CHAPTER TWO

Pain, negative affective states and opioid-based analgesics: Safer pain therapies to dampen addiction

Nicolas Massaly[a,b,c,*], Tamara Markovic[a,b,c], Meaghan Creed[a,b,c,d,e,f], Ream Al-Hasani[a,b,c,g,h], Catherine M. Cahill[i,j,k], and Jose A. Moron[a,b,c,d,e]

[a]Department of Anesthesiology, Washington University in St. Louis, St. Louis, MO, United States
[b]Washington University in St Louis, Pain Center, St. Louis, MO, United States
[c]Washington University in St Louis, School of Medicine, St. Louis, MO, United States
[d]Department of Neuroscience, Washington University in St. Louis, St. Louis, MO, United States
[e]Department of Psychiatry, Washington University in St. Louis, St. Louis, MO, United States
[f]Department of Biomedical Engineering, Washington University in St. Louis, St. Louis, MO, United States
[g]Department of Pharmaceutical and Administrative Sciences, St. Louis College of Pharmacy, St. Louis, MO, United States
[h]Center for Clinical Pharmacology, St. Louis College of Pharmacy and Washington University in St. Louis School of Medicine, St. Louis, MO, United States
[i]Department of Psychiatry and Biobehavioural Sciences, University of California, Los Angeles, CA, United States
[j]Shirley and Stefan Hatos Center for Neuropharmacology, University of California Los Angeles, Los Angeles, CA, United States
[k]Jane & Terry Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, CA, United States
[*]Corresponding author: e-mail address: nmassaly@wustl.edu

Contents

Abstract

Across centuries and civilizations opioids have been used to relieve pain. In our modern societies, opioid-based analgesics remain one of the most efficient treatments for acute pain. However, the long-term use of opioids can lead to the development of analgesic tolerance, opioid-induced hyperalgesia, opioid use disorders, and overdose, which can ultimately produce respiratory depressant effects with fatal consequences. In addition

International Review of Neurobiology, Volume 157
ISSN 0074-7742
https://doi.org/10.1016/bs.irn.2020.09.002

to the nociceptive sensory component of pain, negative affective states arising from persistent pain represent a risk factor for developing an opioid use disorder. Several studies have indicated that the increase in prescribed opioid analgesics since the 1990s represents the root of our current opioid epidemic. In this review, we will present our current knowledge on the endogenous opioid system within the pain neuroaxis and the plastic changes occurring in this system that may underlie the occurrence of pain-induced negative affect leading to misuse and abuse of opioid medications. Dissecting the allostatic neuronal changes occurring during pain is the most promising avenue to uncover novel targets for the development of safer pain medications. We will discuss this along with current and potential approaches to treat pain-induced negative affective states that lead to drug misuse. Moreover, this chapter will provide a discussion on potential avenues to reduce the abuse potential of new analgesic drugs and highlight a basis for future research and drug development based on recent advances in this field.

1. Introduction: Pain and the opioid epidemic

In recent years, North America has faced an opioid epidemic. Over a number of decades, opioid use disorder (OUD), including misuse and abuse of both opioid analgesics and illegal opioid substances, has reached an unprecedented prevalence. In 2018, in the United States, 128 cases of lethal overdose attributed to an opioid (opioid medication, heroin and illegal synthetic opioids) were reported daily. In addition, emergency departments have been dealing with an insurgence of opioid-induced respiratory depression, as well as other opioid use related illnesses such as infectious diseases (Dowell, Haegerich, & Chou, 2016; Volkow & McLellan, 2016). This alarming growth in opioid use and misuse in the North American population correlates with a massive increase in opioid analgesic prescriptions. Currently, more than 178 million Americans experience pain that persists for weeks to years, where the prevalence of chronic pain is 11.2% of the United States adult population (Nahin, 2015).

Since the 19th century following the isolation of morphine from crude opium, many opioid formulations have been designed to engage our endogenous opioid system and provide efficient pain relief. The endogenous opioid system is critical in the modulation of pain signaling, but despite its analgesic properties its engagement also has deleterious side effects such as constipation, nausea, sedation, the development of tolerance, abuse potential, and the induction of respiratory depression. To this day, opioid medications remain the most efficient pain reliever for acute, inflammatory

conditions, nerve-injured induced pain and other persistent conditions (less than 16 weeks in duration from pain onset) (Dowell et al., 2016; Furlan, Chaparro, Irvin, & Mailis-Gagnon, 2011). Recently, and as a result of recommendations described by the Institute of Medicine in 2010 on pain management (Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education, 2011), pain was introduced as the "fifth vital sign" requiring practitioners to provide an effective and sustained pain treatment (Lanser & Gesell, 2001). To provide efficient acute pain management, in 1995 the U.S. Food and Drug Administration (FDA) approved the use of an extended release formulation of oxycodone, Oxycontin®, which was marketed as an opioid with less addictive profile, and potential than previous opioid-based analgesics. The aggressive promotion of Oxycontin® for the treatment of acute, moderate to severe pain relief together with the false belief that opioid-based pain killers possess low abuse liability when used for treating pain led to a vast increase in prescription use (Cochran et al., 2016; Krashin, Murinova, & Sullivan, 2016). In the span of only 15 years, from 1997 to 2012, opioid-based prescriptions rose from 91 million to 255 million units dispensed in the United States. During this period, the number of reported opioid-related lethal overdoses, mainly from prescription opioids, increased exponentially (Dowell et al., 2016). As a consequence, the medical community and federal governments imposed restrictions in the number of opioid based therapy units dispensed from health care providers (Von Korff, Kolodny, Deyo, & Chou, 2011). Following restrictions on opioid analgesic dispensing, along with the threat of litigation facing physicians, and the decision by some general practitioners to stop prescribing opioids, a rapid increase in heroin consumption and illicit opioids has been observed. From 2010 to 2017, deaths from synthetic opioids such as fentanyl increased nearly 10-fold, from 3007 (14.3% of opioid-related death) to 28,466 (59.8%) (https://www.cdc.gov/nchs/data/databriefs/db329_tables-508.pdf). While it is likely that the development of misuse and abuse behaviors often arises from the diversion and recreational use of those opioids, it is been shown that prescription opioid use triggers the development of OUDs in 21–29% of pain patients (Vowles et al., 2015).

To better understand the potential risk for opioid misuse in pain conditions, all aspects of the pain experience must be considered. Pain is comprised of many components including a sensory component (pain intensity and location), an affective component (emotional reaction to the pain) and cognitive component (evaluation of the pain). The intense emotional suffering often present in chronic pain patients correlates with the

development of persistent disabilities in social, professional and self-care activities (Elman, Borsook, & Volkow, 2013), as well as impairments or disturbances in memory, cognition and attention, sleep, and reduced physical functioning (Dahan, van Velzen, & Niesters, 2014). The development of chronic pain drives synaptic adaptations in brain structures where nociceptive and pain-associated affective components are integrated, which contributes to the development of negative affective states (Garland, Froeliger, Zeidan, Partin, & Howard, 2013; Krashin et al., 2016; Massaly, Morón, & Al-Hasani, 2016; Taylor, Becker, Schweinhardt, & Cahill, 2016). Importantly, persistent negative affective states can lead to co-morbid psychiatric disease such as depression and represent a trigger for the development of OUD as well as other drugs of abuse (Hogarth, 2020). Despite the sustained effort of the scientific community to identify novel targets and develop innovative and non-addictive treatments for the relief of chronic pain, this has yet to result in safer analgesics. Current approaches for the development of non-addictive analgesics consist of non-opioid drugs, biased opioid ligands devoid of addictive properties and positive allosteric modulators and are further discussed later in this chapter. Minimizing the occurrence of OUDs driven by prescription opiates for chronic pain and the development of safer pain mediation requires a better understanding of the neurocircuitry of pain and its interaction with opioid-based pain killers. It should be noted that multiple non-pharmacological approaches are currently used to relieve pain and improve quality of life of patients experiencing chronic pain such as cognitive, rehabilitation and physical therapies. Indeed, the integration of several above mentioned approaches has shown high efficiency in chronic pain relief and may help the medical community in decreasing chronic use of opioid analgesics and prevent the development of OUD in pain patients (Koele et al., 2014).

In this review, we will describe our current understanding of the pain neurocircuitry and its interaction with the endogenous opioid system. We will then discuss the impact of chronic and persistent pain on the development of negative affective states, how this may impact opioid misuse and abuse potential, the neurocircuitry mediating these conditions and the role of endogenous opioid systems within them. Lastly, we provide insight on the current and future directions for the development of safer opioid-based analgesics devoid of abuse potential and chronic pain treatment.

2. Pain and the endogenous opioid system

As defined by the International Association for the Study of Pain (IASP) pain is "*an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in term of such damage*." Acute pain is necessary and protective. It serves as a warning signal allowing our bodies to heal while avoiding further injury that may jeopardize our well-being and survival. Pain, thus, primarily helps organisms, through the initiation of defensive and avoidance mechanisms. Noxious stimuli and tissue damage can activate a selective network of peripheral nociceptors projecting (further detailed in the following section), via a spinal relay network, to central brain regions such as cortex, amygdala, bilateral insula, thalamus, anterior cingulate and the prefrontal cortex (Coghill, McHaffie, & Yen, 2003). Within these brain structures, the nociceptive experience acquires an emotional valence which allows an organism to learn and avoid future similar situations.

Despite this obvious protective role, the occurrence of long term adaptive cellular changes within the pain neuroaxis can ultimately lead to the development of chronic pain. Chronic pain is defined as pain lasting at least 3 months, whether associated with an identifiable cause or not (for review Dowell et al., 2016). Preclinical studies and brain imaging in patients experiencing chronic pain reveal neuronal allostatic changes (the process of achieving stability, or homeostasis, through physiological or behavioral change) along pain transmission pathways such as nociceptors phenotype alteration, transcriptome and translatome changes, adaptations in limbic circuits, and interactions between the nervous and immune systems which represent key factors in the development of these chronic states (Ji, Chamessian, & Zhang, 2016; Price et al., 2018). Correlated with those allostatic adaptations, brain structure activity and connectivity are impacted by the presence of chronic pain states (Apkarian, Baliki, & Farmer, 2013; Price et al., 2018). Furthermore, chronic pain states and their negative affective consequences are exacerbated by stress exposure, emotional states, and several other psychological factors (Denk, McMahon, & Tracey, 2014; Garland, 2012). The interaction between long term plastic changes and psychiatric outcomes during chronic pain may explain, at least in part, the ineffectiveness of common therapies. Thus, it is important to understand how pain is encoded and what alterations occur in nociceptive and limbic circuits during chronic pain in order to develop novel and safer analgesics.

Nociceptive sensation is first integrated by activation of peripheral nociceptors projecting to several superficial layers of the spinal dorsal horn as well as in the deeper layers associated with non-noxious sensations. There, nociceptors can transmit the "pain signal" onto second-order dorsal horn neurons that project to the thalamus and subsequently to the somatosensory cortex. The networks from nociceptors to supraspinal centers is defined collectively as the ascending pain pathway which serves as a first-order integration of the pain experience, allowing protective behavior and avoidance learning to prevent further damage (for detailed review Basbaum, Bautista, Scherrer, & Julius, 2009). During pain processing, the activity and efficiency of the spinal projection tracts that relay to different brain structures can be modulated by the activity of local spinal circuits and descending circuits comprised in part by the periaqueductal gray (PAG) neurons projecting to the rostral ventral medulla (RVM) and the locus coeruleus (LC). The RVM and LC send axons to the dorsal horn of the spinal cord to modulate transmission between primary nociceptors and second-order ascending neurons (Basbaum et al., 2009; Heinricher, Tavares, Leith, & Lumb, 2009; Julius & Basbaum, 2001). In addition, several other cortical and subcortical structures play a critical role in pain modulation through descending circuits. The prefrontal cortex (PFC), the anterior cingulate cortex (ACC), the hypothalamus, the insula, the mesolimbic pathway and the amygdala are all involved in the integration of the aversive and emotional component of pain (Tracey & Mantyh, 2007).

Components of the endogenous opioid system are highly expressed CNS sites important for pain processing/transmission, and endogenous opioid signaling is crucial in the modulation of pain. Indeed, both endogenous and exogenous opioid agonists possess potent analgesic properties by inhibiting nociceptive transmission (Besson, 1999; Tracey, 2010). The opioid system is composed of four main receptors: the delta-opioid receptor (DOR), the mu-opioid receptor (MOR) and the kappa-opioid receptor (KOR) and the nociceptin (orphanin FQ) receptor (NOR). These receptors are members of the superfamily of transmembrane G-protein coupled receptors (GPCRs). The MOR and DOR can be activated by the endogenous opioid peptides enkephalins and endorphins, while dynorphin peptide is the main endogenous agonist for the KOR. There are almost 30 peptides that bind to opioid receptors in the central nervous system that are derived from four peptide precursors (pre-prodynorphin, pre-proenkephalin, pre-pronociceptin, and prooopiomelanocortin).

The role of opioid systems in modulating nociception has been investigated using preclinical models during, acute, inflammatory and chronic pain. Until very recently, nociception was assessed using reflexive measures of withdrawal latencies to noxious pressure, thermal, cold and touch stimuli. The presence of hyperalgesia, characterized by an increased response to a normally painful stimulus, and allodynia, defined as painful response to a stimulus that is not normally noxious, represent the main measurable outcomes in animal pain models. To date, engagement of MOR signaling using endogenous or synthetic agonists represent the most efficient analgesic in reversing hyperalgesia and allodynia. Along these lines, most of the current opioid analgesics derived from the *papaver somniferum* opium poppy (morphine, codeine), semi-synthetics based on the structure of thebaine from the opium poppy (oxycodone, hydrocodone), and synthetics with no similarity in chemical structure with any of the poppy alkaloids (methadone, fentanyl) target the MOR to alleviate pain. Interestingly, opioid analgesics do not only modulate nociceptive and reflexive pain signals, but they also alleviate affective and emotional dimensions of pain (Garland et al., 2013). Indeed, motivational pain assays such as conditioned place preference (CPP), Real Time Place Paradigm (RTPP), sucrose preference test, progressive ratio schedule of reinforcement in self-administration approach helped uncovering the role of MOR in the emotional component of pain experience in preclinical models. However, activation of opioid receptors in the peripheral and central nervous systems causes numerous undesirable side effects including vomiting, urinary retention, bradycardia, hypotension, sedation, pruritis, and respiratory depression, which restrict their long-term use and contribute to non-compliance (Arvidsson, Dado, et al., 1995; Arvidsson, Riedl, et al., 1995; Basbaum et al., 2009; Cahill et al., 2014; Mansour, Khachaturian, Lewis, Akil, & Watson, 1988; Zhu, Hsu, & Pintar, 1998).

