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Endogenous opioid systems alterations in pain and opioid use disorder

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Decades of research advances have established a central role for endogenous opioid systems in regulating reward processing, mood, motivation, learning and memory, gastrointestinal function, and pain relief. Endogenous opioid systems are present ubiquitously throughout the central and peripheral nervous system. They are composed of four families, namely the μ (MOPR), κ (KOPR), δ (DOPR), and nociceptin/orphanin FQ (NOPR) opioid receptors systems. These receptors signal through the action of their endogenous opioid peptides β-endorphins, dynorphins, enkephalins, and nociceptins, respectfully, to maintain homeostasis under normal physiological states. Due to their prominent role in pain regulation, exogenous opioids—primarily targeting the MOPR, have been historically used in medicine as analgesics, but their ability to produce euphoric effects also present high risks for abuse. The ability of pain and opioid use to perturb endogenous opioid system function, particularly within the central nervous system, may increase the likelihood of developing opioid use disorder (OUD). Today, the opioid crisis represents a major social, economic, and public health concern. In this review, we summarize the current state of the literature on the function, expression, pharmacology, and regulation of endogenous opioid systems in pain. Additionally, we discuss the adaptations in the endogenous opioid systems upon use of exogenous opioids which contribute to the development of OUD. Finally, we describe the intricate relationship between pain, endogenous opioid systems, and the proclivity for opioid misuse, as well as potential advances in generating safer and more efficient pain therapies.

KEYWORDS

opioids, pain, addicition, opioid use and abuse, opioid use disorder (OUD), reward, endogenous opioids, opioid receptors

Introduction

The intersection between pain and opioid use presents a major dilemma for public health. Efforts to curb the burden of the ongoing opioid crisis continue to be challenged by the need to provide adequate relief for pain patients and at the same time lessen the negative impact of opioid misuse. Pain is extremely prevalent with over half of US adults reporting pain symptoms within the past 3 months (Lucas et al., 2021). Similarly, detriments of opioid abuse are evident in the annual increases in opioid overdose deaths, with the most recent provisional estimates exceeding 80,000 in 2021 (Ahmad et al., 2022). Although the prevalence of problematic opioid use in pain patients is difficult to pin-point for a myriad of reasons (Ballantyne, 2015; Voon et al., 2017), estimates derived from a number of metanalyses suggest rates of problematic prescription opioid use may occur in >80% of pain patients (Minozzi et al., 2013; Ballantyne, 2015; Chou et al., 2015; Vowles et al., 2015; Voon et al., 2017). Collectively, pain and opioid use pose tremendous societal costs, with pain-related health care and lost productivity exceeding $635 billion and opioid abuse-related health care, criminal justice, lost productivity, reduced quality of life, and life lost due to overdose exceeding $1.03 trillion annually (Institute of Medicine Committee on Advancing Pain Research, 2011; Gaskin and Richard, 2012; Florence et al., 2021). Linking the putative relationship between pain and maladaptive opioid use, is the endogenous opioid system, a primary biological substrate of pain and opioid reward. In the present review, we examine how pain and concurrent opioid use may disrupt endogenous opioid system function leading to alterations in reward signaling pathways and ultimately, higher risk for negative outcomes associated with opioid use.

Problematic opioid use in the context of pain

In 2019, the National Survey on Drug Abuse reported that almost all (>96%) instances of opioid misuse, or use deviating from physicians' instructions, was restricted to prescription opioid pain medications (Center for Behavioral Health Statistics and Quality, 2019). This same report indicated that among those that misused prescription opioids, the most common reason for misuse was to relieve physical pain (65%). Based on this evidence and the lack of therapeutic alternatives to prescription opioids suggests that the US is undertreating pain or undermining an overlapping and vulnerable population. The former could have likely been fueled by pain management initiatives in the 1990s that recognized pain as a fifth vital sign (Morone and Weiner, 2013; Meisenberg et al., 2018). This notion encouraged physicians to prioritize pain reduction through the liberalization of opioid prescriptions (Compton and Volkow, 2006; U.S. Department of Health and Human Services, 2019) which led to the initial wave of prescription overdose deaths (Rudd et al., 2016). This was addressed by several opioid diversion and mitigation strategies, including revisions to opioid prescribing practices in 2016 by the Center of Disease Control (CDC) that limit the number of opioid prescriptions (Lappin, 2016; Volkow and McLellan, 2016). Although these efforts appeared to bring prescription overdoses to a plateau, synthetic opioid overdoses (both illicit and prescribed) increased at alarming rates (CDC WONDER, 2018). It is difficult to pin down whether the continued rise in opioid overdoses was driven by the unmet needs of pain patients, growth in illicit markets, or a combination of both. Despite additional government-backed initiatives intended to curb opioid use and facilitate research for pain management alternatives (U.S. Department of Health and Human Services, 2019), the prevalence of chronic pain and opioid overdose deaths continue to rise each year (Goldstick et al., 2021; Zajacova et al., 2021; Ahmad et al., 2022), and have even been amplified by the COVID-19 pandemic (Fallon et al., 2021; Manchikanti et al., 2021; Soares et al., 2021). The National Institute of Health's (NIH) most recent endeavor, the HEAL initiative (Helping to End Addiction Long-term), recognized the need to address the opioid crisis through improvements to pain management (Wandner et al., 2022). As such, our ability to curtail opioid abuse and improve the treatment of pain relies heavily on our capacity to understand the neurobiological mechanisms underlying pain and opioid systems.

According to the International Association for the Study of Pain (IASP), pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Raja et al., 2020). The intersection between these two dimensions of pain—sensation and emotion—present a substantial problem for chronic pain patients on long-term opioid therapy which can play a synergistic role in perpetuating pain, mood disruptions, and problematic opioid use. The occurrence of mood disorders can predict not only opioid misuse liability (NIDA, 2008; Davis et al., 2017; Center for Behavioral Health Statistics and Quality, 2019; Jones and McCance-Katz, 2019; Smit et al., 2020) but also, susceptibility to pain conditions (Viana et al., 2018; Rizvi et al., 2021). Likewise, patients with opioid use disorder (OUD), a chronic and relapsing disorder characterized by persistent and compulsive drug-seeking behavior despite negative outcomes, frequently report comorbidities of chronic pain (up to 65%) and mood disorders (up to 82%) (Davis et al., 2017; Hser et al., 2017; Peciña et al., 2018; Jones and McCance-Katz, 2019; Higgins et al., 2020; Latif et al., 2021). It is therefore not surprising that chronic pain patients are 2–3 times more likely to meet diagnostic criteria for an anxiety, mood, and mental disorders (Pereira et al., 2017) and are at higher risk (>50%) for developing opioid or substance use disorder (Højsted and Sjøgren, 2007; Morasco et al., 2011).

Collectively, the co-occurrence of pain, mood disruptions, and problematic opioid use can have additive effects on the severity and risk for the other. The extensive overlap of these conditions alludes to a common underlying mechanism; and while each of these conditions are associated with dysfunction across multiple biological systems, one potential source of shared functional disruption lies within the endogenous opioid system (Jarcho et al., 2012; Witkin et al., 2014; Peciña et al., 2018; Jones and McCance-Katz, 2019; Toubia and Khalife, 2019).

The endogenous opioid system

Both pain and exogenous opioids can disrupt function of the endogenous opioid system (Roeckel et al., 2016) and similarly, alterations in endogenous opioid activity can predict variations in pain thresholds, opioid-induced analgesia, and the proclivity for opioid misuse and abuse (Corder et al., 2018; Jassar et al., 2019; Llorca-Torralba et al., 2019a; Massaly and Morón, 2019; Bodnar, 2021). The endogenous opioid system plays an important role in analgesia, but it is also critically involved in autonomic regulation, immunological responses, gastrointestinal function, learning and memory, and many other functions (Bodnar, 2021). As such, the endogenous opioid system is crucial for maintaining homeostasis and alterations in its activity are largely state dependent (Darcq and Kieffer, 2018; Valentino and Volkow, 2018). This system is also highly integrated with other biological systems involved in stress regulation, mood, and reward such as the endocannabinoid, serotonin, oxytocin, vasopressin, and dopamine (DA) systems and the hypothalamic adrenal pituitary axis (Leknes and Tracey, 2008; Toubia and Khalife, 2019; Emery and Akil, 2020; Koob, 2020; Bodnar, 2021; Mohammadkhani and Borgland, 2022). Implicitly, the extensive crosstalk between these contributes to the highly adaptive nature of the opioid system and its ability to acutely respond to noxious stimuli. However, chronic perturbations to opioid systems can leave the system vulnerable to dysfunction and have debilitating consequences (Stoeber et al., 2018). Here, we focus on the impact of pain and opioids on function of the endogenous opioid system and reward pathways and examine their putative role in provoking maladaptive patterns of opioid use and OUD.

