Kappa Opioid Signaling at the Crossroads of Chronic Pain and Opioid Addiction

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Abstract

Pain is complex and is a unique experience for individuals in that no two people will have exactly the same physiological and emotional response to the same noxious stimulus or injury. Pain is composed of two essential processes: a sensory component that allows for discrimination of the intensity and location of a painful stimulus and an emotional component that underlies the affective, motivational, unpleasant, and aversive response to a painful stimulus. Kappa opioid receptor (KOR) activation in the periphery and throughout the neuroaxis modulates both of these components of the pain experience. In this chapter we focus on recent findings that KORs contribute to the emotional, aversive nature of chronic pain, including how expression in the limbic circuitry contributes to anhedonic states and components of opioid misuse disorder. While the primary focus is on preclinical pain models, we also highlight clinical or human research where there is strong evidence for KOR involvement in negative affective states associated with chronic pain and opioid misuse.

Keywords

Amygdala; Analgesia; Anhedonia; Antinociception; Biased agonist; Chronic pain; Dopamine; Dynorphin; Emotional component of pain; Endogenous opioid; Inflammatory pain; Kappa opioid receptor; Mesolimbic circuitry; Negative affect; Neuropathic pain; Nociception; Nucleus accumbens; Opioid misuse; Opioid use disorder; Pain; Pain aversion; Peripherally-restricted; Ventral tegmental area

1 Introduction

The family of opioid receptors includes four homologous 7 transmembrane spanning G protein-coupled receptors (GPCRs) denoted kappa, mu, delta, (KOR, MOR, DOR, respectively), and the opioid receptor-like/nociceptin receptor (ORL1). Opioids are also involved in a myriad of other physiological, defensive, and behavioral processes, including autonomic regulation, control of breathing, immune function, gut transit, and itch (Bodnar 2018). In the early years of opioid receptor exploration, researchers understood the addiction liability associated with MOR agonists, and hoped that the identification of compounds targeting the alternate opioid receptors, including KOR, might lead to non-addictive alternatives for pain relief. Unfortunately, while acute activation of DOR and KOR does result in analgesia in preclinical models, KOR agonists produce strongly aversive emotional states. Subsequent research has implicated both dynorphin peptides and KOR activation in the acute and chronic impact of pain, stress, and addiction, though their contribution to each of these issues is complex and likely changes over time. There is now consensus that KOR agonists can produce dysphoria, depressive-like symptoms, and psychotomimetic effects in humans (Kumor et al. 1986; Pfeiffer et al. 1986; Wadenberg 2003) and elicit place aversion and depressive-like behaviors (Shippenberg and Herz 1986; Shippenberg et al. 1993; Bruchas et al. 2010; Knoll and Carlezon 2010; Chavkin and Koob 2016) as well as stimulate drug-seeking (Valdez et al. 2007; Grella et al. 2014; Nygard et al. 2016; Lê et al. 2018)

in rodents. Activation of the KOR system also elicits signs of anxiety and fear in animals and humans (Chartoff and Mavrikaki 2015; Chavkin and Koob 2016; Darcq and Kieffer 2018); however, spinal administration of KOR agonists produce antinociceptive effects in various preclinical pain models. The characterization of the crystal structures of inactive and active states of KOR has provided insights for drug–receptor interactions allowing new concepts for novel drug design (Wu et al. 2012; Che et al. 2018). This structural characterization together with identification of the signaling events that elicit antinociceptive versus dysphoric and psychotomimetic effects has provided extensive advancement in novel chemical entities that hold promise as new pain treatments with minimal aversive effects including depressive or addictive properties. In addition, peripherally restricted compounds, low efficacy ligands, and compounds with mixed mechanisms of action have shown promising results in early clinical trials. In this chapter, we will discuss (1) the involvement of KOR systems in the brain that contribute to pain and negative affective states associated with ongoing persistent pain and (2) the potential involvement of KOR systems in opioid medication misuse and opioid use disorder in the context of concomitant occurrence with chronic pain, given the recent evidence that KOR agonists can trigger drug relapse and that a systematic review confirm that chronic pain patients have high rates (13–38%) of opioid misuse (defined as opioid use contrary to the directed or prescribed pattern of use (Vowles et al. 2015).

2 Functional Upregulation of KOR Systems in Chronic Pain States

One of the first studies to report that dynorphin expression is increased in chronic pain states used a model of polyarthritis produced by intradermal tail injection of *Mycobacterium butyricum* that caused a gradual development of arthritic limbs, hypophagia (reduction of food intake), hypodipsia (reduced thirst), and reductions in thermal and mechanical sensory thresholds. This arthritic model was associated with a significant upregulation of immunoreactive dynorphin in the spinal cord that correlated with both the intensity and time course of mechanical hyperalgesia (Fig. 1) (Millan et al. 1985) and KOR antagonism potentiated this hyperalgesic response (Millan et al. 1987). KOR antagonism also enhanced pain hypersensitivities in a model of neuropathic pain (Xu et al. 2004). Together these data suggest that the dynamic endogenous tone of dynorphin at KORs is an adaptive process to suppress nociceptive transmission associated with tissue injury. Constitutive (global) KOR knockout produced enhanced pain hypersensitivity in a model of chronic inflammatory pain, but interestingly this enhancement was modality specific where mechanical, but not thermal, hypersensitivity was exaggerated in mice lacking KORs (Gavériaux-Ruff et al. 2008). Constitutive KOR knockout mice also exhibited enhanced nociceptive responses in a model of chemical visceral pain (intraperitoneal acidic acid) where abdominal constrictions were significantly greater, although there was no effect of KOR deletion on formalin-induced nocifensive (licking, flinching, guarding) behaviors (Simonin et al. 1998).

Many inflammatory agents (carrageenan, phorbol ester, yeast, and complete Freund's adjuvant) that rapidly induce edema and thermal hyperalgesia increased dynorphin mRNA within 8h and dynorphin A (1–8) peptide in the spinal cord within 48h following tissue injury (Iadarola et al. 1988a). Spinal dynorphin is upregulated in models of preclinical models of neuropathic and inflammatory chronic pain (Fig. 1) (Millan et al. 1985, 1986,

1988; Iadarola et al. 1988a, b; Kajander et al. 1990; Draisci et al. 1991; Malan et al. 2000; Rosén et al. 2000; Wang et al. 2001), as well as elevated in the cerebrospinal fluid of chronic pain patients (Vaerøy et al. 1991; Samuelsson et al. 1993). Moreover, dynorphin peptides can remain elevated for several months concurrent with persistent pain (Iadarola et al. 1988a; Kajander et al. 1990; Malan et al. 2000). Dynorphin is also present in primary afferent nociceptors and dynorphin neuropeptides were shown to be upregulated in dorsal root ganglia neurons in models of chronic pain (Fig. 1) (Calzà et al. 1998; Mika et al. 2010).

KOR agonists have been shown to produce antinociceptive effects in various visceral, inflammatory, and neuropathic pain models, although KOR agonists were found to have no effect on nociceptive responses in models of chronic musculoskeletal pain such as intramuscular acid injection (Sluka et al. 2002). Considering KOR agonists produce motor impairment and hypo-locomotion (Castellano et al. 1988; Bakshi et al. 1990), it is important to dissociate changes in reflexive nociceptive behaviors from potential confounds of motor impairment. The KOR agonist SA14867 (more than 31,000 and 2,200-fold higher affinity for KOR compared to mu and delta opioid receptors) elicited a large therapeutic window of antinociceptive effects relative to sedative/motor effects (as measured by rotarod) compared to other KOR agonists (Tsukahara-Ohsumi et al. 2011), demonstrating that indeed changes in threshold evoked sensory responses are not solely attributed to changes in motor performance.

