The negative affect of protracted opioid abstinence: progress and perspectives from rodent models

Lola Welsch[1],[#], Julie Bailly[1],[#], Emmanuel Darcq[1], Brigitte Lina Kieffer[1]

[1]Douglas Mental Health Institute, Department of Psychiatry, McGill University, Montreal, Quebec, Canada.

Abstract

Opioid use disorders (OUDs) are characterized by the development of a negative emotional state that develops after a history of chronic exposure to opioids, and represents a true challenge for treatment and relapse prevention. Human research has amply documented emotional disruption in individuals with an opioid substance use disorder, at both behavioral and brain activity levels, however brain mechanisms underlying this particular facet of OUDs are only partially understood. Animal research has been instrumental to elucidate genes and circuits adapting to chronic opioids or modified upon acute withdrawal, but research on long-term consequences of opioid exposure, and their relevance to the negative affect of OUDs, remain scarce. Here we overview this literature, with a focus on two questions: (i) do we have behavioral models in rodents, and what do they tell us? and (ii) what do we know about the neuronal populations involved? In sum, behavioral rodent models have successfully recapitulated behavioral signs of the OUD-related negative affect, and several neurotransmitter systems were identified (serotonin, dynorphin, corticotropin-releasing factor, oxytocin). Circuit mechanisms driving the negative mood of prolonged abstinence likely involve the four main reward/aversion brain centers (nucleus accumbens, bed nucleus of the stria terminalis amygdala, habenula and the raphe nucleus), which all express mu opioid receptors (MORs) and directly respond to opioids. Future work will identify the nature of these MOR-expressing neurons throughout reward/aversion networks, characterize their adapted phenotype in opioid abstinent animals and hopefully position these primary events in the broader picture of MORassociated brain aversion networks.

Keywords

Opioid use disorders; mu opioid receptor; opioid withdrawal; mood; rodent behavior; neural circuits

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Corresponding author: Brigitte L. Kieffer, PhD, Douglas Hospital Research Center, Perry Pavilion Room E-3317.1, 6875 boulevard LaSalle, Montreal (Quebec) H4H 1R3, Canada. Phone: 514 761-6131 ext: 3175 Fax: 514 762-3033., brigitte.kieffer@douglas.mcgill.ca.
[#]Equal contribution

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Introduction

Opium extracted from the poppy (*papavum somniferum)*, as well as opioids developed for medicinal purposes have traditionally been associated with huge societal challenges. From opium wars in the late 19th century where British trading policies devastated Chinese economy and produced millions of opium addicted individuals, to heroin prohibition in 1920 and the major subsequent criminality issues, we now face the opioid epidemic recognized as a major public health challenge. The over prescription of opioid painkillers has fostered an alarming increase of transition to synthetic opioid abuse and deaths by overdose (1–4). The extremely powerful pain relieving effects of opioids and their inherent euphoric/rewarding properties all contribute to misuse, eventually leading opioid use disorders (OUDs).

Opioid abuse, as most addictions, is a complex brain disorder that involves adaptations to repeated opioid exposure in several interconnected brain networks (5). These lead to progressive impairment of reward systems that are recruited during binge/intoxication episodes, increasing engagement of aversion brain centers upon recurrent drug withdrawal episodes, enhanced stress- and drug cue-related sensitivity and disrupted executive functions leading to craving and further intoxication episodes. All these aspects contribute to enforce the severity of addiction, and escaping the vicious intoxication/withdrawal/craving cycle is a true challenge. Whether substitution treatment strategies or efforts towards maintaining full abstinence are preferable is debated (6), however a clear goal in OUD treatment is addressing the negative affect of opioid withdrawal and abstinence, which develops after a history of opioid use and shows some of the features of mood disorders (7, 8). This aspect of OUDs is critical, as the urge for relief from this negative emotional state is recognized as a strong negative reinforcer and a major drive for relapse (5, 9).