Opioids

Opioids are natural, synthetic, or semi-synthetic chemicals acting on opioid receptors to produce analgesia among other peripheral effects (Zöllner and Stein, 2007). Opium is a dried milky exudate obtained from the unripe seed pods of the opium poppy, *papaver somniferum* (Brownstein, 1993). Among the dozens of alkaloids found in opium, the pharmacologically relevant constituents include morphine (10–15%), codeine (1–3%, noscapine (4–8%), papaverine (1–3%), and thebaine (1–2%) (Zöllner and Stein, 2007). The antiquity of opium for medicinal use was documented as early as ∼2100 BCE in Sumerian medical tablets (Duarte, 2005). The unrivaled ability of opium to relieve pain was recognized in texts for millennia, but the therapeutic application of opioids was transformed when a young German apothecary's assistant, F.W.A. Sterürner, isolated crystalline morphine (1803–1817), naming it after Greek god of sleep and dreams (Krishnamurti and Rao, 2016). The subsequent invention of the hypodermic syringe needle in the 1850s facilitated the use of morphine for surgical procedures, pain relief, and as an adjunct to general anesthetics (Brownstein, 1993). Since then, the broad application of various opioid analgesics has facilitated a greater understanding of the opioid system and the clinical utility of opioids for pain management.

The existence of opioid receptors was first proposed in the 1950s (Beckett and Casy, 1954), but it was not until the 1970s that different bioassays began to identify stereospecific binding sites for opioids in the brain (Pert and Snyder, 1973; Simon et al., 1973; Terenius, 1973; Martin et al., 1976; Lord et al., 1977). These studies revealed that exogenous opioid ligands produce their narcotic effects through actions at different opioid receptors which led to the discovery that endogenous opioid-like peptides can produce similar effects through their activity at the same peptide receptors (Cox et al., 1976; Hans et al., 1977; Olson et al., 1979). The first evidence of distinct opioid receptor types was determined by detailing the actions of several analgesic drugs. As such, the first two opioid receptor types were named after the prototypic drugs used in these studies to distinguish them, mu (μ) for morphine and kappa (κ) for ketocyclazocine (Martin et al., 1976). Pharmacological analysis revealed a third opioid receptor type in the mouse vas deferens that exhibited a pharmacological profile markedly different from those previously identified (μ and κ) and was accordingly, named delta (δ) to signify this difference (Lord et al., 1977). The heterogeneity of these receptor types was later confirmed when distinct mRNAs for each receptor type were cloned and characterized (Evans et al., 1992; Kieffer et al., 1992; Chen et al., 1993; Yasuda et al., 1993). Together, the μ, κ, and δ opioid receptors (MOPR, KOPR, DOPR, respectively) are considered the classical opioid peptide receptors based on their structural homology and sensitivity to the non-selective opioid receptor antagonist, naloxone (Dietis et al., 2011). A fourth opioid receptor-like (OPRL1) gene was later revealed to encode a receptor with a primary structure analogous to previously identified opioid receptors and yet, it lacked sensitivity to traditional opioid ligands (Bunzow et al., 1994; Mollereau et al., 1994). As such, OPRL1 remained an 'orphan' receptor until two independent groups isolated its endogenous ligand, nociception (Meunier et al., 1995) or orphanin FQ (Reinscheid et al., 1995) (N/OFQ), for which the OPRL1 or N/OFQ opioid receptor is referred to here on as NOPR. While MOPR, KOPR, DOPR,

and NOPR comprise the four major opioid receptor systems due to homology in structure and function, NOPR is often excluded from "classical" opioid receptor types based on its lack of sensitivity to naloxone or prototypical opioid ligands.

Four major opioid peptide families are commonly associated with complimentary opioid receptor systems for which they exhibit preferential activity: β-endorphins (MOPR), dynorphins (KOPR), enkephalins (DOPR), and N/OFQ (NOPR) (Hughes et al., 1977; Nakanishi et al., 1979; Horikawa et al., 1983; Pathan and Williams, 2012; Shenoy and Lui, 2018). However, despite greater selectivity of these endogenous ligands and their respective receptors, the activity of both endogenous and exogenous opioids at distinct receptor types is rarely exclusive to one family and can often activate multiple receptor types to varying degrees (Stein, 2016). Opioid receptors are seven-transmembrane G protein-coupled receptors (GPCR) that generally couple to inhibitory G proteins, thereby reducing signal transduction and neurotransmission by engaging several second- and third-messenger systems and regulating ion channel activity (Zöllner and Stein, 2007; Al-Hasani and Bruchas, 2011; Toll et al., 2016; Corder et al., 2018). Different opioids can also engage biased signaling pathways to preferentially activate GPCR-dependent signaling or β-arrestin-dependent signaling, which can produce analgesia or unwanted side-effects, respectively (Ballantyne and Chavkin, 2020). Allosteric binding sites on opioid receptors, distinct from orthostatic sites or the ligand binding pocket, can also modulate opioid receptor function through activation by various other neurotransmitters and neuropeptides (Kathmann et al., 2006; Burford et al., 2015; Remesic et al., 2017; Livingston and Traynor, 2018). For example, cannabidiol (CBD), an exogenous cannabinoid ligand, can act as a negative allosteric modulator at MOPR or DOPR in rat cerebral cortices to reduce their function (Kathmann et al., 2006). Positive allosteric modulators for MOPR have also been sought after as they may reduce some of the unwanted side-effects attributed to traditional opioid medications or facilitate the activity of endogenous opioids (Burford et al., 2015). Adding another layer of complexity to opioid receptor signaling is the fact that different opioid receptors can associate with each other to form heteromers (e.g., MOPR-DOPR, DOPR-KOPR, KOPR-MOPR). For example, DOPR antagonism of DOPR-MOPR heteromers can act to enhance MOPR agonist-mediated analgesia (Gomes et al., 2004). The complexity of opioid receptor signaling mechanisms shed light on the multiple means by which opioid system function can be disrupted.

Opioid receptors are among the most widely expressed receptors in the central and peripheral nervous systems, although the composition and distribution of different opioid receptor types varies across regions (Corder et al., 2018). In the periphery, opioid receptors expressed in the lungs, heart, kidney, small intestine, and pancreas, can modulate organ function, inflammation, as well as multiple homeostatic processes (Peng et al., 2012). Opioid receptors can also be found in neuroendocrine (adrenals, pituitary), immune (leukocytes), and ectodermal cells, where they can modulate nociception and inflammation (Zöllner and Stein, 2007; Stein, 2013). In the context of pain, opioid receptors are ideally situated among, and connected with, somatosensory neurons of dorsal root ganglion (DRG) and second-order neurons of the dorsal horn of the spinal cord where they transmit ascending nociceptive signals to cortical areas through the spinothalamic, spinoreticular, and spinoparabrachial pathways (Basbaum and Fields, 1984; Marchand, 2008; DosSantos et al., 2017; Ringkamp et al., 2018). Local release of endogenous opioids or acute application of exogenous opioids at injury sites can suppress DRG activity to reduce nociceptive signaling and pain perception (Dickenson et al., 1990; Stein et al., 2003; Spahn et al., 2017; Corder et al., 2018; Massaly et al., 2020). Similarly, top-down regulation by opioid receptor systems within the periaqueductal gray (PAG) and rostral ventral medulla (RVM) can exert descending modulatory control over nociceptive signal transduction (Marchand, 2008; Ringkamp et al., 2018). The level of top-down control over anti-nociceptive responses can also be influenced by opioid receptor systems in other brain regions involved in cognition, affect, sensation, and motivation (Corder et al., 2018; Bannister and Dickenson, 2020; Dickenson et al., 2020). As such, the central and peripheral presence of opioid systems yields the ability of opioid receptors to functionally modulate reward-aversion networks through ascending and descending modes of control, and therefore, play a substantial role in aversive pain states, reward from pain relief, and hedonic balance (Darcq and Kieffer, 2018).

Proper functioning of the endogenous opioid system is essential for survival mechanisms involved in reward- and aversion-based learning and behavior. When the integrity of this system becomes compromised, the ability to integrate opioid reward- and pain aversion-related information will also become impaired. Among the many debilitating consequences associated with compromised opioid system function, is the risk of OUD. After repeated drug exposure, reward-processing centers can undergo neuroadaptations that leave affected individuals with enhanced incentive salience and habit formation, impulsivity, stress reactivity, and negative affect in the absence of drug; thereby producing overall disruptions in motivation (Koob and Volkow, 2010). As a result, maladaptive drug use is perpetuated through cycles of binge/intoxication, withdrawal/negative affect, and preoccupation/craving (Koob and Volkow, 2010). OUD and other substance use disorders are linked with adaptations to the opioid system (Darcq and Kieffer, 2018) because of its central role in reward processing (le Merrer et al., 2009). Therefore, the ability of the opioid system to regulate both pain states and the actions of opioid drugs may exacerbate the risk for the development of OUD in pain patients on long-term opioid therapies. Here, we focus on adaptations

within mesolimbic reward pathways and the putative synergistic effects of pain and opioid use in driving opioid misuse liability.