2.1 Dynorphin Peptides Can Exacerbate Nociceptive Transmission via Non-opioid Mechanisms

Spinal dynorphin peptides have also been associated with exacerbation of pain outcomes. Spinal administration of KOR agonists produce significant changes in the excitability of some superficial nociceptive neurons, where both facilitation and inhibition of excitability and expansion of receptive fields were reported (Hylden et al. 1991). Later studies concluded that inhibitory effects of spinal dynorphins and KOR agonists on C-fiber excitability were mediated via KOR activation, whereas the facilitation induced by dynorphin peptides was not opioid receptor-mediated (Knox and Dickenson 1987). The prodynorphin precursor can be cleaved into various dynorphin peptides, where some peptides (e.g., dynorphin (1–17)) were reported to facilitate NMDA-mediated currents via direct excitatory effects on this ionotropic receptor (Caudle and Dubner 1998). Spinal dynorphin A (2–13) peptide also interacts with bradykinin receptors to promote hyperalgesia (Lee et al. 2015), where blockade of spinal bradykinin receptors also reverses neuropathic pain, but only when there was elevated spinal dynorphin A (2–13) peptides (Lai et al. 2006). Similarly, spinal dynorphin peptides dynorphin A (1–17), dynorphin A (2–17), dynorphin A (2–13), and dynorphin (11–17) produced long-lasting allodynia (painful response to a stimulus that is not normally painful), where effects persisted up to 70 days after a single injection (Vanderah et al. 1996; Laughlin et al. 1997). In these studies naloxone did not reverse the pronociceptive effects of dynorphin peptides, but rather were blocked by NMDA receptor antagonists, and the longer duration of action after a single injection suggests that dynorphin peptides can produce the phenomenon of spinal wind-up that contributes to central sensitization. Additionally, pain hypersensitivity associated with nerve injury recovered in prodynorphin knockout mice, consistent with the report that intrathecal

dynorphin antiserum reversed neuropathic pain (Wang et al. 2001). Similarly, neutralization of dynorphin peptides with antibodies was also shown to attenuate pain hypersensitivities associated with neuropathic pain (Malan et al. 2000; Gardell et al. 2004). These data suggest that the injury-induced upregulation of dynorphin produces pronociceptive effects and is required for the maintenance of persistent neuropathic pain. Indeed, a review argued that a dynorphin targeted gene silencing strategy to block dynorphin upregulation is a rational drug approach for treatment of chronic pain (Podvin et al. 2016). However, generation of mice that specifically ablated dynorphin containing inhibitory (but not excitatory) interneurons enhanced static and dynamic mechanical sensory thresholds in the absence of injury, demonstrating that these neurons normally act to prevent low-threshold mechanical stimuli from activating pain transmission neurons (Duan et al. 2014).

There is the possibility that KORs can also facilitate nociception, as this receptor is expressed on astrocytes, whereby KOR activation in these glial cells triggers their hypertrophy (Xu et al. 2007). Hence, in a model of neuropathic pain, KOR activation on astrocytes was shown to produce proliferation of spinal cord astrocytes via activation of p38 MAP kinase (Xu et al. 2007). The activation and hypertrophy of spinal astrocytes contributes to the maintenance of persistent pain states as well as MOR analgesic tolerance (Eidson and Murphy 2019; Ji et al. 2019; Donnelly et al. 2020). Taken together, spinal dynorphin peptides can either inhibit or facilitate nociceptive transmission; however, the facilitating effects of dynorphins are not mediated by neuronal KORs. Whether they engage astrocyte KORs that contributes to enhanced nociceptor excitability remains unknown.

2.2 Chronic Pain Changes KOR Function and Expression in Supra-Spinal Sites

While early research focused on dynorphin peptides and KORs in peripheral nociceptors and the spinal cord, chronic or persistent pain also increases KOR function in various brain structures. In an arthritic pain model, KOR binding increased in the dorsomedial and dorsolateral periaqueductal gray (PAG) (Millan et al. 1987). However, it is unknown what the functional relevance is of the chronic pain-induced KOR upregulation in the dorsal PAG. The PAG is a key structure in descending modulation (both facilitation and inhibition) of nociception, risk assessment triggering sympathetic and emotional responses as well as the learning and action of defensive and aversive behaviors (Lefler et al. 2020; Mokhtar and Singh 2020). Activation of the dorsolateral sub-region of the PAG produces emotional arousal and a stress response (increased heart rate, blood pressure, and alertness), whereas the ventrolateral sub-region is known for its involvement in modulating nociceptive transmission and opioid-mediated antinociception (Bagley and Ingram 2020). Given that KOR activation in the dorsal PAG causes anxiogenic effects and escape behavior (Maraschin et al. 2017), it would be of interest to determine the extent KOR activation in the ventrolateral region may contribute to aspects of negative affective states associated with chronic pain. Kappa ORs present in the ventrolateral PAG and are partially responsible for oxytocin-induced analgesia (Ge et al. 2002). An elegant study recently demonstrated that KOR activation in the ventrolateral PAG reduced GABAergic transmission onto PAG dopamine neurons, suggesting that KOR activation leads to disinhibition of these neurons to modulate pain transmission (Li and Kash 2019). These ventrolateral PAG dopamine neurons project to the extended amygdala (BNST and CeA), areas known to regulate stress

and anxiety where they contribute to Pavlovian fear conditioning (Matthews et al. 2016) and were proposed to be responsible for aberrant fear memory formation in PTSD patients (Torrisi et al. 2019). In addition, they also contribute to wakefulness where they have reciprocal connections with the sleep–wake regulatory system (Lu et al. 2006). Hence, there is a possibility that KOR modulation of PAG neurons in both the dorsal and ventral regions may contribute to the emotional, affective dimension of the pain response. The subsequent sections in this chapter will focus on how chronic pain alters KOR expression and function in mesolimbic circuitry and the functional consequences of this enhanced KOR system.

It was identified that a group of GABAergic prodynorphin positive neurons (tyrosine hydroxylase negative) in the brain stem (present in both humans and rodents) are poised to regulate pain transmission. LJA5 (lateral pons, juxta A5) projects to the lateral and ventrolateral PAG, the lateral parabrachial nucleus and to lamina I of the spinal cord, and receives input from many stress and sensory areas including the somatosensory and insula cortices, the paraventricular nucleus of the hypothalamus, the dorsomedial nucleus and lateral hypothalamus, central nucleus of the amygdala, periaqueductal gray and lateral parabrachial nucleus (Agostinelli et al. 2021). Whether chronic pain changes the expression of prodynorphin transcript in this specific brain region has yet to be assessed, but these neurons are the only known inhibitory neurons that project directly and selectively to innervate lamina I of the spinal cord, and appose dynorphin neurons in lamina I that project to the parabrachial nucleus (Standaert et al. 1986).

An important component of the pain experience is the negative, affective, emotional component of pain. Narita and colleagues were the first to report the occurrence of an anxiogenic phenotype in mice with chronic pain and that the time line of resolution of negative affect correlated with recovery of sensory pain hyper-sensitivity (Narita et al. 2006). Subsequent studies by Yalcin and colleagues elegantly reported the timeline history/development of various anxiogenic and depressive-like behaviors associated with neuropathic pain in mice (Yalcin et al. 2011). Chronic inflammatory, but not neuropathic pain, produced a significant increase in KOR agonist stimulated [^{35}S]GTPγS binding in membranes prepared from the amygdala at 4 weeks post-injury. In the amygdala, KOR is thought to contribute to anxiety-like behavior, as intracerebral amygdala injection of dynorphin A precipitated an anxiogenic-like phenotype (Narita et al. 2006). Given the overlap in circuitry is involved in pain processing, emotional learning, and fear, it is perhaps not surprising that chronic pain causes an upregulation of KOR systems in limbic brain structures. We recently demonstrated that KOR and dynorphin mRNA transcript were upregulated in the nucleus accumbens (NAc) and ventral tegmental area (VTA) of chronic pain mice, compared to sham controls (Liu et al. 2019), while others also report an upregulation of KOR mRNA in the locus coeruleus (Llorca-Torralba et al. 2020) and prefrontal cortex (Palmisano et al. 2018).