A key goal of the opioid research field is to dissociate the mechanisms underlying opioid analgesia from those responsible for adverse effects produced by MOR activation. At the cellular level, activation of MOR by endogenous or exogenous agonists engages intracellular recruitment of inhibitory guanosine-5′-triphosophate (GTP) binding proteins (Gi/o) and signaling through the beta-arrestin pathway. Upon opioid receptor recruitment, the alpha and beta-gamma subunits of the G-coupled protein can activate intracellular kinases, such as c-Jun and ERK, and inwardly rectifying potassium channels, respectively. Dissociated beta-gamma subunits can bind and inhibit Ca^{2+} channels, decreasing presynaptic calcium currents and

presynaptic neurotransmitter release (Rusin, Giovannucci, Stuenkel, & Moises, 1997; Williams, Christie, & Manzoni, 2001). These signaling cascades subsequently lead to neuronal hyperpolarization and produce analgesia. In addition, activation of the beta-arrestin pathway is sufficient to mediate MOR agonist-induced side effects such as tolerance, respiratory depression and constipation (Bohn et al., 1999; Manglik et al., 2016; Schmid et al., 2017). Thus, the development of G-protein signaling biased-agonists for the MOR, engaging the G-protein pathway with little or no beta-arrestin pathway signaling, have been a main objective to develop safer opioid-based pain medications (Grim et al., 2020; Manglik et al., 2016; Raehal, Walker, & Bohn, 2005). However, the lack of translational efficacy and safety in the development of MOR biased-agonists in human studies and recent preclinical evidence have challenged this model and demonstrated that tolerance and respiratory depression are still observed in beta-2 arrestin knockout mice, suggesting that beta-arrestin pathway may not be necessary for MOR agonist-induced side effects (Kliewer et al., 2019, 2020). Future research will be necessary to further dissect the contribution of G-protein and beta-arrestin pathways to undesirable side effects of MOR agonists.

As nociceptors express MOR peripherally and on their axon terminals within the spinal cord, the development of peripherally restricted MOR agonists, sparing centrally mediated side effects, such as abuse potential and respiratory depression, represent another promising avenue for safer analgesics. Several research groups have been working along those lines on the development of such MOR agonists to provide analgesics that are devoid of misuse potential and lethal side effects. Several studies have demonstrated that topical and subcutaneous administration of loperamide, a peripherally restricted MOR agonist, or its analogs is sufficient to reverse hyperalgesia induced by inflammatory pain (DeHaven-Hudkins et al., 2002; DeHaven-Hudkins & Dolle, 2004; Vadivelu, Mitra, & Hines, 2011). Systemic and local administration of peripherally restricted MOR agonists can also dose-dependently attenuate neuropathic pain-induced hyperalgesia and allodynia (Chung et al., 2012; Guan et al., 2008; Obara et al., 2009; Tiwari et al., 2016), and this analgesic effect is reversed when drugs are co-administered with methyl-naltrexone, a peripherally acting MOR antagonist (Guan et al., 2008). Interestingly, deletion of MOR in nociceptors blocks morphine antinociceptive tolerance and morphine-induced hyperalgesia in uninjured and neuropathic pain conditions, without altering acute morphine antinociception (Corder et al., 2017).

Altogether, these studies establish that peripheral MOR engagement is sufficient but not necessary for opioid-induced changes in sensory nociception. However, if peripherally restricted opioid receptor ligands were effective for pain management, loperamide (Imodium®) would be more widely used, yet there is no firm evidence of loperamide use for pain management. With the objective of blunting centrally mediated reinforcing properties of MOR agonists, a novel category of opioid agonists with actions restricted to the inflammatory site has been recently developed (Spahn et al., 2017). After tissue damage or lesion, the recruitment of inflammatory mediators at the injury site creates a localized acidic milieu (Rodriguez-Gaztelumendi, Spahn, Labuz, Machelska, & Stein, 2018), and a low pKa fentanyl derivate was recently developed to selectively target low pH milieu (Spahn et al., 2017). More specifically, the novel opioid agonist, (±)-*N*-(3-fluoro-1-phenethylpiperidine-4-yl)-*N*-phenyl propionamide (NFEPP), relieves hyperalgesia and allodynia induced by inflammatory and neuropathic pain without inducing commonly observed opioid-induced side effects such as constipation, sedation, and abuse liability (Spahn et al., 2017). While further studies are needed to assess the sufficiency of NFEPP for relief of ongoing non-evoked pain and to assess analgesic tolerance during chronic use, targeting opioids selectively in the inflammatory site represents a novel promising strategy for pain treatment.

MORs are widely distributed throughout the brainstem, midbrain, and forebrain structures where endogenous MOR peptides mediate analgesia. Several studies have used locally targeted microinjections of MOR agonists to uncover brain structures involved in analgesia and the negative affective states arising as consequence of persistent pain. The descending pathway, composed of ventrolateral (vl) PAG to RVM projections, represents a main site of action for the MOR system to modulate nociceptive inputs. MORs are widely expressed in the vlPAG and local infusions of MOR agonists into this structure produces analgesia (Bobeck, McNeal, & Morgan, 2009; Buntin-Mushock, Phillip, Moriyama, & Palmer, 2005; Jacquet & Lajtha, 1974). MOR signaling within the vlPAG is necessary for the development of analgesic tolerance to long-term opioid treatment (Lane, Patel, & Morgan, 2005). The RVM possesses different cell types characterized as ON, OFF, or neutral cells. They differ in their analgesic or pro-nociceptive properties and their response to opioid agonists (Basbaum & Fields, 1984; Fang, Haws, Drasner, Williamson, & Fields, 1989). Briefly, MOR agonists inhibit ON cells while they disinhibit OFF cells to produce antinociception (Fang et al., 1989). The selective engagement of MOR in a cell type-specific

fashion remains an unrealistic task for human chronic pain therapies, with perhaps the exception of intrathecal (spinal) pumps for cancer pain treatment. Our current therapies mostly rely on chronic systemic (primarily oral) administration of MOR agonists, which can lead to aberrant plastic events and produce opioid-induced-hyperalgesia (OIH); a phenomenon that may or may not be a consequence of opioid-induced physical withdrawal (Hayhurst & Durieux, 2016). This particular issue represents a trigger for the development of misuse behavior and relapse to opioid use to relieve the symptoms of OIH, as well as the negative affective states associated with pain and opioid withdrawal.

Opioids, at least in part, exert reinforcing properties by inhibiting GABA release onto dopamine neurons in the ventral tegmental area (VTA) thus leading to increased release of dopamine in various brain regions (Devine, Leone, Pocock, & Wise, 1993; Giuliano, Robbins, Wille, Bullmore, & Everitt, 2013; Le Merrer, Becker, Befort and Kieffer, 2009; Xiao & Ye, 2008). In the VTA, MORs are expressed on GABAergic interneurons and GABAergic terminals arising from the rostromedial tegmental nucleus, and activation of these MORs leads to inhibition of GABA release, thereby removing their tonic inhibition, and increasing dopaminergic transmission from the VTA to efferent structures, including the nucleus accumbens (NAc) (Johnson & North, 1992; Matsui, Jarvie, Robinson, Hentges, & Williams, 2014; Siuda et al., 2015). Interestingly, dopamine is necessary for opioid reward only when animals are opioid-dependent (Hnasko, Sotak, & Palmiter, 2005; Laviolette, Gallegos, Henriksen, & van der Kooy, 2004). Thus, the initial learning of opioid reward as expressed as a conditioned place preference does not require dopamine. However, dopamine is critical for the reinforcing effects of opioids in operant paradigms and changes in dopaminergic neuronal activity represent a basis for the misuse and abuse potential of MOR agonists (Corre et al., 2018; Fields & Margolis, 2015; Wise, 2006). The engagement of mesolimbic dopamine is required for motivational learning and important in assigning salience and valence to the stimuli. Interestingly, local activation of MOR in the NAc core and shell can also increase dopamine release, suggesting both regulation of dopamine terminals by local striatal circuits in this target structure (Hipólito et al., 2015), and a feedback mechanism for MOR signaling onto D1 receptor-expressing medium spiny neurons in the NAc that project back to the VTA (Cui et al., 2014). Stimulation of MORs in the NAc is associated with reinforcement behaviors in rodents (Castro & Berridge, 2014). More specifically, MOR engagement in NAc shell substructures can drive either

rewarding (hot spot) or aversive effects (cold spot) suggesting that there is further complexity in exactly how these receptors can regulate striatal function (Castro & Berridge, 2014). Overall, MOR engagement in the VTA and "hotspot" sub-regions of the NAc shell drive opioid reinforcement.

In contrast to the analgesic and rewarding properties of acute activation of the MOR system (Matsui et al., 2014; Siuda, Carr, Rominger, & Violin, 2017; Wade & Fairbanks, 2014; Wise & Koob, 2014), stimulation of the KOR system leads to dysphoria, anhedonia, and aversive behaviors (Al-Hasani et al., 2015; Bruchas, Land, & Chavkin, 2010; Land et al., 2008, 2009; Leitl, Onvani, et al., 2014; Muschamp & Carlezon, 2013; Shippenberg, Stein, Huber, Millan, & Herz, 1988). Because of these opposing actions, the MOR and the KOR are often referred as opponent systems. However, stimulation of the KOR system by its endogenous opioid ligand dynorphin (Chavkin, James, & Goldstein, 1982) can efficiently relieve itch and injury-induced hyperalgesia (Cowan, Kehner, & Inan, 2015; Ho, Mannes, Dubner, & Caudle, 1997; Kivell & Prisinzano, 2010; Schäfer, Brack, & Stein, 2000; Snyder et al., 2018; Vanderah, 2010). Indeed, KOR agonists applied peripherally reduce nociception in several persistent pain models such as formalin and inflammatory pain models (Antonijevic, Mousa, Schafer, & Stein, 1995; Auh & Ro, 2012; Binder et al., 2001; Cunha et al., 2012; Keïta, Kayser, & Guilbaud, 1995; Obara et al., 2009; Stein, Millan, Shippenberg, Peter, & Herz, 1989). In conditions of chronic pain, a subset of dorsal horn interneurons was shown to increase dynorphin expression (Boyle et al., 2017; Lai, Luo, Chen, & Porreca, 2008; Podvin, Yaksh, & Hook, 2016; Xu et al., 2004), suggesting endogenous adaptations within the KOR system. Peripherally restricted KOR agonists have also demonstrated efficacy in persistent pain and incision models (a more acute pain model) as well as the acetic writhing and itch models (Barber et al., 1994; Binder & Walker, 1998; Caram-Salas et al., 2007; Inan & Cowan, 2004; Snyder et al., 2018; Vanderah et al., 2008, 2004). In addition, recruitment of KORs in several discrete brain structures, such as the dorsal raphe nucleus (DRN) can produce antinociception (Land et al., 2009). While activation of KOR system may potentially represent a promising approach for the treatment of pain, several potential limitations must be considered. Indeed, as mentioned above, enhanced KOR signaling produces aversion, impairs stress coping mechanisms, reduces the reinforcing properties of stimuli and promotes drug reinstatement (Bruchas & Chavkin, 2010; Crowley et al., 2016; Lalanne, Ayranci, Kieffer, & Lutz, 2014; Land et al., 2008; Leitl, Onvani, et al., 2014; Massaly et al., 2019; McCall et al., 2017;

Shippenberg et al., 1988; Shippenberg, Zapata, & Chefer, 2007; Tejeda et al., 2017; Van't Veer & Carlezon, 2013). In addition, KOR signaling is necessary for the development of heroin escalation (Schlosburg et al., 2013) suggesting that engagement of this system may promote misuse and abuse of opioids. Thus, KOR agonists possess limited potential as analgesics due to their negative centrally mediated effects and their potential to increase drug misuse and abuse (Chavkin & Koob, 2016; Schlosburg et al., 2013).

Several recent studies demonstrated that the central KOR system is actively recruited by pain to drive negative affective states and that the use of KOR antagonists may represent a potential avenue for the treatment of pain-induced negative affective states (Liu et al., 2019; Massaly et al., 2019; Narita et al., 2005; Nation et al., 2018; Navratilova et al., 2019; Page et al., 2019; Phelps, Navratilova, Dickenson, Porreca, & Bannister, 2019). Within the NAc, a structure important for the integration of hedonic value of both rewarding and aversive stimuli, the KOR system plays an important role in mediating reward-seeking behaviors (Al-Hasani et al., 2015; Castro & Berridge, 2014; Massaly et al., 2019). In addition, evidence has demonstrated that both inflammatory and chronic pain can recruit KOR signaling in the NAc to drive negative affective states and decrease the reinforcing properties of opioids (Liu et al., 2019; Massaly et al., 2019; Narita et al., 2005). We propose that KOR antagonists may represent a functional substrate to alleviate pain-induced negative states and improve patient well-being. In this way, the development of novel selective, potent and non-addictive KOR antagonists to dampen the negative affect associated with pain could (1) reduce the likelihood of co-morbid psychiatric disorders and (2) avoid the drug misuse potential associated with most opioid analgesics (Hogarth, 2020). Along these lines, buprenorphine is usually administered to treat both pain conditions and OUDs. Buprenorphine is a partial MOR agonist but possesses antagonistic properties at the KOR and DOR. However, despite being considered a safer analgesic than morphine and fentanyl (due to its ability to dampen KOR-induced negative affective states), buprenorphine still retains misuse potential (Jones et al., 2015). Thus, the development of selective KOR antagonists may represent a safer strategy for the development of pain treatments. KOR antagonists such as norBNI and JDTic possess a delayed onset of action that ranges from hours to days, but even minimally effective doses produce antagonist action that can last several weeks. Therefore, the development of KOR antagonists with a shorter "medication-like" duration of action is currently undergoing. While a few short-acting KOR antagonists have been developed

(Guerrero et al., 2019; Page et al., 2019), a thorough characterization of these ligands for pain treatment and OUD, as well as their efficacy in a clinical setting still needs to be determined.

