HHS Public Access

Author manuscript

Neuropharmacology. Author manuscript; available in PMC 2024 June 15.

Published in final edited form as:

Neuropharmacology. 2023 June 15; 231: 109510. doi:10.1016/j.neuropharm.2023.109510.

Pain-related cortico-limbic plasticity and opioid signaling

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Abstract

Neuroplasticity in cortico-limbic circuits has been implicated in pain persistence and pain modulation in clinical and preclinical studies. The amygdala has emerged as a key player in the emotional-affective dimension of pain and pain modulation. Reciprocal interactions with medial prefrontal cortical regions undergo changes in pain conditions. Other limbic and paralimbic regions have been implicated in pain modulation as well. The cortico-limbic system is rich in opioids and opioid receptors. Preclinical evidence for their pain modulatory effects in different regions of this highly interactive system, potentially opposing functions of different opioid receptors, and knowledge gaps will be described here. There is little information about cell type- and circuit-specific functions of opioid receptor subtypes related to pain processing and pain-related plasticity in the cortico-limbic system. The important role of anterior cingulate cortex (ACC) and amygdala in MOR-dependent analgesia is most well-established, and MOR actions in the mesolimbic system appear to be similar but remain to be determined in mPFC regions other than ACC. Evidence also suggests that KOR signaling generally serves opposing functions whereas DOR signaling in the ACC has similar, if not synergistic effects, to MOR. A unifying picture of pain-related neuronal mechanisms of opioid signaling in different elements of the cortico-limbic circuitry has yet to emerge.

Keywords

Amygdala; prefrontal cortex; mesolimbic; neuroplasticity; pain; kappa opioid receptor; mu opioid receptor; delta opioid receptor

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Credit authorship contribution statement

Volker Neugebauer: Conceptualization, Methodology, Investigation, Writing - original draft, review & editing, Supervision, Project administration, Funding acquisition. Guangchen Ji, Vadim Yakhnitsa, Peyton Presto, Nico Antonucci: Methodology, Investigation, Writing - original draft, review and editing. Brianna Mendoza: Methodology, Investigation, Writing - original draft.

Declarations of interest: none

1. Cortico-limbic plasticity in pain

The limbic system is comprised of cortical and subcortical structures, including medial prefrontal cortical regions (mPFC) with anterior cingulate cortex (ACC), and hippocampus and amygdala. Ventral components of the basal ganglia such as nucleus accumbens (NAc) and paralimbic regions such as the insular cortex (IC) interact closely with these cortico-limbic circuits. The cortico-limbic system plays an important role in pain mechanisms and pain modulation, reward and substance abuse (Navratilova et al., 2015a; Taylor, 2018; Thompson and Neugebauer, 2019). Neuroplasticity defined as a functional and/or structural change that outlasts or becomes independent of the initial event, has been shown in different regions of the mPFC (reviewed in Kummer et al., 2020) and amygdala (reviewed in Neugebauer, 2020) in pain models, and there is some evidence for pain-related neuroplasticity in IC (Qiu et al., 2014) and NAc (see Ren et al., 2021). Interactions of ACC and IC with amygdala are largely facilitatory (Jasmin et al., 2003; Zhuo, 2011) whereas those between infra- and pre-limbic mPFC and amygdala involve powerful feedforward inhibition (Cheriyan et al., 2016; Ji et al., 2010; Kiritoshi and Neugebauer, 2018; Thompson and Neugebauer, 2019). Here we focus on preclinical studies of neuroplasticity in the cortico-limbic system in pain as the basis for understanding opioid system functions in these regions (see Figure 1).

1.1 Medial prefrontal cortex (mPFC)

The mPFC serves executive functions, decision-making, memory retrieval, and control of emotions and behavior (Bechara and Damasio, 2005; Euston et al., 2012; Wood and Grafman, 2003). Different subregions are infralimbic, prelimbic and anterior cingulate cortices in rodents and Brodmann areas 25, 32 and 24b, respectively, in primates (van Heukelum et al., 2020). The infra- and pre-limbic cortices receive input primarily from limbic rather than somatosensory regions, including pain-related information from thalamus and amygdala; additionally, the ACC receives thalamo-cortical inputs from all sensory modalities (Gabbott et al., 2006; Hoover and Vertes, 2007). Direct inputs from the spinal cord have also been described (Cliffer et al., 1991). In addition to intra- and inter-cortical projections mainly from layer II/III, the different mPFC subregions project to subcortical targets, including mediodorsal thalamus (mostly layer VI), NAc (layer V of IL and PL more so than ACC), lateral hypothalamus (mainly layer V), different amygdala nuclei (layer II and V), nucleus accumbens (ACC and PL to core; IL to shell) periaqueductal gray (PAG, layer V), ventral tegmental area (VTA, layer V of IL and PL but not ACC), parabrachial nucleus (PB, layer V of IL more so than IL but not ACC), nucleus of the solitary tract (NTS, mostly layer V of IL), rostral ventromedial medulla (RVM, layer V of IL and PL and little ACC), and spinal cord (layer V mostly of PL and ACC) (Ding et al., 2001; Gabbott et al., 2005; Gabbott et al., 2006; Vertes, 2004). These targets include regions involved in pain modulation.

1.1.1 Infralimbic and prelimbic mPFC—Il and PL pyramidal cells have large receptive fields and respond to peripheral noxious stimuli (Ji and Neugebauer, 2011, 2014; Ji et al., 2010). Pain-related neuroplasticity has been shown at the BLA-IL and BLA-PL synapses (Cheriyan and Sheets, 2018; Cheriyan and Sheets, 2020; Ji and Neugebauer, 2010;

Kiritoshi et al., 2016) and hippocampal-PL and thalamic-PL synapses (Kelly et al., 2016; Kelly and Martina, 2018). Input from the BLA generates monosynaptic excitation and polysynaptic inhibition in IL and PL, including in neurons projecting to PAG and amygdala (Cheriyan et al., 2016). Synaptic feedforward inhibition from BLA is increased in layer V pyramidal cells of IL (Kiritoshi et al., 2016) and PL (Ji et al., 2010) in male rats in a model of arthritic pain and in PL neurons in male mice in a model of neuropathic pain (Zhang et al., 2015b). Excitation-inhibition balance is decreased at the BLA-PL but not BLA-IL synapse (Cheriyan and Sheets, 2020) and excitatory glutamatergic transmission from hippocampus and dorsomedial thalamus to layer V PL neurons is decreased in male rats under neuropathic pain conditions (Kelly et al., 2016; Kelly and Martina, 2018). Excitatory cholinergic modulation of layer V PL is also lost (Radzicki et al., 2017) in male rats in neuropathic pain. As a consequence, decreased background and evoked activity (extracellular recordings in anesthetized rats) was found in IL (Ji and Neugebauer, 2014) and PL (Ji and Neugebauer, 2011; Ji et al., 2010) presumed pyramidal neurons in male rats in an arthritis pain model and reduction of excitability (whole-call patch-clamp in mouse brain slice) of PL but not IL neurons in male mice in a neuropathic pain model (Cheriyan and Sheets, 2018). Accordingly, restoring/increasing activity in IL and PL decreased sensory and affective arthritic (Kiritoshi et al., 2016), inflammatory (Wang et al., 2015), and neuropathic (Lee et al., 2015; Zhang et al., 2015b) pain behaviors in male rodents through downstream inhibition of amygdala output (Ji and Neugebauer, 2014) and activation of nucleus accumbens (Lee et al., 2015). It should be noted that there is evidence for increased intracortical excitatory transmission and hyperexcitability of layer II/III pyramidal cells in the PL in male rats in neuropathic pain (Cordeiro Matos et al., 2015; Metz et al., 2009) and increased local excitatory transmission onto PL layer II/III neurons in male rats in an inflammatory pain model (Wang et al., 2015), and these neurons can engage inhibitory connections with layer V neurons. However, decreased excitatory transmission between PL layer II/III and layer V neurons was reported in a neuropathic pain model (Cheriyan and Sheets, 2018) and decreased excitability of PL layer II/III in an inflammatory pain model (Wang et al., 2015) in male rodents. The IL and PL circuitry is complex, and pain-related changes may be region-, cell type- and projection-specific.

1.1.2 Anterior cingulate cortex (ACC)—Neuroplasticity has been shown in ACC in different pain models (reviewed in Bak et al., 2021; Taylor, 2018; Zhuo, 2011). Like IL and PL neurons (see 1.1.1), ACC neurons have large receptive fields and respond to noxious somatic and visceral stimuli and are activated during pain anticipation or pain avoidance behavior (Gao et al., 2006; Hutchison et al., 1999; Koyama et al., 2000; Koyama et al., 2001; Kuo and Yen, 2005; Sikes and Vogt, 1992; Yamamura et al., 1996). In contrast to IL and PL deactivation in pain conditions (see 1.1.1), ACC pyramidal layer V cells and certain layer II/III neurons (intermediate type), but not interneurons, show increased activity in neuropathic pain models in both sexes as measured with electrophysiology or calcium imaging (Blom et al., 2014; Cao et al., 2009; Santello and Nevian, 2015; Zhao et al., 2018). Increased intracortical excitatory glutamatergic synaptic transmission was found in layer II/III pyramidal cells through a presynaptic mechanism in males in inflammatory pain (Bie et al., 2011; Toyoda et al., 2009; Zhao et al., 2006; Zheng, 2010) and pre- and postsynaptic changes in males in neuropathic pain (Toyoda et al., 2009; Xu et al., 2008)

models. In layer V, loss of connectivity between pyramidal cells and interneurons was interpreted to indicate ACC disinhibition in neuropathic male mice (Blom et al., 2014). Changes of several proteins related to synaptic plasticity were also reported in the ACC in male mice under neuropathic pain models, including increases in the expression levels of c-Fos, phosphorylated cyclic-AMP response element binding protein (pCREB), neural cell adhesion molecule 1 (NCAM1), and protein kinase Mzeta (PKMζ) (Bak et al., 2021; Li et al., 2010; Wei et al., 1999; Zhuo, 2011). There is evidence from peripheral nerve block experiments in male rats to suggest that ACC pain-related plasticity persists at least in part independently of primary afferent input (Wei and Zhuo, 2001).

Lesions or functional inactivation, including activation of inhibitory neurons, of the ACC decreases predominantly averse-affective and anxio-depressive aspects of inflammatory and neuropathic pain (Barthas et al., 2015; Chen et al., 2018; Fuchs et al., 2014; LaGraize et al., 2004; Lei et al., 2004; Li et al., 2009; Qu et al., 2011; Ren et al., 2008; Xiao et al., 2013; Xiao and Zhang, 2018), but may also affect the sensory aspects of pain. For example, inhibition of hypersensitivity has been reported with pharmacological or optogenetic inhibition of ACC (Chen et al., 2018; Santello and Nevian, 2015; Tan et al., 2017) or midcingulate cortex (MCC) (Tan et al., 2017) activity in male rodents. Conversely, optogenetic activation of ACC pyramidal neurons in males produces hypersensitivity (Chen et al., 2018) and anxio-depressive behaviors (Barthas et al., 2015); optogenetic activation of MCC pyramidal cells in males induced hypersensitivity but not aversive behavior (Tan et al., 2017). These effects are likely mediated through top-down control systems that involve direct projections to PAG and spinal dorsal horn as well as interactions with IC, thalamus (ventral posterolateral and -medial), amygdala and nucleus accumbens (for recent review see Thompson and Neugebauer, 2019).

1.2 Amygdala

The amygdala is comprised of different nuclei. Lateral, basolateral and central nuclei (LA, BLA, CeA) are of particular importance for sensory and nociceptive processing and pain modulation. A majority of neurons in the lateral and capsular division of the CeA (CeLC) respond to peripheral noxious stimuli primarily with excitation but a population of inhibited neurons has also been found (Bernard et al., 1990, 1992; Goncalves and Dickenson, 2012; Neugebauer and Li, 2002). Nociceptive information reaches the amygdala from the parabrachial nucleus (PB) and from thalamic nuclei (midline, posterior intralaminar/paraventricular, and posterior regions) and cortical regions (mPFC, IC, sensory association cortices) (Neugebauer, 2020). The major if not exclusive source of calcitonin gene-related peptide (CGRP) in the CeA is from the lateral PB (Dobolyi et al., 2005; Harrigan et al., 1994; Palmiter, 2018), which targets almost exclusively the CeLC and delineates what has been termed the “nociceptive amygdala” (Neugebauer et al., 2004). The identification of nociceptive input from the PB to the CeLC as part of a spino-parabrachial-amygdala pain pathway originally triggered the exploration of amygdala processing of nociceptive information and neuroplasticity in pain conditions. Some recent controversy surrounds the relay of spinal nociceptive information from the PB to the CeLC. While there is strong evidence for monosynaptic excitatory projections to the CeLC from neurons in the external lateral PB (Bernard et al., 1989; Bernard et al., 1993; Chiang et al., 2020), including neurons

containing calcitonin gene-related peptide (Palmiter, 2018), these PB projection neurons may not receive nociceptive input directly from spinal dorsal horn neurons (Chiang et al., 2019) but rather through intra-PBN connectivity, involving spinal projections to tachykinin receptor 1 positive neurons in the superior lateral PB (Deng et al., 2020; Huang et al., 2019) and dynorphin-expressing neurons in the dorsal lateral PB that send axons to external lateral PB (Chiang et al., 2020). However, older studies have linked spinal input directly to the external lateral PB (Bernard et al., 1989). Thalamic and cortical inputs target primarily the LA-BLA network but also CeA neurons (Fu et al., 2020) and may contain nociceptive information. That information converges with PB input onto CeA neurons to drive a complex set of largely inhibitory GABAergic and peptidergic neurons and connections. This network includes feedforward inhibition of CeLC neurons driven by direct or indirect, via BLA, cortical (IL > PL) projections (Kiritoshi and Neugebauer, 2018).