To confirm to what extent the upregulation in transcript expression within mesolimbic circuitry translates into an increased function of the receptor, we showed using *ex vivo* autoradiography that KOR agonist-induced [^{35}S]GTPγS autoradio-graphic binding was increased in the NAc and VTA of chronic pain mice (Liu et al. 2019). Enhanced KOR agonist stimulated [^{35}S]GTPγS was also reported in the prefrontal cortex and

somatosensory cortex one month after induction of neuropathic pain (Llorca-Torralba et al. 2020). The enhanced KOR activity was also evidenced by an increase in the phosphorylated state of the KOR in the NAc in the absence of exogenous agonist administration (Liu et al. 2019). Prodynorphin mRNA was increased in the NAc, the prefrontal cortex and anterior cingulate cortex 2 weeks after nerve injury model of neuropathic pain (Palmisano et al. 2018; Liu et al. 2019). Interestingly, which peptide is cleaved from the prodynorphin peptide was suggested to be brain region specific. Hence, bioconversion of dynorphin B produced DYN B (1–7) in cortical areas, whereas it produced dynorphin B (2–13) in the striatum (Bivehed et al. 2017). These data suggest that prodynorphin cleavage to various peptides within specific brain regions can influence whether KOR or non-opioid mediated effects are produced and would presumably influence various aspects of the pain experience.

2.3 Kappa OR Agonist-Induced Place Aversion Is Enhanced in Chronic Pain States

Kappa OR-mediated dysphoric states are evaluated in rodent models using agonist-induced conditioned place aversion (CPA). CPA is evident in [pain-naïve] rodents when conditioned to KOR (unbiased) agonists, non-specific opioid antagonists such as naloxone, or lithium chloride (LiCl, which produces gastrointestinal distress, emesis, and vomiting in humans). KOR agonist-induced CPA can be elicited following systemic administration or microinjection directly into the VTA, NAc, prefrontal cortex, and lateral hypothalamus, but not the dorsal striatum or substantia nigra (Fig. 2a) (Bals-Kubik et al. 1993; Tejeda and Bonci 2018). Microinjection of KOR antagonists into the prefrontal cortex or dorsal raphe nucleus blocked CPA produced by systemic administration of a KOR agonist, suggesting a critical role for these brain regions in the aversive state (Land et al. 2009; Tejeda et al. 2013). Using conditional knockout mice, KORs on dopamine neurons were shown to be sufficient to produce a place aversion (Chefer et al. 2013; Ehrich et al. 2015b) and re-expression of KOR in dopamine neurons using a viral approach recovered KOR-mediated place aversion suggesting that KOR on dopamine neurons is sufficient for KOR-mediated place aversion (Chefer et al. 2013). The activation of KORs on mesolimbic dopamine neurons that are responsible for KOR agonist-induced aversion was subsequently identified to require activation of p38 MAP kinase (Ehrich et al. 2015b), although there was a dissociation between aversion and changes in dopamine release within the ventral striatum.

Despite this strong evidence for KOR on dopamine neurons projecting to the NAc being responsible for KOR-mediated aversion, re-expression of KORs in the dorsal raphe using lentivirus approaches in the KOR knockout mouse also restored KOR agonist-induced aversion, whereas re-expression of a mutant receptor that failed to activate p38 MAP kinase did not restore aversion (Land et al. 2009). Indeed, subsequent studies also reported that KOR activation in serotoninergic dorsal raphe neurons is both necessary and sufficient to mediate KOR agonist aversive behavioral effects as well (Land et al. 2009; Ehrich et al. 2015b). It remains unclear whether the dopamine and serotonin systems integrate to produce the aversive state associated with KOR activation or if there are multiple brain regions that are sufficient to elicit this aversive state. Considering that KORs are expressed on terminals of dopamine neurons projecting to various targets including (but not limited to) the basolateral amygdala (BLA), NAc, and prefrontal cortex, it is not unreasonable to question whether the inhibitory effects on dopamine release to other targets may also contribute

to KOR-mediated aversion, although there are conflicting reports of KOR regulation of dopamine neurons within each of these brain regions (Tejeda and Bonci 2018; Margolis and Karkhanis 2019). KOR agonists also appear to modulate other circuits (independent of monoamines such as dopamine) to produce aversion. Inhibition of glutamate and GABA synaptic transmission in the NAc shell by KOR agonists (Hjelmstad and Fields 2001) was also proposed to contribute to KOR agonist-induced aversion.

Considering chronic pain is a stressor in itself, it is unknown if the associated KOR upregulation is generalizable to all stressors. Stress induced by maternal separation and social isolation increased KOR expression in the amygdala (Nakamoto et al. 2020). However, chronic stress induced by social defeat *decreased* dynorphin transcript in the NAc (Donahue et al. 2015), although acute social defeat stress increased it in this brain region and additionally induced KOR-mediated stress-induced analgesia. Despite the lack of change in prodynorphin transcript in the chronic stress state, this latter study reported that ablating KORs from dopamine neurons using a conditional knockout approach delayed the development of chronic stress-induced anhedonia, as measured by intracranial self-stimulation (ICSS, an operant behavior sensitive to increases and decreases in the reinforcing efficacy of rewarding brain stimulation) of monopolar electrodes within the lateral hypothalamus. This study concluded that the KOR expression on dopamine neurons contributed to an increase in stress resilience. Nevertheless, the findings from this study argue that the dynorphin and KOR upregulation in chronic pain states is not generalizable across all types of chronic stress, but the dial up in function appears to be generalizable to withdrawal associated with chronic drug use (Koob 2020).

To determine the extent KOR aversion may be enhanced in chronic pain, we used the CPA assay. The KOR agonist-induced dose-dependent CPA was shifted to the left in male, but not female, chronic pain mice, suggesting a sex-dependent enhancement of KOR-mediated effects in chronic pain states (Fig. 2b) (Liu et al. 2019). This sex difference is consistent with human imaging data showing that KOR binding is greater in men than women in multiple brain regions, including the anterior cingulate cortex, which is involved in the emotional affective dimension of pain (Vijay et al. 2016). Furthermore, females were shown to be less sensitive than males to the KOR agonist-induced deficits in motivation as measured by ICSS of the medial forebrain bundle and less effective in suppressing evoked NAc dopamine release measured via fast scanning cyclic voltammetry (Conway et al. 2019). Nevertheless, there are conflicting reports of the effects of ongoing pain on KOR-mediated aversion, where the place aversion to a KOR agonist was absent in male rats with persistent ongoing pain induced by complete Freund's adjuvant (Shippenberg et al. 1988). Although it is unclear if the pain may have interfered with the essential cue learning required to elicit a CPA as a positive control was not included in the study. Taken together, chronic pain causes a sex-dependent enhancement of KOR-mediated aversion, although it is unknown if the same circuits are engaged as those in the absence of pain.

3 Kappa OR Modulation of the Affective, Emotional Dimension of Pain

Similar to the use of a CPA protocol to detect a drug-induced aversive state, pairing a painful event (rather than a drug) with contextual cues allows animals to learn the association of

an environment with a painful stimulus. Painful stimuli such as intraplantar formalin or carrageenan, or intraperitoneal injection of acetic acid can produce a pain evoked CPA (Fig. 2c). Optogenetic activation or inhibition of nociceptive neurons using real-time place conditioning paradigms also shows place conditioning to painful stimuli (Daou et al. 2013; Iyer et al. 2014; Park et al. 2015; Beaudry et al. 2017). The aversive component of pain has been captured by other place avoidance paradigms to try to capture pain affect in chronic pain states. LaBuda and Fuchs (2000) reported a place avoidance escape assay whereby the rodent has a conflict between staying in a dark compartment associated with a mechanical stimulus or entering a light compartment with no, or non-painful, sensory stimuli. A CPA can also be produced by combining experimenter-provoked mechanical allodynia during the place conditioning, whereby von Frey filaments are applied to the injured hind paw through a grid floor in the place conditioning apparatus (Hummel et al. 2008). The CPA induced by sensory stimulation in either neuropathic or inflammatory chronic pain models was maintained for at least one month in the absence of further conditioning and non-rewarding doses of morphine given during the pain-paired conditioning sessions attenuated the CPA. But what, if any role does the KOR system have in modifying the affective emotional aversive component of this pain experience?