In humans, chronic use of opioid have been associated with some neuropathology that have been extensively reviewed in (10). Specifically, chronic use of heroin in human may induce neurovascular disorders (11), cerebrovascular effects (12), biochemical modification such as an alteration of G-protein density (13, 14), brain structural alterations (15) and cognitive deficits such as working and visual memory, and processing speed (16). Further, the negative affect of prolonged opioid abstinence is characterized by a loss of motivation for natural rewards (9), heightened stress reactivity (17), an inability to identify and describe emotions, physical and/or emotional pain (18), malaise, dysphoria, sleep disorders (19) and/or chronic irritability. Illustrating the negative affect in opioid use disorders (OUDs), a study showed that a single heroin administration in heroin-dependent patients alleviates their negative emotions and increases feelings of well being, independently from the perceived intoxication and sedation (20). Other examples are observations that abstinent heroin abusers show a bias towards negative expressions (21) and dysregulated emotions correlated with childhood neglect and addiction severity (22).

Human imaging studies investigating opioid effects on the brain have been overviewed recently (23) and discussed (24) in the context of the three stage-addiction cycle framework (5), showing in particular that the negative affect of opioid withdrawal is associated with enhanced beta power activity and increased connectivity strength between amygdala and ventral striatum, two main reward and aversion centers. Also, human neuroimaging was

performed under conditions of protracted opioid abstinence and these studies have also been reviewed (25). Notable are findings that the opioid-abstinent human brain (2 weeks to 7 months) shows alterations of functional connectivity strength between brain networks responsible for cognitive control, reward and stress (26–29). Further, former heroin-dependent individuals, abstinent for more than 3 years, showed reduced positive correlation within the default mode and visual networks (30), as well as altered nucleus accumbens functional connectivity depending on the duration of the abstinence period (31). The latter reports demonstrate that disruption of general brain connectivity and alterations in a main reward center persist, even after multiple years. Together therefore, human research has amply documented emotional disruption in individuals with an opioid substance use disorder, at behavioral as well as brain activity levels. Whether effects are pre-existing or a consequence of the history of opioid exposure, however, remains a difficult question in human research.

Animal research allows dissociating causes and consequences, and is essential to tackle molecular and circuit mechanisms underlying the long-term mood disruption in OUDs. When opioids hit the nervous system, a primary molecular event is the activation of the mu opioid receptor (MOR) (32). A vast literature demonstrates that opioid drugs, used for medicinal and/or recreational purposes, act by stimulating this G protein coupled receptor (reviewed in (33, 34)) that mediates both their therapeutic and adverse effects (35). Repeated MOR activation then triggers within-cell adaptations at signaling and transcriptional level, which tend to limit and counteract receptor signaling, and propagate throughout brain circuits to generate behavioral tolerance and dependence (reviewed in (36–38)). Withdrawal from chronic opioids is an extremely painful physical and emotional experience and, in addition, further abstinence partly restores MOR function so that tolerance diminishes and relapse to opioid use often leads to fatal overdose.

This review focuses on animal research addressing the negative affect of opioid withdrawal and abstinence. Emphasis will be on neurobiological and circuit mechanisms involved in the generation of aversive emotional states in protracted withdrawal – or abstinence - from chronic opioid exposure. We will address two key questions:

1. Do we have valid behavioral models in rodents, and what do they tell us? This first section will overview existing behavioral models and summarize current knowledge of contributing neurotransmitter systems.

2. What do we know about the neuronal populations involved? This second section will focus on selected brain centers relevant to negative affect in OUDs, and overview recently identified neuronal populations in these reward/aversion centers that subserve MOR function and adapt under chronic opioids.

Finally, studies that have uses cell-specific genetic manipulations and opto/chemogenetic methods, are still few in the area of opioid withdrawal and abstinence, and we therefore have added a perspective paragraph discussing a number of potential neuronal populations that possibly contribute to circuit mechanisms underlying the disrupted mood in OUDs.

1. Do we have valid behavioral models in animal, and what do they tell us?

A large number of animal studies have examined acute opioid withdrawal, which is typically precipitated in morphine-dependent animals using a single opioid antagonist administration (naloxone, naltrexone). This procedure readily blocks opioid-occupied MORs, and unmasks physiological adaptations that have developed at molecular, circuit and behavioral levels during the chronic exposure to the drug. Acute MOR blockade in opioid-dependent animals produces massive effects, among which somatic signs of physical withdrawal are most impressive. These effects are reminiscent to those observed in rapid opioid detoxification procedures in humans (39, 40) and demonstrate the striking extent of adaptations to chronic opioids at system-level.

