *et al.* (2015a,b) comment on the role of forebrain MOPr and particularly DOPr in reward and decision making. The main finding that long-term translocation of DOPr to the surface of cholinergic interneurons in the nucleus accumbens shell is associated with the selection and execution of goal-directed actions is particularly interesting although the cellular and molecular mechanisms involved are not yet understood. The review by Klenowski *et al.* (2015) comprehensively addresses the role of DOPr in addiction to a range of drugs. Baimel *et al.* (2015) discusses the interactions between the orexin/hypocretin system and opioids in brain regions related to addiction and potential for modulation addiction to opioids and other drugs.

Therapeutic actions and adverse effects of opioids are not limited to analgesia or other nervous system actions. Reviews and research papers arising from the INRC symposium on 'Opioids in Non-Neuronal Cells' provide a perspective on actions not often considered by those working in the CNS. There is considerable interest and some controversy concerning the influence of opioid therapeutics on tumour progression. Yamamizu *et al.* (2015) discuss evidence and mechanisms whereby opioid κ -receptor (KOPr) agonists are anti-angiogenic so may have tumour suppressing properties. Morphine is commonly used in cancer pain management but there have been concerns that the drug may adversely influence post-operative cancer recurrence and metastasis. Afsharimani *et al.* (2015) provide a critical review of the validity of animal models designed to evaluate the effect of morphine on tumour growth and metastasis and suggest ways to improve current approaches. Another noteworthy action of opioids on non-neuronal cells includes the influence of DOPr

receptor agonists on cutaneous wound healing (Bigliardi *et al.*, 2015).

Ultimately, the value of much of the knowledge of novel opioid mechanisms in the themed issue will be its translation into clinical practice. Avoiding tolerance and dependence, severe side effects and improving efficacy in chronic pain conditions all seem possible but there is a long way to go. For example, careful meta-analyses of weak and strong opioid use in chronic non-cancer pain (Reinecke *et al.*, 2015) found only modest trends for efficacy of opioids and no evidence to support the sole or preferential use of opioids. Hopefully drugs exploiting novel opioid mechanisms will be better. Opioid agonists and antagonists also have an important place in management of addictions. For reviews of opioid treatments for addiction in humans the reader is referred to the recent issue of British Journal of Clinical Pharmacology on Addiction (2014, vol 77, Issue 2. Pp 225–400). In particular, articles by Bell (2014) and Garcia-Portilla *et al.* (2015) on maintenance treatments for opioid addiction and sustained release naltrexone for the management of opioid dependence (Kunøe *et al.*, 2014).

Current opioid therapeutics for chronic pain management and addiction are problematic and still largely rely on drugs developed many decades ago. There is hope that findings in this themed issue will lead to the development of new generation opioid analgesics with improved clinical profiles.

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