The role of KORs in mediating the affective dimension of pain states most likely depends on the duration of pain (acute vs. chronic) or the conditioning protocol used to assess the aversive painful state or more likely the co-occurrence of a negative affective state associated with chronic pain. The CPA produced by intraperitoneal injection of acetic acid was *not* blocked by pretreatment with a KOR antagonist (or KOR agonist) (Bagdas et al. 2016). Electroacupuncture prevented the expression of a CPA to intraplantar injection of complete Freund's adjuvant and this effect was absent in rodents pretreated with a MOR, but not KOR, antagonist injected into the rostral anterior cingulate cortex (Zhang et al. 2012). Indeed, in rats with postsurgical or neuropathic pain, endogenous MOR signaling in the anterior cingulate cortex was necessary for the expression of a conditioned place preference (CPP) to non-opioid pain relieving treatments such as a peripheral nerve block or spinal clonidine (an alpha2-adrenergic agonist) and this receptor activation was also associated with dopamine release in the NAc (Navratilova et al. 2015).

3.1 Kappa OR Ligands Do Not Alter Acute Pain-Induced Aversion or Depression of ICSS

The affective dimension of pain can be captured using ICSS, an operant procedure in which subjects emit a learned response such as a lever press to earn pulses of electrical stimulation to brain reward areas and is reliant on dopamine release in the ventral striatum. Studies have shown that acute visceral pain (Leitl et al. 2014a) and different models of inflammatory pain (formalin or complete Freund's adjuvant) (Leitl et al. 2014b) depressed ICSS. Pain-induced (complete Freund's adjuvant, formalin or lactic acid) depression of ICSS was not prevented by pretreatment with a KOR antagonist (Leitl et al. 2014a, b). Despite the lack of involvement in KOR systems for the expression of acute pain-induced aversion, it does not rule out the possibility that activation of KORs contributes to negative affective states associated with chronic pain states. Indeed, chronic pain is highly co-morbid with mood disorders in clinical populations. KOR agonists activate the HPA axis, and produce pro-depressive and anxiogenic-like effects, whereas KOR antagonists cause opposing effects

in producing anxiolytic-like and anti-depressant effects (Van't Veer and Carlezon 2013). Ablation of KORs from dopamine neurons (Van't Veer and Carlezon 2013) or KORs on BLA glutamatergic neurons that project to the medial prefrontal cortex (Tejeda et al. 2015) results in an anxiolytic phenotype, suggesting that KOR modulation of these circuits is critical to the expression of negative affect. KOR activation within the BLA was necessary for the anxiogenic effect of corticotropin releasing factor (Bruchas et al. 2009) and eliminating KOR from BLA glutamatergic neurons projecting to the BNST also has an anxiolytic phenotype (Crowley et al. 2016). Considerable evidence suggests that the KOR system within the NAc also underlies negative affective states and heightens stress reactivity in various psychiatric disorders. For example, dynorphin expression is increased in the ventral striatum of suicidal individuals (Hurd et al. 1997) and in animal models of depression (Shirayama et al. 2004; Carlezon and Krystal 2016; Tejeda and Bonci 2018).

3.2 Kappa OR Systems Contribute to Ongoing Persistent Pain States

The lack of KOR involvement in acute pain aversion or ICSS depression may be due to the temporal relationship between the onset of pain and development of negative affective-like behaviors. Anxiety and depressive behaviors that accompany chronic pain states in rodents do not typically begin to manifest until weeks 4–8 following injury (Yalcin et al. 2011). Thus, the KOR system may only be engaged following tissue or nerve injury that induces the negative affective-like behaviors (anxiety and depression) versus the initial associated with an acute painful event. This idea is supported by the finding that, in a model of joint pain, KOR knockout mice showed reduced anxiety (elevated plus maze) (Negrete et al. 2016), where global KOR knockout does not produce an anxiolytic phenotype in the absence of ongoing pain (pain-naïve animals) (Kieffer 1999). Thus, there are contradictory findings reported for the involvement of KOR in pain-induced negative affect and pain aversion, but if one considers the temporal relationship with development of co-morbid affective states, the delayed KOR system involvement more closely correlates with negative affective states.

While the CPP paradigm is useful for studying reward and aversion, the interpretation of data in chronic pain states can be somewhat difficult; the effect size of this CPP may be exaggerated if the rodent was experiencing an aversive state in the non-drug paired chamber. To circumvent this confound, we used a one-sided conditioning protocol (Bechara and van der Kooy 1992) to determine whether chronic pain could evoke a CPA in the absence of stimulating the dermatome affected by an injury. Both mice and rats, independent of sex, produced a CPA to ongoing persistent inflammatory and neuropathic pain, whereas sham control animals had no preference to either chamber (Liu et al. 2019). We interpreted these data to suggest that one can capture the ongoing aversive component of chronic pain. In separate cohorts of mice, KOR antagonism with JDTic prevented place aversion in male, but not female, chronic neuropathic pain mice, demonstrating a sex-specific engagement of KORs in pain aversive states (Fig. 2c), which was generalizable to chronic inflammatory pain. It is noteworthy that KOR blockade had no effect on mechanical withdrawal thresholds in sham or chronic pain mice demonstrating that KOR involvement in pain circuitry is restricted to the affective, but not sensory, dimension of chronic pain. This study demonstrated that KOR expression on dopamine neurons was sufficient to produce the chronic pain-induced CPA. In addition to capturing this ongoing pain response, other

studies have shown that the negative reinforcement produced by gabapentin and morphine in chronic pain models was absent in rodents that received KOR antagonists (Liu et al. 2019; Navratilova et al. 2019). One interpretation of these data is that blocking the negative affect by KOR antagonism eliminated the motivation and drive for pain relief produced by gabapentin and morphine. One could even suggest that the alleviation of the negative affective state was the only motivation to seek morphine or gabapentin.

In addition to the contribution of KORs within mesolimbic dopamine neurons to the tonic aversive component of ongoing chronic pain, KORs within the amygdala (CeA and BLA) have also been implicated in modulating the pain experience including pain-induced aversion (Corder et al. 2019; Navratilova et al. 2019; Phelps et al. 2019). In un-injured pain-naïve animals, stress produced allodynia (painful response to something not normally painful) via a KOR-dependent mechanism in the CeA (Xie et al. 2017). The CeA receives both nociceptive sensory input from the spinal cord via the parabrachial nucleus (Chiang et al. 2020) and noradrenergic innervation from the locus coeruleus (also implicated in reinstatement of drug-seeking behavior) (España et al. 2016), making it a central brain region for integrating pain and stress. The lateral CeA has been termed the "nociceptive amygdala" given that neurons in this brain region respond exclusively to noxious stimulation (Neugebauer et al. 2020). Intra-CeA administration of a KOR antagonist had no effect on mechanical hypersensitivity in a rat model of neuropathic pain, but prevented the CPP to intravenous gabapentin, suggesting that KOR blockade in this brain region eliminated the aversiveness of ongoing pain (Navratilova et al. 2019). This latter study also demonstrated that KOR blockade also reduced synaptically evoked CeA neuronal spiking in chronic pain, but not sham control, animals, leading the authors to hypothesize that increased KOR activity produces a tonic disinhibition of CeA output neurons that promotes ongoing aversive aspects of neuropathic pain. While KORs in the CeA do not modulate pain hypersensitivity, they may be involved in the loss of diffuse noxious inhibitor control (descending circuits such as the PAG, locus coeruleus and dorsal raphe nucleus that regulate nociceptive transmission) that occurs in various chronic pain states (Phelps et al. 2019). Another recent study reported that optogenetic activation of CeA neurons suppressed both pain-elicited reflexive and self-recuperating behaviors across sensory modalities and abolished neuropathic pain hypersensitivities, whereas inhibiting CeA neuronal activity exacerbated pain and produced a strong aversion (Hua et al. 2020). Future studies are needed to understand to what extent KOR systems in the extended amygdala also contribute to the pain experience. Figure 3 highlights the anatomical expression and contribution of the dynorphin-KOR system in the sensory and affective components of chronic, persistent pain.