Increased excitatory transmission at the LA-BLA, BLA-CeLC and PB-CeLC synapses has been shown in different pain models using brain slice electrophysiology, which indicates synaptic plasticity (for review see Neugebauer, 2020). Synaptic plasticity at the PB-CeLC synapse was found at the acute stages of pain models (5–6 hours to about 10 days) such as formalin, arthritis (knee), muscle, visceral (colon), and neuropathic pain. Enhanced excitatory transmission at the LA-BLA and BLA-CeLC synapses was found in an acute arthritis model and at the BLA-CeLC synapse also at the acute stage of a neuropathic pain model (see Neugebauer, 2020). A cluster of inhibitory intercalated cells (ITC) mediate feedforward inhibition of CeA neurons, which is decreased in male rats in acute pain conditions (arthritis model) (Ren et al., 2013; Ren and Neugebauer, 2010). Little is known about synaptic plasticity in the amygdala circuitry in chronic pain conditions, but enhanced excitatory transmission was detected at the BLA-CeA synapse in male rats at the chronic stage (4 weeks) of a neuropathic pain model (Ji et al., 2017). As a result, electrophysiological studies in anesthetized rats recorded increased ongoing and evoked activity of neurons in the CeA and BLA of male rats in acute arthritis (3–6 h) (Ji et al., 2017; Neugebauer and Li, 2003) and acute (2–14 days) (Goncalves and Dickenson, 2012) and chronic (4 weeks) (Ji and Neugebauer, 2019; Ji et al., 2017) neuropathic pain. Increased calcium responses to peripheral stimuli, but not ongoing activity, was also detected in BLA neurons of awake male mice at the acute and chronic stages of neuropathic pain (Corder et al., 2019).

Cell type- and projection-specific amygdala functions in pain that are only beginning to emerge and are the focus of current research efforts (Adke et al., 2021; Hein et al., 2021; Ji and Neugebauer, 2020; Li et al., 2022; Li and Sheets, 2018; Li and Sheets, 2020; Mazzitelli et al., 2022; Wilson et al., 2019; Yakhnitsa et al., 2022). PKCδ, somatostatin (SOM) and corticotropin-releasing factor (CRF) positive neurons form the main CeA cell clusters (Fadok et al., 2017; Kim et al., 2017; McCullough et al., 2018; Pomrenze et al., 2015; Sanford et al., 2017). PKCδ and CRF, but not SOM, neurons express CGRP receptors and receive CGRP input from PB (Harrigan et al., 1994; Kim et al., 2017; Ye and Veinante, 2019). It should be noted that while CRF and SOM neurons have long been recognized as CeA output neurons sending descending and ascending projections, respectively, to brainstem, hypothalamic nuclei and basal forebrain regions (Bartonjo and Lundy, 2022; Fadok et al., 2017; Li et al., 2013; Magableh and Lundy, 2014; Penzo et al., 2014; Pomrenze

et al., 2015; Sanford et al., 2017; Ye and Veinante, 2019), PKCδ neurons have recently been shown to project the basal forebrain and some brainstem regions (Singh et al., 2022). PKCδ but not SOM neurons showed increased activity in male mice in a neuropathic pain model (6–14 days) (Adke et al., 2021; Wilson et al., 2019). A subtype of CeM, but not CeL, neurons projecting to the PAG had increased excitability in male and female mice in an acute inflammatory pain model (Li and Sheets, 2018). Analysis of paired-pulse ratio at the PB-CeA synapse indicated decreased synaptic efficacy in SOM positive neurons (capsular and medial CeA) but increased transmission in SOM negative neurons (capsular CeA) in mice of both sexes in a neuropathic pain model (10 days); synaptic efficacy was decreased in CRF positive and CRF negative neurons in the CeL, but increased in CRF positive neurons in CeM (Li and Sheets, 2020).

Studies using various pharmacological or knock-down strategies found that CeA activation generated sensory and emotional affective pain-like behaviors under normal conditions, while CeA inhibition decreased behaviors in models of inflammatory and neuropathic pain (see Neugebauer, 2020). More recently, optogenetic activation of PB input to CeA was shown to generate avoidance behavior (Ito et al., 2021) and to serve as a noxious signal for fear (Sato et al., 2015) in male mice and for avoidance memory in mice of both sexes (Chiang et al., 2020). Aversive learning in male and female mice was also induced by optogenetic activation of calcitonin gene-related peptide (CGRP) containing PB input to CeA (Bowen et al., 2020). Optogenetic activation of CeA-CRF neurons or BLA-CeA produced mechanical hypersensitivity, emotional responses and anxiety-like behaviors and increased activity of nociceptive spinal dorsal horn neurons of male rats under normal conditions (Mazzitelli et al., 2021; Mazzitelli et al., 2022). Conversely, optogenetic inhibition of CeA-CRF neurons or BLA-CeA input decreased emotional responses and spinal dorsal horn activity, but not mechanical hypersensitivity, in male rats in an arthritis pain model (Mazzitelli et al., 2021) and emotional responses and anxiety-like behavior, but not hypersensitivity, in male rats in a neuropathic pain model (Mazzitelli et al., 2022). Chemogenetic activation of CeA-PKCδ neurons increased mechanical hypersensitivity in normal male mice whereas chemogenetic inhibition of CeA-PKCδ neurons inhibited hypersensitivity in a neuropathic pain model. In contrast, chemogenetic inhibition of CeA-SOM neurons produced mechanical hypersensitivity under normal conditions but had no effect in neuropathic male mice (Wilson et al., 2019).

It will be important to determine the cell type- and projection-specific amygdala functions in pain-related neuroplasticity and descending and ascending pain modulation. For example, opposing functions of PKCδ and SOM neurons in the CeLC could reflect a differential pain modulator similar to the ON- and OFF-cells, respectively, in the rostral ventromedial medulla (Chen and Heinricher, 2019). It should be noted, however, that in the context of fear memory formation, PKCδ neurons are considered to act as OFF-cells and SOM as ON-cells, with PKCδ inhibition and SOM activation driving fear responses in mice of both sexes (Ciocchi et al., 2010; Haubensak et al., 2010; Penzo et al., 2014). This complex issue remains to be resolved.

1.3 Mesolimbic dopamine system (nucleus accumbens)

The mesolimbic dopamine system centered on ventral tegmental area (VTA) and nucleus accumbens (NAc) plays a key role in reward mechanisms, and their dysregulation is a critical factor in drug addiction and alcohol use disorder (Koob and Volkow, 2016) and in pain conditions (Borsook et al., 2016; DosSantos et al., 2017; Harris and Peng, 2020; Navratilova and Porreca, 2014). There is strong evidence for decreased dopamine levels in the NAc in pain conditions but increase of dopamine with the alleviation of pain (Navratilova et al., 2015a), although there may be differences between shell and core regions in male mice (Ren et al., 2021). Located in the ventral striatum, the NAc is anatomically and functionally divided into an outer (shell) and central (core) subregion. Principal cells in each region are GABAergic medium spiny neurons that express either D1 or D2 dopamine receptors as part of the direct (D1) or indirect (D2) pathway (Salgado and Kaplitt, 2015). NAc receives dopaminergic projections from VTA (to shell) and substantia nigra (to core) and glutamatergic input from mPFC, IC, ventral hippocampus, midline thalamus, and BLA to shell and core. IL appears to target mainly shell and PL, ACC and IC the core, which also receives CRF input from the CeA (Borrego et al., 2022; Groenewegen et al., 1999; Li et al., 2018; Salgado and Kaplitt, 2015; Stuber et al., 2011; Wright and Groenewegen, 1995). Nociceptive information can reach the NAc through these limbic pathways, but direct input from the spinal cord has also been described (Burstein and Giesler, 1989; Cliffer et al., 1991).

While recordings of nociceptive neurons in NAc appear to be lacking, neuroimaging (fMRI) data in male rats showed decreased activity in NAc core at the onset of a noxious stimulus and signal increase at the offset (Becerra et al., 2013). Preliminary neurochemical and immunohistochemical evidence in transgenic mice points to nociceptive neurons in the NAc shell that show increased responsiveness to touch in a neuropathic pain model (Wojick et al., 2022). Synaptic plasticity in the NAc has been shown in pain models. NMDA receptor-mediated excitatory transmission at the mPFC-NAc (shell) synapse was increased in D1 and D2 neurons in brain slices from neuropathic male mice (7 or 14 days postinduction) (Jing et al., 2022; Wu et al., 2018). Prolonged NMDA receptor kinetics were found in male mice at the acute stage (12 h) of an inflammatory pain model whereas at the later stages (12 days) of inflammatory and neuropathic pain models AMPA receptor-mediated excitatory transmission decreased, resulting in lower AMPA/NMDA ratio in D2 but not D1 NAc (core) neurons (Schwartz et al., 2014). A shift towards calcium permeable AMPA receptors accompanied by decreased excitatory transmission at depolarized potentials was found in the synaptic responses of NAc (core) neurons of male rats in a neuropathic pain model (14 days) (Goffer et al., 2013). Decreased excitatory transmission from IL (and slower NMDA receptor decay time), but increased excitability as a consequence of decreased dopaminergic signaling from VTA, was found in D2 but not D1 NAc (shell) neurons of male mice in a neuropathic pain model (5 days) (Ren et al., 2016). Decreased excitatory transmission from BLA to D2, but not D1, NAc (core) neurons was found in slices from neuropathic male mice (8 days), which was not mediated by dopamine signaling; in contrast, excitatory transmission from PL was increased in D2, but not D1, neurons in the same model (Ren et al., 2021).

Importantly, restoring the observed changes in NMDA receptor function, decreased hypersensitivity and depression-like behaviors in neuropathic male mice (Jing et al., 2022; Wu et al., 2018). Mitigating synaptic changes (decreased excitatory transmission) in D2 NAc neurons prevented the decrease in motivation to earn a natural reward in male mice with inflammatory and neuropathic pain without affecting mechanosensitivity (Schwartz et al., 2014). AMPA potentiators administered into the NAc decreased neuropathic pain-induced depression-like behaviors but not hypersensitivity in male rats (Goffer et al., 2013). Chemogenetic inhibition of hyperexcitable D2 NAc neurons decreased hypersensitivity in neuropathic male mice (Ren et al., 2016). Similarly, optogenetic silencing of D2 or activation of D1 neurons in NAc (shell or core) inhibited thermal hypersensitivity in neuropathic mice (Sato et al., 2022). Inactivation of the NAc (shell) with lidocaine decreased mechanical and thermal hypersensitivity in neuropathic male rats (14 days) (Chang et al., 2014). Interestingly though, optogenetic activation of PL-NAc (core) projections decreased mechanical and thermal hypersensitivity and aversive and depression-like behaviors in male rats in a neuropathic pain model (14 days) (Lee et al., 2015). Similarly, chemogenetic activation of D2 NAc (core) neurons decreased anxiety-like behavior and restored social interaction in neuropathic male mice (8 days; there was no effect, however, on mechanical hypersensitivity (Ren et al., 2021). Increased dopamine release in NAc correlated with pain relief in neuropathic (Kato et al., 2016) and postoperative (Navratilova et al., 2012) male rat pain models, and restoring dopamine levels (with L-DOPA) decreased mechanical hypersensitivity in neuropathic male mice (Ren et al., 2016). Blocking dopaminergic signaling in the NAc with D1 or D2 antagonists attenuated stress-induced analgesia in male rats (Noursadeghi et al., 2022) and the antinociceptive effects of morphine and other interventions in male rats (Altier and Stewart, 1998; Haghparast et al., 2012; Harris and Peng, 2020; Navratilova et al., 2012; see 2.3).

While the important role of the NAc and dopamine signaling in reward and pain relief is now well-established, the functional heterogeneity of this circuitry and cell type- and region-specific changes in pain conditions remain to be explored in terms of behavioral modulation and adaptive or maladaptive functions in pain.

2. Opioid system in cortico-limbic pain plasticity and pain modulation

The focus of this review is on opioid receptor function in pain-related neuroplasticity in corticolimbic circuits discussed in 1. Expression, cellular actions and behavioral effects of Mu, kappa, and delta opioid receptors (MOR, KOR, and DOR) will be described.