Less well studied are consequences of chronic opioid exposure after the drug has cleared out the body -or spontaneous withdrawal-, and in particular the alteration of emotional responses. Remarkably, spontaneous withdrawal from a single morphine exposure produces dysphoria (41), anhedonia (42) and anxiety (43), evaluated 1 week, 1 day and 5 hours after drug exposure, respectively. The later anxiety (startle reflex) persisted long after the single morphine exposure, as a naloxone injection revealed a potentiated startle response as far as 80 days later (44). Long-lasting behavioral adaptations, therefore, develop immediately after the first opioid exposure.

Repeated opioid exposure has even more drastic consequences on hedonic homeostasis and mood states. Table 1 summarizes studies that have examined animals experiencing 6 days to 5 weeks of spontaneous withdrawal from chronic morphine or heroin. Data reporting reinstatement of opioid seeking are not included in this summary, and have been detailed elsewhere (45).

Behavior.—Rodent experiments performed in the first week following spontaneous withdrawal from morphine reveal impaired emotionality in several behavioral tests. Six days-withdrawn rats showed increased immobility in the forced swim test, a measure of depression-like behavior (46). Ten days-morphine withdrawn rats showed reduced sucrose self-administration, indicative of lower motivation for a natural reinforce (47). One and seven-days withdrawn rats showed potentiated stress-induced anxiety, measured in general activity and social behaviors after restraint stress, and anxiety level was a function of dose and duration of opioid exposure (48). Similar to rats, morphine-withdrawn mice showed impaired affective behaviors in elevated plus maze, forced swim and sociability tests after 7 days abstinence from chronic morphine (49). Finally, adolescent mice showed decreased despair behaviour in forced swim 3 but not 9 days after termination of the chronic morphine exposure, whereas adult mice showed increased despair-like behaviour after 9 days only, suggesting that spontaneous withdrawal alters mood differently across age (50).

Rodent models further indicate that the negative affect of opioid withdrawal persists and even increases, as the abstinence period extends. Two weeks-abstinent rats showed impaired place preference for a food-associated context, and five-weeks withdrawn rats exhibited decreased preference for food-associated cues and increased preference for morphine associated cues, demonstrating prolonged effects of opioid abstinence on motivation for a natural reward (51, 52). Another study showed that 4 weeks after termination of a chronic

morphine regimen, mice developed despair-like behavior, decreased social interactions and increased self-grooming in a presence of an unknown interactor (53). These behaviors were not observed after 1-week withdrawal, demonstrating that the alterations of emotional states incubate and develop with time (53). These results were reproduced in heroin-dependent mice, and these behavioral modifications remained as far as 7 weeks post-heroin (54). Increased anxiety-like behavior was also reported in 4-week morphine abstinent mice, measured in marble burying and novelty suppressed feeding tests (55), or using the open field and the elevated plus maze (56).

Together therefore, existing rodent models are able to reasonably recapitulate major features characterizing the negative affect of opioid withdrawal and prolonged abstinence. In the future, it may be critical to investigate the negative affect induced by long-term oxycodone withdrawal, the more often over-prescribed opioid in North America. Note that, beyond negative affect, other long-term effects including cognitive alterations are observed in humans (25) and detectable in rodents (53, 54), however these effects are beyond the scope of this review and have been incompletely investigated in animal research.

Neurotransmitter systems and genes.—Using these models, neurotransmitter systems underlying mood-related neurodaptations were identified (Table 1). The corticotropin-releasing factor (CRF) is a stress–related neuropeptide, which was associated to drug use in humans often in relation to a stress history, and rodent research showed a key role for the CRF system in the etiology and maintenance of addiction (reviewed in (57), and see (58, 59), for recent examples in nicotine and alcohol research). In the early abstinence period (first week), the anxiogenic effect of intracerebroventricular administered corticotropin-releasing factor (CRF) was reduced or enhanced at low and high dose, respectively, in morphine-withdrawn rats (60). This was observed both 1 and 7 days after exposure, and therefore also implicates CRF and stress-associated circuitry in the emotional regulation of opioid withdrawal. Oxytocin receptor blockage using systemic carbetocin attenuated anxiety and depressive-like behaviors, as well as impaired sociability, in 7-days withdrawn mice demonstrating altered oxytocinergic system function (49). In a parallel study by the same group, increased mGluR5 expression was observed in the 7-days withdrawn mice, and a similar reduction of emotional impairments was found upon mGluR5 antagonist administration, indicating a metabotropic glutamate regulation of affective state in early morphine abstinence (61). Finally, pharmacological increase of serotonin (5HT) levels using fluoxetine abolished morphine place preference in 5-days withdrawn rats and this effect was reproduced by local fluoxetine infusion in the nucleus accumbens (62), indicating early engagement of 5HT transmission.