4   Is There Potential for KOR Antagonism as a Management Strategy for Chronic Pain-Associated Negative Affect?

The dysphoric and negative affective states induced by KOR activation generated promise for KOR antagonists as a novel treatment strategy for mood disorders and pharmacotherapy for substance use disorders. A review is available summarizing the completed clinical trials that evaluated safety and effectiveness of KOR antagonists for treatments of substance use and mood disorders (Carlezon and Krystal 2016). Pharmacokinetic studies and potential

drug interactions with ethanol were evaluated for the KOR antagonist LY2456302 in healthy subjects (Lowe et al. 2014) as was safety, tolerability, and pharmacokinetics of oral doses of JDTic, which was prematurely stopped due to cardiac adverse events (Buda et al. 2015). One mechanism implicated in KOR-mediated aversion and negative effects on mood is the modulation of mesolimbic dopamine circuitry (Van't Veer and Carlezon 2013). This circuitry plays a central role in motivational processes and incorporates dopaminergic neurons in the VTA that project to the NAc (Berridge and Kringelbach 2013, 2015; Zarrindast and Khakpai 2015). KORs are known to modulate this circuitry by inhibiting dopamine release at dopaminergic nerve terminals within the NAc (Spanagel et al. 1992; Ebner et al. 2010; Cahill et al. 2014; Ehrich et al. 2015b; Chartoff et al. 2016). Considering that systems involved in affective aspects of pain processing and other affective and motivational systems interact extensively (Jarcho et al. 2012; Elman et al. 2013), there is potential that KOR blockade may prove to be a novel pain management strategy.

Epidemiological evidence shows that chronic pain is second only to bipolar disorder as the major cause of suicide among all medical illnesses (Asmundson and Katz 2009; Elman et al. 2013) and that mood disorders are highly co-morbid in chronic pain patients, where the prevalence of depression ranges between 30 and 80%, depending on the pain etiology (Bair et al. 2003; Howe and Sullivan 2014). It is consistently reported that co-morbid psychopathology in patients with chronic pain exhibit increased pain intensity and increased pain-related disability (Jamison and Edwards 2013; Martel et al. 2014), thus managing negative affect holds promise in reducing pain ratings in patients with chronic pain. We, and others, identified that mesolimbic circuitry dysfunction (including dopamine neurotransmission) precipitates mood disorders, impairs motivated behavior, and likely contributes to chronic pain (Narita et al. 2005; Cahill et al. 2014; Hipólito et al. 2015; Taylor et al. 2015; Borsook et al. 2016; Evans and Cahill 2016; Cahill and Taylor 2017; Liu et al. 2019; Massaly et al. 2019). There is compelling evidence that KORs within the ventral striatum underlies negative affective states and heightens stress reactivity in psychiatric diseases (Ebner et al. 2010; Knoll and Carlezon 2010). Supporting this thesis is the report that prodynorphin mRNA was increased in the ventral striatum of victims of suicide (Hurd et al. 1997), although no difference in dynorphin levels in cerebral spinal fluid was found in patients with non-suicide self-injurious behavior, yet this group did have lower levels of other endogenous opioids (Stanley et al. 2010).

Preclinical and human subject research have identified strong correlations between dysfunction of this mesolimbic circuitry and chronic pain (Jarcho et al. 2012; Elman et al. 2013; Borsook et al. 2016; Evans and Cahill 2016; Taylor et al. 2016; Cahill and Taylor 2017). The increase in extracellular dopamine following intra-VTA or systemic administration of MOR agonist is absent in chronic neuropathic pain (Ozaki et al. 2002; Taylor et al. 2015) and inflammatory pain states (Narita et al. 2005; Hipólito et al. 2015), which correlates with the loss of opioid reward as measured by CPP following intra-VTA or systemic administration of MOR agonists (Ozaki et al. 2002; Taylor et al. 2015). Using *in vivo* microdialysis in awake, freely moving animals, we demonstrated that blocking KORs recovered the loss of opioid-induced dopamine release in the NAc associated with neuropathic pain (Liu et al. 2019). This finding is consistent with previous reports that blocking KORs recovered opioid-evoked dopamine release in the formalin model of

inflammatory pain (Narita et al. 2005). Interestingly, the morphine-evoked increases in NAc extracellular dopamine can be blocked by administration of a KOR agonist into the NAc but not the VTA (Spanagel et al. 1992), implying that KORs within the ventral striatum are important in the negative modulation of mesolimbic dopamine dependent motivation produced by MOR agonists such as morphine. Given that hypo-dopaminergic states contribute to chronic pain (Borsook et al. 2016; Taylor et al. 2016) and mood disorders co-morbid with chronic pain (Elman et al. 2013), recovering rewarding effects is an important component of alleviating chronic pain. While KOR antagonism had no effect on opioid reward in pain-naive cohorts, it restored DAMGO-induced CPP in chronic pain animals (Liu et al. 2019). This study further highlights the involvement of NAc KORs in chronic pain-induced negative affective states. Using an inflammatory model of chronic pain induced by complete Freund's adjuvant, Massaly and colleagues showed that the reduced motivation for sucrose self-administration (via progressive ratio testing) required the engaged dynorphin neurons in the NAc and was prevented by KOR antagonism (Massaly et al. 2019). Taken together, KORs contribute to the hypo-dopaminergic tone and reward-related behaviors in chronic pain without altering sensory pain hypersensitivities, suggesting that KOR antagonists may be an effective treatment in pain management for chronic pain patients.

5 Evidence That KOR Systems May Contribute to Drug-Seeking Behavior in Chronic Pain States

As noted above, mood disorders are highly co-morbid in chronic pain patients (Bair et al. 2003; Howe and Sullivan 2014) and are a risk factor for the development of opioid use disorder (OUD) (Evans and Cahill 2016). A systematic review reported that chronic pain patients have high rates (13–38%) of opioid misuse (defined as opioid use contrary to the directed or prescribed pattern of use, regardless of the presence or absence of harm or adverse effects) (Vowles et al. 2015). This is consistent with reports where electronic health records of >5,000 patients with opioid use disorder revealed the majority of patients reported chronic pain preceded their opioid use disorder, and 85% of this cohort had a co-morbid mental disorder (Hser et al. 2017), a finding recently duplicated by another study (Higgins et al. 2020). The high abuse rates of therapeutic opioids have fueled a strong debate on the treatment practices of using prescription opioids and whether pain is a major factor in addiction susceptibility. With the overwhelming evidence that negative affective states drive opioid use disorder (Evans and Cahill 2016), including in chronic pain patients, it is expected that chronic pain states lead to activation of KOR systems that are involved in stress-induced reinstatement of opioid drug-seeking behavior. However, how KOR systems modulate drug-seeking behavior in chronic pain states has not been explored, but there are various clinical trials that have reported the effectiveness of KOR partial agonism or antagonism in modulating substance use disorders (Table 1).

As noted above, there is overlapping expression of the KOR and its endogenous ligands dynorphins within reward and stress pathways, which contributes to the ability of this system to alter stress- and reward-related signaling in the brain (Bruchas et al. 2010; Wee and Koob 2010; Crowley and Kash 2015). Drug relapse can be produced by a stressful

event, presentations of cues associated with drug taking, as well as the drug itself (drug-priming). A number of studies have implicated KORs in stress-induced relapse/reinstatement of drug-seeking behavior (Table 2). KOR antagonists block stress-induced reinstatement, while KOR agonists, such as U50,488, induce reinstatement of cocaine (Beardsley et al. 2005; McLaughlin et al. 2006; Redila and Chavkin 2008; Polter et al. 2014; Heinsbroek et al. 2018), nicotine (Jackson et al. 2013; Nygard et al. 2016), and alcohol (Funk et al. 2014, 2019a, b; Lê et al. 2018) seeking behavior. Stress caused by injection of yohimbine (Zhou et al. 2013) or food deprivation (Sedki et al. 2015) precipitated reinstatement of heroin drug-seeking, is also blocked by pretreatment with the KOR antagonist nor-BNI.