μ Opioid receptor

The role of MOPR in mediating opioid-dependent analgesia and reward provides support for the abundance of research on this opioid receptor family. The analgesic effects of MOPR activity are attributed to their hyperpolarizing effects and suppression of neuronal activity. This is regulated by $G_{\alpha i}$-mediated inhibition of cAMP production (Raffa et al., 1994), activation of G protein-coupled inwardly rectifying potassium (GIRK) channels (Ikeda et al., 2000), $G_{\beta\gamma}$ -mediated inhibition of L-type calcium channels (Bourinet et al., 1996), and inhibition of voltage-dependent calcium channels (VDCC) (Saegusa et al., 2000). Alternatively, β-arrestins can modulate MOPR signaling by decoupling the receptor from G proteins and facilitating receptor internalization (Siuda et al., 2017; Cong et al., 2021). β-arrestins can also engage multiple intracellular signaling cascades independent of G proteins (Macey et al., 2006) and biased signaling mechanisms through β-arrestins or G proteins often produce distinct effects (discussed below).

Endogenous MOPR agonists, like β-endorphins, can be locally released at injury sites to provide acute pain relief through their signaling at the MOPR (Hassan et al., 1993; Truong et al., 2003; Stein et al., 2009). Similarly, acute administration of exogenous MOPR agonists, like morphine, can provide both pain relief and reinforcement. Evidence from positron emission tomography (PET) studies in humans demonstrate that acutely painful stimuli increase MOPR activity in multiple brain regions, including those implicated in nociception and reward processing, such as the PAG and the nucleus accumbens (NAc), respectively (Zubieta et al., 2001, 2002; Bencherif et al., 2002). Relative to pain-free conditions, acute pain enhances MOPR activity while its activity is decreased under conditions of chronic pain. In animal models of neuropathic pain, MOPR expression is downregulated in the spinal cord, DRG, and several cortical regions in the days and weeks following injury (Porreca et al., 1998; Zhang et al., 1998; Rashid et al., 2004; Pol et al., 2006; Thompson et al., 2018). Similarly, patients with chronic lower back pain exhibit lower circulating levels of β-endorphin (Bruehl et al., 2012, 2014, 2017, 2013; Rhodin et al., 2013), while deficits in MOPR binding potential have been linked with multiple pain conditions including fibromyalgia, chronic migraine, trigeminal neuropathic pain, and chronic lower back pain (Harris et al., 2007; DosSantos et al., 2012; Hagelberg et al., 2012; Martikainen et al., 2013; Schrepf et al., 2016; Jassar et al., 2019; Toubia and Khalife, 2019). Therefore, the function of the MOPR system can differ depending on the persistence of pain conditions, losing efficacy over time.

Importantly, MOPR activity can contribute to both sensational and emotional aspects of pain. In healthy controls, baseline MOPR binding can predict pain thresholds, such that lower MOPR binding in multiple cortical regions is associated with higher pain sensitivity (Zubieta et al., 2001, 2002; Hagelberg et al., 2012). Moreover, MOPR binding is negatively correlated with affective pain ratings (Zubieta et al., 2001, 2002), adding further support to the idea that MOPR activity can modulate sensory and affective components of pain. In patients with various chronic pain conditions, the ability of MOPR binding to predict pain sensitivity is similar. For example, patients with trigeminal neuropathic pain exhibit reduced MOPR binding in the NAc which is negatively correlated with pain ratings (DosSantos et al., 2012). Consistent with this relationship, reduced MOPR binding in the prefrontal cortex is associated with migraine severity (DaSilva et al., 2014). Similar results have been recapitulated in rodent models of neuropathic pain. Months after spared nerve injury, rats show reduced MOPR availability and expression in the insula, caudate putamen, and motor cortices, and these levels are correlated with deficits in sucrose preference, a measure of anhedonia (Thompson et al., 2018). Together, these findings indicate that chronic pain disrupts MOPR function to negatively regulate sensory and affective components of pain.

The MOPR system is also influenced by acute or chronic exposure to exogenous opioids. In patients undergoing surgery under general anesthesia, plasma β-endorphin levels are increased, and this effect is inhibited by administration of fentanyl, a potent MOPR agonist (Dubois et al., 1982; Cork et al., 1985). Fentanyl administration also induces MOPR phosphorylation in the striatum of mice at sites involved in receptor desensitization and internalization (Macey et al., 2006), suggesting that acute opioid exposure can have rapid effects on receptor desensitization and tolerance. In contrast, MOPR antagonism increases β-endorphin levels (Hargreaves et al., 1986), adding further support to the idea that endogenous β-endorphin release is regulated by MOPR activity. Chronic opioid exposure can have detrimental effects on endogenous opioid production and MOPR system function. For example, chronic morphine treatment reduces expression levels of the β-endorphin precursor protein, proopiomelanocortin (POMC), in rats (Bronstein et al., 1990; Wardlaw et al., 1996; Przewlocki, 2004), and reduces MOPR density in β-endorphin-expressing neurons of the hypothalamus (site of synthesis) in guinea pigs (Zhang et al., 1996). As such, chronic exposure to exogenous MOPR agonists reduce MOPR system function by reducing endogenous production of MOPR agonists (β-endorphins) and overall MOPR availability. Chronic opioid exposure can also alter function of remaining MOPR by producing a switch in MOPR G-protein coupling from Gi/o to Gs, leading to activation of adenylyl cyclase rather than inhibition (Wang et al., 2005). MOPR activation and subsequent phosphorylation by GPCR kinases can also lead to the recruitment of β-arrestins,

which—in conjunction with many other effectors—leads to MOPR receptor desensitization and internalization (Koch and Höllt, 2008; Roeckel et al., 2016; Corder et al., 2017; Derouiche et al., 2020; Massaly et al., 2021). MOPR phosphorylation at sites involved in receptor desensitization and internalization are observed in mice seven days after partial sciatic nerve ligation, a manipulation that produces tolerance to both the analgesic and conditioned reinforcing properties of morphine (Petraschka et al., 2007). Together, these disruptions to endogenous opioid production and MOPR function in response to chronic opioid exposure can lead to long-term plasticity underlying the development of opioid-induced hyperalgesia, analgesic tolerance, and negative affect, contributing to problematic opioid use.

The ability of pain and exogenous opioids to modify MOPR system function can lead to alterations within the mesolimbic reward pathway that may "prime" the system to be more vulnerable to the abuse of opioids, alcohol, and other substances of abuse (Contet et al., 2004). Opioid activity at MOPR produces rewarding effects by hyperpolarizing GABAergic inputs onto ventral tegmental area (VTA) DA neurons, thereby disinhibiting DA release (Elman and Borsook, 2016; Mitsi and Zachariou, 2016; Stoeber et al., 2018). Local infusion of MOPR agonists in the VTA is sufficient to produce reinforcing behaviors and conditioned reward-seeking behavior (Devine and Wise, 1994). Additionally, VTA MOPR function is necessary for opioid-dependent reward (Cui et al., 2014). Based on the ability of opioids to provide both positive reinforcement and pain relief, it seems evident that pain-induced alterations on MOPR signaling within mesolimbic circuits may facilitate tendencies toward opioid abuse (Koob, 2020). A large body of evidence indicates that pain augments opioid reward thresholds by disrupting DA transmission within the mesolimbic system (Hipólito et al., 2015; Martikainen et al., 2015; Taylor et al., 2016; Selley et al., 2020; Ren et al., 2021). This is regulated at least partly by deficits in MOPR system function (Markovic et al., 2021). Preclinical studies have shown that inflammatory and nerve injury pain reduces MOPR agonist efficiency at silencing VTA GABAergic transmission (Hipólito et al., 2015; Taylor et al., 2015), thus decreasing the ability of MOPR agonists to disinhibit VTA DA neurons (Ozaki et al., 2004, 2003, 2002; Hipólito et al., 2015) and evoke DA release in the nucleus accumbens (NAc) (Niikura et al., 2010; Hipólito et al., 2015; Taylor et al., 2015). These pain-induced deficits in mesolimbic function significantly dampen the rewarding properties of MOPR agonists. For example, rats with sciatic nerve ligation exhibit reduced placed preference induced by intra-VTA administration of the MOPR agonist, DAMGO, or systemic administration of morphine—an effect paralleled by attenuated MOPR binding in the VTA (Niikura et al., 2008). Consistent with this idea, chronic pain patients at low risk for opioid misuse exhibit less pain-induced activation of MOPR in the NAc, and this effect is associated with fewer mood disturbances and negative affect (Ballester et al., 2022). Taken together, MOPR signaling is a primary mechanism by which opioids yield high potential for abuse. As such, the MOPR system has received interest as therapeutic target for the treatment of chronic pain and OUD since the 1960s. Methadone, a long-acting MOPR agonist, has been used as a substitution therapy for chronic pain patients with long-term opioid therapy and maintenance treatment for patients with OUD (Kreek, 1973, 1991, 2000; Ferrari et al., 2004; Axelrod and Reville, 2007; Shi et al., 2008; Mattick et al., 2009; Kreek et al., 2010). The unique pharmacokinetic profile of methadone (slow onset, slow offset) yields a useful strategy to target the MOPR system while reducing the potential for opioid abuse, but the efficacy of these treatments is often limited by inter-individual variability, resources, and appropriate implementation (Dole and Nyswander, 1976; Ward et al., 2009; Kreek et al., 2010). As such, recent approaches have examined allosteric modulators of MOPR and biased signaling mechanisms as a means of offsetting the negative side effects of opioid pain medications (Manglik et al., 2016). A better understanding of how different pain conditions alter MOPR function with consideration of the interplay with ongoing opioid use will aid the development of future pharmacotherapeutic targeting strategies.