2.1 Medial prefrontal cortex (mPFC)

Opioid receptors have been shown to be densely distributed throughout the rodent neocortex, with striking differences in laminar distributions reported by early autoradiographic studies. In the rat, MORs were found to be predominately distributed in laminae I and IV of the cerebral cortex (subregions not specified) whereas DORs were primarily located in laminae II, III, and V, with a relatively equivalent distribution of MORs and DORs in lamina VI (Goodman et al., 1980). In the mouse, MORs are prominent in laminae I, IV, and VI of the frontal cortex (subregions not specified) while DORs are found in all layers (Moskowitz

and Goodman, 1984). Laminar distributions of KORs were not investigated in either study. MORs in the mPFC are extensively localized on GABAergic interneurons (Férézou et al., 2007; Taki et al., 2000) to regulate mPFC output that is known to modulate the reward circuitry centered on signaling from the VTA to NAc, where MOR activation facilitates dopamine release through disinhibition (Fields and Margolis, 2015; Trigo et al., 2010). Cellular distributions of KORs within the mPFC have not been well characterized, though KOR are found on VTA dopaminergic neurons (Chefer et al., 2013) and BLA glutamatergic neurons (Tejeda et al., 2015) that project to the mPFC. Though little information is available regarding DOR cellular distributions, conditional knockout of the DOR gene in GABAergic neurons in the forebrain (ACC and unspecified frontal cortical region) of male mice revealed a preservation of some DOR activity, suggesting that DORs may also be located on mPFC excitatory neurons (Chung et al., 2015). Another study found both MORs and DORs to be localized to cell bodies and neurite-like processes in cultured cells (suggested to be both pyramidal and non-pyramidal neurons from morphological analysis) from male mouse frontal cortex brain slices containing the PL, IL, and ACC, with some cells showing co-localization of both receptors predominately in the region of the cell soma (Olianas et al., 2012). The differential cellular distributions may have important functional implications. Opioid receptor location in the mPFC as well as their involvement in adjacent neuronal circuitries support a role in the modulation of pain and pain-related emotional-affective behaviors.

2.1.1 Infralimbic and prelimbic mPFC—Actions in both prelimbic and infralimbic mPFC regions have been implicated in opioid-related processing (Reiner et al., 2019). While there is evidence for opioid receptor functioning in the mPFC, including infra- and prelimbic regions and their connections, in pain modulation, little is known about cell type- and circuit-specific actions of individual opioid receptor types and their role in pain-related neuroplasticity.

2.1.1.1 MOR: Both endogenous and exogenous MOR signaling can be linked to plasticity of interneurons in the mPFC. Chronic systemic administration of morphine (MOR agonist) increased the dendritic branching of SOM interneurons and the dendritic elongation of parvalbumin (PV) interneurons in the mPFC of male mice (Wang et al., 2019). Similarly, endogenous MOR knockdown in the mPFC with a small hairpin RNA (shRNA) viral vector decreased total dendrite length and impaired dendritic complexity of SOM but not PV interneurons, suggesting MOR signaling in SOM interneurons may contribute to their dendritic development (Wang et al., 2019). As PL and IL inhibitory signaling (Jones and Sheets, 2020; Kiritoshi et al., 2016), including SOM and PV interneurons (Jones and Sheets, 2020; Shiers et al., 2018), is involved in cognitive deficits associated with chronic pain, and MORs are expressed in interneurons in this regions (see 2.1), MOR signaling in the mPFC circuitry may influence pain-related processing. One study found that concomitant activation of MOR (with [D-Ala^2, *N*-MePhe^4, Gly-ol]-enkephalin, DAMGO) and DOR (with ([D-Pen^2,D-Pen^5]enkephalin, DPDPE) potentiated dopamine D1-like receptor signaling in male mouse mPFC brain slices that contained the PL, IL, and ACC (Olianas et al., 2012). This finding may suggest that MOR and DOR in these regions can strengthen dopamine D1

receptor modulation of glutamatergic transmission, a function that is critical in neuroplastic processes such as long-term potentiation (Gurden et al., 2000).

Systemic morphine-induced analgesia involved decreased purinergic signaling in the PL in the formalin pain model (Zeng et al., 2021). Intraplantar formalin triggered a slow but sustained increase in adenosine 5'-triphosphate (ATP) in the mouse PL, which was decreased by systemic injection of morphine (Zeng et al. 2021). Furthermore, infusion of ATP into PL weakened antinociceptive effects of morphine, whereas intra-PL delivery of a selective P2X7 receptor antagonist (Brilliant Blue G) partially mimicked morphine's antinociceptive effects in the formalin test and, like presumed blockade of P2X4 receptors, enhanced morphine analgesia in morphine-tolerant male mice (Zeng et al., 2021). In contrast, systemic injection of a MOR agonist and serotonin-norepinephrine reuptake inhibitor (tramadol) had no acute effect on neuronal firing activity of PL pyramidal neurons in anesthetized male rats (Hasanpour Razmanjani and Reisi, 2022). Systemic application of morphine inhibited the spontaneous firing of the majority (63%) of PL neurons in anesthetized male rats, an effect that was reversed by systemic application of naloxone (Giacchino and Henriksen, 1996). However, electrophoretic application of a MOR agonist (DAMGO) inhibited spontaneous activity in only 38% of neurons, with most showing no change (Giacchino and Henriksen, 1996). Pyramidal cells and interneurons were not distinguished in that study. These findings may suggest the involvement of additional circuitry in mPFC-related MOR signaling.

Descending projections from mPFC to the PAG, where MOR activation inhibits GABAergic transmission to disinhibit output to the RVM to suppress pain behaviors (Vaughan and Christie, 1997; Vaughan et al., 1997), may be involved in the reported potentiation of opioid analgesia by off-label agents. For example, systemic coadministration of morphine and disulfram, an inhibitor of acetaldehyde dehydrogenase that is typically used to promote abstinence in alcohol use disorder, caused an increase in mechanical and thermal withdrawal thresholds that was attributed to an increase in MOR activation efficacy by disulfram in brain systems that include mPFC (unidentified region), PAG and RVM in male rats (de Corde-Skurska et al., 2021). Conversely, blocking MOR signaling in the mPFC has pain facilitating effects. Intra-mPFC (PL) delivery of a MOR antagonist (naloxonazine) increased the intensity of both the first and second phases of formalin-induced orofacial pain behaviors in male rats; this blockade was strong enough to prevent the antinociception by a non-steroidal anti-inflammatory drug (diclofenac) (Tamaddonfard et al., 2020). MOR signaling in PL and descending pathways may also be involved in placebo analgesia. The PL is one of the brain regions activated during placebo analgesia induced by a gabapentin-based conditioning approach in male rats in the spinal nerve ligation (SNL) model of neuropathic pain (Zeng et al., 2018). Microinfusion of a MOR antagonist (naloxone) into PL blocked placebo analgesia in the SNL model and disrupted functional coupling between PL and PAG (Zeng et al., 2018). Chemogenetic and optogenetic inhibition of mPFC (possibly IL) CRF neurons that project to the NAc or a CRF receptor 1 antagonist in the NAc were able to block morphine conditioned place preference (CPP) in neuropathic (chronic constriction injury, CCI) but not sham male mice (Kai et al., 2018), implicating an mPFC to NAc pathway in neuropathic pain-related MOR signaling.

On the input side, the firing rate of dopaminergic VTA neurons projecting to the mPFC (region not specified but possibly IL) decreased in brain slices from male mice with chronic mild stress (CMS)-induced depression (Liu et al., 2018). Intra-VTA morphine significantly increased the firing rate of VTA projection neurons recorded in anesthetized CMS, but not stress-naïve, mice and relieved depressive-like behaviors in the tail suspension, social interaction and sucrose preference tests but increased thermal nociception (decreased paw withdrawal latency) (Liu et al., 2018). Morphine-induced nociceptive responses were prevented by blocking brain-derived neurotrophic factor (BDNF) in VTA but not mPFC, suggesting that MOR in the mesolimbic reward circuitry can differentially regulate depression and nociceptive behaviors and related mPFC functions.

There is evidence to implicate hereditary factors, non-neuronal mechanisms, and sexual dimorphism in the role of mPFC in MOR signaling. Parental morphine exposure in male and female rats prior to mating resulted in reduced spontaneous activity of unidentified PL neurons and in decreased thermal (hot plate test) and visceral (acetic acid writhing test) nociception and decreased nocifensive behavior in the first and second phase of the formalin test in male offspring of morphine-abstinent rats compared to those from naïve parents (Ashabi et al., 2018). Significantly enhanced antinociceptive effects of systemic morphine and upregulation of MOR signaling in NAc but not mPFC were also found in the offspring of morphine-abstinent rats (Ashabi et al., 2018). The data implicate hereditary factors in altered mPFC function in pain-related MOR signaling. Proteomic analysis suggests that glial cells may also be linked to MOR signaling in the PL mPFC. In the PL of male rats with mechanical and thermal hyperalgesia induced by a MOR agonist (fentanyl), downregulation of five types of myelin-related proteins was found, and blockade of oligodendrocyte apoptosis with a caspase 3 inhibitor (z-DEVD-fmk) in the PL mPFC prevented fentanyl-induced hyperalgesia (Wang et al., 2022). Considering that oligodendrocytes (and other glia) express MOR (Stiene-Martin et al., 2001), it is reasonable to conclude that PL glial cells may contribute to MOR-related signaling. Finally, it is important to note that MOR signaling mechanisms in the mPFC may differ with regard to sex, leading to potential sexual dimorphisms in pain processing in this region. Intravenous self-administration with a potent MOR agonist (remifentanil) led to sex-specific differences in the excitability and synaptic modulation of PL layer 5/6 pyramidal neurons recorded in brain slices. Whereas remifentanil treatment caused a long-lasting hypoexcitable state in males and females, decreased excitability occurred on a faster timeline in females while hypoexcitability was preceded by hyperexcitability in males (Anderson et al., 2021). Different synaptic mechanisms were involved in hypoexcitability of PL pyramidal cells in males and females. Decreased excitatory synaptic transmission mediated by AMPA-type glutamate receptors was recorded in females, whereas the hyper- and hypoactive states in males were driven by decreased and increased $GABA_B$ receptor signaling, respectively (Anderson et al., 2021). No significant effects on neuronal excitability were observed in IL pyramidal cells, suggesting region-specific differences in MOR signaling (Anderson et al., 2021). Chemogenetic activation of PL pyramidal cells mitigated remifentanil-induced cognitive deficits in an extradimensional shift test and restored neuronal excitability and synaptic regulation in PL pyramidal neurons (Anderson et al., 2021). Together, the data may suggest sex-specific MOR-related pain modulatory mechanisms involving mPFC, explain

previously reported sex differences in response to opioid-related pain management (Huhn et al., 2018, 2019), and provide support for tailoring opioid-related therapeutic strategies to biological sex in chronic pain patients.

2.1.1.2 KOR: KOR signaling in the mPFC involves presynaptic inhibition of glutamatergic transmission including onto NMDA receptor-expressing neurons. In the PL mPFC (laminae V and VI of the cingulate cortex, area 3) of male rats, KORs were found to be primarily localized on axons and axon terminals, with a small proportion associated with dendritic shafts and glial processes, and KOR-labeled axons contacted NMDA NR1 subunit-immunoreactive postsynaptic targets (Svingos and Colago, 2002). KOR activation with a selective agonist (U69,593) decreased frequency, but not amplitude, of glutamatergic miniature excitatory postsynaptic potentials (mEPSP) in layer V pyramidal neurons (likely PL and ACC) recorded in brain slices from male rats (Tejeda et al., 2013). However, this modulation may be input-specific as systemic U69,593 decreased monosynaptic field excitatory postsynaptic potentials (fEPSPs) in mPFC neurons recorded in anesthetized male rats when evoked by BLA but not hippocampal (fornix) stimulation (Tejeda et al., 2015). Intra-mPFC application of U69,593 reduced both electrical and optogenetic BLA-evoked glutamatergic fEPSPs in mPFC neurons, an effect that was blocked by systemic administration of a KOR antagonist (nor-binaltorphimine, nor-BNI) (Tejeda et al., 2015). Intra-mPFC (PL/ACC) administration of U69,593 also decreased extracellular dopamine levels in male rats, whereas administration of nor-BNI increased extracellular dopamine levels; these effects were not observed in mice line lacking KOR in dopaminergic neurons, suggesting an action of KOR on mesocortical dopaminergic terminals (Tejeda et al., 2013). Therefore, KOR signaling in the mPFC may regulate glutamatergic and dopaminergic inputs including through a tonically active system, though constitutive mPFC KOR activity may decline with age (Sirohi and Walker, 2015).