While there is significant promise in the potential for KOR antagonists to attenuate drug relapse, distinct mechanisms have been shown to underlie reinstatement due to either cue, drug-priming or stress. For example, context-induced reinstatement of oxycodone was blocked by MOR, but not KOR antagonists (Bossert et al. 2019), albeit low dose naloxone (0.03 mg/kg) increased heroin drug intake and elevated ICSS thresholds (above already elevated baseline levels) when stimuli was paired with the naloxone treatment (Kenny et al. 2006). Additionally, social defeat-induced stress produced KOR-mediated anhedonia, as measured by ICSS (Donahue et al. 2015). Other studies show that KOR antagonism *did not affect* morphine (Glick et al. 1995) or heroin (Negus et al. 1993) self-administration or context-induced reinstatement of oxycodone self-administration (Bossert et al. 2019). Furthermore, KOR agonists decreased cocaine intake and cocaine drug-seeking (Glick et al. 1995; Schenk et al. 1999; Morani et al. 2009), as well as cocaine or amphetamine-induced reinstatement in mice (Schenk and Partridge 2001) and non-human primate (Negus et al. 1997; Mello and Negus 2000; Rüedi-Bettschen et al. 2010). Similarly, KOR agonists reduced oxycodone self-administration in non-human primates (Zamarripa et al. 2020a), decreased morphine self-administration in mice (Glick et al. 1995) and blocked oxycodone CPP in male rats (Zamarripa et al. 2020b). Considering ongoing pain is a stressor in itself, it is unknown to what extent KOR systems contribute to stress- and drug-priming-induced reinstatement under conditions of chronic pain. However, one study reported that post-operative pain (incisional model) suppressed morphine-primed reinstatement in self-administration studies and KOR antagonism reversed this inhibition (Table 2) (Nwaneshiudu et al. 2020).

6   Conclusions

The dynorphin-KOR system is a near ubiquitously expressed receptor system found throughout the brain and body that has been implicated in a wide array of physiology and behaviors, including nociceptive processing, chronic pain states, and emotional regulation/dysregulation. It remains a prime target for the potential development of novel therapeutics for the treatment of acute and chronic pain, in the absence of abuse liability. However, likely due to the widespread expression of both the endogenous dynorphin peptides and KOR, designing appropriate pharmacotherapies has proved challenging, due to many unwanted physical and affective side effects. Over the past few decades, researchers have developed a deeper understanding of dynamic signaling capabilities involved with both dynorphin and KOR under various physiological conditions, as well as within and between various tissues and brain regions. This knowledge has resulted in the potential development of both

biased agonists and peripherally restricted compounds targeting KOR for the alleviation of pain. Furthermore, while KOR agonists have long been considered the ultimate goal for drug development, due to the upregulation of KOR observed in the chronic pain states, researchers have found some success in using KOR antagonists to decrease the affective dimension of pain. This has opened another avenue of research into the role of dynorphin and KOR in emotional dysregulation following chronic pain and/or opioid use.

Acknowledgements

Abbreviations

ACTH	Adrenocorticotropic hormone
BLA	Basolateral amygdala
BNST	Bed nucleus of the stria terminalis
CeA	Central nucleus of the amygdala
CPA	Conditioned place aversion
CPP	Conditioned place preference
CRF	Corticotropin-releasing hormone
DOR	Delta opioid receptor
GABA	Gamma-aminobutyric acid
GPCRs	G-protein coupled receptors
ICSS	Intracranial self-stimulation
JDTic	$C_{28}H_{39}N_3O_3$ kappa opioid antagonist
KOR	Kappa opioid receptor
LiCl	Lithium chloride
MAP	Mitogen-activated protein
MK801	Dizocilpine, NMDA antagonist
MOR	Mu opioid receptor
nor-BNI	Nor-binaltorphimine, kappa opioid antagonist
NMDA	Nucleus accumbens NAc

ORL1	Opioid receptor-like/nociceptin receptor
PAG	Periaqueductal gray
VTA	Ventral tegmental area

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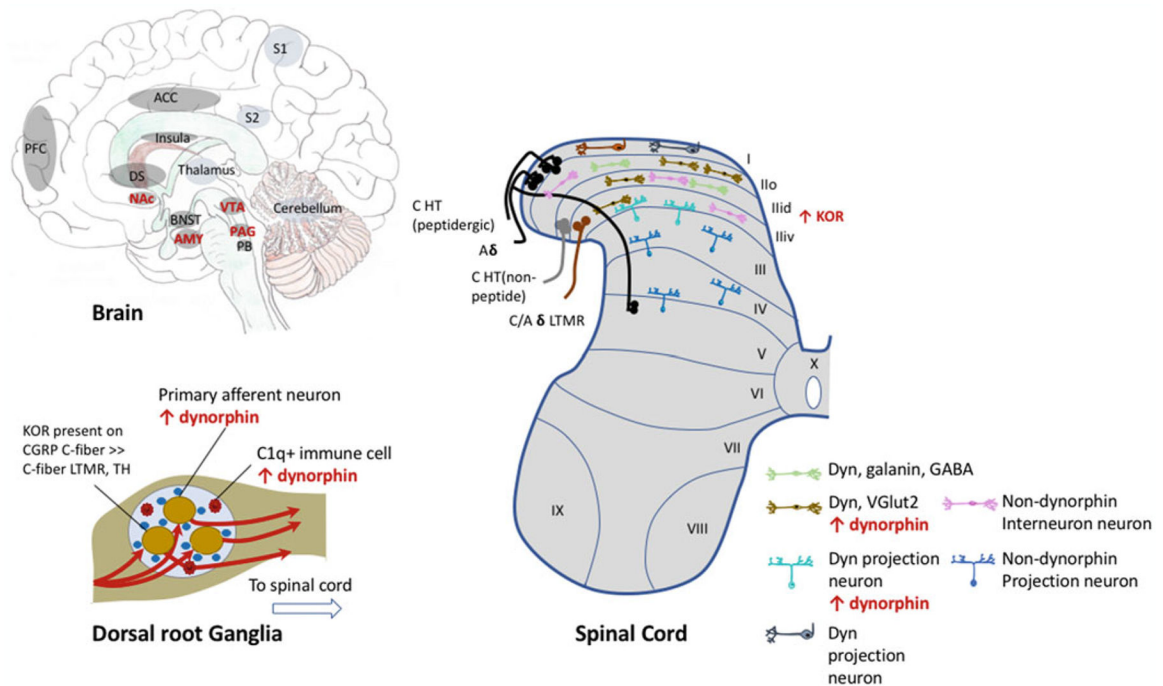
Fig. 1.

Evidence for increased dynorphin or KOR function or expression in various peripheral or central nervous system brain regions in chronic pain states. *Dorsal Root Ganglia*: Following nerve injury, dynorphin is present in primary afferent neurons, where it is not expressed under pain-naïve conditions (Sapio et al. 2020), is produced by C1q+ immune cells (Mika et al. 2010). *Spinal Cord*: Neurons in the spinal cord are organized into laminae, where ascending projection neurons are enriched in lamina I and throughout lamina II-V, whereas lamina II primarily consists of interneurons, including dynorphin containing inhibitory or excitatory neurons. Projection neurons make up 5 distinct circuits that relay sensory information to the brain. The spinothalamic pathway is known for transmitting pain information to the thalamus, and subsequently to the somatosensory cortex (S1) to provide information about pain intensity and location. Nociceptive projection neurons in lamina I relay pain information to specific brainstem (e.g., lateral parabrachial nucleus) and thalamic nuclei, which further project to areas involved in the affective, emotional component of pain such as the amygdala and hypothalamus. Primary afferent nociceptors including C-fiber and A-delta HT (high threshold) project to lamina I and outer lamina II (IIo), while low-threshold mechanoreceptor (LTMR) neurons project to inner lamina II. Prodynorphin immunoreactivity is present in galanin-positive, GABAergic interneurons in lamina I/II (Sardella et al. 2011) and glutamatergic (VGlut2+) (Nahin et al. 1992) interneurons that synapse with projection neurons in lamina III, that also contain dynorphin, where a recent study showed that the dynorphin containing neurons was 88% GABA to 12% glutamatergic (Duan et al. 2014). Dynorphin is upregulated following tissue or nerve injury in excitatory dynorphin-containing interneurons and dynorphin-containing projection neurons (Iadarola et al. 1988a; Ruda et al. 1988; Sapio et al. 2020). It is unclear whether dynorphin expression within dynorphin projection neurons in lamina I is modified in chronic pain states. There is an increase in KOR expression and function within the spinal cord have also been described.