The DOR system represents another potential opioid target for the management of pain states. DORs are highly expressed in forebrain regions (Mansour et al., 1988) and while DOR activation exhibits low analgesic properties in acute pain models, activation of the DOR system provides substantial analgesia in chronic pain conditions (Cahill, Holdridge, & Morinville, 2007; Pradhan, Befort, Nozaki, Gavériaux-Ruff, & Kieffer, 2011). Peripheral application of DOR agonists promotes analgesia in animal models of inflammatory pain (Gendron et al., 2006; Gendron, Mittal, Beaudry, & Walwyn, 2015; Pradhan et al., 2009; Zhang & Bao, 2012) and neuropathic pain (Zhang & Bao, 2012). Unlike opioid-based MOR analgesics, DOR agonists possess fewer side effects (Bodnar, 2020; Gavériaux-Ruff & Kieffer, 2011; Gendron et al., 2015) and most importantly, exhibit no abuse potential (Negus, Gatch, Mello, Zhang, & Rice, 1998). In chronic pain states (i.e., neuropathic pain models or migraine), DOR stimulation demonstrates high analgesic potential (Cahill, Morinville, Hoffert, O'Donnell, & Beaudet, 2003; Fraser, Pradhan, Clarke, & Wahlestedt, 2000; Gavériaux-Ruff, Karchewski, Hever, Matifas, & Kieffer, 2008; Gendron et al., 2006; Hurley & Hammond, 2000; Nadal, Baños, Kieffer, & Maldonado, 2006; Pradhan et al., 2009). Further supporting the role of DORs as analgesics, genetic ablation of these receptors enhances injury-induced hyperalgesia and allodynia (Gavériaux-Ruff et al., 2008; Nadal et al., 2006). Moreover, chronic use of DOR agonists does not induce physical dependence or withdrawal upon treatment cessation (Brandt, Furness, Rice, Fischer, & Negus, 2001). The anxiolytic properties of DOR activation also make it a promising target (similar to KOR antagonism) for improving mood of chronic pain patients. It is well known that negative mood states are not only predictors of opioid misuse, but it also impacts the pain experience, such that co-morbid anxiety or depression exaggerates pain intensity and negatively impacts quality of life (Jamison & Edwards, 2013; Martel, Dolman, Edwards, Jamison, & Wasan, 2014). In addition, DOR agonists have great potential as a therapeutic treatment for chronic migraine (Pradhan, Smith, Zyuzin, & Charles, 2014). However, DOR agonists have been associated with convulsions, which has terminated many clinical development studies (Broom et al., 2002a, 2002b; Chung et al., 2015, Comer et al., 1993; Danielsson et al., 2006; Dykstra, Schoenbaum, Yarbrough, McNutt, & Chang, 1993;

Jutkiewicz, Baladi, Folk, Rice, & Woods, 2006). These negative consequences are an important factor to consider for their use as analgesics in vivo and in clinical settings, although there is evidence that non-internalizing ligands do not share this convulsive side effect (Vicente-Sanchez et al., 2018).

As mentioned above, DOR activation has little or no effect on nociception in pain-naïve and acute phasic pain, as compared to MOR activation (Gallantine & Meert, 2005). Yet, there is still interest in a combination of peripherally restricted agonists for both MOR and DOR as a potential pain relief strategy (Bruce et al., 2019; Günther et al., 2018). In addition to its analgesic properties, DOR signaling alters the development of tolerance to the analgesic effects of MOR agonists. For example, tolerance to the analgesic properties of MOR agonists is abolished in DOR knockout animals or when combined with the use of DOR antagonists (Abdelhamid, Sultana, Portoghese, & Takemori, 1991; Beaudry, Gendron, & Morón, 2015; Váradi et al., 2016; Zhu et al., 1999). Furthermore, DOR antagonists decrease the reinforcing properties of MOR agonist-based analgesics (Abdelhamid et al., 1991; Billa, Xia, & Morón, 2010; Morón et al., 2010; Váradi et al., 2016). Despite this promise, an argument has been made that since DOR is required for hippocampal-dependent learning, ablation or antagonism of DOR could impair associative learning that contributes to the analgesic tolerance of morphine (Cahill & Ong, 2018).

3. Pain-induced alterations in opioid consumption

Pain and pleasure have opposite hedonic value, and thus can both guide our motivational decisions and learning to either avoid or seek emotional experiences. From a behavioral standpoint, reinforcing stimuli such as pleasant odors, music, palatable food and sexual behavior can decrease pain sensitivity and negative affect (Leknes & Tracey, 2008). While pain generates aversive states that disrupt homeostatic balance, pain relief produces negative reinforcement (King et al., 2009; Navratilova & Porreca, 2014). Interestingly, clinical reports suggest that opioids produce significant reinforcement by the relief of pain-induced negative affect; for example, patients with chronic pain have reported reduction in their experience of affective aversive states following morphine use while the nociceptive pain sensation was still present (Price, Von der Gruen, Miller, Rafii, & Price, 1985). This provides further evidence that negative affect is an important part of the pain experience and plays a major role in patients' quality of life.

The persistence of pain-induced negative affective states can trigger allostatic changes in limbic and emotion-related brain structures (Baliki & Apkarian, 2015; Leknes & Tracey, 2008) which over time can lead to the development of anxiety and/or major depression (Elman et al., 2013; Yalcin & Barrot, 2014). Additionally, pain itself can impair reward processing and the patient's ability to enjoy daily activities, characteristic of an anhedonic state (Elman et al., 2013; Leknes & Tracey, 2008).

Preclinical evidence demonstrates that both acute and chronic pain indeed impact reward-induced positive reinforcement (Cahill et al., 2013; Elvemo, Landrø, Borchgrevink, & Håberg, 2015; Hipólito et al., 2015; Leitl, Onvani, et al., 2014; Leknes & Tracey, 2008; Martin & Ewan, 2008; Navratilova & Porreca, 2014; Porreca & Navratilova, 2017; Taylor et al., 2016). Given the fact that opioid-based analgesics possess positive reinforcing properties that can lead to OUD, it is critical to understand the role of pain on the abuse potential of these medications.

Clinical studies have reported that a subset of patients with chronic pain develop misuse and overuse patterns of opioid consumption (Passik, Messina, Golsorkhi, & Xie, 2011). Thus, several preclinical behavioral paradigms have been developed to assess the impact of pain on the reinforcing properties of opioids and the neuronal mechanisms underlying pain-induced negative affect. Many models of pain and voluntary consumption of opioid in animal models have been used to uncover those mechanisms. Unfortunately, the plethora of models led to discrepancy and conflicting results on the consequences of pain on opioid consumption. One of the first reports on the interaction between pain and opioid consumption investigated the reinforcing properties of fentanyl in rats experiencing inflammatory pain (induced by *Mycobacterium butyricum* injection in the tail base) and reported that ongoing inflammatory pain increases voluntary drinking of fentanyl when compared to control animals (Colpaert, Meert, De Witte, & Schmitt, 1982; Colpaert et al., 2001). These results have been replicated in rats by the same group (Colpaert et al., 2001) and others (Kupers & Gybels, 1995). However, using a similar voluntary drinking operant task in, another group reported that inflammatory, chemotherapy-induced and neuropathic pain reduced motivation to seek and consume fentanyl in mice (Wade et al., 2013). It should be noted that in the latter study conducted in mice, the overall locomotor activity of pain animals tended to be lower than controls, which may confound interpretation of the results. To this end, a separate experiment in the same study showed that pain does not impact reinforcing properties of natural rewards as compared to opioids

(Wade et al., 2013). Since then, additional reports have demonstrated that pain can impact the hedonic value of opioids, without changing food seeking and consumption behaviors (Hipólito et al., 2015; Taylor et al., 2015).

To further assess the potential rewarding properties of opioids under pain conditions other approaches such as conditioned place preference (CPP) and intravenous drug self-administration (IVSA) have been used. Conditioned place preference consists of repeated pairing of a specific context with drug, such that the animal associates the interoceptive cues of the drug with the contextual cues. Using this model in adult rats, inflammatory pain has been shown to lower the number of morphine-context conditioning sessions necessary to elicit a preference for the drug context (Zhang et al., 2014), as well as leftward shift in the dose response curve for morphine-induced CPP for male rats in a model of neuropathic pain (Cahill et al., 2013) and inflammatory pain (Sufka, 1994). However, many other reports demonstrate that the rewarding properties of morphine are decreased in both adult rats and mice experiencing inflammatory, neuropathic and, cancer pain (Betourne et al., 2008; Narita et al., 2005; Niikura et al., 2008; Ozaki, Narita, Iino, Miyoshi, & Suzuki, 2003; Ozaki et al., 2002; Taylor et al., 2015). While CPP is a widely used model to assess rewarding properties of stimuli, it has some limitations, especially when studying opioids in pain conditions as central opioid actions in the brain or spinal cord that are important in mediating anti-hyperalgesia and analgesia (i.e., negative reinforcement). As mentioned above, the analgesic properties of opioids may be sufficient to trigger preference for the drug-paired context, thus introducing a confound between the negative reinforcement of pain relief and the rewarding properties of the drug itself. Furthermore, CPP is dependent on non-voluntary drug exposure and thus, despite its translational value, possesses a limited face validity when compared to patients voluntarily consuming opioids to relieve the nociceptive and negative emotional aspects of pain. In this regard, the operant intracranial self-stimulation (ICSS) model can be used to integrate voluntary seeking of reinforcing stimulations during pain conditions (Moerke & Negus, 2019). ICSS is an operant paradigm in which animals press a lever triggering a contingent electrical stimulation. This approach can be used to test abuse liability of drugs where electrical stimuli are delivered in the medial forebrain bundle of the lateral hypothalamus or the VTA, driving excitatory inputs to the mesolimbic dopaminergic neurons in the VTA and thus promoting DA release in nucleus accumbens (Negus & Moerke, 2019).

Acute oxycodone or morphine administration increases the frequency of responding for ICSS, whereas natural or naloxone precipitated opioid withdrawal suppressed ICSS responding (Altarifi & Negus, 2011; Wiebelhaus, Walentiny, & Beardsley, 2016). Acute pain induced by intraperitoneal administration of dilute acid did not alter medial forebrain bundle ICSS frequency (Miller, Altarifi, & Negus, 2015), nor altered medial forebrain bundle ICSS in male or female rats affected by chemotherapy-induced (paclitaxel) neuropathic pain (Legakis & Negus, 2018). However, treatment of the neuropathic pain induced by the chemotherapeutic drug showed that as morphine tolerance developed to the anti-allodynic effects, reward increased as evidenced by changes in ICSS frequency (Legakis & Negus, 2018). Although, morphine and cocaine produced similar effects on ICSS responding in the medial forebrain bundle, but paraventricular nucleus of the hypothalamus ICSS was facilitated to a greater extent by morphine than cocaine, and the effects of either drug were unaltered in neuropathic pain rats induced by spinal nerve ligation (Ewan & Martin, 2012). Interestingly, VTA ICSS was not altered by the presence of neuropathic pain in rats, but oxycodone, methadone, fentanyl and hydromorphine facilitation of VTA ICSS in controls rats was absent in neuropathic pain rats (Ewan & Martin, 2011). Although, post-surgical pain induced by paw incision initially decreased VTA ICSS for the first 2 days after injury (Ewan & Martin, 2014). Taken together, a significant number of studies agree that the occurrence of chronic pain does not alter ICSS stimulation frequency, independent of the brain region of stimulation, however, it does alter the responses to opioids.

Intravenous self-administration represents the gold standard model to assess the reinforcing properties and abuse potential of drugs. This approach allows assessment of drug-seeking and drug intake in an operant paradigm. Self-titer, rate of drug intake and escalation of drug intake can be measured during single sessions or across days and weeks (Tsibulsky & Norman, 2005), allowing studies of opioid analgesic intake during the development and maintenance of pain states. One study demonstrated that morphine consumption is not altered during the first 10 days of IVSA after pain induction ($1\,mg\,kg^{-1}$ per injection). Interestingly, after a period of withdrawal (assessed up to 13 days after termination of morphine access), animals experiencing neuropathic pain demonstrated significantly higher rates of morphine-seeking and morphine consumption than control animals, when the amount of morphine obtained per injection was lowered to $0.2\,mg\,kg^{-1}$ (Hou, Cai, & Pan, 2015). In contrast and using the same IVSA approach, another

group demonstrated that morphine self-administration was lower in animals experiencing inflammatory pain (Lyness, Smith, Heavner, Iacono, & Garvin, 1989). While these results again seem contradictory, it is important to note that the in the study by Hou and collaborators, animals were trained to self-administer morphine before the induction of pain, while the study by Lyness and collaborators tested the acquisition of morphine self-administration after pain induction. Importantly, it has been shown that heroin, morphine, methadone, fentanyl, and hydromorphone consumption (using the IVSA procedure) is lower in rats with neuropathic pain induced by sciatic nerve ligation (SNL) compared to sham animals (Martin, Kim, Buechler, Porreca, & Eisenach, 2007). In this study, full pharmacological characterization of the impact of pain on the reinforcing properties of opioids showed that while IVSA of low doses of each opioid (heroin, morphine, methadone, fentanyl, and hydromorphone) compound was lower in pain conditions, the reinforcing properties of higher doses were unaltered—with pain animals consuming a total amount of opioid per self-administration session similar to that achieved by control animals (Martin et al., 2007). This result is similar to another recent report showing that induction of inflammatory pain following initial heroin self-administration, decreased the number of low-dose heroin reinforcers consumed per self-administration session. Interestingly, in this study by Hipólito and collaborators, IVSA of heroin was significantly increased when rats were exposed to very high doses of the opioid (Hipólito et al., 2015). Together, these studies demonstrate that during inflammatory and chronic pain states, the opioid dose-response relationship for its reinforcing properties is shifted to the right (such as animals in pain doubled the intake of a very high dose of heroin, whereas control animals didn't alter the intake of the same dose. Conversely, animals in pain significantly decreased the intake of the lower dose of heroin). While this can lead to lower drug consumption for low-titer opioid analgesics in the short run (acute and short opioid exposure to treat perioperative pain, for example), it highlights an increased risk for the development of OUD in patients that develop tolerance and are exposed to higher concentrations of opioid analgesics.

4. Circuits underlying pain-induced negative affect and OUD

There is an increased risk for the development of OUD in patients with long-term persistent pain and opioid access, which is likely related

to plastic changes occurring within the central nervous system that drive the emergence of negative affective states (Garland et al., 2013; Martin & Ewan, 2008; Massaly et al., 2016). Clinical and preclinical studies have pinpointed several brain structures involved in the affective dimension of pain: for example, the ACC is highly involved in processing the affective and emotional components of pain (Becerra, Navratilova, Porreca, & Borsook, 2013; Vogt, 2005). Functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET) studies have revealed that the endogenous MOR system is engaged in the ACC during persistent pain and affective pain relief states (Borras et al., 2004; Zubieta et al., 2005). Early studies have uncovered that pain unpleasantness rating in patients is tightly correlated with the activity of the ACC (Rainville, Duncan, Price, Carrier, & Bushnell, 1997). Additionally, preclinical studies confirmed that MOR signaling within the ACC is necessary to alleviate ongoing pain in rodents (Navratilova et al., 2015). In line with these results, microinfusions of MOR agonists locally in the ACC reduce pain-induced negative affect without altering the expression of mechanical allodynia (LaGraize, Borzan, Peng, & Fuchs, 2006). Altogether, these findings point toward a major role for the ACC in the integration and maintenance of negative affective states induced by pain.

