## Editorial

# The behavioural pharmacology of opioids

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Opiates have been used for both recreational and medical purposes by humans for thousands of years. The 'recreational and medical' in the previous sentence also describe the two main issues in opioid research today. On the one hand, opiates are among the most powerful and effective painkillers, which is the most prominent cause for their widespread medicinal use. On the other hand, the euphorigenic effects of opiates – as well as the tolerance and dependence that ensues upon their repeated use – are widely recognized to inspire their abuse and, ultimately, addiction. Indeed, addiction to opiates has been a recognized medical problem for nearly two centuries now. More recently, the epidemic increase in prescription opioid use, abuse, and addiction, in particular in North America, has caused massive societal and medical problems. The 'opioid epidemic' has again laid bare the benefits and risks to our society of medicinal as well as recreational opioid use. For researchers (and for society), the main question remains whether it is possible to treat pain with opiates in such a way that the risk for addiction is minimized. With this in mind, we are pleased to devote this Special Issue to the Behavioural Pharmacology of Opioids.

This Special Issue contains three review papers on fascinating and original topics related to opioid use, and fifteen empirical papers addressing a wide range of problems across the whole spectrum of opioid effects.

The first review article, by Ren and Lotfipour, considers the role of the gut-brain axis in opioid use. The gut microbiome has come to be recognized as exerting a significant and bi-directional influence on brain activity (as explored in detail in a recent Special Issue of Behavioural Pharmacology). Inter alia, gut bacteria influence circuits involved in stress, reward, and motivation, while substance use influences the gut microbiome, providing a basis for significant gut-brain interactions in drug addiction. This review summarizes the influence of gut microbiota on factors that influence opioid addiction, including incentive salience, reward, tolerance, withdrawal, stress, and executive function. It presents clinical and preclinical evidence supporting a bidirectional relationship between gut microbiota and opioid-related behaviours and discusses possible mechanisms by which this gut-brain communication influences opioid use. The authors suggest that a better understanding of these issues could contribute to the development of therapeutic interventions for opioid dependence and addiction.

The second review, by Varastehmoradi and colleagues, addresses another issue that has increased recently in importance, that is, the role of cognitive-affective bias in mood regulation, and its potential modulation by opioids. Emotions are known to influence a wide range of cognitive processes, and negative affective biases are a key feature of major depressive disorder, which may present concurrently with other cognitive deficits and be of particular relevance in treatment-resistant patients. This useful review describes the underlying neurocircuitry of affective cognition, outlines the role of opioid receptors in affective cognition, executive function, and major depressive disorder, and summarizes the evidence that supports a modulatory role for opioid drugs on negative affective bias, with a focus on kappa-opioid receptor antagonists that are currently in development for their potential clinical use in treatment-resistant depression.

In the third review, Martinez and Abalo consider one of the core areas of opioid pharmacology, that is, analgesia, from an unusual angle: the prospects for pain control by peripherally acting opioids, thereby avoiding the abuse liability associated with centrally acting opioid analgesics. Following from the identification of peripherally located mu, delta and kappa opioid receptors that can mediate anti-nociceptive effects, research aimed at optimizing these effects while minimizing central opioid actions has led to a range of novel strategies. These include massive molecules that cannot easily cross lipid membranes, substrates of glycoprotein P (an extrusion pump that prevents CNS penetration), nanocarriers that release the analgesic agent at the site of inflammation and pain, and pH-sensitive opioid agonists that selectively activate at those sites. The authors express the hope that these novel developments will soon lead to benefits to patients – in the form of pain management approaches with improved safety profiles.

The first four empirical papers also deal with the classic opioid issue of pain and analgesia. The first, by Tobaldini and colleagues, considers the relationship between pain- and stress-induced analgesia. Pain-induced analgesia is known to involve opioid mechanisms in the nucleus accumbens and nicotinic cholinergic mechanisms in the rostral ventromedial medulla. This study used


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intra-accumbens and intra-medulla injections to demonstrate that the same mechanisms are involved in stress-induced analgesia. In the second study, Leonard and Kangas used an operant conflict technique to examine whether co-administration of a benzodiazepine could decrease the dose of an opioid, oxycodone, needed to achieve analgesia ('opioid-sparing'). This effect was observed, but only over a limited dose range, which was felt to provide insufficient evidence to take this forward into the clinic. More encouraging results are reported by Ulker and colleagues. They studied whether MP1104, a novel agonist at mu, delta and kappa receptors that has been reported to show anti-nociceptive effects in an acute pain model, would show similar effects in a chronic model, that is, the formalin test. They found that MP1104 was anti-nociceptive in both phases of the formalin test, and that these effects were blocked by pre-treatment with either a delta or a kappa antagonist. Finally, Qin and colleagues report on a novel strategy to prevent tolerance to opioid analgesia. They found that tolerance was accompanied by an increase in the expression of heat shock protein 70 (Hsp70) in the peri-aqueductal grey, and that tolerance could be suppressed or enhanced by pharmacological or genomic modulators of Hsp70, pointing to a potentially interesting novel target for drug development.