In pain conditions, alterations in mPFC KOR signaling may influence neuroplasticity related to opioid reward. mRNA levels of dynorphin, an endogenous ligand for KOR, were increased in the mPFC (subregion not specified) of male mice with morphine conditioning and a hindpaw incision pain model compared to that of sham mice, while no differences were present after recovery from incisional injury (Nwaneshiudu et al., 2020). In this study, blockade of KOR with systemic nor-BNI also led to an enhancement of morphine conditioning behavior in injured animals; together, this may suggest a potential protective role for mPFC KOR activation in acute pain when primed for morphine reward. U69,593-stimulated [35S]GTPγS binding increased in the mPFC (subregions not differentiated) in brain slices from male rats 7 days after CCI induction; however, no significant differences in binding were found between 30 day-CCI and sham animals (Llorca-Torralba et al., 2020), suggesting that KOR-related neuroplasticity in the mPFC may play a more critical role at the acute stage of neuropathic pain. Anxiolytic effects of mPFC KOR blockade have also been reported, as intra-mPFC (likely PL) infusion of nor-BNI in naïve male mice increased time spent in the center of the open field test (OFT), whereas systemic nor-BNI administration did not have a significant effect on anxiety-like behavior (Tejeda et al., 2015). Intra-mPFC nor-BNI microinjection in male rats also blocked conditioned place aversion (CPA) produced by systemic U69,593 (Tejeda et al., 2013). Since pain has an averse-

affective component and is often comorbid with anxiety, shared neurobiological mechanisms in the mPFC may contribute to pain modulation and emotional network neuroplasticity (Vachon-Presseau et al., 2016), which could be regulated by blockade of mPFC KOR signaling. However, the role of KOR signaling in mPFC subregions in pain-related behaviors and neuroplasticity remains to be determined, and data suggest rather complex KOR actions in the mPFC related to pain, anxiety, and brain reward processing.

As with MOR, potential sexual dimorphism has been reported for KOR-related nociceptive mechanisms in the mPFC. In a mouse model of Fabry disease, a condition commonly associated with painful neuropathy (Burand and Stucky, 2021), downregulation of prodynorphin and KOR mRNA levels in the mPFC (region not specified) of males but upregulation in females was measured, and males, but not females, displayed mechanical and thermal hypersensitivity in the plantar aesthesiometer and Hargreaves tests, respectively, compared to wild type (Rullo et al., 2021). Interestingly, the same trend was not seen at the protein level – females displayed an increase but males showed no difference in mPFC KOR protein levels in the disease model compared to wild type (Rullo et al., 2021). The data suggest that early dysregulation of the dynorphinergic KOR system may contribute to the nociceptive symptoms of Fabry disease, possibly in a sex-dependent way. Overall, it is not clear if KOR signaling in mPFC is protective or harmful with regard to pain and pain-related neuroplasticity.

2.1.1.3 DOR: The DOR system has been implicated in sensory and affective pain regulation (Cahill et al., 2022; Gavériaux-Ruff and Kieffer, 2011; Nadal et al., 2006) but pain-related neuronal and behavioral effects of DOR signaling in the mPFC remain to be determined.

Like MOR signaling, DOR-related mechanisms in the mPFC may affect interneuron plasticity. Following DOR downregulation with shRNA, SOM but not PV mPFC (likely PL) interneurons demonstrated decreased total dendrite length and dendritic complexity; however, DOR but not MOR knockdown impaired dendritic morphology in SOM interneurons following a single morphine injection in male mice (Wang et al., 2019). These results suggest that while both MOR and DOR are critically involved in mPFC dendrite development, the endogenous signaling mechanisms may have differential roles regarding dendritic remodeling in response to exogenous activation. DORs in the mPFC may also have associations with MORs with regard to dopaminergic transmission, as one study reported that concomitant activation of DOR (with [D-Pen^2,D-Pen^5]enkephalin, DPDPE) and MOR (DAMGO), but not KOR (U50,488), in the male mouse mPFC enhanced dopamine D1-like receptor signaling in brain slices that included IL, PL and ACC, and a large percentage of dopamine D1 receptor positive cells expressed DOR and/or MOR immunoreactivity in neuronal cell bodies and processes of mPFC primary cell cultures with substantial co-localization of DORs and MORs (Olianas et al., 2012). As these two receptors have been shown to form heterodimers with novel functional properties (George et al., 2000), potential DOR-MOR interactions may influence opioid-related neurotransmission in the mPFC.

Little has been investigated with regard to DOR signal transduction in the mPFC under pain conditions. A DOR agonist (DPDPE) decreased [35S]GTPγS binding significantly

in the mPFC (subregions not differentiated) in brain slices from male rats 30 days after CCI induction relative to 7 days after induction after a non-significant increase at 7 days compared to sham controls (Llorca-Torralba et al., 2020); this may suggest that DOR-related activity changes in the mPFC are associated with early rather than chronic stages of the neuropathic condition. Neuronal effects of DOR signaling in the mPFC have been studied under normal conditions but not in pain models. In brain slices from male mice, a DOR agonist (KNT-127) significantly decreased the frequency, but not amplitude, rise time, or decay time, of spontaneous and miniature excitatory postsynaptic currents (EPSCs) in PL pyramidal cells, and this effect was blocked by a DOR antagonist (naltrindole, NTI) (Yamada et al., 2021). KNT-127 also significantly increased the paired-pulse ratio, suggesting that DOR activation decreases glutamate transmission through a presynaptic site of action. KNT-127 decreased excitability of PL pyramidal neurons in the PL mPFC measured as the reduction in the number of action potentials and firing threshold (Yamada et al., 2021). Administration of KNT-127 into the PL mPFC of male mice decreased anxiety-like behavior (OFT) and glutamate, but not GABA, release induced by a sodium channel activator (veratrine) (Saitoh et al., 2018). KNT-127 administration into PL mPFC also decreased veratrine-induced c-Fos expression in the amygdala (LA, BLA and CeA) (Saitoh et al., 2018). KNT-127 alone had no effect. Inhibitory effects of DOR activation in the PL mPFC may therefore contribute to pain modulation but this remains to be determined.

2.1.2 Anterior cingulate cortex (ACC)—Endogenous opioid neurotransmission in the ACC plays an important role in pain modulation. The ACC has one of the highest levels of opiate ligand binding in the CNS, and MOR and DOR, but less so KOR, are localized in the ACC (Mansour et al., 1987; Tempel and Zukin, 1987; Vogt et al., 2001; Zubieta et al., 2001). Neuroimaging (PET) studies in humans found evidence for increased release of endogenous opioids in the ACC during acute experimental pain in healthy subjects (muscle pain induced by hypertonic saline (Scott et al., 2007) and heat pain (Sprenger et al., 2006)) and in patients with peripheral or central neuropathic pain (Maarrawi et al., 2007), fibromyalgia (Harris et al., 2007) and migraine during a spontaneous migraine attack (DaSilva et al., 2014), supporting a role of endogenous opioid function in the modulation of pain. Preclinical studies also found that release of endogenous opioids in the rodent ACC is necessary for the relief of the aversiveness of ongoing pain (Navratilova et al., 2015a).

2.1.2.1 MOR: MOR is expressed at high levels in superficial and deep layers of the ACC though differences are noted between studies (Mansour et al., 1987; Tempel and Zukin, 1987; Vogt et al., 2001; Wang et al., 2018; Zubieta et al., 2001). A greater number of functional DAMGO receptor sites was reported on axons than on somata and proximal dendrites (Vogt et al., 2001). Converging evidence from clinical PET studies measuring binding of MOR radiotracers suggests increased opioid release and MOR activation in the ACC of healthy subjects undergoing sustained experimental muscle pain (Scott et al., 2007; Zubieta et al., 2001) and in patients diagnosed with a variety of pain conditions such as fibromyalgia (Harris et al., 2007; Schrepf et al., 2016), migraine (DaSilva et al., 2014), and post-stroke pain (Willoch et al., 2004). Activation of the MOR system on the ACC was associated with reductions in affective ratings of the pain experience (McGill Pain Questionnaire affective scores) (Zubieta et al., 2001). Neuroimaging PET studies also

found that increased ACC activity (regional blood flow) correlated with MOR-mediated antinociceptive effects of exogenous opioids (remifentanil) and placebo analgesia during noxious heat stimulation in normal subjects (Petrovic et al., 2002; Wager et al., 2007).

Evidence from preclinical studies also implicates endogenous opioids and MOR signaling in the ACC in affective rather than sensory pain relief (Navratilova et al., 2015a). In male rats with postsurgical pain (incision model) or neuropathic pain (SNL model), blockade of ACC opioid signaling with naloxone or ablation of ACC MOR expressing neurons with the cytotoxic ribosome inhibitor dermorphin-saporin inhibited conditioned place preference (CPP) and NAc dopamine release resulting from non-opioid pain-relieving treatments such as peripheral nerve block or intrathecal administration of an α2-adrenergic agonist (clonidine), but had no effect on mechanical and thermal hypersensitivity (Navratilova et al., 2015b). Thus, ACC opioid and MOR signaling is required for pain relief by non-opioid treatments through the activation of reward circuits. MOR blockade with β-funaltrexamine (β-FNA) in the ACC also prevented CPP and NAc dopamine release induced by morphine administration into the amygdala (CeA) in neuropathic male rats (SNL model). Therefore, endogenous MOR signaling in the ACC is involved in affective pain relief by MOR activation in the CeA through a functional connection from CeA to ACC (Navratilova et al., 2020).

Injection of morphine into the ACC decreased aversive but not sensory pain behaviors in models of neuropathic (SNL model) and postsurgical pain (Gomtsian et al., 2018; LaGraize et al., 2006; Navratilova et al., 2015a; Navratilova et al., 2015b). Morphine in the ACC decreased the aversiveness of noxious cutaneous stimulation in male SNL rats measured as escape/avoidance behavior in the light-dark test (LaGraize et al., 2006) and produced CPP and dopamine release in the NAc in male rats with postinjury and SNL pain but not in uninjured rats (Navratilova et al., 2015b). ACC morphine-induced CPP in SNL rats was blocked by pretreatment of NAc with a dopamine receptor blocker (α-flupenthixol). Morphine in the ACC did not affect mechanical (von Frey or Randall-Selitto) or thermal (Hargreaves or hot plate) hypersensitivity (Gomtsian et al., 2018; LaGraize et al., 2006; Navratilova et al., 2015a; Navratilova et al., 2015b). However, mechanical (Randall-Selitto) and thermal (hot plate) antinociceptive effects of ACC morphine have also been reported; they were blocked by β-FNA and were decreased in a neuropathic pain model (CCI) compared to normal male rats, possibly due to the downregulation of MOR expression measured at the mRNA level (Wang et al., 2020). Still, evidence suggests that MOR signaling in the ACC relieves predominantly the aversiveness of pain and activates reward/motivation circuits.

At the cellular level, systemic administration of morphine inhibited laser-heat stimulus evoked activity of ACC neurons in awake male and female rats measured with single-unit multi-array recordings (Kuo and Yen, 2005; Wang et al., 2009). In brain slices from male rats with complete Freund's adjuvant (CFA)-induced inflammatory pain, a MOR agonist (DAMGO) decreased evoked glutamatergic transmission in layer II/III neurons, and this effect was blocked by a MOR antagonist (CTAP). The effect was due to a presynaptic action because DAMGO increased paired-pulse ratio and decreased frequency, but not amplitude, of mEPSCs (Zheng, 2010).

2.1.2.2 KOR/DOR: KOR expression in ACC is more uniformly distributed across different layers but at a lower level than MOR whereas DOR expression in ACC is strong in superficial and deep layers (Mansour et al., 1987; Tempel and Zukin, 1987) though segregation of DOR and MOR neurons in different ACC layers of the ACC has been reported with DOR expression prominent in layer II/III and MOR in layer V (Wang et al., 2018). PET studies in humans showed that KOR binding is greater in men than women in multiple brain regions, including ACC (Vijay et al., 2016). There is also evidence for lateralization of the endogenous opioid system in the human ACC. In radioimmunoassays, levels of opioid peptides Leu-enkephalin-Arg (LER, DOR/MOR agonist) and Met-enkephalin-Arg-Phe (MEAP, KOR/MOR agonist) were lateralized to the left and right ACC, respectively (Watanabe et al., 2015), which may be linked to the lateralization of higher functions and their modulation, such as positive and negative emotions and pain (Brügger et al., 2011; Kim et al., 2012; Knoll and Carlezon, 2010; Shippenberg, 2009; Symonds et al., 2006).

Pain-related functions and cellular actions of KOR signaling in the ACC are largely unknown. Administration of a KOR agonist (U69,593) into the ACC of naïve male mice and rats by microdialysis decreased dopamine, glutamate and GABA levels and induce conditioned place aversion whereas a KOR antagonist (nor-BNI) enhanced dopamine release and blocked U69,593-mediated conditioned place aversion (Tejeda et al., 2013). Consistent with presynaptic KOR actions, U69,593 decreased the mEPSP frequency, but not amplitude, in ACC layer V pyramidal cells in brain slices (Tejeda et al., 2013).