The mesolimbic pathway is a key brain circuit involved in the development of opioid addiction and, because of its alterations during chronic and persistent pain states, it represents an ideal candidate for mechanistic studies on pain and opioid misuse co-morbidities (Cui et al., 2014; Fields & Margolis, 2015). The mesolimbic dopamine pathway is composed of dopaminergic projections from the VTA projecting to the striatum, including the NAc (Morales & Margolis, 2017). The dopaminergic projections to the NAc are involved in reward and aversion processing (Becerra & Borsook, 2008) and also mediates pain-induced negative affect. However, it should be noted that dopaminergic neurons co-release other neurotransmitters such as glutamate and GABA, also involved in integration of reward and aversion. In addition, non-dopaminergic neurons originating from the VTA are also involved in these processes (see Morales & Margolis, 2017 for extensive review). It is well established that neuroplastic changes in mesolimbic circuitry, including molecular and cellular changes within the mesolimbic dopamine system, lead to the genesis of negative affect (Koob & Le Moal, 2001; Koob & Volkow, 2010, 2016; Wise & Koob, 2014). Both natural rewards and drugs of abuse, including opioids, activate this pathway and trigger accumbal dopamine release (Devine et al., 1993;

Giuliano et al., 2013; Hipólito et al., 2015; Taylor et al., 2015). Interestingly, those drug-induced dopaminergic responses are blunted in detoxified abusers (Volkow & Morales, 2015; Volkow et al., 1997). Patients experiencing chronic pain show reduced NAc activity and alterations in reward evaluation, decision making, and motivation tasks (Apkarian et al., 2004; Verdejo-García, López-Torrecillas, Calandre, Delgado-Rodríguez, & Bechara, 2009; Walteros et al., 2011). Furthermore, the resolution of pain is negatively associated with NAc activity in chronic pain patients (Baliki, Geha., Fields, & Apkarian, 2010), suggesting a dysregulation of dopaminergic function during persistent pain states. As noted above, positive stimuli and opioids cause release of dopamine in the NAc via inhibition of GABA release onto VTA dopamine neurons. Thus, the observed decrease in MOR function in GABAergic projections onto the VTA during pain impairs opioid-induced disinhibition of dopaminergic neurons, which in turn decreases opioid reinforcing properties (Hipólito et al., 2015; Niikura, Narita, Butelman, Kreek, & Suzuki, 2010; Ozaki et al., 2002). Similarly, a positive correlation has been observed between alterations in opioid reinforcing properties during pain states and dopaminergic transmission within the NAc (Hipólito et al., 2015; Narita et al., 2005; Niikura et al., 2008; Ozaki et al., 2002; Taylor et al., 2015). Furthermore, pain relief produces MOR-dependent dopamine release within the NAc, further corroborating the interactions between opioid systems and dopamine-dependent reinforcement processes (Navratilova et al., 2012). In addition to MOR, KORs can also locally alter dopamine release within the NAc (Muschamp & Carlezon, 2013; Nestler & Carlezon, 2006; Van't Veer & Carlezon, 2013). Recent work demonstrated that neuropathic pain recruits KOR signaling in the NAc to reduce dopaminergic activity and induce negative affective states (Liu et al., 2019). Another laboratory demonstrated that not only KOR recruitment but also dynorphin-containing neurons in the NAc were sufficient and necessary to drive pain-induced depression of motivational states (Massaly et al., 2019). These observations support the notion that dynorphin acting on KORs in the NAc is responsible for blunting morphine-induced dopamine release and for the development of morphine CPP under inflammatory pain conditions (Narita et al., 2005). Altogether, these studies demonstrate that KOR signaling represents a potential target to prevent negative affective states induced by pain which could ultimately reduce or mitigate the emergence of OUDs (Cahill et al., 2014; Chavkin & Koob, 2016; Liu et al., 2019; Massaly et al., 2019, 2016). It must also be noted that despite its high potential to treat these

different disorders, former studies have demonstrated that subcutaneous injection of the KOR antagonist, norBNI, does not reverse pain-induced decrease in lever presses during ICSS procedure (Leitl, Potter, et al., 2014; Leitl, Onvani, et al., 2014). This lack of effect may be explained by the simultaneous analgesic and aversive properties of systemically administered KOR agonists that readily cross the blood-brain barrier. Indeed, if KOR antagonists relieve negative affective centrally, their peripheral action may blunt KOR-mediated endogenous analgesia and thus mask negative affect relief, that should be reflected in altered ICSS responding. In addition, KOR stimulation in discrete substructures of the NAc drive opposite hedonic effects (Castro & Berridge, 2014). Overall, we posit that targeted inhibition of KOR signaling in pain states represents a promising strategy to dampen negative affective states and reduce the development of OUD in patients using opioid-based analgesics (Cahill et al., 2014; Chavkin, 2011; Liu et al., 2019; Massaly et al., 2019, 2016).

In addition to the mesolimbic pathway, the amygdala is another brain area that undergoes neuroplastic changes during persistent pain states and in turn drives alterations in reinforcing and rewarding properties of opioids (Carrasquillo & Gereau, 2007; Crock et al., 2012; Janak & Tye, 2015; Narita et al., 2006). Both the central nucleus of the amygdala and the basolateral amygdala (BLA) are key players in the integration of affect, mood, fear disorders as well as reinforcement (Pare & Duvarci, 2012; Veinante, Yalcin, & Barrot, 2013). Recent studies have elegantly uncovered neuronal ensembles in the amygdala that are necessary for the expression of the emotional component of noxious stimuli (Corder et al., 2019). This study holds promising potential for future treatment of negative affective states that accompany ongoing pain and thus decrease both the development of co-morbid psychiatric disorders and opioid drug misuse potential. This is especially interesting as projections from the BLA to the NAc modulate dopamine-mediated neuronal responses to both stress and opioid reward salience (Lintas et al., 2011, 2012; Namburi et al., 2015; Stuber et al., 2011). Blocking MOR in the lateral amygdala using MOR antagonist beta-funaltrexamine reverses pain-induced reductions in heroin intake in rats with neuropathic pain (Martin et al., 2011). Further, inhibition of amygdala GABAergic neurons with MOR agonists reduces foot-shock aversive conditioning reactions and disinhibits the descending brainstem pain modulation pathway (Han, Soleiman, Soden, Zweifel, & Palmiter, 2015; Namburi et al., 2015; Winters et al., 2017). These studies further implicate the amygdala as an important regulation center for pain and negative affect. Other work has

shown that inflammatory pain promotes KOR signaling in the amygdala to drive negative affective states (Nation et al., 2018; Navratilova et al., 2019). Hence, manipulating MOR and KOR signaling in the amygdala holds promising therapeutic potential for the treatment of pain-induced negative affect and anhedonia.

5. Development of safer analgesics approaches for chronic pain

The pain research community aims to develop the Holy Grail of analgesics—a drug with significant analgesic properties that is devoid of abuse potential. Current pain treatments with opioid medications are mostly limited by their abuse potential and the respiratory depression events that may arise from misuse or overdose. There are several ongoing drug development projects funded by the NIH Heal Initiative to develop new pharmaceutical compounds devoid of those deleterious side effects. Several research groups have been focusing on the development of MOR and KOR biased agonists. This strategy leverages the fact that signal transduction from opioid GPCRs through either G-protein or beta-arrestin may lead to distinct behavioral outcomes. For example, mice lacking beta-arrestin protein do eexhibit an analgesic response to opioid treatment but not respiratory depression, tolerance and opioid reinforcement (Bohn et al., 1999). This finding prompted the design of MOR agonists biased toward G-protein signaling to produce efficient analgesics devoid of side effects (Gupta et al., 2016; Kingwell, 2015; Manglik et al., 2016; White et al., 2014). While these biased MOR compounds represent a promising approach for the improvement of pain treatment, recent evidence using beta-arrestin knockout mice demonstrate that both morphine and fentanyl still retain respiratory depressant potential (Kliewer et al., 2020). This underscores the necessity for more in-depth examination on the characterization of these biased compounds, their mechanism of action and their full set of effects.

Another exciting strategy for pain treatment points toward the use of opioid receptor heterodimers as drug targets to reach maximal analgesic efficiency. High-throughput screening approaches have identified many compounds that are being tested for their analgesic properties as well as their safety profile, mostly as agonists of the MOR/DOR heterodimers (Bruce et al., 2019; Fujita, Gomes, & Devi, 2014, 2015). The development of selective milieu MOR agonist has also been investigated: for example, as mentioned above, a fentanyl derivate with decreased pKA allows selective

activity on MOR in a low pH milieu (Rodriguez-Gaztelumendi et al., 2018; Spahn et al., 2017). The authors took advantage of the acidic nature of the inflammatory milieu and demonstrate that NFEPP has higher efficiency at low pH and selectively reverses hyperalgesia and allodynia without inducing commonly observed opioid side effects (Rosas, Huang, Roth, & Dockendorff, 2019; Spahn et al., 2017). Lastly, the development of KOR antagonists to decrease negative affective states induced by persistent pain represents a potential promising avenue (Cahill et al., 2014; Chavkin, 2011; Liu et al., 2019; Massaly et al., 2019; Navratilova et al., 2019). Improving the treatment of prolonged negative affective states may decrease the incidence or severity of psychiatric co-morbidities associated with pain, and may also reduce opioid abuse potential.

In addition to opioid pharmacology, chronic pain treatment still employs a combination of nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, anticonvulsants, local anesthetics, alpha-2 adrenoreceptors agonists, NMDA antagonists and more recently, in certain states, cannabinoids (Derry, Derry, & Moore, 2013; Eilers, Philip, Bickler, McKay, & Schumacher, 2001; Graff-Radford, Shaw, & Naliboff, 2000; Loftus et al., 2010; Lunn, Hughes, & Wiffen, 2014; Moore, Derry, Aldington, Cole, & Wiffen, 2015; Pirbudak, Sevinç, Maralcan, & Kiliç, 2014; Smith, Deshpande, Collins, Katz, & Losina, 2016; Wang et al., 2015; Whiting et al., 2015; Wiffen et al., 2017). All these pharmacological agents are routinely used to try and dampen the nociceptive and emotional component of acute and chronic pain without the use of opioid-based analgesics. Some treatments such as ketamine and cannabinoids have been shown to also decrease opioid intake during perioperative care (Boehnke, Litinas, & Clauw, 2016; Cengiz et al., 2014; Cichewicz, 2004; Zakine et al., 2008). However, despite their "safer" profiles and analgesic properties, cannabinoids and NMDA antagonists (Ketamine) still retain misuse potential and need to be closely monitored by health care providers even if their life-threatening potential remains lower than opioid-based analgesics.

6. Conclusions

The widespread use of opioid-based analgesics has been a major factor in the emergence of the opioid epidemic. While the diversion of these pills for recreational use by pain-free individuals may have contributed in this process, one-fifth of chronic pain patients treated with opioid-based medications develop OUD. Even more than the sensory component of chronic

pain conditions, the persistence of negative affective states associated with chronic pain represents an important trigger for abuse potential in patients treated with increasing doses of opioids over the long-term. Thus, the development of non-addictive pharmacological analgesics and non-pharmacological approaches is critical for the treatment of the emotional component of pain. Decreasing the occurrence and persistence of negative affect associated with chronic pain conditions would indeed dampen both the development of co-morbid neuropsychiatric diseases and the abuse potential of opioid-based analgesics. In parallel, the development of pain treatments devoid of abuse potential will be necessary to reduce pain analgesics diversion and reduce the proportion of chronic pain patients with a high risk of abuse that are exposed to opioid medications. Overall, these efforts are necessary for optimizing and developing novel safe and effective strategies for treating chronic pain.

References

Abdelhamid, E. E., Sultana, M., Portoghese, P. S., & Takemori, A. E. (1991). Selective blockage of delta opioid receptor prevents the development of morphine tolerance and dependence in mice. *The Journal of Pharmacology and Experimental Therapeutics*, *258*, 299–303.

Al-Hasani, R., McCall, J. G., Shin, G., Gomez, A. M., Schmitz, G. P., Bernardi, J. M., et al. (2015). Distinct subpopulations of nucleus accumbens dynorphin neurons drive aversion and reward. *Neuron*, *87*, 1063–1077.

Altarifi, A. A., & Negus, S. S. (2011). Some determinants of morphine effects on intracranial self-stimulation in rats: Dose, pretreatment time, repeated treatment, and rate dependence. *Behavioural Pharmacology*, *22*, 663–673.

Antonijevic, I., Mousa, S., Schafer, M., & Stein, C. (1995). Perineurial defect and peripheral opioid analgesia in inflammation. *The Journal of Neuroscience*, *15*, 165–172.

Apkarian, A. V., Baliki, M. N., & Farmer, M. A. (2013). Predicting transition to chronic pain. *Current Opinion in Neurology*, *26*, 360–367.

Apkarian, A. V., Sosa, Y., Krauss, B. R., Thomas, P. S., Fredrickson, B. E., Levy, R. E., et al. (2004). Chronic pain patients are impaired on an emotional decision making task. *Pain*, ***108***, 129–136.

Arvidsson, U., Dado, R., Riedl, M., Lee, J., Law, P., Loh, H., et al. (1995). Delta-opioid receptor immunoreactivity: Distribution in brainstem and spinal cord, and relationship to biogenic amines and enkephalin. *The Journal of Neuroscience*, *15*, 1215–1235.

Arvidsson, U., Riedl, M., Chakrabarti, S., Lee, J., Nakano, A., Dado, R., et al. (1995). Distribution and targeting of a mu-opioid receptor (MOR1) in brain and spinal cord. *The Journal of Neuroscience*, *15*, 3328–3341.

Auh, Q.-S., & Ro, J. Y. (2012). Effects of peripheral κ opioid receptor activation on inflammatory mechanical hyperalgesia in male and female rats. *Neuroscience Letters*, *524*, 111–115.

Baliki, M. N., & Apkarian, A. V. (2015). Nociception, pain, negative moods, and behavior selection. *Neuron*, *87*, 474–491.

Baliki, M. N., Geha, P. Y., Fields, H. L., & Apkarian, A. V. (2010). Predicting value of pain and analgesia: Nucleus accumbens response to noxious stimuli changes in the presence of chronic pain. *Neuron*, ***66***, 149–160.