Brain: Many brain regions show increased KOR function in chronic pain states (highlighted in red text). *ACC* Anterior cingulate cortex, *AMY* amygdala, *BNST* bed nucleus of the stria terminalis, *DS* dorsal striatum, *NAc* nucleus accumbens, *PAG* periaqueductal gray, *PB* parabrachial nucleus, *PFC* prefrontal cortex, *S1* somatosensory cortex, *S2* secondary somatosensory cortex, *VTA* ventral tegmental area. A detailed description of spinal neurons in nociceptive transmission has been described (Todd 2010; Peirs and Seal 2016)
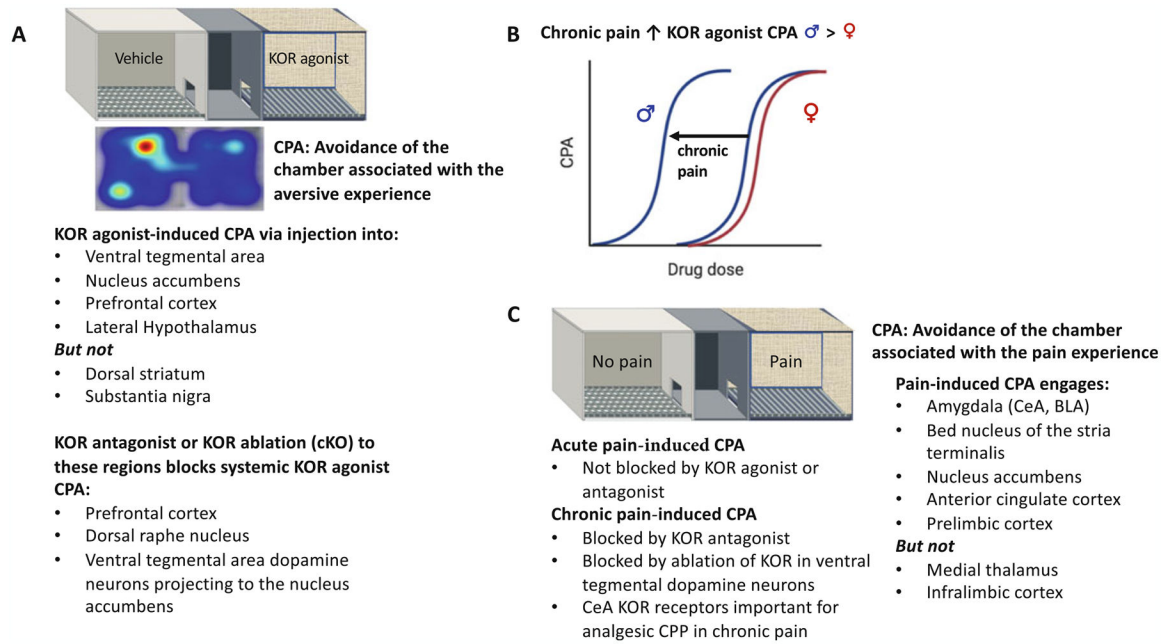
Fig. 2.
Use of conditioned place preference protocols to measure kappa opioid receptor agonist mediated aversion and pain-induced aversion. (**a**) KOR agonist-induced place aversion (CPA) can be generated by intracerebral injection into specific brain regions, whereas genetic ablation of KORs from specific brain regions eliminates place aversion following systemic agonist administration. (**b**) Chronic pain enhances KOR agonist-induced place aversion in male, but not female, mice. (**c**) Pain-induced aversion where an acute pain stimulus is used for conditioning is not blocked by either KOR agonists or antagonists, however, KOR antagonists block CPA in chronic pain states. Brain regions important for the expression of pain-induced place aversion include the amygdala, bed nucleus of the stria terminalis, nucleus accumbens, anterior cingulate cortex, and prelimbic cortex
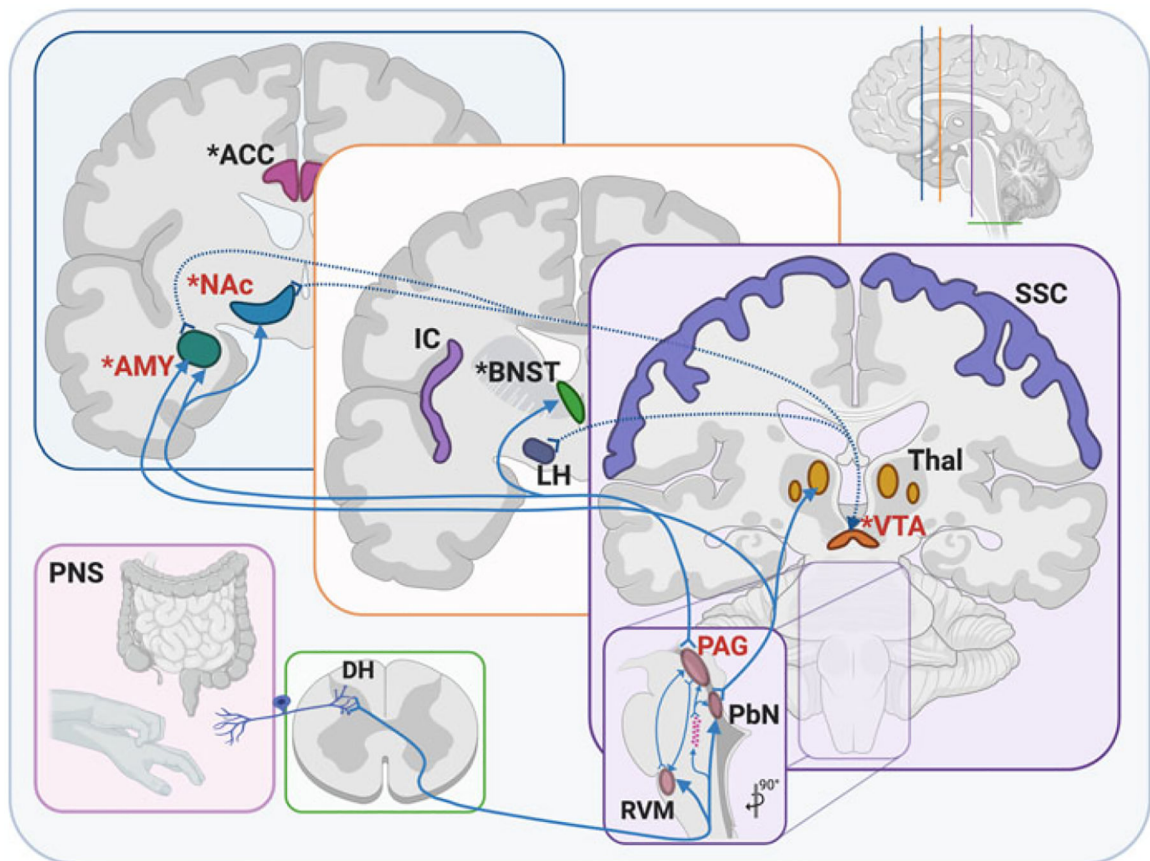
Fig. 3.
Anatomical expression and contribution of the dynorphin-KOR system in the sensory and affective components of chronic, persistent pain. KORs are present on peripheral sensory inputs from skin and visceral targets, where they synapse onto the DH of the spinal cord. Within the spinal cord, KORs are concentrated in the lamina II of the superficial DH. From here, sensory information is sent via ascending connections into numerous brain stem nuclei, including the RVM, PbN, and a cluster of LJA5 cells. From there, sensory information is relayed into midbrain regions, including PAG and VTA, where KORs are concentrated and shown to be upregulated following chronic pain. Connections from the brain stem and midbrain are further relayed to numerous forebrain areas, including PbN to Thal and AMY, as well as PAG to AMY, BNST, and NAc, all regions shown to contribute to the affective dimension of pain. KOR is also increased in NAc and AMY following chronic pain. Other regions involved in the affective and/or sensory dimensions of pain are the ACC, IC, and SSC, though the connectivity and specific contribution of KOR is not yet fully understood. *areas known to be involved in affective pain; red text: areas where KOR activity is increased following chronic pain; dotted arrows: known dynorphin connections; pink stars: LJA5 cells. *ACC* anterior cingulate cortex, *AMY* amygdala, *BNST* bed nucleus of the stria terminalis, *DH* dorsal horn, *IC* insular cortex, *LH* lateral hypothalamus, *NAc* nucleus accumbens, *PAG* periaqueductal gray, *PbN* parabrachial nucleus, *PNS* peripheral nervous

system (sensory components), *RVM* rostral ventromedial medulla, *SSC* somatosensory cortex, *Thal* thalamic nuclei, *VTA* ventral tegmental area

