EDITORIAL

Emergent areas of opioid pharmacology

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This themed issue of the British Journal of Pharmacology stems from an International Narcotics Research Conference (INRC) Meeting held in July 2016 at The Assembly Rooms in Bath, UK.

Opium has been used in society for thousands of years and in more recent times opioid drugs have become a mainline treatment for moderate to severe pain, but these drugs are also well known for their ability to lead to drug abuse and death due to opioid poisoning. There are four opioid receptors named μ, δ, κ and nociceptin, and all are GPCRs. Therapeutically, opioid drugs such as morphine are also of pharmacological interest as they represent (along with e.g. β-adrenoceptor agonists) one of the few major classes of therapeutic drug that are agonists at GPCR targets. This explains in part the interest in opioid tolerance and its relationship to GPCR desensitization mechanisms. Nevertheless, opioid receptor antagonist drugs are also important drugs, with for example naloxone being an essential drug to reverse opioid agonist-induced respiratory depression in opioid

overdose. Apart from these generally widely recognised aspects of opioids, in recent years other less familiar aspects of endogenous opioid systems and opioid drug action have emerged. These lesser known but increasingly important areas represent the central theme of this issue of British Journal of Pharmacology.

The immune system and its relationship to opioid function is one such emergent area. Plein and Rittner (2017) report that whilst it is generally belived that opioid drugs exert an immunosuppressive effect in patients, some immune cells also release opioid peptides which can reduce inflammation and pain. However further studies at the clinical and epidemiological level are required to determine the importance of such interactions to the patient. Opioid drugs are often prescribed to manage pain in cancer, but as described by Boland and Pockley (2017) opioids can also affect the entry of immune cells into the tumour micro-environment. Some of these effects vary with the exact opioid drug being employed whilst some of the effects of opioid drugs on immune cells may be mediated by non-opioid receptor mechanisms. Their review highlights that further studies are needed to determine clinical outcomes in defined cancer patient groups.

Opioid receptors, particularly μ receptors, are well expressed in the mammalian brain emotion circuitry. As discussed by Nummenmaa and Tuominen (2017) both endogenous opioid systems and exogenous opioid drugs are considered to contribute to a wide array of positive and negative emotions, and thus are suggested to play an important role in in psychological and psychosomatic resilience. Pellissier *et al.* (2017) describe how in μ opioid receptor null mice, the behavioural defecits observed are similar to those observed in

patients with autism spectrum disorder (ASD), such as poor social interactions. It is suggested that altered μ opioid receptor function may contribute to this pathology in ASD.

Whilst opioids have long been known for their ability to suppress acute pain, nevertheless new aspects of this theme continue to surface, for example in the area of chronic pain. There is an important relationship between pain and reward, with the obvious problem of dealing with opioid pain therapy in subjects with substance abuse disorder, as discussed by Wilson-Poe and Morón (2017). In particular more work is needed to understand the interaction between chronic pain and the brain's reward system. On the other hand Jones and Brown (2017) argue for the application of quantitative computational models to analyse neuroplasticity in chronic pain. They discuss the role of predictive mechanisms in different types of plasticity, and evidence for their modulation by endogenous opioids. One further contribution to the discussion of opioids in chronic pain is provided by Maldonado *et al.* (2017), who describe the effects of various gene knockouts in mice of components of the opioid system (receptors or peptides) on models of chronic pain. The data from such studies have suggested, for example, the development of novel opioid drugs which target multiple opioid receptor subtypes. This latter theme is returned to again in this editiorial below.

Other emergent themes in the opioid field include the use of the neurohypophyseal peptide oxytocin or other oxytocinergic drugs to treat opioid addiction and co-existing affective disorders, as described by Zanos *et al.* (2017). Oxytocin is known for its strong effects on mediating reward, social interaction, stress and learning/memory, and whilst the preclinical data support the use of oxytocinergics to manage drug addicition, further clinical studies are

needed to take this concept forward. Another field of interest coming to the fore is the complex regulation of neuronal systems within subdomains of brain nuclei previously considered to be relatively homogenous. For the ventral tegmental area, as discussed by Thomas et al. (2017), both μ and κ opioid receptors regulate distinct populations in this nuclei, the former regulating presynaptic activity and the latter postsynaptic dopaminergic neuronal activity. The precise selectivity of endogenous opioid peptides and exogenous opioid drugs is therefore critical in determining the functional output of such brain regions.

Finally new aspects of the molecular pharmacology of opioid receptors are gaining increasing interest. Molecular Dynamics simulations afford an unprecedented and increasingly important insight into the dynamic interaction of ligands with opioid receptors, ligand-induced conformational changes, as well as the likely nature of the interactions in receptor dimers (Marino et al. 2017). These *in silico* studies have been made possible by the availability of crystal structures of the opioid receptors. Small molecule allosteric modulators, particularly at mu and delta opioid receptors, have been identified with the idea of modifying the effects of endogenous opioids and avoiding many of the adverse effects seen with exogenous opioid drugs (Livingston and Traynor, 2017). Allosteric modulators interact with regions of the receptor other than the orthosteric site occupied by the endogenous opioid peptides or most exogenous ligands, and can exert positive or negative effects on signalling (Positive Allosteric Modulators or PAMs, and Negative Allosteric Modulators or NAMs, respectively). Other emerging approaches in an attempt to enhance the effectiveness of opioid drug therapy whilst limiting the adverse effects include the targeting of multiple opioid receptors with a single chemical entity (Günther *et al.,*

2017). The drug dihydroetorphine for example is a strong agonist at μ, δ and κ receptors whilst subtler effects include those of nalfurafine, a κ receptor agonist with weak effects at μ and δ receptors and which exerts antipruritic as well as analgesic effects. This theme is developed by Almatroudi *et al.* (2017) who report a mixed κ/μ receptor antagonist, BU10119, which has potential as a treatment for depression and stress-related disorders, and the work of Dietis *et al.* (2018) who report on the analgesic actions and tolerance liability of the experimental drug UFP-505, which has μ agonist activity along with very weak partial agonism/antagonism at δ receptors.

This themed section highlights the diversity of current research in opioid pharmacology. No longer are opioids involved only in pain and euphoria but are increasingly being implicated in a wide range of physiological systems and disease states. The organizers would like to thank all the presenters and sponsors of INRC 2016 (tinyurl.com/yacasw9u), especially BPS and NIDA, for making it such a stimulating conference.

Conflict of interest

The author C.P. Bailey wishes to acknowledge that he is a co-author of the paper by Almatroudi *et al.* (2017).

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