After a longer period of spontaneous withdrawal (4 weeks), morphine-withdrawn mice showed persistent decreased of 5HT tissue levels in the dorsal raphe, and chronic administration of fluoxetine (5HT uptake blocker) during abstinence prevented the development of despair-like behaviour and social interaction deficits (53), implicating adaptations of 5HT neurotransmission. This was also observed in a similar experiment that used heroin instead of morphine (54). Both fluoxetine and norbinaltorphimine (norBNI, a kappa opioid receptor antagonist) were able to prevent and reverse emotional deficits of heroin abstinence, when administration was performed during abstinence (prevention) or

after 4 weeks (reversal) when emotional alterations have established (63). This set of studies demonstrated the implication of two neurotransmitter systems that are notoriously involved in negative mood and aversive states, as 5HT deficits are typically associated with major mood disorders (64, 65) and the kappa opioid system is known to mediate dysphoria and depressive-like behaviors (66, 67). Another indication implicating 5HT is the observation that lorcaserin, a 5HT2C receptor agonist, reduces behavioural sensitization and naloxone-precipitated withdrawal after both morphine (68), and heroin (69) exposure, however this drug was not tested in the context of prolonged spontaneous withdrawal. Finally within-system (opioid system) adaptations were observed in 4-weeks abstinent rats, which had formerly escalated their oxycodone self-administration, and an alteration of MOR and kappa opioid receptor protein levels was reported in the striatum and hippocampus (70).

Transcriptional adaptations were reported in the brains of 4-week abstinent mice, opening the way to studying many more neurotransmitter and signalling pathways. Expression analysis of a hundred MOR-dependent genes (71) in the extended amygdala showed highly differing transcript modifications when comparing morphine-dependent mice with morphine-withdrawn mice, uncovering long-term molecular consequences of prior chronic opioid exposure (72). Of interest was the observation that animals exposed to either morphine, D9-tetrahydrocannabinol, alcohol or nicotine showed very distinct gene expression changes during the chronic treatment, whereas a common gene alteration pattern emerged after 4 weeks abstinence that possibly reflects a unitary signature of protracted abstinence (72). These commonly regulated transcripts encode known (CB1 and dopamine D1 receptors) and orphan (GPR88) G protein coupled receptors, cellular signaling molecules (phosphodiesterase 10A) and transcription factors (NR4A1, FOXP1 and BCL11B), belonging to huntingtin-centered (striatum function), Creb/ERK (neuroadaptation), glutamate/glucocorticoid (stress) and NFkB (inflammation) gene pathways. Worthwhile noting, genes patterns in cocaine abstinence were very different (55). Whether these genes are biomarkers or feasible targets to address the negative affect of opioid withdrawal is open for investigation.

Similar studies may be developed for other brain regions also involved in reward deficits, stress responses and mood control. Altogether, and beyond the traditionally studied neurotransmitter systems (5), novel molecular targets may be of interest to study the negative affect, and a next step will be to study their potential causal roles in aversive states of opioid abstinence. To our knowledge, only one example was reported. Knockdown of Wnt7a, a signaling protein involved in synaptic plasticity, in the medial insular cortex was able to alleviate high anxiety levels observed in 4-week morphine abstinent mice (56).