Table 1

Clinical trials that KOR partial agonism or antagonism improves substance use disorder (pain is noted). Nalmefene (Selincro®), a mu opioid receptor inverse agonist with weak partial KOR agonist properties, is used in the treatment of alcohol use disorder. Buprenorphine (partial mu opioid agonist, ORL-1 agonist, KOR antagonist/partial KOR agonist, and delta opioid antagonist) and naloxone (Zubsolv®, Suboxone®) combination has been used for treating opioid use disorder (Heo and Scott 2018) and this combination was reported to reduce pain. Buprenorphine in combination with samidorphan (MOR antagonist) showed beneficial effects over placebo to reduce symptoms in major depressive disorder patients who had inadequate responses to antidepressants, although this drug combination was recently rejected by the US Food and Drug Administration. Polymorphisms in the KOR gene are associated with opioid dependence. Previous reviews have discussed the safety and efficacy of buprenorphine for the treatment for chronic pain (Davis et al. 2018; Pergolizzi and Raffa 2019) or opioid use disorder (Parida et al. 2019)

Species	Sex	Protocol	KOR ligand	Brain region	Model	Outcome	Ref
Human	M/F	Phase IV clinical trial	Nalmefene	na	EtOH-dependent outpatients	↓ Heavy drinking days ↓ Total EtOH consumption	(Barrio et al. 2018)
Human	M/F	Double-blind Multicenter Randomized	Nalmefene	na	AUD (>60 g/day M >40 g/day F)	↓ Heavy drinking days ↓ Total EtOH consumption	(Miyata et al. 2019)
Human	M/F	FMRI Placebo controlled, double-blind	Nalmefene	Putamen, angular gyrus, supramarginal gyrus, (↔amygdala)	AUD	↑ BOLD to emotional faces in areas responsible for empathy and social cognition, attentional shift happy > fearful	(Vollstädt-Klein et al. 2019)
Human	M/F	Double-blind, placebo control trial	Nalmefene	na	AUD	↓ Heavy drinking days	(Mason et al. 1999)
Human	Male	FMRI with i.v. EtOH (6% v/v to achieve 80 mg/dL)	Nalmefene	Striatum	Heavy drinkers	↓ BOLD during reward anticipation	(Quelch et al. 2017)
Human			ORPK1 gene polymorphism (rsJ0958350- rs7016778-rsJ2675595)	na	Methadone maintenance for OUD	Polymorphism was associated with opioid withdrawal	(Wang et al. 2014)
Human			ORPK1 gene polymorphism (rs997917, rs6985606)	na	Methadone maintenance for OUD	Polymorphism was associated with opioid dependence	(Albonaim et al. 2017)
Human			ORPK1 gene polymorphism (KOR 36G > T SNP, rs6473797, rsI6918842, rs3802279)	na	Heroin-dependence	Polymorphism was associated with heroin dependence	(Yuferov et al. 2004; Gerra et al. 2007; Levran et al. 2008; Yuanyuan et al. 2018)
Human	Male	Suicide ideation for inpatients	Buprenorphine (sublingual)	na	OUD and major depressive disorder	↓ Suicide ideation	(Ahmadi et al. 2018)
Human	M/F	Multicenter double-blind placebo controlled trial	Buprenorphine/ samidorphan (not approved by FDA)	na	Major depressive disorder	↓ Depression (HAM-D, 17-item scale, Montgomery-Åsberg depression rating	(Ehrich et al. 2015a; Fava et al. 2016)

Species	Sex	Protocol	KOR ligand	Brain region	Model	Outcome	Ref
						scale and the clinical global impressions severity scale)	
Human	M/F	OUD	Buprenorphine-naloxone	na	OUD	↓ Pain intensity (in non-chronic pain cohorts)	(Becker et al. 2015)
Human	M/F	In patient oxycodone selfadministration	Buprenorphine-naloxone	na	OUD/chronic pain transitioning from opioid to Bup/Nx	↓ Pain ratings when switched to Bup/Nx ↔ between placebo and oxycodone preference, those that showed oxycodone preference had lower Bup/Nx dose, more withdrawal and more pain	(Roux et al. 2013)
Human	M/F	Pilot clinical trial	Buprenorphine-naloxone	na	OUD/chronic pain transitioning from opioid to Bup/Nx	↓ Average and worse pain after switching to Bup/Nx	(Rosenblum et al. 2012)
Human	M/F	Postsecondary analysis of randomized trials	Buprenorphine-naloxone	na	OUD	>50% reported pain at baseline Improvement in pain correlated with increased retention of treatment	(Shulman et al. 2020)
Human	M/F	Open-label randomized	Buprenorphine-naloxone	na	OUD	↔Pain intensity, affective pain or sensory pain but women had greater affective pain than men	(Latif et al. 2019)
Human	M/F	Postsecondary analysis of randomized trials	Buprenorphine-naloxone	na	OUD	Patients with flare-up pain were at higher risk of relapse	(Griffin et al. 2016)
Human	M/F	Postsecondary analysis of randomized trial	Buprenorphine-naloxone	na	OUD with chronic pain	↓ Pain over course of 12 week treatment, those with high pail volatility were more likely to relapse	(Worley et al. 2015, 2017)
Human	Male	Case study (40 year+ with chronic pain)	Buprenorphine-naloxone	na	Chronic pain with long-term opioid use	↓ Pain, improved function and quality of life	
Human	Male	Randomized trial	Buprenorphine-naloxone vs. methadone	na	Chronic pain and OUD	↓ Pain at 6 months	(Neumann et al. 2013)

Table 2

Evidence that KOR activation contributes to stress-induced reinstatement of opioid seeking behavior in preclinical models

KOR ligand	Species	Sex	Drug of abuse/protocol	Stressor/pain	Main outcome	Reference	Pain component
Nor-BNI	Sprague Dawley rats	Male	Heroin IVSA and stress-induced reinstatement	Yohimbine (YOH)	KOR blockade reduced reinstatement	(Zhou et al. 2013)	No
Nor-BNI	Sprague Dawley rats	Male	Heroin IVSA and stress-induced reinstatement	Food deprivation	KOR blockade reduced reinstatement	(Sedki et al. 2015)	No
Nor-BNI	Mouse (C57Bl/6)	Male	Morphine CPP and drug-prime reinstatement	Incisional postsurgical pain model	KOR blockade enhanced drug-primed reinstatement	(Nwaneshiudu et al. 2020)	Yes
LY2456302	Sprague Dawley rats	Male	Oxycodone IVSA and cue-induced reinstatement	None	KOR blockade had no effect on reinstatement	(Bossert et al. 2019)	No
CJ-15208 (Cyclo[Pro-Sar-Phe-D-Phe]) or Nor-BNI	Mouse (C57Bl/6)	Male	Morphine CPP and stress-induced reinstatement	Forced swim stress	Both drug interventions prevented reinstatement	(Brice-Tutt et al. 2020; Ferracane et al. 2020)	No
Buprenorphine + naltrexone	Sprague Dawley rats	Male	Morphine CPP and drug-prime reinstatement	None	The combination blocked drug-primed reinstatement	(Cordery et al. 2014)	No
Dezocine (partial MOR agonist, KOR antagonist) or buprenorphine	Sprague Dawley rats	Male	Morphine CPP and drug-prime reinstatement	None	Both drug interventions prevented reinstatement	(Wu et al. 2019)	No
Nor-BNI	Sprague Dawley rats	Male	Morphine CPP and drug-prime reinstatement	None	KOR blockade did not alter drug-primed reinstatement	(He et al. 2019)	No