κ Opioid receptor

In contrast to the rewarding effects exerted by MOPR activity, the KOPR system is often attributed to dysphoria, anhedonia, and aversion (Spanagel et al., 1992; Darcq and Kieffer, 2018; Liu et al., 2019; Massaly et al., 2019; Cahill et al., 2022b). The opioid peptide, dynorphin, and its activity at KOPR have been implicated in negative affect, pain, analgesia, stress, and addiction (Bruchas et al., 2009; Darcq and Kieffer, 2018). A large body of evidence demonstrates that pain increases dynorphin mRNA expression and peptide production in the spinal cord of rodents and humans (Iadarola et al., 1988; Millan et al., 1988, 1985; Samuelsonn et al., 1993; Xu et al., 2004; Podvin et al., 2016; Liu et al., 2019). Following the onset of pain, the increase in dynorphin parallels the development of hyperalgesia and KOPR antagonism can facilitate hyperalgesic responses (Millan et al., 1987; Xu et al., 2004). This suggests that the dynorphin-kappa system is actively recruited under pain conditions to suppress nociceptive transmission. However, the ability of KOPR activity to suppress hyperalgesic responses may be dependent on the cell populations activated by dynorphin. For example, spinally restricted dynorphin signaling at KOPR expressed in astrocytes, rather than neurons, can produce nociceptive responses (Chartoff and Mavrikaki, 2015; Cahill et al., 2022b). In this regard, astrocytic KOPR activation can trigger hypertrophy in spinal astrocytes to facilitate the persistence of pain and the development of MOPR analgesic tolerance (Donnelly et al., 2020).

Pain can also trigger dynorphin-mediated KOPR activity in supraspinal regions. Pain induced adaptations to KOPR function within mesolimbic pathways may represent a primary mechanism by which pain can lead to the emergence of negative affect and altered motivational states. Indeed, pain conditions increase dynorphin expression and KOPR activity in multiple supraspinal sites including the VTA and NAc (Narita et al., 2005; Tejeda et al., 2017; Liu et al., 2019; Massaly et al., 2019; Navratilova et al., 2019; Wawrzczak-Bargieła et al., 2020). Although genetic deletion of KOPR or KOPR antagonism fails to alter pain-induced hyperalgesia, these manipulations can effectively restore pain-induced anhedonia and aversion (Narita et al., 2005; Tejeda et al., 2017; Liu et al., 2019; Massaly et al., 2019; Navratilova et al., 2019; Vergara et al., 2020). Recent evidence suggests that KOPR activity in NAc may be important for the transition from acute to chronic pain. Using hind paw injections of prostaglandin E2 to induce a persistent hyperalgesic state in rats, KOPR manipulations did not affect mechanical sensitivity during the induction phase (14 daily injections) (Vergara et al., 2020). Rather, intra-NAc KOPR agonists or antagonists facilitated or inhibited the persistence of hyperalgesia, respectively (Vergara et al., 2020). The findings suggest that the KOPR system may play an important role in pain chronification (Borsook et al., 2016).

Dynorphin recruitment under conditions of pain and the ability of KOPR activity to drive the transition from acute to chronic pain, suggest that KOPR may also be important for the development of comorbidities associated with persistent pain states such as negative affect and motivational deficits (Al-Hasani et al., 2015; Hipólito et al., 2015; Taylor et al., 2015; Elman and Borsook, 2016; Liu et al., 2019; Massaly et al., 2019). In general, KOPR agonists produce aversion and are associated with negative affect across species. In humans, KOPR agonists have psychotomimetic effects and produce dysphoria and hallucinations (Pfeiffer et al., 1986; Ranganathan et al., 2012) while increasing circulating stress hormone levels of cortisol (Ur et al., 1997). Similarly, in rodent models, both systemic and intracranial injections of KOPR agonists are sufficient to produce a conditioned place aversion (CPA) (Chefer and Ba, 2013; Tejeda et al., 2013) and increases in circulating levels of the stress hormone, corticosterone (Hayes and Stewart, 1985; Iyengar et al., 1986). These findings indicate that dynorphin-mediated activation of KOPR is acutely aversive and stimulates HPA axis activity, a putative mechanism contributing to negative affect associated with pain conditions. In support of this, increases in NAc dynorphin are found in suicidal individuals (Hurd et al., 1997) and animal models of depression (Carlezon and Krystal, 2016; Tejeda and Bonci, 2019). Importantly, these effects appear to be driven by the ability of KOPR activity to attenuate DA release in the NAc (Chefer and Ba, 2013; Conway et al., 2019; Escobar et al., 2020).

Dynorphin recruitment in mesolimbic pathways under conditions of pain leads to motivational deficits. For example, our lab showed that inflammatory pain increases KOPR function and recruits dynorphin-containing neurons in the NAc shell (Massaly et al., 2019). In this work, we found that the recruitment of NAc shell dynorphin neurons and activity at KOPR is both necessary and sufficient to drive pain-induced motivational deficits for natural rewards (Massaly et al., 2019). These effects also translate to motivational deficits for opioid drug reward. In models of neuropathic or inflammatory pain, morphine-induced conditioned place preference (CPP) scores are attenuated but can be restored by intra-NAc infusions of KOPR antagonists (Narita et al., 2005; Liu et al., 2019). Moreover, pain reduced opioid-evoked DA release in the NAc, an effect restored by intra-systemic KOPR antagonism (Narita et al., 2005; Liu et al., 2019). This suggests that pain-induced recruitment of dynorphin significantly decreases opioid reward processing. Importantly, KOPR antagonism does not impact opioid reward or dopamine release in the absence of pain (Liu et al., 2019), further implicating the state-dependent role of dynorphin. Opioid exposure, in the absence of pain, can perturb KOPR function in a manner similar to pain. For example, opioid self-administration or chronic opioid exposure increases prodynorphin (dynorphin precursor) levels in the NAc (Nylander et al., 1995; Trujillo et al., 1995; Solecki et al., 2009; Schlosburg et al., 2013). Based on this, pain patients on long-term opioid therapies may have compounding effects of pain and opioid use on KOPR dysfunction, exacerbating motivational deficits, negative affect, and leading to increased risk for maladaptive opioid use. Consistent with this idea, genetic polymorphisms to the prodynorphin gene have been linked with increased risk for OUD (Clarke et al., 2012).