2. What do we know about the neuronal populations involved?

Opioid drugs stimulate MORs throughout the peripheral and central nervous system, where the receptor is broadly distributed (Figure 1A and Refs (73, 74), and therefore alter the activity of several overlapping neuronal networks involved in pain, reward and mood regulation. It is well established that the acute opioid action on pain circuits reduces the sensory, emotional and cognitive experience of pain (75), and that their activities on the dopamine mesocorticolimbic circuitry (notably ventral tegmental area, nucleus accumbens)

and other hedonic hotspots (e.g. lateral hypothalamus, septum) facilitate reward processing and increase hedonic tone (34, 76). In addition, opioid drugs directly act on aversion brain centers, where MORs are also expressed at high density but have been less studied (32). These brain centers, known to contribute to stress-related responses (extended amygdala) and emotional states (notably the dorsal raphe nucleus/5HT system) (77), are increasingly engaged as addiction develops and participate in the aversive experience of withdrawal and abstinence. Finally, MORs are present at low density in the cortex. Although MOR function at the level of cortical networks is virtually unknown, the stimulation of cortical MORs may alter motivational states and inhibitory controls (prefrontal cortex), and modulate integration of aversive experiences (e.g. anterior cingulate and insular cortices), also involved in chronic pain, see (75).

Overall, chronic opioid exposure alters all these brain centers (summarized in Figure 1A) either due to direct MOR stimulation or via system-level adaptations. Deciphering circuit mechanisms and neuronal populations that reshape reward/aversion processing (78, 79) after chronic exposure to opioids is critical to understand the negative affect of long-term opioid withdrawal. Below we summarize the current – and still limited- evidence on (i) MOR function in identified neuronal populations from these brain centers, which is relevant to OUDs and (ii) reported adaptations to chronic opioids in neurons from those circuits.

MOR function in OUD-relevant brain circuitry/neurons.—MOR function in opioid reward and motivation has been well studied. Abundant pharmacology and electrophysiology literature has established that MORs expressed in GABAergic interneurons of the ventral tegmental area (VTA) mediate opioid reward through disinhibition of dopamine (DA) neuron activity (34). Genetic manipulations of the *Oprm1* gene in mice have further revealed roles for the MOR expressed in D1 dopamine receptor-type neurons of the striatum (direct pathway of the mesolimbic DA circuitry) in opioid reward and seeking. MOR rescue in D1 neurons of MOR knockout mice was sufficient to restore morphine place preference and also partially restored remifentanil self-administration demonstrating that, in addition to VTA receptors, MORs in brain areas receiving DA neuron projections could also contribute to opioid reward (80). Further, the conditional MOR knockout in these neurons altered motivation to obtain heroin and palatable food, pointing at a specific role of this receptor population in the regulation of motivation (81). Finally DA-independent opioid reward is also well-documented (82–85), but MOR-expressing neurons responsible for these effects, outside the traditionally studied VTA-striatum pathway have not been identified, as yet.

The study of MOR function in aversion centers is only beginning. In particular, MOR is highly expressed in the medial part of the habenula (MHb) (86), a brain center particularly active in anticipation of aversive outcomes (87–89) and considered a key aversion center in addiction and depression research (90–92). In general, the habenula complex is important to regulate information flow from forebrain to midbrain (87, 88, 90). The MHb receives inputs from the posterior septum (triangularis septum and septofimbria septum), nucleus accumbens and diagonal band of Broca and sends outputs to the interpeduncular nucleus (87, 88, 90) and asymmetrical projections to the lateral Hb have been described (93). A recent study analyzed behavioral consequences of a genetic MOR deletion targeted to

Chnrb4-positive neurons of the MHb. While rewarding effects of morphine and motivation for palatable food were intact in mutant mice, naloxone-induced place aversion (94) was reduced in both naïve and morphine-dependent mice, and naloxone-precipitated physical withdrawal was attenuated in morphine dependent animals (95). These data reveal a brain site and neuronal population, in which MOR blockade normally produces highly aversive effects, both emotional and somatic. Therefore, in addition to facilitating reward, endogenous MOR activity may limit aversive states through inhibition of these MHb neurons.

While most studies addressed MOR function in opioid reward or acute opioid withdrawal, one study only searched for MORs implicated in long-term opioid withdrawal and associated mood disruption. Local genetic MOR deletion in the dorsal raphe nucleus (DRN) prevented the development of depressive-like behavior and social interaction deficits normally observed in 4 week-heroin abstinent mice (54). Otherwise physical withdrawal and working memory deficits developed as expected, indicating that heroin-induced adaptations of MOR signaling in this main 5HT center profoundly and specifically alter mood during abstinence. The precise MOR-expressing neurons of the DRN responsible for emotional deficits have not been identified, as yet.