Barber, A., Bartoszyk, G. D., Bender, H. M., Gottschlich, R., Greiner, H. E., Harting, J., et al. (1994). A pharmacological profile of the novel, peripherally-selective kappa-opioid receptor agonist, EMD 61753. *British Journal of Pharmacology*, *113*, 1317–1327.

Basbaum, A. I., Bautista, D. M., Scherrer, G., & Julius, D. (2009). Cellular and molecular mechanisms of pain. *Cell*, *139*, 267–284.

Basbaum, A. I., & Fields, H. L. (1984). Endogenous pain control systems: Brainstem spinal pathways and endorphin circuitry. *Annual Review of Neuroscience*, 7, 309–338.

Beaudry, H., Gendron, L., & Morón, J. A. (2015). Implication of delta opioid receptor subtype 2 but not delta opioid receptor subtype 1 in the development of morphine analgesic tolerance in a rat model of chronic inflammatory pain. *The European Journal of Neuroscience*, *41*, 901–907.

Becerra, L., & Borsook, D. (2008). Signal valence in the nucleus accumbens to pain onset and offset. *European Journal of Pain*, *12*, 866–869.

Becerra, L., Navratilova, E., Porreca, F., & Borsook, D. (2013). Analogous responses in the nucleus accumbens and cingulate cortex to pain onset (aversion) and offset (relief) in rats and humans. *Journal of Neurophysiology*, *110*, 1221–1226.

Besson, J. M. (1999). The neurobiology of pain. *Lancet*, *353*, 1610–1615.

Betourne, A., Familiades, J., Lacassagne, L., Halley, H., Cazales, M., Ducommun, B., et al. (2008). Decreased motivational properties of morphine in mouse models of cancerous- or inflammatory-chronic pain: Implication of supraspinal neuropeptide FF2 receptors. *Neuroscience*, *157*, 12–21.

Billa, S. K., Xia, Y., & Morón, J. A. (2010). Disruption of morphine conditioned place preference by delta-2-opioid receptor antagonist: Study of mu- and delta-opioid receptor expression at the synapse. *The European Journal of Neuroscience*, *32*, 625–631.

Binder, W., Machelska, H., Mousa, S., Schmitt, T., Rivière, P. J., Junien, J. L., et al. (2001). Analgesic and antiinflammatory effects of two novel kappa-opioid peptides. *Anesthesiology*, *94*, 1034–1044.

Binder, W., & Walker, J. S. (1998). Effect of the peripherally selective κ-opioid agonist, asimadoline, on adjuvant arthritis. *British Journal of Pharmacology*, *124*, 647–654.

Bobeck, E. N., McNeal, A. L., & Morgan, M. M. (2009). Drug dependent sex differences in periaqueducatal gray mediated antinociception in the rat. *Pain*, *147*, 210.

Bodnar, R. J. (2020). Endogenous opiates and behavior: 2017. *Peptides*, *124*, 170223.

Boehnke, K. F., Litinas, E., & Clauw, D. J. (2016). Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. *The Journal of Pain*, *17*, 739–744.

Bohn, L. M., Lefkowitz, R. J., Gainetdinov, R. R., Peppel, K., Caron, M. G., & Lin, F. T. (1999). Enhanced morphine analgesia in mice lacking beta-arrestin 2. *Science*, *286*, 2495–2498.

Borras, M. C., Becerra, L., Ploghaus, A., Gostic, J. M., DaSilva, A., Gonzalez, R. G., et al. (2004). fMRI measurement of CNS responses to naloxone infusion and subsequent mild noxious thermal stimuli in healthy volunteers. *Journal of Neurophysiology*, *91*, 2723–2733.

Boyle, K. A., Gutierrez-Mecinas, M., Polgár, E., Mooney, N., O'Connor, E., Furuta, T., et al. (2017). A quantitative study of neurochemically defined populations of inhibitory interneurons in the superficial dorsal horn of the mouse spinal cord. *Neuroscience*, *363*, 120–133.

Brandt, M. R., Furness, M. S., Rice, K. C., Fischer, B. D., & Negus, S. S. (2001). Studies of tolerance and dependence with the delta-opioid agonist SNC80 in rhesus monkeys responding under a schedule of food presentation. *Journal of Pharmacology and Experimental Therapeutics*, ***299***, 629–637.

Broom, D. C., Jutkiewicz, E. M., Folk, J. E., Traynor, J. R., Rice, K. C., & Woods, J. H. (2002a). Nonpeptidic delta-opioid receptor agonists reduce immobility in the forced swim assay in rats. *Neuropsychopharmacology*, ***26***, 744–755.

Broom, D. C., Nitsche, J. F., Pintar, J. E., Rice, K. C., Woods, J. H., & Traynor, J. R. (2002b). Comparison of receptor mechanisms and efficacy requirements for delta-agonist-induced convulsive activity and antinociception in mice. *Journal of Pharmacology and Experimental Therapeutics*, ***303***, 723–729.

Bruce, D. J., Peterson, C. D., Kitto, K. F., Akgün, E., Lazzaroni, S., Portoghese, P. S., et al. (2019). Combination of a δ-opioid receptor agonist and loperamide produces peripherally-mediated analgesic synergy in mice. *Anesthesiology*, *131*, 649–663.

Bruchas, M. R., & Chavkin, C. (2010). Kinase cascades and ligand-directed signaling at the kappa opioid receptor. *Psychopharmacology*, *210*, 137–147.

Bruchas, M. R., Land, B. B., & Chavkin, C. (2010). The dynorphin/kappa opioid system as a modulator of stress-induced and pro-addictive behaviors. *Brain Research*, *1314*, 44–55.

Buntin-Mushock, C., Phillip, L., Moriyama, K., & Palmer, P. P. (2005). Age-dependent opioid escalation in chronic pain patients. *Anesthesia and Analgesia*, *100*, 1740–1745.

Cahill, C. M., Holdridge, S. V., & Morinville, A. (2007). Trafficking of delta-opioid receptors and other G-protein-coupled receptors: Implications for pain and analgesia. *Trends in Pharmacological Sciences*, *28*, 23–31.

Cahill, C. M., Morinville, A., Hoffert, C., O'Donnell, D., & Beaudet, A. (2003). Up-regulation and trafficking of delta opioid receptor in a model of chronic inflammation: Implications for pain control. *Pain*, *101*, 199–208.

Cahill, C. M., & Ong, E. (2018). Evidence and function relevance of native DOR-MOR heteromers. *Handbook of Experimental Pharmacology*, *247*, 115–127.

Cahill, C. M., Taylor, A. M. W., Cook, C., Ong, E., Morón, J. A., & Evans, C. J. (2014). Does the kappa opioid receptor system contribute to pain aversion? *Frontiers in Pharmacology*, *5*, 253.

Cahill, C. M., Xue, L., Grenier, P., Magnussen, C., Lecour, S., & Olmstead, M. C. (2013). Changes in morphine reward in a model of neuropathic pain. *Behavioural Pharmacology*, *24*, 207–213.

Caram-Salas, N. L., Reyes-García, G., Bartoszyk, G. D., Araiza-Saldaña, C. I., Ambriz-Tututi, M., Rocha-González, H. I., et al. (2007). Subcutaneous, intrathecal and periaqueductal grey administration of asimadoline and ICI-204448 reduces tactile allodynia in the rat. *European Journal of Pharmacology*, *573*, 75–83.

Carrasquillo, Y., & Gereau, R. W. (2007). Activation of the extracellular signal-regulated kinase in the amygdala modulates pain perception. *The Journal of Neuroscience*, *27*, 1543–1551.

Castro, D. C., & Berridge, K. C. (2014). Opioid hedonic hotspot in nucleus accumbens shell: Mu, delta, and kappa maps for enhancement of sweetness "liking" and "wanting". *The Journal of Neuroscience*, *34*, 4239–4250.

Cengiz, P., Gokcinar, D., Karabeyoglu, I., Topcu, H., Cicek, G. S., & Gogus, N. (2014). Intraoperative low-dose ketamine infusion reduces acute postoperative pain following total knee replacement surgery: A prospective, randomized double-blind placebo-controlled trial. *Journal of the College of Physicians and Surgeons–Pakistan*, *24*, 299–303.

Chavkin, C. (2011). The therapeutic potential of κ-opioids for treatment of pain and addiction. *Neuropsychopharmacology*, *36*, 369–370.

Chavkin, C., James, I. F., & Goldstein, A. (1982). Dynorphin is a specific endogenous ligand of the kappa opioid receptor. *Science*, *215*, 413–415.

Chavkin, C., & Koob, G. F. (2016). Dynorphin, dysphoria, and dependence: The stress of addiction. *Neuropsychopharmacology*, *41*, 373–374.

Chung, C., Carteret, A. F., McKelvy, A. D., Ringkamp, M., Yang, F., Hartke, T. V., et al. (2012). Analgesic properties of loperamide differ following systemic and local administration to rats after spinal nerve injury. *European Journal of Pain*, *16*, 1021–1032.

Chung, P. C. S., Keyworth, H. L., Martin-Garcia, E., Charbogne, P., Darcq, E., Bailey, A., et al. (2015). A novel anxiogenic role for the delta opioid receptor expressed in GABAergic forebrain neurons. *Biological Psychiatry*, **77**, 404–415.

Cichewicz, D. L. (2004). Synergistic interactions between cannabinoid and opioid analgesics. *Life Sciences*, *74*, 1317–1324.

Cochran, G., Bacci, J. L., Ylioja, T., Hruschak, V., Miller, S., Seybert, A. L., et al. (2016). Prescription opioid use: Patient characteristics and misuse in community pharmacy. *Journal of the American Pharmaceutical Association*, *56*, 248–256.e6.

Coghill, R. C., McHaffie, J. G., & Yen, Y.-F. (2003). Neural correlates of interindividual differences in the subjective experience of pain. *Proceedings of the National Academy of Sciences of the United States of America*, *100*, 8538–8542.

Colpaert, F. C., Meert, T., De Witte, P., & Schmitt, P. (1982). Further evidence validating adjuvant arthritis as an experimental model of chronic pain in the rat. *Life Sciences*, *31*, 67–75.

Colpaert, F. C., Tarayre, J. P., Alliaga, M., Bruins Slot, L. A., Attal, N., & Koek, W. (2001). Opiate self-administration as a measure of chronic nociceptive pain in arthritic rats. *Pain*, *91*, 33–45.

Comer, S. D., Hoenicke, E. M., Sable, A. I., McNutt, R. W., Chang, K. J., De Costa, B. R., et al. (1993). Convulsive effects of systemic administration of the delta opioid agonist BW373U86 in mice. *Journal of Pharmacology and Experimental Therapeutics*, ***267***, 888–895.

Corder, G., Ahanonu, B., Grewe, B. F., Wang, D., Schnitzer, M. J., & Scherrer, G. (2019). An amygdalar neural ensemble that encodes the unpleasantness of pain. *Science*, *363*, 276–281.

Corder, G., Tawfik, V. L., Wang, D., Sypek, E. I., Low, S. A., Dickinson, J. R., et al. (2017). Loss of μ opioid receptor signaling in nociceptors, but not microglia, abrogates morphine tolerance without disrupting analgesia. *Nature Medicine*, *23*, 164–173.

Corre, J., van Zessen, R., Loureiro, M., Patriarchi, T., Tian, L., Pascoli, V., et al. (2018). Dopamine neurons projecting to medial shell of the nucleus accumbens drive heroin reinforcement. *eLife*, *7*, e39945.

Cowan, A., Kehner, G. B., & Inan, S. (2015). Targeting itch with ligands selective for κ opioid receptors. *Handbook of Experimental Pharmacology*, *226*, 291–314.

Crock, L. W., Kolber, B. J., Morgan, C. D., Sadler, K. E., Vogt, S. K., Bruchas, M. R., et al. (2012). Central amygdala metabotropic glutamate receptor 5 in the modulation of visceral pain. *The Journal of Neuroscience*, *32*, 14217–14226.

Crowley, N. A., Bloodgood, D. W., Hardaway, J. A., Kendra, A. M., McCall, J. G., Al-Hasani, R., et al. (2016). Dynorphin controls the gain of an amygdalar anxiety circuit. *Cell Reports*, *14*, 2774–2783.

Cui, Y., Ostlund, S. B., James, A. S., Park, C. S., Ge, W., Roberts, K. W., et al. (2014). Targeted expression of μ-opioid receptors in a subset of striatal direct-pathway neurons restores opiate reward. *Nature Neuroscience*, *17*, 254–261.

Cunha, T. M., Souza, G. R., Domingues, A. C., Carreira, E. U., Lotufo, C. M., Funez, M. I., et al. (2012). Stimulation of peripheral kappa opioid receptors inhibits inflammatory hyperalgesia via activation of the PI3Kγ/AKT/nNOS/NO signaling pathway. *Molecular Pain*, *8*, 10.

Dahan, A., van Velzen, M., & Niesters, M. (2014). Comorbidities and the complexities of chronic pain. *Anesthesiology*, *121*, 675–677.

Danielsson, I., Gasior, M., Stevenson, G. W., Folk, J. E., Rice, K. C., & Negus, S. S. (2006). Electroencephalographic and convulsant effects of the delta opioid agonist SNC80 in rhesus monkeys. *Pharmacology Biochemistry and Behavior*, ***85***, 428–434.

DeHaven-Hudkins, D. L., Cowan, A., Cortes Burgos, L., Daubert, J. D., Cassel, J. A., DeHaven, R. N., et al. (2002). Antipruritic and antihyperalgesic actions of loperamide and analogs. *Life Sciences*, *71*, 2787–2796.