The reinforcing and rewarding effects of the opioids, which play an important role in opioid abuse (and therefore represent a significant unwanted effect of medicinally useful opioids) were examined in two pharmacological and two behavioural studies. Yue and colleagues studied the effects of Toll-like receptor 4 (TLR4) antagonists in a model of opioid craving. They found that, in animals trained to self-administer the mu-opioid agonist remifentanil, different TLR4 antagonists only inconsistently prevented reinstatement of extinguished responding by an injection of heroin; moreover, drug- and food-reinforced responding were similarly affected, suggesting that this is unlikely to be a viable strategy to prevent relapse. In a related study with a more positive outcome, Nazari-Serenjeh and colleagues examined the role of dopamine D1 and D2 receptors in reinstatement of an extinguished morphine-conditioned place preference. They report that reinstatement by food deprivation and a sub-threshold dose of morphine was suppressed by a D1 receptor agonist injected into the CA1 region of hippocampus, suggesting that the D1 receptor might be a target for treatment of opiate addiction. A behavioural study by Robertson and Jutkiewicz examined the ability of remifentanil to support conditioned reinforcement. They tested the extent to which a remifentanil-associated stimulus would support a previously unlearned nose-poke operant response over a prolonged period of extinction. The results showed both dose-dependency and individual differences in susceptibility to conditioned reinforcement, supporting the importance of Pavlovian conditioning in the maintenance of drug abuse. Maguire and colleagues used a behavioural economic framework to study a technical aspects of the reinforcing effects of remifentanil. Using a self-administration paradigm, they varied the 'price' (fixed ratio values) of remifentanil infusions and varied the order in which different ratios were presented. They found that order of presentation had no effect on the elasticity of demand for remifentanil, confirming the primacy of price as a determinant of reinforcer effectiveness.

Two further behavioural economic studies addressed the effects of mu-opioid drugs on impulsivity. It is known that opioids can increase impulsive choice in preclinical studies, which is considered a model of risky behaviour by human opioid abusers. Hunt and colleagues investigated the behavioural mechanism of this effect. They showed that the mu-opioid oxycodone dose-dependently decreased preference for a larger reinforcer, without affecting other measures of performance or general motivation. This suggests that a decreased sensitivity to reinforcement magnitude could underlie impulsivity and risky choice. Minervini & France used delay-discounting and matching-to-sample tasks to investigate interactive effect of morphine and a cannabinoid CB1/CB2 receptor agonist, CP55940 in monkeys. They found that the effects of the two drugs were essentially additive, suggesting that a cannabinoid-opioid mixture could potentially be used as an opioid-sparing combination for pain relief without increasing risk of adverse side-effects.

The next three studies examined the role of opioids in binge consumption of food or alcohol. Awad and colleagues studied the role of mu-opioid receptors (MORs) in binge eating, by examining sweet solution intake under conditions of limited access in mice with genetic deletion of the MOR. Limited access increased food intake and weight gain relative to continuous access, but these effects were smaller in MOR knock-out animals. Morales and colleagues used a version of the drinking-in-the-dark paradigm to generate binge consumption of ethanol, sucrose and saccharin in mice. Administration of the MOR antagonist naltrexone reduced intakes of preferred, highly concentrated EtOH, sucrose, and saccharin, both alone and in combination. Together, these two studies provide strong evidence for an involvement of MORs in binge consumption. The third study, by Gibula-Tarlowska and Kotlinska, showed that a novel anti-opioid peptide, kisspeptin, could prevent or reverse learning deficits and impairment of cognitive flexibility induced in rats by withdrawal from 11 to 13 days of 'binge-like' ethanol exposure. Thus, anti-opioid treatments not only counteract bingeing but can also ameliorate its adverse consequences.

The focus of the two final studies is the sensitization that occurs with repeated intermittent opioid administration. The increased locomotion and stereotyped behaviours seen in morphine-sensitized rats has been proposed as a model of mania. Scheggi and colleagues report that,

consistent with this proposal, sensitized rats also showed an enhanced motivation to work for sucrose, along with an increased dopaminergic response to sucrose consumption in the nucleus accumbens shell. They also observed an increased expression of hyperpolarization-activated cyclic nucleotide-gated channels in the ventral tegmental area that could potentially explain the increased dopaminergic activity. Finally, Madison and colleagues studied sensitization in relation to opioid use disorder. Using a battery of behavioural tests to classify mice as socially avoidant or socially exploring, they found that avoidant mice showed lesser locomotor sensitization to morphine but greater anxiogenesis and hyperalgesia. Their data provides scientific support the widely held notion that individual differences in levels of sociability level might contribute to the development of problematic opioid use.

The Behavioural Pharmacology of Opioids is an area that will continue to be of great scientific and societal concern until such time as there are improved and safer alternatives to the use of classical morphine-like opioids for pain management. The 18 contributions to this Special Issue illustrate the broad expanse of research area. We hope that you will enjoy reading these articles as much as we enjoyed editing this Special Issue.

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