Impaired neuronal activities upon chronic opioids.—Two studies from the same group investigated VTA neuron adaptations in rats that have experienced a history of chronic morphine exposure, followed by variable periods of spontaneous withdrawal. In contrast to naïve rats, an acute morphine challenge failed to increase DA neuron firing in 24h- and 2 weeks-withdrawn animals, demonstrating that VTA DA neurons show long-lasting tolerance to the acute effect of morphine (96). Further *in vivo* recordings of GABAergic neurons in the tail of the VTA (tVTA) projecting onto the DA neurons did not reveal any morphine tolerance for these latter neurons in the 2-weeks abstinent rats. However, further optogenetic manipulations of tVTA GABAergic neurons showed their ability to inhibit, but not disinhibit, DA cells after 2 weeks withdrawal, an adaptive mechanism that may contribute to the negative affect of opioid abstinence (97).

Another study revealed a thalamic-NAc circuit, which mediates aversive behavioral effects of opioid withdrawal (98). Specifically, opto-silencing paraventricular thalamic (PVT)-NAc neurons in morphine-dependent mice reduced physical signs of naloxone-precipitated withdrawal, and suppressed the learned place aversion measured 1 and 7 days after the withdrawal episode. Chemogenetic silencing of these neurons also reduced conditioned place aversion elicited by 16h spontaneous withdrawal. It will be important in the future to investigate how PVT-NAc neurons adapt and evolve along protracted withdrawal, as they may well contribute to the negative affect of opioid abstinence. Finally, a recent study investigated the role of neurons from the lateral habenula (LHb) projecting to the raphe in morphine-dependent mice (99). Remarkably, chemogenetic inhibition of these neurons promoted social avoidance elicited by naloxone-precipitated withdrawal, an effect requiring cytokine signaling. It is therefore possible that adaptations of these LHb-raphe neurons also contribute to the negative emotional state of long-term withdrawal.

In sum, these reports point at a number of neuronal populations within OUD-relevant circuits, which possibly drive aversive states of opioid abstinence. In fact, many more neuronal circuits regulating reward and aversion processing and expressing MORs (Figure 1A and (32)) are likely involved, and studying them all would be a daunting task. Below, we have identified a number of other candidates, now approachable using opto/chemogenetic approaches.

Perspectives: candidate neuronal populations driving negative affect in OUDs.

Alterations of neuronal populations that shape reward/aversion processing may all potentially contribute to the negative emotional state of opioid abstinence. We may anticipate that their adaptations to chronic opioid exposure would gradually hinder reward processing and facilitate the expression of aversive states, and that their sustained modification in turn would create the emergence of intractable negative mood.

In a prospective exercise, we have selected a number of studies that have used optogenetic stimulation in real-time place preference testing (RT-PT, most classically used) and optical self-stimulation paradigms, as well as emotional – related testing (less frequent) to identify and demonstrate a role for neurons from the NAc, amygdala (BLA and CeA), DRN and BNST in approach/avoidance behavior and reward processing. The neural populations, which we discuss, are schematized in Figure 1B and data are summarized in Supplementary information and Supplementary Table S1.

These results together show dual reward/aversion function for several neuronal populations, which belong to the four main OUD-reward/aversion centers. Of note, the interpretation of optogenetic data is based on the assumption that optostimulation reproduces physiological patterns of neuronal firing, which may not always be the case, however we can reasonably speculate that these neurons could be candidates to opioid-mediated dysregulation, and deserve further studies in opioid–dependent or withdrawn animals.

Conclusion

Animal models have many limitations (100), as it is difficult to address the complexity of individual variabilities, social determinants or environment stressors that characterize in human patients suffering from OUDs. However, rodent research has successfully established behavioral models that recapitulate a number of behavioral signs of OUD-related negative affect. Several neurotransmitter systems including neuropeptides (dynorphin, CRF, oxytocin) and bioamines (5HT), known to be implicated in aversive states of drug withdrawal (5), are also contributing to the longer-term negative affective state of protracted opioid abstinence. Several brain regions contribute to this negative syndrome and include the NAc, the amygdala, BNST and the DRN, however the precise neuronal populations involved remain poorly identified. In fact, the literature on circuit mechanisms driving the growing negative mood of prolonged is still limited. Future work will identify the nature of MOR-expressing neurons that directly respond to repeated opioid stimulation throughout reward/aversion networks, characterize their adapted phenotype in opioid abstinent animals and