DeHaven-Hudkins, D. L., & Dolle, R. E. (2004). Peripherally restricted opioid agonists as novel analgesic agents. *Current Pharmaceutical Design*, *10*, 743–757.
Denk, F., McMahon, S. B., & Tracey, I. (2014). Pain vulnerability: A neurobiological perspective. *Nature Neuroscience*, *17*, 192–200.
Derry, C. J., Derry, S., & Moore, R. A. (2013). Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain. *The Cochrane Database of Systematic Reviews*, *2013*, CD010210.
Devine, D. P., Leone, P., Pocock, D., & Wise, R. A. (1993). Differential involvement of ventral tegmental mu, delta and kappa opioid receptors in modulation of basal mesolimbic dopamine release: In vivo microdialysis studies. *The Journal of Pharmacology and Experimental Therapeutics*, *266*, 1236–1246.
Dowell, D., Haegerich, T. M., & Chou, R. (2016). CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA*, *315*, 1624–1645.
Dykstra, L. A., Schoenbaum, G. M., Yarbrough, J., McNutt, R., & Chang, K. J. (1993). A novel delta opioid agonist, BW373U86, in squirrel monkeys responding under a schedule of shock titration. *Journal of Pharmacology and Experimental Therapeutics*, ***267***, 875–882.
Eilers, H., Philip, L. A., Bickler, P. E., McKay, W. R., & Schumacher, M. A. (2001). The reversal of fentanyl-induced tolerance by administration of "small-dose" ketamine. *Anesthesia and Analgesia*, *93*, 213–214.
Elman, I., Borsook, D., & Volkow, N. D. (2013). Pain and suicidality: Insights from reward and addiction neuroscience. *Progress in Neurobiology*, *109*, 1–27.
Elvemo, N. A., Landrø, N. I., Borchgrevink, P. C., & Håberg, A. K. (2015). Reward responsiveness in patients with chronic pain. *European Journal of Pain*, *19*, 1537–1543.
Ewan, E. E., & Martin, T. J. (2011). Rewarding electrical brain stimulation in rats after peripheral nerve injury: Decreased facilitation by commonly abused prescription opioids. *Anesthesiology*, *115*, 1271–1280.
Ewan, E. E., & Martin, T. J. (2012). Intracranial self-stimulation of the paraventricular nucleus of the hypothalamus: Increased faciliation by morphine compared to cocaine. *Anesthesiology*, *116*, 1116–1123.
Ewan, E. E., & Martin, T. J. (2014). Differential suppression of intracranial self-stimulation, food-maintained operant responding, and open field activity by paw incision and spinal nerve ligation in rats. *Anesthesia and Analgesia*, *118*, 854–862.
Fang, F. G., Haws, C. M., Drasner, K., Williamson, A., & Fields, H. L. (1989). Opioid peptides (DAGO-enkephalin, dynorphin A(1-13), BAM 22P) microinjected into the rat brainstem: Comparison of their antinociceptive effect and their effect on neuronal firing in the rostral ventromedial medulla. *Brain Research*, *501*, 116–128.
Fields, H. L., & Margolis, E. B. (2015). Understanding opioid reward. *Trends in Neurosciences*, *38*, 217–225.
Fraser, G. L., Pradhan, A. A., Clarke, P. B., & Wahlestedt, C. (2000). Supraspinal antinociceptive response to [D-Pen(2,5)]-enkephalin (DPDPE) is pharmacologically distinct from that to other delta-agonists in the rat. *The Journal of Pharmacology and Experimental Therapeutics*, *295*, 1135–1141.
Fujita, W., Gomes, I., & Devi, L. A. (2014). Revolution in GPCR signalling: Opioid receptor heteromers as novel therapeutic targets: IUPHAR review 10. *British Journal of Pharmacology*, *171*, 4155–4176.
Fujita, W., Gomes, I., & Devi, L. A. (2015). Heteromers of μ-δ opioid receptors: New pharmacology and novel therapeutic possibilities. *British Journal of Pharmacology*, *172*, 375–387.
Furlan, A., Chaparro, L. E., Irvin, E., & Mailis-Gagnon, A. (2011). A comparison between enriched and nonenriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain. *Pain Research & Management*, *16*, 337–351.

Gallantine, E. L., & Meert, T. F. (2005). A comparison of the antinociceptive and adverse effects of the mu-opioid agonist morphine and the delta-opioid agonist SNC80. *Basic & Clinical Pharmacology & Toxicology*, ***97***, 39–51.

Garland, E. L. (2012). Pain processing in the human nervous system: A selective review of nociceptive and biobehavioral pathways. *Primary Care*, *39*, 561–571.

Garland, E. L., Froeliger, B., Zeidan, F., Partin, K., & Howard, M. O. (2013). The downward spiral of chronic pain, prescription opioid misuse, and addiction: Cognitive, affective, and neuropsychopharmacologic pathways. *Neuroscience and Biobehavioral Reviews*, *37*, 2597–2607.

Gavériaux-Ruff, C., Karchewski, L. A., Hever, X., Matifas, A., & Kieffer, B. L. (2008). Inflammatory pain is enhanced in delta opioid receptor-knockout mice. *The European Journal of Neuroscience*, *27*, 2558–2567.

Gavériaux-Ruff, C., & Kieffer, B. L. (2011). Delta opioid receptor analgesia: Recent contributions from pharmacology and molecular approaches. *Behavioural Pharmacology*, *22*, 405–414.

Gendron, L., Lucido, A. L., Mennicken, F., O'Donnell, D., Vincent, J.-P., Stroh, T., et al. (2006). Morphine and pain-related stimuli enhance cell surface availability of somatic δ-opioid receptors in rat dorsal root ganglia. *The Journal of Neuroscience*, *26*, 953–962.

Gendron, L., Mittal, N., Beaudry, H., & Walwyn, W. (2015). Recent advances on the δ opioid receptor: From trafficking to function. *British Journal of Pharmacology*, *172*, 403–419.

Giuliano, C., Robbins, T. W., Wille, D. R., Bullmore, E. T., & Everitt, B. J. (2013). Attenuation of cocaine and heroin seeking by μ-opioid receptor antagonism. *Psychopharmacology*, *227*, 137–147.

Graff-Radford, S. B., Shaw, L. R., & Naliboff, B. N. (2000). Amitriptyline and fluphenazine in the treatment of postherpetic neuralgia. *The Clinical Journal of Pain*, *16*, 188–192.

Grim, T. W., Schmid, C. L., Stahl, E. L., Pantouli, F., Ho, J.-H., Acevedo-Canabal, A., et al. (2020). A G protein signaling-biased agonist at the μ-opioid receptor reverses morphine tolerance while preventing morphine withdrawal. *Neuropsychopharmacology*, *45*, 416–425.

Guan, Y., Johanek, L. M., Hartke, T. V., Shim, B., Tao, Y.-X., Ringkamp, M., et al. (2008). Peripherally acting mu-opioid receptor agonist attenuates neuropathic pain in rats after L5 spinal nerve injury. *Pain*, *138*, 318–329.

Guerrero, M., Urbano, M., Kim, E.-K., Gamo, A. M., Riley, S., Abgaryan, L., et al. (2019). Design and synthesis of a novel and selective kappa opioid receptor (KOR) antagonist (BTRX-335140). *Journal of Medicinal Chemistry*, *62*, 1761–1780.

Günther, T., Dasgupta, P., Mann, A., Miess, E., Kliewer, A., Fritzwanker, S., et al. (2018). Targeting multiple opioid receptors—Improved analgesics with reduced side effects? *British Journal of Pharmacology*, *175*, 2857–2868.

Gupta, A., Gomes, I., Bobeck, E. N., Fakira, A. K., Massaro, N. P., Sharma, I., et al. (2016). Collybolide is a novel biased agonist of κ-opioid receptors with potent antipruritic activity. *Proceedings of the National Academy of Sciences of the United States of America*, *113*, 6041–6046.

Han, S., Soleiman, M. T., Soden, M. E., Zweifel, L. S., & Palmiter, R. D. (2015). Elucidating an affective pain circuit that creates a threat memory. *Cell*, *162*, 363–374.

Hayhurst, C. J., & Durieux, M. E. (2016). Differential opioid tolerance and opioid-induced hyperalgesia: A clinical reality. *Anesthesiology*, *124*, 483–488.

Heinricher, M. M., Tavares, I., Leith, J. L., & Lumb, B. M. (2009). Descending control of nociception: Specificity, recruitment and plasticity. *Brain Research Reviews*, *60*, 214–225.

Hipólito, L., Wilson-Poe, A., Campos-Jurado, Y., Zhong, E., Gonzalez-Romero, J., Virag, L., et al. (2015). Inflammatory pain promotes increased opioid self-administration: Role of dysregulated ventral tegmental area μ opioid receptors. *The Journal of Neuroscience*, *35*, 12217–12231.

Hnasko, T. S., Sotak, B. N., & Palmiter, R. D. (2005). Morphine reward in dopamine-deficient mice. *Nature*, *438*, 854–857.
Ho, J., Mannes, A. J., Dubner, R., & Caudle, R. M. (1997). Putative kappa-2 opioid agonists are antihyperalgesic in a rat model of inflammation. *The Journal of Pharmacology and Experimental Therapeutics*, *281*, 136–141.
Hogarth, L. (2020). Addiction is driven by excessive goal-directed drug choice under negative affect: Translational critique of habit and compulsion theory. *Neuropsychopharmacology*, *45*, 720–735.
Hou, Y.-Y., Cai, Y.-Q., & Pan, Z. Z. (2015). Persistent pain maintains morphine-seeking behavior after morphine withdrawal through reduced MeCP2 repression of Glua1 in rat central amygdala. *The Journal of Neuroscience*, *35*, 3689–3700.
Hurley, R. W., & Hammond, D. L. (2000). The analgesic effects of supraspinal μ and δ opioid receptor agonists are potentiated during persistent inflammation. *The Journal of Neuroscience*, *20*, 1249–1259.
Inan, S., & Cowan, A. (2004). Kappa opioid agonists suppress chloroquine-induced scratching in mice. *European Journal of Pharmacology*, *502*, 233–237.
Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education. (2011). *Relieving pain in America: A blueprint for transforming prevention, care, education, and research*. Washington (DC), USA: National Academies Press.
Jacquet, Y. F., & Lajtha, A. (1974). Paradoxical effects after microinjection of morphine in the periaqueductal gray matter in the rat. *Science*, *185*, 1055–1057.
Jamison, R. N., & Edwards, R. R. (2013). Risk factor assessment for problematic use of opioids for chronic pain. *The Clinical Neuropsychologist*, *27*, 60–80.
Janak, P. H., & Tye, K. M. (2015). From circuits to behaviour in the amygdala. *Nature*, *517*, 284–292.
Ji, R.-R., Chamessian, A., & Zhang, Y.-Q. (2016). Pain regulation by non-neuronal cells and inflammation. *Science*, *354*, 572–577.
Johnson, S. W., & North, R. A. (1992). Opioids excite dopamine neurons by hyperpolarization of local interneurons. *The Journal of Neuroscience*, ***12***, 483–488.
Jones, J. D., Sullivan, M. A., Vosburg, S. K., Manubay, J. M., Mogali, S., Metz, V., et al. (2015). Abuse potential of intranasal buprenorphine versus buprenorphine/naloxone in buprenorphine-maintained heroin users. *Addiction Biology*, *20*, 784–798.
Julius, D., & Basbaum, A. I. (2001). Molecular mechanisms of nociception. *Nature*, *413*, 203–210.
Jutkiewicz, E. M., Baladi, M. G., Folk, J. E., Rice, K. C., & Woods, J. H. (2006). The convulsive and electroencephalographic changes produced by nonpeptidic delta-opioid agonists in rats: Comparison with pentylenetetrazol. *Journal of Pharmacology and Experimental Therapeutics*, ***317***, 1337–1348.
Keïta, H., Kayser, V., & Guilbaud, G. (1995). Antinociceptive effect of a kappa-opioid receptor agonist that minimally crosses the blood-brain barrier (ICI 204448) in a rat model of mononeuropathy. *European Journal of Pharmacology*, *277*, 275–280.
King, T., Vera-Portocarrero, L., Gutierrez, T., Vanderah, T. W., Dussor, G., Lai, J., et al. (2009). Unmasking the tonic-aversive state in neuropathic pain. *Nature Neuroscience*, *12*, 1364–1366.
Kingwell, K. (2015). Pioneering biased ligand offers efficacy with reduced on-target toxicity. *Nature Reviews Drug Discovery*, *14*, 809–810.
Kivell, B., & Prisinzano, T. E. (2010). Kappa opioids and the modulation of pain. *Psychopharmacology*, *210*, 109–119.
Kliewer, A., Schmiedel, F., Sianati, S., Bailey, A., Bateman, J. T., Levitt, E. S., et al. (2019). Phosphorylation-deficient G-protein-biased μ-opioid receptors improve analgesia and diminish tolerance but worsen opioid side effects. *Nature Communications*, ***10***, 367.

Kliewer, A., Gillis, A., Hill, R., Schmidel, F., Bailey, C., Kelly, E., et al. (2020). Morphine-induced respiratory depression is independent of β-arrestin2 signalling. *British Journal of Pharmacology*, *177*, 2923–2931.

Koele, R., Volker, G., van Vree, F., van Gestel, M., Köke, A., & Vliet Vlieland, T. (2014). Multidisciplinary rehabilitation for chronic widespread musculoskeletal pain: Results from daily practice. *Musculoskeletal Care*, *12*, 210–220.

Koob, G. F., & Le Moal, M. (2001). Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology*, *24*, 97–129.

Koob, G. F., & Volkow, N. D. (2010). Neurocircuitry of addiction. *Neuropsychopharmacology*, *35*, 217–238.

Koob, G. F., & Volkow, N. D. (2016). Neurobiology of addiction: A neurocircuitry analysis. *Lancet Psychiatry*, *3*, 760–773.

Krashin, D., Murinova, N., & Sullivan, M. (2016). Challenges to treatment of chronic pain and addiction during the "opioid crisis". *Current Pain and Headache Reports*, *20*, 65.

Kupers, R., & Gybels, J. (1995). The consumption of fentanyl is increased in rats with nociceptive but not with neuropathic pain. *Pain*, *60*, 137–141.

LaGraize, S. C., Borzan, J., Peng, Y. B., & Fuchs, P. N. (2006). Selective regulation of pain affect following activation of the opioid anterior cingulate cortex system. *Experimental Neurology*, *197*, 22–30.

Lai, J., Luo, M., Chen, Q., & Porreca, F. (2008). Pronociceptive actions of dynorphin via bradykinin receptors. *Neuroscience Letters*, *437*, 175–179.

Lalanne, L., Ayranci, G., Kieffer, B. L., & Lutz, P.-E. (2014). The kappa opioid receptor: From addiction to depression, and back. *Frontiers in Psychiatry*, *5*, 170.

Land, B. B., Bruchas, M. R., Lemos, J. C., Xu, M., Melief, E. J., & Chavkin, C. (2008). The dysphoric component of stress is encoded by activation of the dynorphin kappa-opioid system. *The Journal of Neuroscience*, *28*, 407–414.

Land, B. B., Bruchas, M. R., Schattauer, S., Giardino, W. J., Aita, M., Messinger, D., et al. (2009). Activation of the kappa opioid receptor in the dorsal raphe nucleus mediates the aversive effects of stress and reinstates drug seeking. *Proceedings of the National Academy of Sciences of the United States of America*, *106*, 19168–19173.

Lane, D. A., Patel, P. A., & Morgan, M. M. (2005). Evidence for an intrinsic mechanism of antinociceptive tolerance within the ventrolateral periaqueductal gray of rats. *Neuroscience*, *135*, 227–234.

Lanser, P., & Gesell, S. (2001). Pain management: The fifth vital sign. *Healthcare Benchmarks*, *8*(68–70), 62.