The role of the KOPR system in pain-related mood disturbances and negative affect make this system an appealing target from a treatment perspective (Roeckel et al., 2016; Jassar et al., 2019; Llorca-Torralba et al., 2019b). Although systemic KOPR agonists can produce analgesia, many undesirable effects including hallucinations, impaired stress-coping skills, and deficits in reward-driven motivation, limit their clinical utility as therapeutic alternatives to traditional exogenous opioids (Jarcho et al., 2012; Davis et al., 2017; Jones and McCance-Katz, 2019; Toubia and Khalife, 2019; Emery and Akil, 2020). However, pharmacotherapies with partial agonist properties at KOPR have been examined in clinical trials for treatment of alcohol use disorder (AUD). Nalmefene, a MOPR inverse agonist and weak partial KOPR agonist can effectively reduce alcohol consumption and heavy drinking days (Barrio et al., 2018; Miyata et al., 2019), while improving emotional processing in AUD patients (Vollstädt-Klein et al., 2019). On the other hand, considering the upregulated KOPR signaling in supraspinal sites driving negative affective states under pain conditions, the development of KOPR antagonists may yield promising therapeutic potential for the treatment or prevention of neuropsychiatric disorders comorbid with pain (Ghozland et al., 2002; Liu et al., 2019; Escobar et al., 2020;

Ji et al., 2021; Cahill et al., 2022b). Buprenorphine is a KOPR antagonist/partial agonist, a partial MOPR and NOPR agonist, and DOPR antagonist with higher efficacy in the periphery than centrally (Bloms-Funke et al., 2000; Lutfy and Cowan, 2004). As such, this treatment provides higher levels of analgesia while sparing many of the negative side-effects associated with traditional opioid medications (Cowan et al., 1977; Lutfy and Cowan, 2004; Koppert et al., 2005; Gudin and Fudin, 2020). The ability of buprenorphine to reduce depressive symptoms has been demonstrated in patients with treatment resistant depression (Karp et al., 2014) and patients with comorbid depression and OUD (Yovell et al., 2016; Ahmadi et al., 2018a). Adding further support to this strategy, buprenorphine is also effective in reducing pain severity in experimentally-induced pain (Koppert et al., 2005) and pain patients (Pergolizzi and Raffa, 2019; Gudin and Fudin, 2020). In patients with OUD and pain symptoms, combinatorial therapeutic approaches with buprenorphine and naloxone can effectively reduce pain severity (Worley et al., 2017, 2015; Shulman et al., 2020). The ability of similar strategies to curb opioid use and craving are less consistent (Blondell et al., 2010; Ahmadi et al., 2018b; Parida et al., 2019). However, evidence suggests that the efficacy of buprenorphine as a substitution therapy for OUD is dependent on the dose and rate of tapering (Walsh et al., 1994; Sturgeon et al., 2020), but concerns remain for the potential for abuse (Cicero et al., 2018). To advance KOPR targeting strategies, it will be critical for future research to dissociate the analgesic properties of spinal KOPR and the emotional component of pain mediated by supraspinal KOPR. Biased ligands and peripherally restricted pharmacotherapeutics targeting KOPR will be important developments for treating the mood disruptions in the context of pain.

δ Opioid receptor

The DOPR system plays an important role in pain, analgesia, and negative affective states (Quirion et al., 2020). Similar to KOPR, the functional role of the DOPR system may be selectively dependent on pain states. In rodent models of inflammatory or neuropathic pain, DOPR expression increases in the dorsal horn of the spinal cord and DRG neurons (Cahill et al., 2003; Morinville et al., 2004a; Kabli and Cahill, 2007). The recruitment of DOPR in pain conditions appears to have an inhibitory influence over nociception because genetic deletion of DOPR, but not MOPR, exacerbates and prolongs thermal and mechanical sensitivity in mice with inflammatory pain (Gavériaux-Ruff et al., 2008). Similarly, conditional knock-out of DOPR in the peripheral nociceptive neurons exacerbates mechanical sensitivity in conditions of inflammatory or neuropathic pain (Gaveriaux-Ruff et al., 2011). Moreover, systemic, or local DOPR agonism effectively reduces mechanical and thermal hyperalgesia in wild-type, but not DOPR knock-out, mice, adding further support to the anti-nociceptive role of DOPR (Gaveriaux-Ruff et al., 2011). Importantly, the role of DOPR in nociception is dependent on the presence of pain. In the absence of pain, DOPR activity has negligible effects on analgesia; but in the presence of neuropathic or inflammatory pain, DOPR agonists can reduce thermal and mechanical pain sensitivity (Cahill et al., 2001; Gendron et al., 2007a,b; Normandin et al., 2013). DOPR agonists have also been shown to attenuate migraine associated-pain in preclinical models *via* signaling through calcitonin gene-related peptide (Moye et al., 2021). The weak antinociceptive effects of DOPR agonists in pain naïve animals results from low levels of DOPR expression in plasma membrane. In conditions of pain, the density of DOPR increases at the membrane and cell surface in spinal cord regions and DRG neurons (Quirion et al., 2020). The ability of pain to increase DOPR trafficking is a potential cellular mechanism to explain the pain selective analgesic properties of DOPR agonists. DOPR trafficking is controlled by constitutive pathways involving dynamic remodeling of actin filaments of the cytoskeleton (Mittal et al., 2013) or regulated signaling pathways involving G-protein receptor kinases (GRKs) (Quirion et al., 2020), but the precise mechanisms of DOPR trafficking remain unclear. The DOPR system can modulate nociceptive components of pain not only through neuronal mechanisms, but astrocytic mechanisms as well. For example, deletion of astrocytic DOPR decreases cold allodynia in neuropathic pain while mechanical allodynia is not affected (Reiss et al., 2021). In contrast, DOPR activity in somatostatin-expressing neurons of the dorsal horn of the spinal cord can reduce mechanical, but not thermal, sensitivity in neuropathic pain models (Wang et al., 2018). Therefore, DOPR can modulate distinct elements of the nociceptive experience based on their activity in different cellular populations.

The DOPR system has also received a lot of attention for its role in emotional regulation of mood disorders like anxiety and depression. For example, genetic ablation of DOPR or DOPR antagonists has anxiogenic effects in animal models, while DOPR agonists produce opposite effects (Filliol et al., 2000; Saitoh et al., 2005; Narita et al., 2006a,b; Perrine et al., 2006; Bilkei-Gorzo et al., 2007; Chu Sin Chung and Kieffer, 2013). Similarly, DOPR agonists are associated with higher latency for immobility in the forced swim task, a measure of depressive-like behavior in rodent models (Filliol et al., 2000; Jutkiewicz et al., 2006; Torregrossa et al., 2006), suggesting that pain-related recruitment of DOPR may function to offset mood dysregulation in pain. Unlike MOPR, DOPR activity is not rewarding in the absence of pain. DOPR agonists can elicit CPP in mice with peripheral nerve injury, but not sham controls, while DOPR antagonists selectively produce CPA in mice with pain (Cahill et al., 2022a). This demonstrates the pain state-dependent role of DOPR and suggests that DOPR activation acts as negative reinforcer by alleviating pain rather than producing positive reinforcement.

Given the ability of the DOPR system to modulate analgesic responses and negative affect while sparing any properties that may lead to abuse, DOPR have been investigated for their potential role in curbing opioid use (Quirion et al., 2020). Exogenous opioid exposure can regulate DOPR trafficking in a similar way to the induction of pain. For example, morphine exposure increases DOPR expression at the cell surface of DRG or cortical neurons (Cahill et al., 2001; Morinville et al., 2004b; Gendron et al., 2006). DOPR may also play an important role in the development of analgesic tolerance to exogenous opioids because genetic deletion of DOPR or DOPR antagonists can prevent the development of analgesic tolerance to morphine (Zhu et al., 1999; Abul-Husn et al., 2007; Beaudry et al., 2015). However, the role of DOPR in regulating opioid reward is less clear. DOPR knock-out or DOPR antagonists can facilitate morphine-induced locomotor sensitization (Chefer and Shippenberg, 2009; Billa et al., 2010), a measure of drug responsivity manifesting after repeated drug exposures. However, similar DOPR manipulations have been shown to reduce morphine CPP (Chefer and Shippenberg, 2009; le Merrer et al., 2009, 2011; Billa et al., 2010). These effects may not be attributed to reductions in opioid reinforcement, *per se,* as these manipulations fail to alter morphine self-administration (David et al., 2008; le Merrer et al., 2011). Instead, DOPR may play an important role in drug-cue associated learning.

DOPR signaling is necessary for cued value-based decisions making, particularly within the NAc shell (Laurent et al., 2014, 2012). This effect is driven by distinct anatomical regulation of DA transmission in the NAc by DOPR (Saigusa et al., 2017), such that DOPR agonists in the NAc core increase extracellular DA, while decreasing DA release in the NAc shell (Hirose et al., 2005; Hipólito et al., 2008; Saigusa et al., 2017). Adding another layer of complexity to DOPR-mediated effects on DA release, is that distinct DOPR subtypes (DOPR-1 and DOPR-2) can differentially regulate DA release through their interactions with MOPR. While stimulation of either subtype can have an inhibitory influence over MOPR-mediated slow increases DA release, the precise mechanisms underlying these effects are less clear. For example, stimulation of DOPR-1, not DOPR-2, can activate MOPR causing rapid increases in extracellular DA. However, DOPR agonists can also facilitate DA release independent of MOPR or DOPR, possibly by regulating sodium channel activity (Murakawa et al., 2004; Hirose et al., 2005; Saigusa et al., 2017). In contrast, DOPR-2, not DOPR-1, may play an important role in the development of analgesic tolerance (Beaudry et al., 2015). Future research delineating the precise role of DOPR in mesolimbic circuits will be crucial to exploit on the therapeutic potential of targeting the DOPR system for pain and opioid abuse. Interestingly, gene polymorphisms to the DOPR encoding gene have been linked with increased risk for drug dependence, further strengthening the need for untangling the DOPR system from the behavioral to the genetic level (Zhang et al., 2008; Crist et al., 2013). Moreover, because DOPR agonists have lower abuse liability than MOPR agonists (Stevenson et al., 2005), the DOPR system may represent a useful target for managing pain states during long-term opioid therapy. While the analgesic properties and anxiolytic effects of DOPR agonists are desirable for improving mood states of chronic pain patients, it should be noted that activation of DOPRs can lead to convulsions which may limit their clinical utility (Pradhan et al., 2011). As such, advancing clinical use of DOPR-based ligands will likely be dependent on the development of biased-ligands or dimer-specific drugs capable of DOPR heteromized with other GPCRs (Chu Sin Chung and Kieffer, 2013). Nevertheless, the DOPR system represents a promising target for the development of chronic pain therapies with improved analgesia and minimal unwanted side-effects attributed to traditional opioid medications.