hopefully position these primary events in the broader picture of MOR-associated brain aversion networks (101). In the context of the opioid epidemic, this knowledge will help developing the much-needed innovative approaches for OUD prevention (102–104) and treatment (105).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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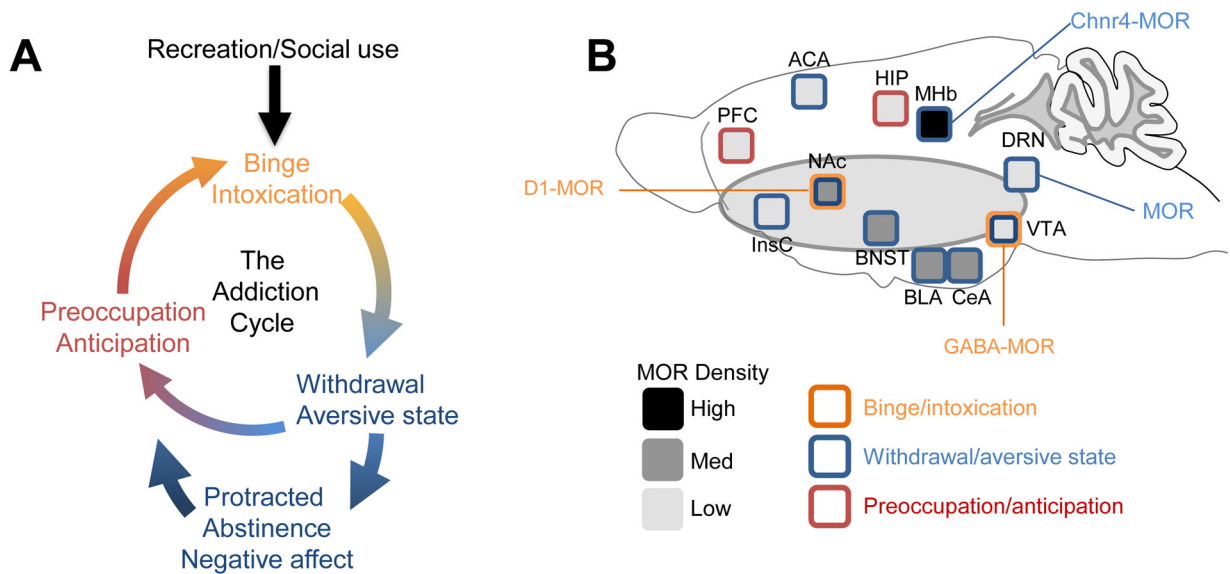
Figure 1. MOR-expressing brain centers traditionally studied in addiction, including OUDs.
A. The addiction cycle is conceptualized as a 3-stage cycling process, and applies to OUDs. Addiction develops when recreational use switches to binge/intoxication episodes. Each of these events is followed by withdrawal when the opioid drug clears out, and the development of an aversive state. A preoccupation/anticipation stage follows, where the urge for relief from withdrawal, as well as cue-induced craving, causes the next intoxication episode. When withdrawal is maintained for a long time, the negative affect increases with time, making abstinence difficult to sustain. **B**. MOR function in brain centers involved in OUDs. Brain regions are represented as colored squares (orange, binge/intoxication; blue, withdrawal/ aversive state; red, preoccupation/anticipation), and MOR expression levels are indicated in light grey to black. The NAc, Amygdala (CeA and BLA), BNST and DRN are major contributing brain centers in the context of aversive aspects of addiction (see also Figure 2). MORs in GABAergic interneurons of the VTA (GABA-MOR) facilitate dopamine release and drug reward (34). MORs in the striatum, expressed mainly in D1R-type neurons (D1-MOR), regulate opioid reward and the motivation for opioid consumption (33, 80). MORs in the MHb (Chnrb4-MOR) reduce aversive states, which are revealed by naloxone blockade (95). MORs in the DRN drive adaptations leading to depressive-like states and social withdrawal in protracted heroin abstinence (54). ACA, anterior cingulate cortex; BNST, bed nucleus of the stria terminalis; BLA, basolateral amygdala; CeA, central amygdala; DRN, dorsal raphe nucleus; HIP, hippocampus; InsC, insular cortex; MHb, medial habenula; PFC, prefrontal cortex; NAc, nucleus accumbens; VTA, ventral tegmental area. Adapted from (5).
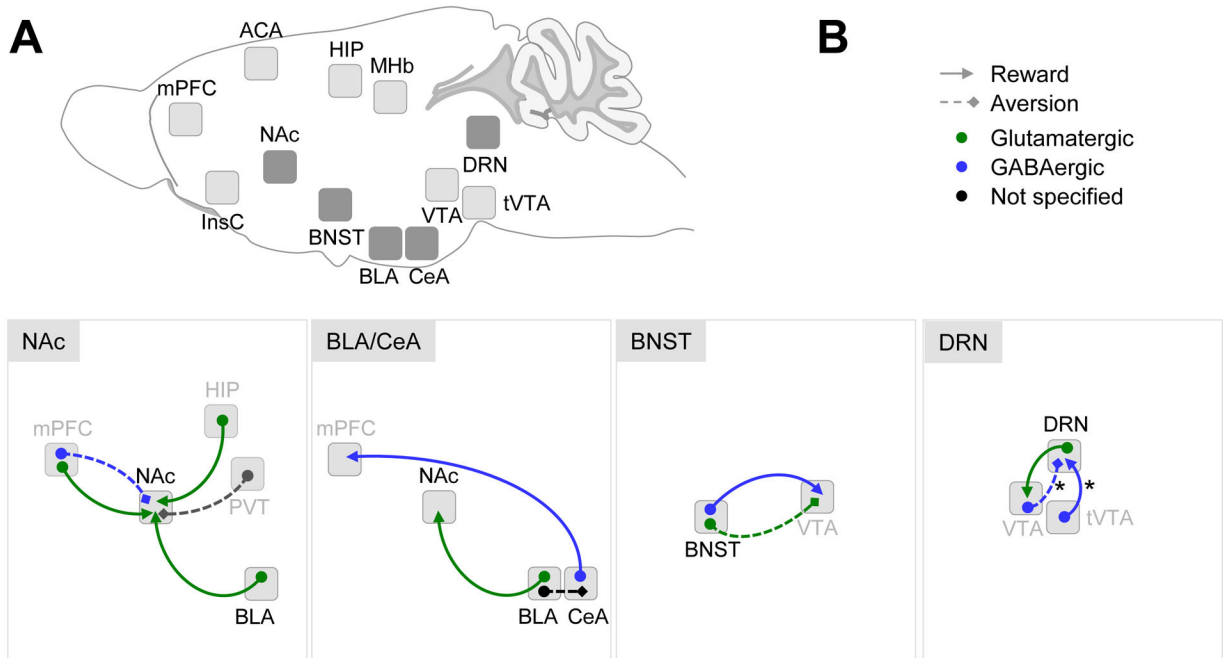
Figure 2. Neuronal populations involved in reward/aversion responses in four major aversion brain centers.