Laviolette, S. R., Gallegos, R. A., Henriksen, S. J., & van der Kooy, D. (2004). Opiate state controls bi-directional reward signaling via GABAA receptors in the ventral tegmental area. *Nature Neuroscience*, *7*, 160–169.

Le Merrer, J., Becker, J. A. J., Befort, K., & Kieffer, B. L. (2009). Reward processing by the opioid system in the brain. *Physiological Reviews*, ***89***, 1379–1412.

Legakis, L. P., & Negus, S. S. (2018). Repeated morphine produces sensitization to reward and tolerance to anti-allodynia in male and female rats with chemotherapy-induced neuropathy. *The Journal of Pharmacology and Experimental Therapeutics*, *365*, 9–19.

Leitl, M. D., Onvani, S., Bowers, M. S., Cheng, K., Rice, K. C., Carlezon, W. A., et al. (2014). Pain-related depression of the mesolimbic dopamine system in rats: Expression, blockade by analgesics, and role of endogenous κ-opioids. *Neuropsychopharmacology*, *39*, 614–624.

Leitl, M. D., Potter, D. N., Cheng, K., Rice, K. C., Carlezon, W. A., & Negus, S. S. (2014). Sustained pain-related depression of behavior: Effects of intraplantar formalin and complete freund's adjuvant on intracranial self-stimulation (ICSS) and endogenous kappa opioid biomarkers in rats. *Molecular Pain*, *10*, 62.

Leknes, S., & Tracey, I. (2008). A common neurobiology for pain and pleasure. *Nature Reviews. Neuroscience*, *9*, 314–320.

Lintas, A., Chi, N., Lauzon, N. M., Bishop, S. F., Gholizadeh, S., Sun, N., et al. (2011). Identification of a dopamine receptor-mediated opiate reward memory switch in the basolateral amygdala-nucleus accumbens circuit. *The Journal of Neuroscience*, ***31***, 11172–11183.

Lintas, A., Chi, N., Lauzon, N. M., Bishop, S. F., Sun, N., Tan, H., et al. (2012). Inputs from the basolateral amygdala to the nucleus accumbens shell control opiate reward magnitude via differential dopamine D1 or D2 receptor transmission. *European Journal of Neuroscience*, ***35***, 279–290.

Liu, S. S., Pickens, S., Burma, N. E., Ibarra-Lecue, I., Yang, H., Xue, L., et al. (2019). Kappa opioid receptors drive a tonic aversive component of chronic pain. *The Journal of Neuroscience*, *39*, 4162–4178.

Loftus, R. W., Yeager, M. P., Clark, J. A., Brown, J. R., Abdu, W. A., Sengupta, D. K., et al. (2010). Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. *Anesthesiology*, *113*, 639–646.

Lunn, M. P. T., Hughes, R. A. C., & Wiffen, P. J. (2014). Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. *Cochrane Database of Systematic Reviews*, *4*, CD007115.

Lyness, W. H., Smith, F. L., Heavner, J. E., Iacono, C. U., & Garvin, R. D. (1989). Morphine self-administration in the rat during adjuvant-induced arthritis. *Life Sciences*, *45*, 2217–2224.

Manglik, A., Lin, H., Aryal, D. K., McCorvy, J. D., Dengler, D., Corder, G., et al. (2016). Structure-based discovery of opioid analgesics with reduced side effects. *Nature*, *537*, 185–190.

Mansour, A., Khachaturian, H., Lewis, M. E., Akil, H., & Watson, S. J. (1988). Anatomy of CNS opioid receptors. *Trends in Neurosciences*, *11*, 308–314.

Martel, M. O., Dolman, A. J., Edwards, R. R., Jamison, R. N., & Wasan, A. D. (2014). The association between negative affect and prescription opioid misuse in patients with chronic pain: The mediating role of opioid craving. *The Journal of Pain*, *15*, 90–100.

Martin, T. J., Buechler, N. L., Kim, S. A., Ewan, E. E., Xiao, R., & Childers, S. R. (2011). Involvement of the lateral amygdala in the antiallodynic and reinforcing effects of heroin in rats after peripheral nerve injury. *Anesthesiology*, *114*, 633–642.

Martin, T. J., & Ewan, E. (2008). Chronic pain alters drug self-administration: Implications for addiction and pain mechanisms. *Experimental and Clinical Psychopharmacology*, *16*, 357–366.

Martin, T. J., Kim, S. A., Buechler, N. L., Porreca, F., & Eisenach, J. C. (2007). Opioid self-administration in the nerve-injured rat relevance of antiallodynic effects to drug consumption and effects of intrathecal analgesics. *Anesthesiology*, *106*, 312–322.

Massaly, N., Copits, B. A., Wilson-Poe, A. R., Hipólito, L., Markovic, T., Yoon, H. J., et al. (2019). Pain-induced negative affect is mediated via recruitment of the nucleus accumbens kappa opioid system. *Neuron*, *102*, 564–573.e6.

Massaly, N., Morón, J. A., & Al-Hasani, R. (2016). A trigger for opioid misuse: Chronic pain and stress dysregulate the mesolimbic pathway and kappa opioid system. *Frontiers in Neuroscience*, *10*, 480.

Matsui, A., Jarvie, B. C., Robinson, B. G., Hentges, S. T., & Williams, J. T. (2014). Separate GABA afferents to dopamine neurons mediate acute action of opioids, development of tolerance, and expression of withdrawal. *Neuron*, *82*, 1346–1356.

McCall, J. G., Siuda, E. R., Bhatti, D. L., Lawson, L. A., McElligott, Z. A., Stuber, G. D., et al. (2017). Locus coeruleus to basolateral amygdala noradrenergic projections promote anxiety-like behavior. *eLife*, *6*, e18247.

Miller, L. L., Altarifi, A. A., & Negus, S. S. (2015). Effects of repeated morphine on intracranial self-stimulation in male rats in the absence or presence of a noxious pain stimulus. *Experimental and Clinical Psychopharmacology*, *23*, 405–414.
Moerke, M. J., & Negus, S. S. (2019). Interactions between pain states and opioid reward assessed with intracranial self-stimulation in rats. *Neuropharmacology*, *160*, 107689.
Moore, R. A., Derry, S., Aldington, D., Cole, P., & Wiffen, P. J. (2015). Amitriptyline for neuropathic pain in adults. *Cochrane Database of Systematic Reviews*, *7*, CD008242.
Morales, M., & Margolis, E. B. (2017). Ventral tegmental area: Cellular heterogeneity, connectivity and behaviour. *Nature Reviews Neuroscience*, *18*, 73–85.
Morón, J. A., Gullapalli, S., Taylor, C., Gupta, A., Gomes, I., & Devi, L. A. (2010). Modulation of opiate-related signaling molecules in morphine-dependent conditioned behavior: Conditioned place preference to morphine induces CREB phosphorylation. *Neuropsychopharmacology*, *35*, 955–966.
Muschamp, J. W., & Carlezon, W. A. (2013). Roles of nucleus accumbens CREB and dynorphin in dysregulation of motivation. *Cold Spring Harbor Perspectives in Medicine*, *3*, a012005.
Nadal, X., Baños, J.-E., Kieffer, B. L., & Maldonado, R. (2006). Neuropathic pain is enhanced in delta-opioid receptor knockout mice. *The European Journal of Neuroscience*, *23*, 830–834.
Nahin, R. L. (2015). Estimates of pain prevalence and severity in adults: United States, 2012. *The Journal of Pain*, *16*, 769–780.
Namburi, P., Beyeler, A., Yorozu, S., Calhoon, G. G., Halbert, S. A., Wichmann, R., et al. (2015). A circuit mechanism for differentiating positive and negative associations. *Nature*, *520*, 675–678.
Narita, M., Kaneko, C., Miyoshi, K., Nagumo, Y., Kuzumaki, N., Nakajima, M., et al. (2006). Chronic pain induces anxiety with concomitant changes in opioidergic function in the amygdala. *Neuropsychopharmacology*, *31*, 739–750.
Narita, M., Kishimoto, Y., Ise, Y., Yajima, Y., Misawa, K., & Suzuki, T. (2005). Direct evidence for the involvement of the mesolimbic kappa-opioid system in the morphine-induced rewarding effect under an inflammatory pain-like state. *Neuropsychopharmacology*, *30*, 111–118.
Nation, K. M., De Felice, M., Hernandez, P. I., Dodick, D. W., Neugebauer, V., Navratilova, E., et al. (2018). Lateralized kappa opioid receptor signaling from the amygdala central nucleus promotes stress-induced functional pain. *Pain*, *159*, 919–928.
Navratilova, E., Ji, G., Phelps, C., Qu, C., Hein, M., Yakhnitsa, V., et al. (2019). Kappa opioid signaling in the central nucleus of the amygdala promotes disinhibition and aversiveness of chronic neuropathic pain. *Pain*, *160*, 824–832.
Navratilova, E., & Porreca, F. (2014). Reward and motivation in pain and pain relief. *Nature Neuroscience*, *17*, 1304–1312.
Navratilova, E., Xie, J. Y., Meske, D., Qu, C., Morimura, K., Okun, A., et al. (2015). Endogenous opioid activity in the anterior cingulate cortex is required for relief of pain. *The Journal of Neuroscience*, *35*, 7264–7271.
Navratilova, E., Xie, J. Y., Okun, A., Qu, C., Eyde, N., Ci, S., et al. (2012). Pain relief produces negative reinforcement through activation of mesolimbic reward-valuation circuitry. *Proceedings of the National Academy of Sciences of the United States of America*, *109*, 20709–20713.
Negus, S. S., Gatch, M. B., Mello, N. K., Zhang, X., & Rice, K. (1998). Behavioral effects of the delta-selective opioid agonist SNC80 and related compounds in rhesus monkeys. *The Journal of Pharmacology and Experimental Therapeutics*, *286*, 362–375.
Negus, S. S., & Moerke, M. J. (2019). Determinants of opioid abuse potential: Insights using intracranial self-stimulation. *Peptides*, *112*, 23–31.
Nestler, E. J., & Carlezon, W. A. (2006). The mesolimbic dopamine reward circuit in depression. *Biological Psychiatry*, *59*, 1151–1159.

Niikura, K., Narita, M., Butelman, E. R., Kreek, M. J., & Suzuki, T. (2010). Neuropathic and chronic pain stimuli downregulate central mu-opioid and dopaminergic transmission. *Trends in Pharmacological Sciences*, *31*, 299–305.

Niikura, K., Narita, M., Narita, M., Nakamura, A., Okutsu, D., Ozeki, A., et al. (2008). Direct evidence for the involvement of endogenous β-endorphin in the suppression of the morphine-induced rewarding effect under a neuropathic pain-like state. *Neuroscience Letters*, *435*, 257–262.

Obara, I., Parkitna, J. R., Korostynski, M., Makuch, W., Kaminska, D., Przewlocka, B., et al. (2009). Local peripheral opioid effects and expression of opioid genes in the spinal cord and dorsal root ganglia in neuropathic and inflammatory pain. *Pain*, *141*, 283–291.

Ozaki, S., Narita, M., Iino, M., Miyoshi, K., & Suzuki, T. (2003). Suppression of the morphine-induced rewarding effect and G-protein activation in the lower midbrain following nerve injury in the mouse: Involvement of G-protein-coupled receptor kinase 2. *Neuroscience*, *116*, 89–97.

Ozaki, S., Narita, M., Narita, M., Iino, M., Sugita, J., Matsumura, Y., et al. (2002). Suppression of the morphine-induced rewarding effect in the rat with neuropathic pain: Implication of the reduction in μ-opioid receptor functions in the ventral tegmental area. *Journal of Neurochemistry*, *82*, 1192–1198.

Page, S., Mavrikaki, M. M., Lintz, T., Puttick, D., Roberts, E., Rosen, H., et al. (2019). Behavioral pharmacology of novel kappa opioid receptor antagonists in rats. *The International Journal of Neuropsychopharmacology*, *22*, 735–745.

Pare, D., & Duvarci, S. (2012). Amygdala microcircuits mediating fear expression and extinction. *Current Opinion in Neurobiology*, *22*, 717–723.

Passik, S. D., Messina, J., Golsorkhi, A., & Xie, F. (2011). Aberrant drug-related behavior observed during clinical studies involving patients taking chronic opioid therapy for persistent pain and fentanyl buccal tablet for breakthrough pain. *Journal of Pain and Symptom Management*, *41*, 116–125.

Phelps, C. E., Navratilova, E., Dickenson, A. H., Porreca, F., & Bannister, K. (2019). Kappa opioid signaling in the right central amygdala causes hind paw specific loss of diffuse noxious inhibitory controls in experimental neuropathic pain. *Pain*, *160*, 1614–1621.

Pirbudak, L., Sevinç, A., Maralcan, G., & Kiliç, E. (2014). Pain management with intrathecal clonidine in a colon cancer patient with opioid hyperalgesia: Case presentation. *Ağrı*, *26*, 93–96.

Podvin, S., Yaksh, T., & Hook, V. (2016). Emerging role of spinal dynorphin in chronic pain, a therapeutic perspective. *Annual Review of Pharmacology and Toxicology*, *56*, 511–533.

Porreca, F., & Navratilova, E. (2017). Reward, motivation and emotion of pain and its relief. *Pain*, *158*, S43–S49.

Pradhan, A. A. A., Becker, J. A. J., Scherrer, G., Tryoen-Toth, P., Filliol, D., Matifas, A., et al. (2009). In vivo delta opioid receptor internalization controls behavioral effects of agonists. *PLoS One*, *4,5*. https://doi.org/10.1371/journal.pone.0005425. e5425.

Pradhan, A. A., Befort, K., Nozaki, C., Gavériaux-Ruff, C., & Kieffer, B. L. (2011). The delta opioid receptor: An evolving target for the treatment of brain disorders. *Trends in Pharmacological Sciences*, *32*, 581–590.

Pradhan, A. A., Smith, M. L., Zyuzin, J., & Charles, A. (2014). δ-Opioid receptor agonists inhibit migraine-related hyperalgesia, aversive state and cortical spreading depression in mice. *British Journal of Pharmacology*, *171*, 2375–2384.

Price, T. J., Basbaum, A. I., Bresnahan, J., Chambers, J. F., De Koninck, Y., Edwards, R. R., et al. (2018). Transition to chronic pain: Opportunities for novel therapeutics. *Nature Reviews. Neuroscience*, *19*, 383–384.

Price, D. D., Von der Gruen, A., Miller, J., Rafii, A., & Price, C. (1985). A psychophysical analysis of morphine analgesia. *Pain*, *22*, 261–269.