Nociceptin/orphanin FQ opioid receptor

The role of the NOPR system in pain is complex (Toll et al., 2016). In animal models of inflammatory pain, neuropathic pain, and fibromyalgia, NOPR expression and respective endogenous peptide, nociceptin/orphanin FQ (N/OFQ), are upregulated in DRG neurons, spinal tissue, and supraspinal sites (Andoh et al., 1997; Briscini et al., 2002; Dagnino et al., 2019). The ability of NOPR to regulate nociception is related to crosstalk between the NOPR system and stress systems and anatomical distinctions in NOPR function in spinal versus supraspinal sites. Early studies found that intracerebroventricular administration of N/OFQ reduced hot plate and tail flick latencies, suggesting a pro-nociceptive role of supraspinal NOPR activity (Meunier et al., 1995). However, subsequent studies determined that this pro-nociceptive effect was solely related to stress-induced analgesia (Mogil et al., 1996a,b; Morgan, 1997; Rizzi et al., 2001, 2007), a phenomenon triggering the release of endogenous opioids. The pro-nociceptive effects supraspinal N/OFQ are driven partially by antagonistic effects at MOPR, DOPR, and KOPR (Mogil et al., 1996a,b) as well as non-opioid components of stress-induced analgesia (Rizzi et al., 2001). On the contrary, intrathecal administration of N/OFQ produces anti-nociceptive effects and potentiates the effects of morphine (Xu et al., 1996; Yamamoto et al., 1997), indicating the role of NOPR signaling in pain is anatomically specific. Intrathecal administration of N/OFQ or NOPR agonists reduce pain sensitivity in animal models of neuropathic and inflammatory pain (Hao et al., 1998; Ko and Naughton, 2009; Tzschentke et al., 2017). Similar effects are observed with systemic NOPR agonists on mechanical allodynia in preclinical models of cancer-induced bone pain (Sliepen et al., 2021).

NOPR function also varies depending on the persistence of pain. Genetic deletion of NOPR does not alter acute pain

sensitivity but exacerbates hyperalgesic responses in conditions of persistent inflammatory pain (Depner et al., 2003; Rizzi et al., 2011). However, significant differences in NOPR supraspinal distribution and localization is observed between species, particularly between preclinical animal models and non-human primates/humans (Florin et al., 2000; Berthele et al., 2003). As such, the effects of NOPR manipulations in preclinical models of pain may not directly translate to clinical populations (Spetea et al., 2022). Because cellular adaptations within the NOPR system and anatomical distribution of NOPR vary across species and different pain models, future research is required to uncover how recruiting/silencing NOPR signaling can efficiently treat pain symptoms in a more individualized setting.

When considering the clinical utility of targeting the NOPR system for treating opioid abuse in pain patients, it is important to highlight that NOPR activity is neither rewarding nor aversive (Devine et al., 1996). This significantly adds to the therapeutic potential of targeting the NOPR system since NOPR manipulations mitigate abuse potential while sparing negative side-effects. NOPR agonists reduce extracellular release of DA in the NAc (Murphy et al., 1996; Lutfy et al., 2001a), suggesting an inhibitory influence of NOPR activity over drug reward. Indeed, intracerebroventricular administration of N/OFQ or NOPR agonists block the acquisition of CPP for morphine, cocaine, alcohol, and methamphetamine (Ciccocioppo et al., 2000; Kotlińska et al., 2002, Kotlinska et al., 2003; Sakoori and Murphy, 2004; Zaveri et al., 2018). This evidence further solidifies the therapeutic potential of the NOPR system in mitigating opioid abuse and substance use disorders in general. Recent studies found that local administration of N/OFQ in the central amygdala attenuates escalation of oxycodone self-administration (Kallupi et al., 2020). These effects may be attributed to site-specific NOPR regulation as intracerebroventricular administration of N/OFQ fails to reduce heroin self-administration (Walker et al., 1998.). Further adding to this complexity is that the effects of NOPR manipulations have inconsistent effects on alcohol self-administration (Ciccocioppo et al., 1999, 2004; Kuzmin et al., 2004; Economidou et al., 2008). One possibility is that NOPR function may be important for drug-associated memory formation given that NOPR activity can negatively impact memory (Moulédous, 2019). In this regard, NOPR activity may impact the formation of drug-context association (conditioned place preference) rather than impact drug reinforcement and thus, instrumental drug-seeking behavior. This would align with findings demonstrating that NOPR agonists effectively block the acquisition of morphine CPP, but not its expression (Shoblock et al., 2005). The precise mechanisms underlying the effects of pain and opioid use on NOPR function remain unclear, but emerging evidence indicates that NOPR agonists, like cebranopadol, have high analgesic efficacy in chronic pain, delayed development of analgesic tolerance, and lower abuse potential (Linz et al., 2014; Tzschentke et al., 2019). Therefore, it will be important for ongoing research endeavors to fully characterize the role of NOPR in the context of pain and opioid misuse liability and determine whether this opioid system is a therapeutic target with clinical utility.

Opioid system dysfunction by exogenous opioids

Chronic exogenous opioid use can lead to the development of tolerance, a progressive decrease in opioid efficacy which can be mitigated by increasing opioid doses (Lee et al., 2011). Pain patients on long-term opioid therapy typically require increasing doses of opioids to achieve the same level of analgesia (Williams et al., 2001; Zernig et al., 2007; Hayes et al., 2020). In addition to analgesia, tolerance to other opioid-induced effects, like euphoria, sedation, nausea, respiratory depression, and constipation, can also develop over time, albeit not at the same rate (Hayhurst and Durieux, 2016). For example, the development of analgesic and euphoric tolerance occurs on a faster time scale than tolerance to respiratory depression (Ling et al., 1989; Volkow et al., 2018), which contributes to the heightened risk of overdose for opioid users with escalating opioid doses (Kaplovitch et al., 2015; Hayes et al., 2019, 2020). Furthermore, the rate at which tolerance develops often depends on genetic variability and differential responses to different opioid ligands, duration of exposure, and route of administration (Dumas and Pollack, 2008; Ballantyne and Koob, 2021).

Tolerance

The development of tolerance stems from desensitization of the opioid system and inflammatory immune responses within peripheral and central nervous systems (Zhu et al., 1999; Dumas and Pollack, 2008; Koch and Höllt, 2008; Matsui et al., 2014; Corder et al., 2017; Lueptow et al., 2018; Eidson and Murphy, 2019). Following activation, opioid receptors can be phosphorylated by GPCR kinases, which triggers G-protein uncoupling and binding of β-arrestins (Dumas and Pollack, 2008; Zhou et al., 2021). β-arrestin pathway signaling causes desensitized receptors to remain inactive at the plasma membrane, facilitates their endocytosis and subsequent degradation or recycling. As such, these cellular mechanisms represent a critical component in facilitating the development of tolerance at multiple levels (Hutchings et al., 1997; Bohn et al., 2000; Koch and Höllt, 2008; Zhou et al., 2021). Biased agonists, that preferentially activate G-protein signaling cascades with minimal β-arrestin pathway activity, have received great interest as therapeutic alternatives with the thought that such ligands may minimize the development of tolerance and other unwanted side-effects (Ballantyne and Chavkin, 2020). In

mice with genetic deletion of the β-arrestin2 isoform, acute morphine prolongs analgesia while reducing the unwanted side-effects of respiratory depression and constipation, while chronic morphine treatment reduces MOPR desensitization and the development of tolerance (Bohn et al., 1999, 2000; Raehal et al., 2011). These findings led to the development of functionally selective MOPR agonists, like oliceridine, which exhibit preference for G protein-biased signaling and produce less respiratory depression in preclinical models compared to non-selective agonists (DeWire et al., 2013). However, subsequent studies found that opioid-induced respiratory depression and constipation may occur independent of β-arrestins (Kliewer et al., 2020) and G-protein selectivity may worsen some side effects (Kliewer et al., 2019). Although negative side-effects remained during clinical trials (Hertz, 2018), the risk for respiratory depression with oliceridine was lower than morphine (Dahan et al., 2020). Similar findings were found for another biased-MOPR agonist, PZM21 (Graeme Henderson et al., 2018), further highlighting the need to better understand biased opioid ligand signaling mechanisms and their role tolerance.