Some evidence suggests that DOR signaling in the ACC has inhibitory effects on neuronal activity and behaviors in pain models. In neuropathic male mice with sciatic nerve ligation, DOR dysfunction measured by agonist-induced G protein activation and astrogliosis due to impaired DOR-mediated astrocyte differentiation was found in the ACC, and these changes were linked to anxiety-like behaviors (EPM and light-dark test) (Narita et al., 2006b). Administration of a DOR agonist ([D-Ala2, D-Leu5]-enkephalin, DADLE) into ACC reversed CFA-induced conditioned place avoidance, but not thermal hypersensitivity, in male rats and decreased phosphorylation of NMDA receptor subunits GluN1, GluN2A, GluN2B, NMDA, but not AMPA, receptor-mediated currents and discharge frequency of ACC pyramidal cells in rat brain slices, suggesting that DOR activation alleviates affective pain by decreasing activity of ACC pyramidal cells (Ma et al., 2022). In brain slices from normal male and female mice, DPDPE inhibited local inhibitory transmission from PV interneurons to ACC layer V pyramidal cells through an action on DOR on PV interneurons without affecting excitatory inputs from medial thalamus, and this disinhibition resulted in increased excitability (action potential firing) of ACC pyramidal cells. MOR activation with DAMGO decreased excitatory thalamic inputs and ACC pyramidal excitability (Birdsong et al., 2019). Neuronal mechanisms of DOR signaling in the ACC and potential changes and behavioral consequences in pain conditions and pain-related neuroplasticity remain to be determined.

2.2 Amygdala

The amygdala plays an important role in opioid analgesia manning (Bagley and Ingram, 2020; Helmstetter et al., 1998; Manning, 1998; Manning and Mayer, 1995a, b; McGaraughty et al., 2004; McGaraughty and Heinricher, 2002). MOR, DOR and KOR that are all expressed at various levels in the amygdala but may have different functions. MOR signaling in the amygdala is linked to analgesia, reward and the regulation of fear, anxiety and related behaviors (Bagley and Ingram, 2020; Bodnar, 2022; Tershner and Helmstetter, 2000; Wilson and Junor, 2008; Zhang et al., 2013). Amygdala DOR is also involved in anxiolysis (Klenowski et al., 2015). In contrast, amygdala KOR signaling has anxiogenic and aversive behavioral effects (Cahill et al., 2014; Limoges et al., 2022).

2.2.1 MOR—MORs are expressed in all nuclei of the amygdala and at high levels in the BLA (Mansour et al., 1987) and on ITC cells (Wang et al., 2018; Winters et al., 2017). MOR immunoreactivity in the BLA is found on dendritic spines and axon terminals and also in Golgi apparatus (Zhang et al., 2015a). MOR can act presynaptically at excitatory synapses in CeM neurons (Zhu and Pan, 2005) and CeLC neurons (Kissiwaa et al., 2020) but also on terminals of inhibitory synapses in CeL and on postsynaptic sites where there was some co-expression with CRF receptors in male mice (Jaferi and Pickel, 2009). Given the opposite intracellular signal mechanisms of MOR and CRF-receptors through Gi and Gs proteins, respectively, MOR signaling including through endogenous opioids may counterbalance the excitatory effects of CRF as has been shown for stress responses in male rats in the locus coeruleus (Curtis et al., 2001; Valentino and Van Bockstaele, 2001). In the BLA, MOR expression is lower and has been found on pyramidal cells and interneurons as well as on excitatory synaptic terminals in male rats, and as a result there could be inhibitory and dis-inhibitory effects of MOR on BLA output neurons (Zhang et al., 2015a).

Neuronal effects of MOR signaling in the amygdala have been studied under normal conditions but not in pain models. Brain slice electrophysiology showed hyperpolarization and decreased input resistance mostly in interneurons in the rat LA with methionine-enkephalin (ME) or DAMGO (Sugita et al., 1993), and these effects were blocked with naloxone and CTOP (Sugita and North, 1993). DAMGO increased spike adaptation in rat LA pyramidal neurons by potentiating Kv1.2-mediated voltage-dependent potassium currents through the activation of the phospholipase A2-arachidonic acid-lipoxygenases signaling pathway (Faber and Sah, 2004). ME or endogenous opioids also produced an outward current in male rat ITC cells by activating a potassium conductance, which was blocked by a MOR antagonist (CTAP) (Winters et al., 2017). Likewise, DAMGO hyperpolarized ITC cells from male mice (Blaesse et al., 2015). DAMGO also inhibited CeL and CeM neurons, including those projecting to PB, by inducing postsynaptic potassium currents in male rat brain slices (Chieng et al., 2006).

MOR can also regulate excitatory and inhibitory transmission in the amygdala. DAMGO decreased excitatory inputs from dorsal midline thalamus to BLA pyramidal cells and CeL neurons as well as feedforward excitation of CeM neurons in mice brain slices (Goedecke et al., 2019). DAMGO inhibited BLA-evoked excitatory transmission in ITC cells (Winters et al., 2017), CeLC neurons (Kissiwaa et al., 2020) and in CeM neurons (Zhu and Pan,

2005), and also PB-evoked excitatory transmission in CeLC neurons (Kissiwaa et al., 2020) through a presynaptic action in male rat brain slices. DAMGO induced long-term depression in dorsomedial striatum neurons by activating MOR on excitatory inputs from BLA in male mice brain slices (Muñoz et al., 2020). In male rat brain slices, DAMGO decreased inhibitory GABAergic, but not excitatory glutamatergic, transmission (mIPSCs and evoked IPSCs) in BLA neurons projecting to the CeA through a presynaptic action that involved Kv1.1 and Kv1.2 potassium channels, and this effect was blocked by a MOR antagonist (CTAP) (Finnegan et al., 2006). DAMGO also decreased GABAergic transmission between ITC and CeM neurons by hyperpolarizing ITC cells in male mouse brain slices without affecting excitatory transmission from BLA to ITC or CeM (Blaesse et al. 2015), although another study in male rat brain slices reported presynaptic inhibition of excitatory transmission from BLA to ITC with DAMGO that was blocked by CTAP (Winters et al., 2017). DAMGO or morphine decreased evoked GABAergic transmission (IPSPs) in CeA neurons in male rat brain slices through a presynaptic mechanism without affecting membrane properties (Bajo et al., 2011). A MOR antagonist (CTOP) increased inhibitory transmission suggesting tonic activation of MOR. The different pre- and postsynaptic MOR actions on excitatory and inhibitory elements of the complex amygdala circuitry do not yield a clear picture yet and remain to be explored in pain conditions.

This is important because of evidence for decreased MOR signaling measured as DAMGO-stimulated [^{35}S]GTPγS binding to amygdala cell membranes in mouse models of inflammatory (CFA) and neuropathic (sciatic nerve ligation) pain in males (Narita et al., 2006a). MOR expression in the amygdala was downregulated in males in a rat surgical (incision) pain model combined with perioperative stress through microRNA (miRNA-339-5p)-mediated posttranscriptional regulation (Zhu et al., 2022). In addition to pain-related changes in MOR signaling there is also evidence for MOR-induced amygdala neuroplasticity. Prenatal (days 11–18 post-conception) systemic morphine application decreased and increased MOR density expression in the BLA and CeA, respectively, in male but not female rats (Vathy et al., 2003). Systemic morphine treatment of newborn rats on postnatal days 1–4, but not after day 22, decreased MOR binding in the BLA (Tempel, 1991). Intermittent systemic morphine treatment induced FosB/DeltaFosB transcription factor expression in limbic brain regions of male mice, including BLA and CeA (Kaplan et al., 2011). Chronic escalating, but not single, morphine application in male mice significantly altered expression of genes involved in neuroplasticity, including neurogenesis, cell growth, and signaling proteins such as G protein-coupled receptors, scaffolding and signaling proteins, and neuropeptides (Befort et al., 2008).

MOR signaling in the amygdala is antinociceptive and inhibits averse-affective behaviors through a mechanism that involves at least in part descending modulation of the PAG-RVM circuitry. Morphine injections into BLA decreased thermal nociception (increased tail-flick latency) (Helmstetter et al., 1995; McGaraughty and Heinricher, 2002) and increased activity of RVM OFF-cells while decreasing RVM-ON cell activity in naïve male rats (McGaraughty and Heinricher, 2002). The antinociceptive effects (tail-flick test) of DAMGO injected into BLA of male rats were decreased by lidocaine injection into PAG or RVM and blocked by lesion of PAG or RVM (Helmstetter and Tershner, 1994; Helmstetter et al., 1998). Morphine or β-endorphin injected into BLA or CeA increased tail-flick latencies

and shock-evoked jump thresholds in male rats and this effect was blocked by blocking opioid receptors in the PAG (Pavlovic et al., 1996). MOR activation was more effective on the jump test than tail-flick test, suggesting modulation of the affective pain component, which is also supported by a study showing that DAMGO injection into CeA inhibited conditioned place aversion induced in male rats by an inflammatory pain condition (CFA) but did not affect heat hyperalgesia (paw withdrawal latency) in this pain model (Zhang et al., 2013). Interestingly, administration of morphine into right but not left CeA produced conditioned place preference (CPP) in neuropathic male rats (SNL model) without affecting mechanical hypersensitivity (Navratilova et al., 2020), suggesting lateralized modulation consistent with pain-related neuroplasticity in the right but not left CeA (Allen et al., 2020; Neugebauer, 2020). Bilateral lesion of the CeA, but not BLA, abolished systemic morphine-induced antinociception in the tail-flick and formalin tests in male rats (Manning and Mayer, 1995a, b), suggesting that the CeA is required for morphine-induced antinociception including the suppression of spinally mediated nociceptive reflexes. Conversely, systemic naltrexone increased Fos expression in the CeA (especially CeLC) in naïve mice and the effect was greater in a model of latent sensitization, and CTAP injection into the CeA precipitated mechanical hypersensitivity in male and female mice (Cooper et al., 2022). Chemogenetic silencing of MOR expressing PB neurons that project to CeA decreased nociceptive behaviors in male and female mice in the formalin test, jumps in the hotplate test, and anxiety-like behaviors in the EPM, suggesting that MOR on excitatory nociceptive inputs could modulate affective pain behaviors through effects on CeA (Liu et al., 2022).

In healthy humans, a PET study using a MOR radiotracer ([^{11}C] carfentanil) found that sustained masseter muscle pain induced the release of endogenous opioids in the amygdala to activate MOR, which was associated with decreased sensory and affective pain ratings (Zubieta et al., 2001). Using a similar approach, placebo analgesia was shown to increase heat pain-induced MOR activation in limbic regions including the right amygdala whereas placebo-induced anticipatory opioid decrease was detected in the left amygdala (Wager et al., 2007). Placebo analgesia involving MOR activation may be linked to neuroimmune mechanisms. Using [^{11}C] carfentanil, a PET study in healthy humans subjected to experimental masseter muscle pain found that placebo analgesia-induced MOR activation in the left amygdala and NAc correlated with decreased plasma levels of a pro-inflammatory cytokine (IL-18) (Prossin et al., 2022).

2.2.2 KOR—KOR expressing cells are located in CeA while little expression is observed in BLA or ITC (Fallon and Leslie, 1986; Gomes et al., 2020; Hurd, 1996; Le Merrer et al., 2009; Mansour et al., 1996; Marchant et al., 2007; Peckys and Landwehrmeyer, 1999). KORs expression in CeA can be pre- and post-synaptic (Chieng et al., 2006; Gilpin et al., 2014). KOR activation with U69,593 increased or decreased GABAergic transmission (spontaneous IPSCs) in different sets of BLA neurons in brain slices from adolescent (30–40 days) but not adult (>60 days) male rats through a presynaptic action but had no effect on excitatory transmission (Przybysz et al., 2017; Varlinskaya et al., 2020). This effect was blocked in the presence of TTX suggesting a network action of KOR signaling. Another KOR agonist (U50,488H) decreased excitatory synaptic transmission and blocked long-term potentiation (field potentials) evoked in BLA neurons by stimulation

of LA afferents in male mouse brain slices (Huge et al., 2009). In CeM neurons from male rats, U69,593 decreased inhibitory transmission presynaptically (Gilpin et al., 2014; Przybysz et al., 2017), and this effect was not age-dependent (Przybysz et al., 2017). Similarly, U69,593 increased excitability of CRF neurons in the CeL in male rat brain slices through synaptic disinhibition, i.e., inhibition of feedforward inhibition driven by optical activation of PB input (Hein et al., 2021). U69,593 had no effect on PB-evoked excitatory synaptic transmission on CeA-CRF neurons (Hein et al., 2021) and on unidentified CeLC neurons (Kissiwaa et al., 2020). Single-unit recordings in anesthetized transgenic male rats showed that stereotaxic administration of U69,593 increased the responsiveness of CeA neurons to noxious mechanical stimuli and this effect was reversed by optogenetic silencing of CRF neurons in the CeA (Ji and Neugebauer, 2020). As a consequence of CeA neuronal activation by U69,593, activity of spinal dorsal horn neurons to innocuous and noxious mechanical stimuli increased (Ji and Neugebauer, 2020), suggesting that descending facilitation from CeA-CRF neurons is under the control of KOR signaling.