Raehal, K. M., Walker, J. K. L., & Bohn, L. M. (2005). Morphine side effects in beta-arrestin 2 knockout mice. *The Journal of Pharmacology and Experimental Therapeutics*, *314*, 1195–1201.

Rainville, P., Duncan, G. H., Price, D. D., Carrier, B., & Bushnell, M. C. (1997). Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science*, *277*, 968–971.

Rodriguez-Gaztelumendi, A., Spahn, V., Labuz, D., Machelska, H., & Stein, C. (2018). Analgesic effects of a novel pH-dependent μ-opioid receptor agonist in models of neuropathic and abdominal pain. *Pain*, *159*, 2277–2284.

Rosas, R., Huang, X.-P., Roth, B. L., & Dockendorff, C. (2019). β-Fluorofentanyls are pH-sensitive Mu opioid receptor agonists. *ACS Medicinal Chemistry Letters*, *10*, 1353–1356.

Rusin, K. I., Giovannucci, D. R., Stuenkel, E. L., & Moises, H. C. (1997). Kappa-opioid receptor activation modulates Ca2+ currents and secretion in isolated neuroendocrine nerve terminals. *The Journal of Neuroscience*, *17*, 6565–6574.

Schäfer, M., Brack, A., & Stein, C. (2000). Dynorphin a peptides. *Molecular Diagnosis & Therapy*, *13*, 161–166.

Schlosburg, J. E., Whitfield, T. W., Park, P. E., Crawford, E. F., George, O., Vendruscolo, L. F., et al. (2013). Long-term antagonism of κ opioid receptors prevents escalation of and increased motivation for heroin intake. *The Journal of Neuroscience*, *33*, 19384–19392.

Schmid, C. L., Kennedy, N. M., Ross, N. C., Lovell, K. M., Yue, Z., Morgenweck, J., et al. (2017). Bias factor and therapeutic window correlate to predict safer opioid analgesics. *Cell*, *171*, 1165–1175.e13.

Shippenberg, T. S., Stein, C., Huber, A., Millan, M. J., & Herz, A. (1988). Motivational effects of opioids in an animal model of prolonged inflammatory pain: Alteration in the effects of kappa- but not of mu-receptor agonists. *Pain*, *35*, 179–186.

Shippenberg, T. S., Zapata, A., & Chefer, V. I. (2007). Dynorphin and the pathophysiology of drug addiction. *Pharmacology & Therapeutics*, *116*, 306–321.

Siuda, E. R., Copits, B. A., Schmidt, M. J., Baird, M. A., Al-Hasani, R., Planer, W. J., et al. (2015). Spatiotemporal control of opioid signaling and behavior. *Neuron*, ***86***, 923–935.

Siuda, E. R., Carr, R., Rominger, D. H., & Violin, J. D. (2017). Biased mu-opioid receptor ligands: A promising new generation of pain therapeutics. *Current Opinion in Pharmacology*, *32*, 77–84.

Smith, S. R., Deshpande, B. R., Collins, J. E., Katz, J. N., & Losina, E. (2016). Comparative pain reduction of oral non-steroidal anti-inflammatory drugs and opioids for knee osteoarthritis: Systematic analytic review. *Osteoarthritis and Cartilage*, *24*, 962–972.

Snyder, L. M., Chiang, M. C., Loeza-Alcocer, E., Omori, Y., Hachisuka, J., Sheahan, T. D., et al. (2018). Kappa opioid receptor distribution and function in primary afferents. *Neuron*, *99*, 1274–1288.e6.

Spahn, V., Del Vecchio, G., Labuz, D., Rodriguez-Gaztelumendi, A., Massaly, N., Temp, J., et al. (2017). A nontoxic pain killer designed by modeling of pathological receptor conformations. *Science*, *355*, 966–969.

Stein, C., Millan, M. J., Shippenberg, T. S., Peter, K., & Herz, A. (1989). Peripheral opioid receptors mediating antinociception in inflammation. Evidence for involvement of mu, delta and kappa receptors. *The Journal of Pharmacology and Experimental Therapeutics*, *248*, 1269–1275.

Stuber, G. D., Sparta, D. R., Stamatakis, A. M., van Leeuwen, W. A., Hardjoprajitno, J. E., Cho, S., et al. (2011). Excitatory transmission from the amygdala to nucleus accumbens facilitates reward seeking. *Nature*, ***475***, 377–380.

Sufka, K. J. (1994). Conditioned place preference paradigm: A novel approach for analgesic drug assessment against chronic pain. *Pain*, *58*, 355–366.

Taylor, A. M. W., Becker, S., Schweinhardt, P., & Cahill, C. (2016). Mesolimbic dopamine signaling in acute and chronic pain: Implications for motivation, analgesia, and addiction. *Pain*, *157*, 1194–1198.

Taylor, A. M. W., Castonguay, A., Taylor, A. J., Murphy, N. P., Ghogha, A., Cook, C., et al. (2015). Microglia disrupt mesolimbic reward circuitry in chronic pain. *The Journal of Neuroscience*, *35*, 8442–8450.

Tejeda, H. A., Wu, J., Kornspun, A. R., Pignatelli, M., Kashtelyan, V., Krashes, M. J., et al. (2017). Pathway- and cell-specific kappa-opioid receptor modulation of excitation-inhibition balance differentially gates D1 and D2 accumbens neuron activity. *Neuron*, *93*, 147–163.

Tiwari, V., Yang, F., He, S.-Q., Shechter, R., Zhang, C., Shu, B., et al. (2016). Activation of peripheral μ-opioid receptors by dermorphin [D-Arg2, Lys4] (1-4) amide leads to modality-preferred inhibition of neuropathic pain. *Anesthesiology*, *124*, 706–720.

Tracey, I. (2010). Getting the pain you expect: Mechanisms of placebo, nocebo and reappraisal effects in humans. *Nature Medicine*, *16*, 1277–1283.

Tracey, I., & Mantyh, P. W. (2007). The cerebral signature for pain perception and its zmodulation. *Neuron*, *55*, 377–391.

Tsibulsky, V. L., & Norman, A. B. (2005). Real time computation of in vivo drug levels during drug self-administration experiments. *Brain Research. Brain Research Protocols*, *15*, 38–45.

Vadivelu, N., Mitra, S., & Hines, R. L. (2011). Peripheral opioid receptor agonists for analgesia: A comprehensive review. *Journal of Opioid Management*, 7, 55–68.

Vanderah, T. W. (2010). Delta and kappa opioid receptors as suitable drug targets for pain. *The Clinical Journal of Pain*, *26*(Suppl. 10), S10–S15.

Vanderah, T. W., Largent-Milnes, T., Lai, J., Porreca, F., Houghten, R. A., Menzaghi, F., et al. (2008). Novel D-amino acid tetrapeptides produce potent antinociception by selectively acting at peripheral kappa-opioid receptors. *European Journal of Pharmacology*, *583*, 62–72.

Vanderah, T. W., Schteingart, C. D., Trojnar, J., Junien, J.-L., Lai, J., & Riviere, P. J.-M. (2004). FE200041 (D-Phe-D-Phe-D-Nle-D-Arg-NH2): A peripheral efficacious kappa opioid agonist with unprecedented selectivity. *The Journal of Pharmacology and Experimental Therapeutics*, *310*, 326–333.

Van't Veer, A., & Carlezon, W. A. (2013). Role of kappa-opioid receptors in stress and anxiety-related behavior. *Psychopharmacology*, *229*, 435–452.

Váradi, A., Marrone, G. F., Palmer, T. C., Narayan, A., Szabó, M. R., Le Rouzic, V., et al. (2016). Mitragynine/corynantheidine pseudoindoxyls as opioid analgesics with Mu agonism and delta antagonism, which do not recruit β-arrestin-2. *Journal of Medicinal Chemistry*, *59*, 8381–8397.

Veinante, P., Yalcin, I., & Barrot, M. (2013). The amygdala between sensation and affect: A role in pain. *Journal of Molecular Psychiatry*, *1*, 9. https://doi.org/10.1186/2049-9256-1-9.

Verdejo-García, A., López-Torrecillas, F., Calandre, E. P., Delgado-Rodríguez, A., & Bechara, A. (2009). Executive function and decision-making in women with fibromyalgia. *Archives of Clinical Neuropsychology*, ***24***, 113–122.

Vicente-Sanchez, A., Dripps, I. J., Tipton, A. F., Akbari, H., Akbari, A., Jutkiewicz, E. M., et al. (2018). Tolerance to high-internalizing δ opioid receptor agonist is critically mediated by arrestin 2. *British Journal of Pharmacology*, *175*, 3050–3059.

Vogt, B. A. (2005). Pain and emotion interactions in subregions of the cingulate gyrus. *Nature Reviews. Neuroscience*, *6*, 533–544.

Volkow, N. D., & McLellan, A. T. (2016). Opioid abuse in chronic pain—Misconceptions and mitigation strategies. *The New England Journal of Medicine*, *374*, 1253–1263.

Volkow, N. D., & Morales, M. (2015). The brain on drugs: From reward to addiction. *Cell*, *162*, 712–725.
Volkow, N. D., Wang, G.-J., Fowler, J. S., Logan, J., Gatley, S. J., Hitzemann, R., et al. (1997). Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subjects. *Nature*, *386*, 830–833.
Von Korff, M., Kolodny, A., Deyo, R. A., & Chou, R. (2011). Long-term opioid therapy reconsidered. *Annals of Internal Medicine*, *155*, 325–328.
Vowles, K. E., McEntee, M. L., Julnes, P. S., Frohe, T., Ney, J. P., & van der Goes, D. N. (2015). Rates of opioid misuse, abuse, and addiction in chronic pain: A systematic review and data synthesis. *Pain*, *156*, 569–576.
Wade, C. L., & Fairbanks, C. A. (2014). The self-administration of analgesic drugs in experimentally induced chronic pain. *Current Topics in Behavioral Neurosciences*, *20*, 217–232.
Wade, C. L., Krumenacher, P., Kitto, K. F., Peterson, C. D., Wilcox, G. L., & Fairbanks, C. A. (2013). Effect of chronic pain on fentanyl self-administration in mice. *PLoS One*, *8*, e79239.
Walteros, C., Sánchez-Navarro, J. P., Muñoz, M. A., Martínez-Selva, J. M., Chialvo, D., & Montoya, P. (2011). Altered associative learning and emotional decision making in fibromyalgia. *The Journal of Psychosomatic Research*, ***70***, 294–301.
Wang, Z. Y., Shi, S. Y., Li, S. J., Chen, F., Chen, H., Lin, H. Z., et al. (2015). Efficacy and safety of duloxetine on osteoarthritis knee pain: A meta-analysis of randomized controlled trials. *Pain Medicine*, *16*, 1373–1385.
White, K. L., Scopton, A. P., Rives, M.-L., Bikbulatov, R. V., Polepally, P. R., Brown, P. J., et al. (2014). Identification of novel functionally selective κ-opioid receptor scaffolds. *Molecular Pharmacology*, *85*, 83–90.
Whiting, P. F., Wolff, R. F., Deshpande, S., Di Nisio, M., Duffy, S., Hernandez, A. V., et al. (2015). Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA*, *313*, 2456–2473.
Wiebelhaus, J. M., Walentiny, D. M., & Beardsley, P. M. (2016). Effects of acute and repeated administration of oxycodone and naloxone-precipitated withdrawal on intracranial self-stimulation in rats. *The Journal of Pharmacology and Experimental Therapeutics*, *356*, 43–52.
Wiffen, P. J., Derry, S., Bell, R. F., Rice, A. S., Tölle, T. R., Phillips, T., et al. (2017). Gabapentin for chronic neuropathic pain in adults. *Cochrane Database of Systematic Reviews*, *6*, CD007938.
Williams, J. T., Christie, M. J., & Manzoni, O. (2001). Cellular and synaptic adaptations mediating opioid dependence. *Physiological Reviews*, *81*, 299–343.
Winters, B. L., Gregoriou, G. C., Kissiwaa, S. A., Wells, O. A., Medagoda, D. I., Hermes, S. M., et al. (2017). Endogenous opioids regulate moment-to-moment neuronal communication and excitability. *Nature Communications*, *8*, 14611.
Wise, R. A. (2006). Role of brain dopamine in food reward and reinforcement. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *361*, 1149–1158.
Wise, R. A., & Koob, G. F. (2014). The development and maintenance of drug addiction. *Neuropsychopharmacology*, *39*, 254–262.
Xiao, C., & Ye, J.-H. (2008). Ethanol dually modulates GABAergic synaptic transmission onto dopaminergic neurons in ventral tegmental area: Role of mu-opioid receptors. *Neuroscience*, ***153***, 240–248.
Xu, M., Petraschka, M., McLaughlin, J. P., Westenbroek, R. E., Caron, M. G., Lefkowitz, R. J., et al. (2004). Neuropathic pain activates the endogenous κ opioid system in mouse spinal cord and induces opioid receptor tolerance. *The Journal of Neuroscience*, *24*, 4576–4584.
Yalcin, I., & Barrot, M. (2014). The anxiodepressive comorbidity in chronic pain. *Current Opinion in Anaesthesiology*, *27*, 520–527.

Zakine, J., Samarcq, D., Lorne, E., Moubarak, M., Montravers, P., Beloucif, S., et al. (2008). Postoperative ketamine administration decreases morphine consumption in major abdominal surgery: A prospective, randomized, double-blind, controlled study. *Anesthesia and Analgesia*, *106*, 1856–1861.

Zhang, X., & Bao, L. (2012). Interaction and regulatory functions of μ- and δ-opioid receptors in nociceptive afferent neurons. *Neuroscience Bulletin*, *28*, 121–130.

Zhang, Z., Tao, W., Hou, Y.-Y., Wang, W., Lu, Y.-G., & Pan, Z. Z. (2014). Persistent pain facilitates response to morphine reward by downregulation of central amygdala GABAergic function. *Neuropsychopharmacology*, *39*, 2263–2271.

Zhu, Y., Hsu, M.-S., & Pintar, J. E. (1998). Developmental expression of the μ, κ, and δ opioid receptor mRNAs in mouse. *The Journal of Neuroscience*, *18*, 2538–2549.

Zhu, Y., King, M. A., Schuller, A. G. P., Nitsche, J. F., Reidl, M., Elde, R. P., et al. (1999). Retention of supraspinal delta-like analgesia and loss of morphine tolerance in δ opioid receptor knockout mice. *Neuron*, *24*, 243–252.

Zubieta, J.-K., Bueller, J. A., Jackson, L. R., Scott, D. J., Xu, Y., Koeppe, R. A., et al. (2005). Placebo effects mediated by endogenous opioid activity on μ-opioid receptors. *The Journal of Neuroscience*, *25*, 7754–7762.