NOPR signaling appears to play facilitative role in the development of tolerance in the context of pain. As previously mentioned, NOPR expression increases after the induction of pain in spinal and supraspinal sites (Andoh et al., 1997; Briscini et al., 2002; Dagnino et al., 2019) which, under conditions of chronic pain, can suppress hyperalgesic responses (Depner et al., 2003; Rizzi et al., 2011). Based on this, it is somewhat surprising that N/OFQ potentiates the development of opioid tolerance. Genetic ablation of the endogenous peptide, nociceptin, N/OFQ, its receptor (NOPR), or blocking NOPR signaling using an exogenous antagonist, prevents and reverses the development of morphine tolerance (Ueda et al., 1997; Lutfy et al., 2001b; Chung et al., 2006; Scoto et al., 2010). These likely are attributed to the antagonistic properties of N/OFQ at other opioid receptors (Mogil et al., 1996b). NOPR can also undergo desensitization after chronic or acute stimulation (Donica et al., 2013). While these findings suggest that pain-induced upregulation of the NOPR system underlies attenuated analgesic responses to exogenous opioids, they also suggest that targeting the NOPR system may be a useful target to treat vulnerabilities in opioid tolerance, escalation, and abuse in pain patients.

The development of tolerance can also develop in response to the recruitment of neuroinflammatory mediators. Long-term opioid use triggers neuroinflammatory responses in the CNS to increase neuronal excitability which can contribute to tolerance (Eidson and Murphy, 2019; Zhang et al., 2020; Zhou et al., 2021). In particular, the ventrolateral PAG (vlPAG) is a critical hub in which descending control over nociceptive signaling is negatively affected by chronic opioid use. Chronic intra-vlPAG opioid agonist administration is sufficient to produce tolerance to systemically administered opioids. Similarly, blocking vlPAG opioid receptor-mediated signaling can prevent the development of tolerance to chronic systemic administration of exogenous opioids (Lane et al., 2004; Morgan et al., 2006; Meyer et al., 2007; Loyd et al., 2008; Macey et al., 2009; Bobeck et al., 2012; Eidson and Murphy, 2019). Opioid-induced activation of toll-like receptor 4 (TLR4) in astrocytes and microglia within the spinal cord or PAG triggers inflammatory responses through activation of nuclear factor kappa B (NFκB) and the release of pro-inflammatory cytokines such as tumor necrosis factor α (TNFα) and interleukins, IL-1β and IL-6 (Raghavendra et al., 2002; Eidson et al., 2016; Liang et al., 2016; Eidson and Murphy, 2019; Wang et al., 2020). This release in cytokines leads to down-regulation of GABA receptors resulting in increased function of glutamate receptor systems. Consequently, hyper-excitability in nociceptive pathways acts to oppose the analgesic actions of opioids, resulting in tolerance (DeLeo et al., 2004; Eidson and Murphy, 2019; Zhou et al., 2021). Based on the role of cytokines in opioid tolerance, significant efforts have been directed toward the development of treatments that may inhibit opioid-induced cytokine production (Namba et al., 2021). For example, manipulations inhibiting TNF signaling through TLR4 can prevent morphine tolerance and associated hyperexcitability (Shen et al., 2011; Eidson et al., 2016; Wang et al., 2020). As such, modulation of TNF signaling represents a promising adjunctive therapy to curb the development of opioid tolerance. Taken together, opioid tolerance manifests through adaptations to endogenous opioid and inflammatory systems, but a better understanding of the relationship between these systems will facilitate our ability to identify novel therapeutic targets to overcome the development of opioid tolerance.

Opioid-induced hyperalgesia

In contrast to the development of tolerance, chronic opioid use can also result in opioid-induced hyperalgesia (OIH), a paradoxical increase in pain sensitivity either at the initial source of pain or elsewhere (Chu et al., 2008; Hay et al., 2009; Roeckel et al., 2016). While the phenomenon of tolerance represents a reduction in drug potency and creates a rightward shift in analgesic opioid dose response curves, OIH increases pain sensitivity modeled by a significant downward shift in analgesic dose response (Chu et al., 2008). It is, thus, distinct from tolerance in that escalating opioid doses may exacerbate the development of OIH in the long-term. However, both tolerance and OIH are associated with hyperexcitability in glutamatergic systems and up-regulation of pro-inflammatory molecules at spinal synapses and supraspinal regions, like the RVM (Bederson et al., 1990; Kaplan and Fields, 1991; Kovelowski et al., 2000; Vanderah et al., 2001). OIH is a pro-nociceptive process that can be observed independently of tolerance through acute exposure to ultra-low opioid doses. However, the development of OIH is more often observed after

the development of tolerance, following chronic exposure to higher, analgesic doses (Drdla et al., 2009; Silverman, 2009; Lee et al., 2011; Hayhurst and Durieux, 2016; Roeckel et al., 2016).

Opioid-induced hyperalgesia is driven by cellular adaptations in pronociceptive signaling pathways, particularly within glutamatergic systems (Lee et al., 2011). Opioid agonists increase cellular excitability underlying OIH by inhibiting glutamate transporter systems (Mao et al., 2002). The resulting abundance in synaptic glutamate can lead to NMDA receptor-dependent long-term potentiation (LTP) at primary afferents and second-order spinal neurons resulting in sensitization of pain signaling pathways (Drdla et al., 2009; Silverman, 2009; Heinl et al., 2011; Drdla-Schutting et al., 2012; Roeckel et al., 2016; Corder et al., 2018). Adding to this, previous reports from our lab found that OIH is driven by insertion of GluA4-containing AMPA receptors in the dorsal horn of the spinal cord (Cabañero et al., 2013). Similar to the development of tolerance, OIH is also associated with opioid-dependent production and release of nociceptive signaling molecules from microglia and astrocytes such as pro-inflammatory cytokines, chemokines, ATP, nitric oxide, and others detailed elsewhere (Chu et al., 2008; Lee et al., 2011; Roeckel et al., 2016). Consequent release of the neuropeptide, cholecystokinin (CCK) in the RVM has been shown to have 'anti-opioid' actions that facilitate pronociceptive pathways contributing to OIH (Kaplan and Fields, 1991; Kovelowski et al., 2000; Friedrich and Gebhart, 2003; Heinricher and Neubert, 2004). The NMDA receptor-dependent hyperexcitability associated with OIH has been targeted in efforts to mitigate the impact of opioids on central sensitization. For example, low-dose ketamine (non-selective NMDA receptor antagonist) administration in conjunction with opioid analgesics can prevent the development of OIH in animal models and clinical patients with postoperative pain (Célèrier et al., 2000; Maher et al., 2017). Similarly, methadone, a potent MOPR agonist and weak NMDA receptor antagonist, has been examined as a substitute for opioid therapies and can effectively reduce opioid-induced OIH (Sjøgren et al., 1994; Shimoyama et al., 1997; Davis and Inturrisi, 1999; Axelrod and Reville, 2007). While the efficacy of methadone maintenance treatment (MMT) is less reliable in patients with opioid dependence or a prior history of abuse, MMT reduce instances of heroin use, drug craving, and criminal activity (Dole and Nyswander, 1965, 1976; Shi et al., 2008; Mattick et al., 2009; Ward et al., 2009; Lee et al., 2011). Despite this, moral reservations among some groups precipitated shifts in the treatment goals initially outlined for long-term MMT advising sufficient dosing and instead, goals were centered around achieving abstinence and using less-than-effective doses, which compromised treatment outcomes and funding for MMT research (Dole and Nyswander, 1976; Ward et al., 2009). As such, OIH remains a barrier to effective treatment with opioids. Further research delineating the mechanisms mediating the physiological and behavioral effects of opioids and whether pain affects these properties will help facilitate the development of novel and safer pharmacotherapies to improve patient care and well-being.

Pain, opioids, and reward

The mesolimbic pathway integrates both aversive and rewarding properties of external stimuli (Bromberg-Martin et al., 2010). Activation of the mesolimbic pathway by rewarding stimuli results in phasic DA release from the VTA into the NAc to reinforce goal-directed behaviors (Fibiger et al., 1987; Berridge and Robinson, 1998; Becerra and Borsook, 2008; Pignatelli and Bonci, 2015). As described previously, opioids reliably activate mesolimbic DA pathway and thus promote motivational salience (Matsui et al., 2014; Galaj et al., 2020; Doyle and Mazei-Robison, 2021). In conditions of pain, the ability of opioids to trigger comparable responses is significantly reduced. Furthermore, the motivational salience of opioid reward may be driven by hedonic pleasure (positive reinforcement) or pain relief (negative reinforcement) (Koob, 2020). Similar to exogenous opioids in pain-naïve conditions, relief from pain itself can elicit increases in DA release and reinforce motivated behaviors (Martin et al., 2006; Leknes et al., 2011; Navratilova et al., 2015; Eikemo et al., 2021). As such, the presence of pain may perpetuate maladaptive patterns of opioid use.