In models of neuropathic (SNL) (Navratilova et al., 2019) or functional (morphine priming followed by a stressor) (Yakhnitsa et al., 2022) pain, a KOR antagonist (nor-BNI) decreased synaptically evoked spiking of CeL neurons and excitability of CeL-CRF neurons in rat brain slices from SNL but not control male rats. This effect was mediated through a presynaptic action to increase feedforward inhibition driven by optogenetic and electrical stimulation of PB input. There was no effect on excitatory synaptic transmission. The data suggest tonic KOR-mediated disinhibition of CeA (including CRF) neurons in pain conditions. In anesthetized male rats, nor-BNI administered into CeA decreased ongoing activity and responses of CeA neurons to peripheral mechanical stimulation (Yakhnitsa et al., 2022).

Administration of U69,593 into the right CeA in naïve male rats increased vocalizations to noxious stimuli, and induced anxiety-like behaviors in the open field test and avoidance in the conditioned place “preference” test, but had no effect on mechanical thresholds in the paw pressure test (Hein et al., 2021). CRF neurons were involved in the KOR mediated behavioral effects because they were blocked by optogenetic silencing of CeA-CRF neurons. In neuropathic male rats (SNL model), administration of nor-BNI into the right CeA eliminated aversiveness and therefore blocked conditioned place preference to intravenous gabapentin but had no effect on mechanosensitivity in the von Frey test (Navratilova et al., 2019). Nor-BNI administered into right CeA also decreased vocalizations evoked by noxious stimuli and anxiety-like behavior in the elevated plus maze in males in a rat functional pain model (morphine priming plus stressor) but had mixed effects on mechanical hypersensitivity, showing inhibitory effects in the von Frey test but not paw pressure test (Yakhnitsa et al., 2022). Nor-BNI administration into the right but not left CeA prevented mechanical hypersensitivity (von Frey test) in males in an injury-free rat model of medication overuse (sumatriptan priming with stressor) (Xie et al., 2017) and also decreased mechanical hypersensitivity (von Frey test) in males in a rat model of trigeminal neuropathic pain (infraorbital CCI) but had no significant effect on anxiety-like behavior (elevated plus maze) (Turnes et al., 2022). The role and mechanisms of KOR signaling in the amygdala in sensory aspects of pain remain to be determined.

Nor-BNI administration into the right but not left CeA of male rats restored impaired diffuse noxious inhibitory controls (DNIC) induced by capsaicin injected into the forepaw as a conditioning stimulus in models of neuropathic (SNL) (Phelps et al., 2019) and functional (morphine priming with subsequent stressor) pain where dynorphin A levels were increased (Nation et al., 2018). Outcome measures for DNIC modulation included mechanosensitivity (paw pressure test) and spinal nociceptive processing (responses of dorsal horn neurons to mechanical stimuli).

There is evidence for pain-related changes in KOR signaling in the amygdala. In males in the rat model of medication overuse (sumatriptan priming with stressor), stress-evoked increases of dynorphin levels and phosphorylation of KOR were detected in both the left and right CeA (Xie et al., 2017). Phosphorylation could involve MAP kinase activation because of the inhibitory effects of a MAP kinase inhibitor (U0126) injected into the CeA (Xie et al., 2017), and increased dynorphin release is likely downstream of CRF activation (Bruchas et al., 2009). In a transgenic mouse model of Fabry disease, male but not female mice showed mechanical (plantar aesthesiometer) and thermal (Hargreaves test) hypersensitivity and there was a decrease of prodynorphin mRNA levels in the amygdala of males but an increase in females, suggesting sex-specific adaptation to pain (Rullo et al., 2021). In a mouse model of inflammatory pain (CFA), a significant increase of [^{35}S]GTPγS binding to amygdala cell membranes stimulated by a KOR agonist (ICI199,441) was found in males (Narita et al., 2006a). Increased KOR signaling and activation found in different pain models and inhibitory effects of KOR blockade in the amygdala point to the amygdala KOR system as an important pain mechanism and potentially useful target.

2.2.3 DOR—DOR expression is high in many brain areas including the amygdala (Mansour et al., 1987; Peckys and Landwehrmeyer, 1999). DOR neurons are mainly found in the BLA (Wang et al., 2018) whereas DOR expression in the CeA is mostly on axon terminals (Wilson et al., 2002) but has also been identified on dendrites, mainly on CRF neurons (Reyes et al., 2017). Neuronal DOR expression is also supported by immunohistochemistry and in situ hybridization of enkephalin mRNA in BLA and CeA (Zhang and McDonald, 2016). A DOR agonist (ICI174864) or endogenously released opioids acting on DOR inhibited glutamatergic transmission from BLA to ITC through a presynaptic action in male rats (Winters et al., 2017). A DOR1 agonist (DPDPE), but not DOR2 agonist (deltorphin II), inhibited excitatory transmission from BLA and PB to CeL neurons through a presynaptic action in male mouse brain slices (Zhou et al., 2021). Deltorphin II inhibited excitatory transmission evoked from BLA, but not PB, in a subset of CeLC neurons from male rats (Kissiwaa et al., 2020). In males in a mouse model of inflammatory pain (CFA), DPDPE decreased the increased excitatory transmission onto CeL neurons at 4 days whereas deltorphin II had inhibitory effects on PB-CeL transmission at 7 days, suggesting a functional switch from D1 to D2 (Zhou et al., 2021). Neither agonist had an effect at 21 days. Consistent with deceased DOR function in pain, [^{35}S]GTPγS binding to amygdala cell membranes stimulated by a DOR agonist (SNC80) was suppressed in mouse models of inflammatory (CFA) and neuropathic (sciatic nerve ligation) pain at the 4 week time point, and this was linked to anxiety-like behaviors (light-dark test and elevated plus maze) in males in these pain models because injection of a DOR antagonist

(naltrindole) had anxiogenic effects (Narita et al., 2006a). On the other hand, administration of DPDPE into the CeA had pronociceptive effects (decreasing mechanical thresholds) in normal male mice but not in the pain model and had no effect on anxiety-like behaviors (open field and elevated plus maze tests) in either condition (Zhou et al., 2021). Deltorphin II administration into CeA had no effect on mechanical nociception in either condition but had anxiolytic effects in the CFA model (7 days but not 4 days) whereas a DOR2 antagonist (naltriben), but not a DOR1 antagonist (BNTX), had anxiogenic effects at that stage (Zhou et al., 2021). The data suggest a link of DOR signaling in the amygdala to anxiety-like behaviors in pain, but the modulation of pain-related amygdala processing, plasticity and behaviors remains to be determined.

2.3 Mesolimbic dopamine system (nucleus accumbens)

Pain relief depends heavily on the reward system (Fields and Margolis, 2015; Leknes and Tracey, 2008; Porreca and Navratilova, 2017). Analgesic effects of opioids are strongly related to dopamine signaling in the mesolimbic NAc system. Dopaminergic signaling and the NAc play an important role in drug addiction and modulation of opioid-induced analgesia (Apkarian et al., 2013; Harris and Peng, 2020; Navratilova et al., 2015a). Blockade of dopamine D2 receptors in the NAc shell reduced the analgesic efficacy of morphine and substance P analogues administered in the ventral tegmental area in experimental male rats (Altier and Stewart, 1998). Conversely, dopamine signaling in NAc can be modulated by opioids. All opioid receptor subtypes (MOR, DOR and KOR) are expressed in NAc and MOR and DOR can colocalize on dendrites of NAc neurons (Gerfen et al., 1990; Meng et al., 1993; Meshul and McGinty, 2000; Svingos et al., 1998; Svingos et al., 1999; Svingos et al., 1997). There is evidence for differential functions of different NAc opioid receptor subtypes in pain processing as described below (2.3.1 and 2.3.2).

2.3.1 MOR and DOR—Opioid signaling in NAc is crucial for dopamine turnover. Stimulation of MOR and DOR with agonists in NAc provokes rapid extracellular dopamine release in the NAc measured by in vivo microdialysis (Di Chiara and Imperato, 1988; Fusa et al., 2005; Hipolito et al., 2008; Saigusa et al., 2017; Spanagel et al., 1992; Yokoo et al., 1994). Dopamine increase following activation of MOR and DOR is subregion-specific as it was observed in the core but not shell subregion in male rats (Hipolito et al., 2008). Administration of agonists for MOR (DAMGO), DOR1 (DPDPE) and DOR2 (DSLET) into NAc significantly increased the extracellular levels of dopamine in a dose-related manner that was partially naloxone-sensitive. An interaction between two DORs subtypes, DOR1 and DOR2, and MOR was also suggested. MOR activation engaged DOR1 to activate DOR2 and DOR1, but not DOR2, activated MOR causing the rapid increase in extracellular dopamine in male rats (Hirose et al., 2005).

Accumulating evidence points to the importance of NAc in opioid-mediated antinociception. Intra-NAc activation of MOR with microinjection of morphine induced sensory antinociception (Dill and Costa, 1977; Yu and Han, 1990), and the analgesic effects of morphine given systemically or into the habenula were reversed by intra-NAc administration of an opioid receptor antagonist (naloxone) in male animals (Dill and Costa, 1977; Ma et al., 1992), suggesting that habenula and NAc do not act independently in the antinociceptive

circuitry. Co-activation, but not individual activation, of MOR and DOR in NAc with DAMGO and DPDPE, respectively, produced antinociception measured as attenuation of the jaw-opening reflex in male rats (Schmidt et al., 2002). In males in a rat model of neuropathic pain (sciatic nerve ligation), intra-NAc administration of morphine markedly reduced hypersensitivity to mechanical and thermal stimuli as reflected in the increased latency of paw withdrawal reflexes (Bian and Yu, 2015). Interestingly, in males in a mouse model of neuropathic pain (CCI), mRNA levels of DOR, but not MOR, markedly increased in the ipsilateral NAc, and levels of proenkephalin, a ligand for MOR and DOR, were also elevated, suggesting pain-related plasticity in opioid NAc signaling (Wawrzczak-Bargiela et al., 2020). Conversely, blocking MOR and DOR in NAc produced pronociceptive effects. Either a specific MOR antagonist (CTOP) or a DOR antagonist (naltrindole) injected bilaterally into NAc blocked antinociception measured as attenuation of the jaw-opening reflex that was induced by intrathecally delivered DAMGO into the lumbar region of male rats (Gear and Levine, 2011) or by subdermal capsaicin injection into the plantar surface of the male rat paw (Schmidt et al., 2002). Antinociceptive effects of MORs and DORs can be attributed to dopamine receptor activation in NAc. Subdermal capsaicin evoked heterosegmental pain-induced antinociception in male rats that was reduced by bilateral intra-NAc pretreatment with either naloxone or a dopamine receptor antagonist (flupentixol) (Gear et al., 1999).

Pain, particularly chronic pain, is associated with negative affective states such as anxiety and depression. Activation of MOR and DOR in NAc with a high affinity agonist (UFP-512) administered into NAc of naïve male rats produced antidepressant-like behavior in the forced swim test and anxiolytic like behavior in the elevated plus maze and novelty-induced hypophagia tests (Kabli et al., 2014). Bilateral intra-NAc pretreatment with a MOR antagonist (CTOP) and a DOR antagonist (naltrindole) abolished antidepressant- and anxiolytic-like effects of UFP-512 (Kabli et al., 2014).

2.3.2 KOR—The mesolimbic KOR system has been implicated in reward, stress and nociception. Activation of KOR in NAc by pharmacological agents or by the endogenous ligand dynorphin, reduces motivational value of rewards and provokes aversion and depression-like behaviors that can be attributed to inhibition of dopamine release. Intra NAc microdialysis application of a KOR agonist (U69,593) decreased dopamine efflux in the dialysate by 50% whereas administration of a KOR antagonist (nor-BNI) increased dopamine levels in male rats dose-dependently (Spanagel et al., 1992). KORs on dopaminergic neurons are necessary for the development of aversive behaviors. Transgenic male mice with deletion of KOR on dopaminergic neurons did not develop conditioned place aversion (CPA) to systemically applied U69,593, and dopamine levels collected by microdialysis in the NAc were reduced (Chefer et al., 2013). In male rats in the formalin pain model, systemic morphine-induced dopamine release in the microdialysis probe in NAc was significantly decreased and this decrease was KOR dependent since intra-NAc microinjection of an antibody against dynorphin A restored the morphine effect on dopamine levels (Narita et al., 2005).

KOR activation in NAc produces negative affective anxiety- and depression like behaviors. A KOR agonist (U50,488) microinjected into NAc had anxiogenic effects in male mice

in elevated place maze and light-dark tests. Anxiogenic effects were prevented by intra-NAc pretreatment with a KOR antagonist (nor-BNI) (Wang et al., 2016). Local intra-NAc microinjections of U50,488 or dynorphin derivative E-2078 produced strong conditioned place aversion in male rats (Bals-Kubik et al., 1993; Wee and Koob, 2010). Dynorphin can also be released by optical stimulation of dynorphin-containing neurons in the NAc shell region of transgenic male mice (Al-Hasani et al., 2015). Region-specific behavioral effects were found and could be observed in the same animal. Photoactivation of dynorphin neurons in the ventral NAc shell provoked real-time place aversion whereas photoactivation of dorsal NAc shell neurons evoked real-time place preference behavior, while neither intervention induced anxiety-like behavior in the open field test (Al-Hasani et al., 2015). Optical activation of dynorphin-containing neurons in the ventral NAc of transgenic male and female mice also decreased motivation to self-administer sucrose while driving real-time place aversion (Massaly et al., 2019). Chemogenetic silencing of dynorphin containing neurons in male rats restored motivation for sucrose reward, and intra-NAc administration of a low dose of nor-BNI prevented aversive behavior induced by stimulation of dynorphin neurons, implicating KOR signaling (Massaly et al., 2019).

In an inflammatory pain condition (intradermal CFA injection) in mice of both sexes, optical stimulation of dynorphin neurons in the NAc shell region produced similar real-time place aversion as under normal conditions but required a higher dose of nor-BNI to block the effect, which suggests enhanced KOR signaling in the NAc in pain conditions by activation of dynorphin neurons to increase dynorphin levels and drive negative affective pain behaviors (Massaly et al., 2019). Activation of KOR signaling in NAc has pronociceptive effects. Antinociception (jaw-opening reflex) induced by subdermal capsaicin injection in the rat hind paw was blocked with intra-NAc administration of U69,593 but not nor-BNI. U69,593 also blocked the antinociceptive effects of DAMGO and DPDPE in male rats, suggesting opposing interactions between KOR and MOR/DOR signaling (Schmidt et al., 2002). In male mice in neuropathic pain (CCI model), mRNA expression of KOR and DOR as well as their endogenous ligands, prodynorphin and proenkephalin, was significantly upregulated, suggesting plasticity of the NAc opioidergic system in pain (Wawrzczak-Bargiela et al., 2020).

KOR signaling in the mesolimbic dopamine circuit has also been implicated in stress and depression. A single immobilization stress or forced swim test resulted in increased immunoreactivity of dynorphin (A and B) in NAc of male rats (Shirayama et al., 2004). Microinjections of nor-BNI into NAc prevented the depressive phenotype in the learned helplessness model, and these effects were stronger after infusion into NAc shell rather than core (Nestler and Carlezon, 2006; Shirayama et al., 2004).

Little is known about cell type and specific circuitry of opioid receptor subtypes in NAc related to pain processing but in slices containing NAc from naïve male and female mice, differential regulation by KOR of dopamine D1 and D2 medium spiny neurons (MSNs) has been demonstrated. U69,593 inhibited D1 MSNs more strongly than D2 MSNs. Excitatory drive from amygdala, but not hippocampus, to NAc was reduced in D1 MSN by KOR activation whereas presynaptic KOR inhibited inhibitory inputs (disinhibition) from both

amygdala and hippocampus to D2 MSN (Tejeda et al., 2017). The relevance of these actions for pain processing in the mesolimbic system remain to be determined.

3. Conclusions

While the cortico-limbic system is an important target for opioid actions in pain modulation, reward mechanisms and related functions, the cellular and circuit actions of different opioids receptors and behavioral consequences of opioid receptor signaling in different elements of the cortico-limbic system are not fully understood. Data discussed in this review are summarized in Table 1. The ACC has consistently been implicated in the affective component of pain, and endogenous opioid signaling in the ACC plays a critical role in pain modulation. High levels of MOR and DOR rather than KOR are found in the ACC. MOR activation mitigates averse-affective pain behaviors and similar if not synergistic effects have been reported for DOR whereas the role of KOR in this area is largely unknown. The picture is less clear for the PL and IL regions of the mPFC in part because of the complexity of their functions in pain. The amygdala plays an important role in averse-affective behaviors and pain modulation and is rich in opioid receptors and endogenous ligands. MOR and KOR serve opposing functions whereas DOR signaling is less clear and appears to undergo a change from normal to pain conditions. Data are not quite clear about the role of amygdala MOR and KOR signaling in sensory compared to averse-affective pain behaviors. In the NAc, a key element of the central reward system, opioid signaling interacts with the dopaminergic system in addiction control and analgesia. All opioid receptor subtypes are expressed in NAc and MOR and DOR can colocalize on dendrites of NAc neurons. MOR and DOR have opposing functions to KOR on dopamine signaling and behaviors in pain models.

In conclusion, modulation of pain-related neuroplasticity by opioid signaling in cortico-limbic circuits and underlying synaptic and cellular mechanisms are largely understudied areas, though MOR and DOR signaling in the ACC and KOR signaling in the amygdala have been linked to inhibitory and disinhibitory neuronal effects, respectively. Since evidence suggests that changes in cortico-limbic circuits contribute to emotional affective and cognitive aspects of pain and possibly sensory pain modulation, it is important to determine opioid receptor subtype functions and pain-related changes in these brain regions to provide the knowledge basis for the development of novel and improved therapeutic strategies.

Acknowledgments

Work in the authors' lab is supported by National Institute of Health (NIH) grants R01 NS038261 (VN), R01 NS106902 (VN), R01 NS109255 (GJ), R01 NS118731 (VN), R01 NS120395 (VN), R01 NS129552 (VN), Garrison Family Foundation and Giles McCrary Endowed Chair in Addiction Medicine (VN).

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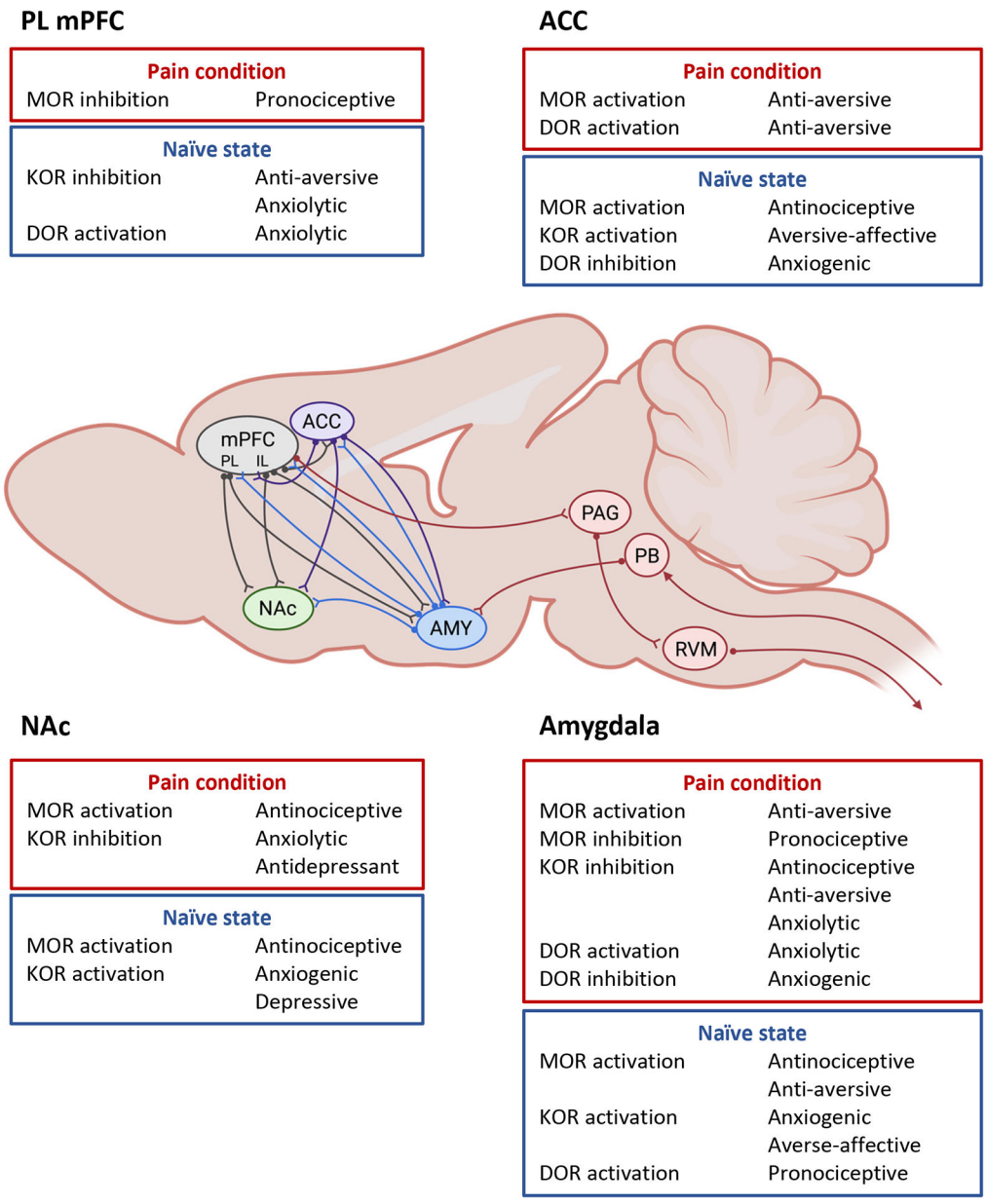

Figure 1.

Key effects of MOR, KOR and DOR modulation in different elements of the cortico-limbic system. ACC, anterior cingulate cortex, IL, infralimbic, mPFC, medial prefrontal cortex, NAc, nucleus accumbens, PAG, Periaqueductal gray, PB, Parabrachial nucleus, PL, prelimbic, RVM, Rostral ventromedial medulla. Diagram shows main connections between cortico-limbic areas and brainstem connections.

Table 1.

Behavioral effects of MOR, KOR, and DOR drugs in preclinical studies

Receptor	Drug Type	Compound	Route of Administration	Subregion	Species	Sex	Pain Model	Behavioral Effect	Behavioral Test	References
Systemic										
MOR	Agonist	Morphine	i.p.	-	Mouse	Male	Formalin	Antinociceptive	Licking and biting time	Zeng 2021
			i.p.		Mouse	Male	CCI	Increased preference behavior	CPP	Kai 2018
			Oral		Rat	Both	Naïve	Antinociceptive (in male offspring)	Hot plate test, acetic acid writhing test	Ashabi 2018
							Formalin		Licking time	
			s.c.		Mouse	Male	Hindpaw incision	Increased preference behavior	CPP	Nwaneshiudu 2020
			i.v.		Rat	Male	SNL	Antinociceptive	von Frey test	Navratilova 2015b
								Increased preference behavior	CPP	
			i.p.		Rat	Male	SNL	Antinociceptive	von Frey test	LaGraize 2006
								Decreased avoidance behavior	LDB	
			i.p.		Rat	Male	NMDA-induced CeA lesion	No effect	Formalin test	Manning 1995a
							NMDA-induced BLA lesion	Antinociceptive		
			i.p.		Rat	Male	NMDA-induced CeA lesion	No effect	Tail flick test	Manning 1995b
		Fentanyl (long-term)	s.c.		Rat	Male	Naïve	Pronociceptive	von Frey test, Hargreaves test	Wang 2022
		Remifentanil (long-term)	i.v.		Mouse	Female	Naïve	Increased cognitive deficits	ED shift task	Anderson 2021
						Male		No effect		
						Female	Naïve	Increased depressive-like behavior	FST	
						Male		No effect		

Receptor	Drug Type	Compound	Route of Administration	Subregion	Species	Sex	Pain Model	Behavioral Effect	Behavioral Test	References
	Agonist + antagonist	Morphine + naloxone	s.c. + intra-NAc microinjection		Rat	Male	Naïve	Pronociceptive	Hot plate test	Dill 1977
			s.c. + intra-CN microinjection					No effect		
			s.c. + intra-GP microinjection					No effect		
	Agonist + acetaldehyde dehydrogenase inhibitor	Morphine + disulfram	Oral		Rat	Male	Naïve	Antinociceptive	Randall-Selitto test, tail flick test	de Corde-Skurska 2021
	Antagonist + agonist	Naloxone + morphine	i.p. + intra-ACC microinjection		Rat	Male	SNL	No effect	von Frey test	LaGraize 2006
								No effect	LDB	
KOR	Agonist	U69,593 (long-term)	s.c.		Rat	Male	Naïve	Increased aversion behavior	CPA	Tejeda 2013
		U69,593	s.c.		Mouse	Male	KOR KO on dopaminergic neurons	Decreased aversive behavior	CPA	Chefer 2013
	Antagonist	nor-BNI	s.c.		Rat	Male	Naïve	No effect	OFT	Tejeda 2015
DOR	Antagonist	NTI	s.c.		Mouse	Male	Naïve	Increased anxiety-like behavior	LDB, EPM	Narita 2006b
mPFC										
MOR	Agonist	Morphine	Microinjection	ACC	Rat	Male	Incision model	Increased preference behavior	CPP	Navratilova 2015b
								No effect	von Frey test	
							SNL	Increased preference behavior	CPP	
								No effect	von Frey test	
			Microinjection	ACC	Rat	Male	SNL	No effect	von Frey test	LaGraize 2006
								Decreased avoidance behavior	LDB	
			Microinjection	rostral ACC, caudal ACC	Rat	Male	SNL	No effect	Tail flick assay, von Frey test, Randall-Selitto test, Hargreaves test	Gomtsian 2018
				rostral ACC				Increased preference behavior	CPP	