Pain disrupts mesolimbic DA function contributing to maladaptive effects on reward processing. Deficits in DA signaling, or administration of DA receptor antagonists reduce approach behaviors and hedonic responses to rewarding stimuli (Frank et al., 2016; Nguyen et al., 2019). In rodent models of inflammatory and nerve injury pain, motivated behaviors for natural and drug rewards, such as opioids, are significantly impaired (Schwartz et al., 2014; Hipólito et al., 2015; Taylor et al., 2015; Massaly et al., 2019). This pain-induced decrease in motivation is strongly correlated with blunted DA signaling in the mesolimbic pathway (Cahill et al., 2013; Schwartz et al., 2014; Hipólito et al., 2015). These findings parallel clinical studies in which pain-induced negative emotional states positively correlates with reductions in DA neurotransmission and maladaptive changes in NAc function (Lee and Tracey, 2010; Jarcho et al., 2012; Martikainen et al., 2015; Makary et al., 2020). Importantly, pain-related alterations in DA signaling are also associated with deficits in emotional and sensory processing. For example, deficits in DA receptor binding potential in the NAc are observed in patients with lower back pain, which can predict the severity of negative affect and pain (Baliki et al., 2010; Martikainen et al., 2015). In line with this, DA transporter activity, a mechanism important for clearing DA from the synaptic cleft, is increased in the NAc of animal models of chronic neuropathic

or inflammatory pain (Ren et al., 2015, 2021; Selley et al., 2020). Moreover, morphine-induced DA release in the NAc is suppressed by sciatic nerve ligation (Niikura et al., 2008). These changes in mesolimbic DA function strongly impact reward thresholds which may contribute to pain-related occurrences of negative affect and enhanced vulnerability for opioid abuse (Massaly et al., 2019, 2021). Supporting this, pain patients are more likely to initiate and continue opioid treatment if they have a cooccurring mood disorder (Halbert et al., 2016).

Opioid abuse susceptibility in pain states is likely exacerbated by a rightward shift in opioid reinforcement thresholds due to pain-related deficits in mesolimbic pathway function. In lower back pain patients, the propensity for risky monetary behavior is associated with altered connectivity of the NAc (Berger et al., 2014). The severity of pain is also associated with increased impulsivity in humans and rodent models (Wakaizumi et al., 2019; Cunha et al., 2020). These would suggest that pain patients are predisposed to developing problematic opioid use. Although it is recognized that chronic pain patients receiving prescription opioids are at high risk for opioid dependence (Ballantyne, 2015), the prevalence of maladaptive opioid use in pain patients has been difficult to determine based on confounding outcome measurements (i.e., mortality) and imprecise or poorly defined terminology (i.e., "abuse," "misuse," "addiction") (Vowles et al., 2015). Opioid "misuse," or use contrary to the prescribed pattern, occurs in up to 29% of pain patients receiving opioid medications while "addiction," or continued use despite negative consequences, can occur in up to 12% (Vowles et al., 2015). Opioid "abuse," or aberrant drug taking behavior often predictive of maladaptive opioid use has been reported in 46–81% of pain populations (Butler et al., 2004; Wilsey et al., 2008; Vowles et al., 2015). However, there remains a general consensus that high-quality research on this relationship is lacking (Ballantyne, 2015; Voon et al., 2017; Nadeau et al., 2021). Nevertheless, qualitative evidence from clinical literature indicates that negative outcomes associated with opioid use can be instigated by pain severity (Grol-Prokopczyk, 2017; Zajacova et al., 2021), duration of opioid use (Chung et al., 2019; Jantarada et al., 2021), escalating opioid doses (Zernig et al., 2007; Kaplovitch et al., 2015), comorbid anxiety and depression (Peciña et al., 2018; Emery and Akil, 2020; Rogers et al., 2020), discontinuation of opioid medications (Mark and Parish, 2019; Stein et al., 2021), and inherent risk factors like sex (Manubay et al., 2015; McHugh, 2020) or genetics (Kendler et al., 2003; Agarwal et al., 2017). Evidence from patients with pain and long-term opioid use have been critical in identifying potential risk factors for maladaptive opioid use but have yielded minimal impacts on either public health concern.

Determining the level of synergy between pain, long-term opioid use, and opioid misuse can be difficult for many reasons, but preclinical pain models of opioid self-administration provide a translational means to better understand how pain may provoke motivational shifts to alter opioid misuse liability. Although pain-induced dysfunction of mesolimbic reward pathways produces clear deficits in motivation for natural rewards (Massaly et al., 2019, 2021; Reiner et al., 2019), the effects of pain on opioid motivation are more complex. Evidence from self-administration studies suggest that the ability of pain to effect opioid self-administration is related to the chronicity of pain, selected opioid/dose, and the duration of daily opioid exposure. For example, chronic arthritic pain has biphasic effects on rates of oral fentanyl self-administration, that interestingly, follow the time-course of pain progression (Colpaert et al., 2001, 1982). Specifically, one week after the onset of pain there are no effects on fentanyl consumption but, during successive weeks, fentanyl intake dramatically increases—peaking at 2–3 weeks – and declines to baseline levels several weeks later. Importantly, the time course of fentanyl consumption rates parallels the time course of progressive pain sensitivity (Colpaert et al., 1982, 2001). Similarly, spinal cord injury has time-dependent effects on long-access morphine self-administration in rats. In this regard, pain reduces morphine intake 24 h after the induction of pain, then peaks at 14–21 days before normalizing 35–42 days later (Woller et al., 2014). These findings indicate that the persistence of pain is an important driver of opioid consumption. Adding further support to this, acute pain manipulations with capsaicin or lactic acid do not alter rates of fentanyl or heroin self-administration, but persistent inflammatory pain-induced reductions in fentanyl vs. food choice procedures match controls by one week after the induction of pain (Reiner et al., 2021). Notably, a small study found that arthritic pain reduced self-administration of relatively high doses of morphine with 24-h access for weeks following pain onset (Lyness et al., 1989) while another found that multiple forms of chronic pain attenuated oral fentanyl self-administration and discrimination in mice (Wade et al., 2013). These findings allude to the notion that pain may produce a shift opioid dose-response. Consistent with this, our lab found that inflammatory pain reduces heroin intake at low doses, but increases intake when doses are high (Hipólito et al., 2015). Our findings suggest that these effects are driven by deficits in VTA DA cell excitability (Hipólito et al., 2015) and this is exemplified by evidence showing that pain reduces the ability of low-dose opioids to facilitate VTA intracranial self-stimulation (Ewan and Martin, 2011). Spinal nerve ligation also produces a rightward shift in dose-response for multiple opioids, but the time-dependency of these effects has not been examined (Martin et al., 2007). Taken together, evidence from preclinical pain models of opioid abuse suggest that chronic pain can increase motivation for high opioid doses in a time-dependent manner that parallels the progression of pain. It will be important for

future studies to evaluate whether the time- and dose-dependent effects of pain on opioid consumption are related to time-dependent disruptions in mesolimbic pathway function.

Conclusions

Pain conditions, chronic opioid use, and withdrawal from chronic opioid use disrupt the endogenous opioid system function at spinal and supraspinal levels to negatively impact pain thresholds, opioid sensitivity, mood, and reward sensitivity. These physiological and behavioral alterations, particularly among opioid systems and mesolimbic reward pathways, may contribute to persistent use of opioid medications in an attempt to alleviate adverse physical and emotional states, thereby creating a susceptibility for opioid misuse. In addition, other mediating factors outside the scope of this review contribute to individual variabilities in pain perception and opioid sensitivity like sex differences (Huhn et al., 2018; Pisanu et al., 2019), genetic (Tremblay and Hamet, 2010; Mogil, 2012), and epigenetic mechanisms (Liang et al., 2015; Browne et al., 2019) and likely influence proclivity for opioid abuse in the context of pain. Neuroadaptive processes produced by pain conditions and long-term opioid use have compounding effects on negative outcomes, like the development of tolerance or opioid-induced hyperalgesia. An understanding of the synergy between these processes remains incomplete, but the ability to curb the opioid crisis and the prevalence of pain relies heavily on the ability to identify safer pharmacotherapeutic alternatives derived from a better comprehension of pain- and opioid-induced adaptations to opioid systems and functional neurocircuitry.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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