Receptor	Drug Type	Compound	Route of Administration	Subregion	Species	Sex	Pain Model	Behavioral Effect	Behavioral Test	References
				caudal ACC				No effect		
			Microinjection	ACC	Rat	Male	CCI	Antinociceptive	Randall-Selitto test, hot plate test	Wang 2020
	Agonist + antagonist	Morphine + naloxone						No effect		
		Morphine + β-FNA						No effect		
	Antagonist	Naloxonazine	Microinjection	PL	Rat	Male	Orofacial formalin	Pronociceptive	Face rubbing	Tamaddonfard 2020
		Naloxone	Microinfusion	PL	Rat	Male	SNL	Pronociceptive	von Frey test	Zeng 2018
			Microinjection	ACC	Rat	Male	Incision model	Decreased preference behavior	CPP	Navratilova 2015b
								No effect	von Frey test	
							SNL	Decreased preference behavior	CPP	
								No effect	von Frey test	
	Antagonist + agonist	β-FNA + morphine	Microinjection + i.v.					Antinociceptive	von Frey test	
								Decreased preference behavior	CPP	
	Selective ablation of MOR-expressing neurons	Derm-SAP	Microinjection					Decreased preference behavior	CPP	
								No effect	Hargreaves test	
	Antagonist + agonist	β-FNA + morphine	Microinjection	right ACC + right CeA	Rat	Male	SNL	Decreased preference behavior	CPP	Navratilova 2020
KOR	Antagonist	nor-BNI	Microinfusion	PL	Rat	Male	U69,593-conditioned	Decreased aversion behavior	CPA	Tejeda 2013
			Microinfusion	PL	Rat	Male	Naïve	Decreased anxiety-like behavior	OFT	Tejeda 2015
DOR	Agonist	DADLE	Microinjection	rostral ACC	Rat	Male	CFA	Decreased aversion behavior	CPA	Ma 2022
								No effect	Hot plate test	
		KNT-127	Microinfusion	PL	Mouse	Male	Naïve	No effect	OFT	Saitoh 2018
	Agonist + sodium channel activator	KNT-127 + veratrine						Decreased anxiety-like behavior		
	Antagonist	Naltrindole	Microinjection	ACC	Mouse	Male	Naïve	Increased anxiety-like behavior	LDB, EPM	Narita 2006b

Receptor	Drug Type	Compound	Route of Administration	Subregion	Species	Sex	Pain Model	Behavioral Effect	Behavioral Test	References
Amygdala										
MOR	Agonist	Morphine	Microinjection	right CeA	Rat	Male	SNL	No effect	von Frey test, Randall-Selitto test	Navratilova 2020
								Increased preference behavior	CPP	
				left CeA				No effect	von Frey test, Randall-Selitto test, CPP	
			Microinjection	BLA	Rat	Male	Naïve	Antinociceptive	Tail flick test	Helmstetter 1995
			Microinjection	BLA	Rat	Male	Naïve	Antinociceptive	Tail flick test, jump test	Pavlovic 1996
				CeA						
			Microinfusion	BLA	Rat	Male	Naïve	Antinociceptive	Tail flick test	McGaraughty 2002
		DAMGO	Microinjection	BLA	Rat	Male	Naïve	Antinociceptive	Tail flick test	Helmstetter 1998
			Microinjection	CeA	Rat	Male	CFA	Decreased aversion behavior	CPA	Zhang 2013
								No effect	Hargreaves test	
		β-endorphin	Microinjection	BLA	Rat	Male	Naïve	Antinociceptive	Tail flick test, jump test	Pavlovic 1996
				CeA						
	Agonist + antagonist	Morphine + naltrexone	Microinjection	BLA + PAG				No effect		
		β-endorphin + naltrexone								
	Antagonist	CTAP	Microinjection	CeA	Mouse	Both	Plantar incision model	Pronociceptive	von Frey test	Cooper 2022
	Chemogenetic inhibition of MOR-expressing PB input neurons	AAVDJ-EF1a-DIO-hM4D(Gi)-mCherry	Microinjection	CeA	Mouse	Both	Formalin	Antinociceptive	Hot plate test	Liu 2022
								Decreased anxiety-like behavior	EPM	
KOR	Agonist	U69,593	Microinfusion	right CeA	Rat	Male	Naïve	Increased emotional-affective responses	Vocalizations to noxious stimulus	Hein 2021
								Increased anxiety-like behavior	OFT	
								Decreased preference behavior	CPP	

Receptor	Drug Type	Compound	Route of Administration	Subregion	Species	Sex	Pain Model	Behavioral Effect	Behavioral Test	References
								No effect	Paw pressure test	
	Antagonist	nor-BNI	Microinfusion	right CeA	Rat	Male	SNL	Decreased gabapentin-induced preference behavior	CPP	Navratilova 2019
								No effect	von Frey test	
			Microinfusion	right CeA	Rat	Male	Functional pain model	Decreased emotional-affective responses	Vocalizations to noxious stimulus	Yakhnitsa 2022
								Decreased anxiety-like behavior	EPM	
								Antinociceptive	von Frey test	
								No effects	Paw pressure test	
			Microinfusion	right CeA	Rat	Male	Medication overuse model	Antinociceptive	von Frey test	Xie 2017
				left CeA				No effect		
			Microinfusion	right CeA	Rat	Male	Infraorbital CCI	Antinociceptive	von Frey test	Turnes 2022
								No effect	EPM	
				left CeA				No effect	von Frey test, EPM	
			Microinjection	right CeA	Rat	Male	SNL + capsaicin	Antinociceptive	Randall-Selitto test	Phelps 2019
				left CeA				No effect		
			Microinjection	right CeA	Rat	Male	Functional pain model	Antinociceptive	Randall-Selitto test	Nation 2018
				left CeA				No effect		
DOR	Agonist	DPDPE	Microinfusion	CeA	Mouse	Male	Naïve	Pronociceptive	von Frey test	Zhou 2021
								No effect	OFT, EPM	
							CFA	No effect	von Frey test, OFT, EPM	
		Deltorphin II					Naïve	No effect	von Frey test, OFT, EPM	
							CFA	No effect	Von Frey test	
								Decreased anxiety-like behavior	OFT, EPM	
	DOR1 antagonist	BNTX						No effect		

Receptor	Drug Type	Compound	Route of Administration	Subregion	Species	Sex	Pain Model	Behavioral Effect	Behavioral Test	References
	DOR2 antagonist	Naltriben						Increased anxiety-like behavior		
	Antagonist	Naltrindole	Microinjection	BLA	Mouse	Male	CFA CCI	Increased anxiety-like behavior	LDB, EPM	Narita 2006a
NAc										
MOR	Agonist	Morphine	Microinjection	n.s.	Rat	Male	Naïve	Antinociceptive	Hot plate test	Dill 1977
			Microinfusion	n.s.	Rat	Male	SNL	Antinociceptive	Hot plate test, Randall-Selitto test	Bian 2015
		DAMGO	Microinjection	n.s.	Rat	Male	Naïve	No effect	Jaw-opening reflex	Schmidt 2002
	Antagonist	CTOP	Microinjection	n.s.	Rat	Male	DAMGO-induced antinociception	Pronociceptive	Jaw-opening reflex	Gear 2011
			Microinjection	n.s.	Rat	Male	Capsaicin-induced antinociception	Pronociceptive	Jaw-opening reflex	Schmidt 2022
			Microinjection	n.s.	Rat	Male	UFP-512-induced anxiolytic and antidepressant effects	Increased anxiety- and depressive-like behavior	EPM, novelty-induced hypophagia test	Kabli 2014
		Naloxone	Microinjection	n.s.	Rat	Male	Capsaicin-induced antinociception	Pronociceptive	Jaw-opening reflex	Gear 1999
	Dopamine receptor antagonist + agonist	α-flupenthixol + morphine	Microinjection	NAc + rostral ACC	Rat	Male	SNL	Decreased preference behavior	CPP	Navratilova 2015b
MOR + DOR	Agonist + agonist	DAMGO + DPDPE	Microinjection	n.s.	Rat	Male	Naïve	Antinociceptive	Jaw-opening reflex	Schmidt 2002
		UFP-512	Microinjection	n.s.	Rat	Male	Naïve	Decreased anxiety- and depressive-like behavior	EPM, novelty-induced hypophagia test	Kabli 2014
KOR	Photoactivation of dynorphin neurons	-	Optical activation	ventral NAc shell	Mouse	Both	Naïve	Decreased motivation Increased aversion behavior	Sucrose self-administration Real-time place aversion	Massaly 2019

Receptor	Drug Type	Compound	Route of Administration	Subregion	Species	Sex	Pain Model	Behavioral Effect	Behavioral Test	References
				NAc shell cold spot	Rat	Male	CFA	Increased aversion behavior		
			Photostimulation	ventral NAc shell	Mouse	Male	Naïve	Increased aversion behavior	Real-time place aversion	Al-Hasani 2015
								No effect	OFT	
				dorsal NAc shell				Increased preference behavior	Real-time place preference	
								No effect	OFT	
	Photoactivation of dynorphin neurons + antagonist	nor-BNI	Microinjection	NAc shell cold spot	Rat	Male	CFA	Decreased aversion behavior	Real-time place aversion	Massaly 2019
	Agonist	U69,593	Microinjection	n.s.	Rat	Male	Capsaicin-induced antinociception	Pronociceptive	Jaw-opening reflex	Schmidt 2022
							DAMGO-induced antinociception			
							DPDPE-induced antinociception			
		E-2078	Microinjection	n.s.	Rat	Male	Naïve	Increased aversion behavior	CPA	Bals-Kubik 1993
		U50,488	Microinjection	n.s.	Mouse	Male	Naïve	Increased anxiety-like behavior	EPM, LDB	Wang 2016
	Antagonist	nor-BNI					U50,488-induced anxiety-like behavior	Decreased anxiety-like behavior	EPM	
			Microinfusion	NAc shell	Rat	Male	Learned helplessness model	Decreased depressive-like behavior	Conditioned avoidance test	Shirayama 2004
			Microinjection	ventral NAc shell	Mouse	Both	Dynorphin neuron stimulation	Decreased aversive behavior	Real-time place aversion	Massaly 2019
	Chemogenetic silencing of dynorphin neurons	Dyn2.0-hM4Di-IRES-mCherry	Microinjection	NAc shell cold spot	Rat	Male	Naïve	Increased motivation	Sucrose self-administration	

Receptor	Drug Type	Compound	Route of Administration	Subregion	Species	Sex	Pain Model	Behavioral Effect	Behavioral Test	References
DOR	Agonist	DPDPE	Microinjection	n.s.	Rat	Male	Naïve	No effect	Jaw-opening reflex	Schmidt 2002
	Antagonist	Naltrindole	Microinjection	n.s.	Rat	Male	DAMGO-induced antinociception	Pronociceptive	Jaw-opening reflex	Gear 2011
			Microinjection	n.s.	Rat	Male	Capsaicin-induced antinociception	Pronociceptive	Jaw-opening reflex	Schmidt 2002
			Microinjection	n.s.	Rat	Male	UFP-512-induced anxiolytic and antidepressant effects	Increased anxiety- and depressive-like behavior	EPM, novelty-induced hypophagia test	Kabli 2014

β-FNA, β-funaltrexamine; BNTX, 7-benzylidenenaltrexone; CCI, chronic constriction injury; CeA, central nucleus of the amygdala; CFA, complete Freund's adjuvant; CMS, chronic mild stress; CN, caudate nucleus; CPA, conditioned place aversion; CPP, conditioned place preference; CTOP, [Cys2-Tyr3-Orn5-Pen7]-amide; DADLE, [D-Ala2, D-Leu5]-enkephalin; DAMGO, D-Ala2,N-Me-Phe^{4},Gly^{5}-ol]-enkephalin; Derm-SAP, dermorphin-saporin; DPDPE, D-Pen^{2,5} enkephalin D-Pen^{2,5}-enkephalin; ED, extradimensional shift task; EPM, elevated plus maze; FST, forced swim test; GP, globus pallidus; i.p., intraperitoneal; i.v., intravenous; KO, knock out; LDB, light/dark box; mPFC, medial prefrontal cortex; NMDA, N-methyl-D-aspartate; nor-BNI, nor-binaltorphimine; n.s., not specified; NTI, naltrindole; OFT, open field test; PB, parabrachial nucleus; PL, prelimbic; RVM, rostral ventromedial medulla; s.c., subcutaneous; SNL, spinal nerve ligation; TST, tail suspension test; UFP-512, (H-Dmt-Tic-NH-CH(CH$_2$-COOH)-Bid); vlPAG, ventrolateral periaqueductal gray