A. Brain template representing brain regions of interest to study the negative affect of protracted opioid abstinence. ACA, anterior cingulate area; BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; DRN, dorsal raphe nucleus; HIP, hippocampus; InsC, insular cortex; MHb, medial habenula; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; PVT, paraventricular thalamus; tVTA, tail of the ventral tegmental area; VTA, ventral tegmental area. **B**. Summary of data obtained from selected optogenetic studies focused on the NAc, BLA/CeA, BNST and DRN. Photostimulation of the identified neuronal populations produce approach (arrow) or avoidance (dashed arrow) behavior in real-time preference testing. Glutamatergic neurons are in green, GABAergic neurons in blue and unspecified neuron types in black. *, photo-inhibition produced the opposite behavior. Other affect-related behaviors are also reported in these studies (see Supplementary information and Supplementary Table 1).

Table 1.

Emotional deficits after spontaneous opioid withdrawal.

The table summarizes behavioral modifications in rodents that have experienced a history of chronic opioid exposure, followed by spontaneous withdrawal (no more drug on board). Opioid regimen, duration of withdrawal and behavioral tests are indicated. Despair-like behavior in FST and TST relate to measures of immobility time. Some of the studies have examined brain sites, neurotransmitter mechanisms or potential genes involved. The vast rodent literature reporting effects of naloxone-precipitated withdrawal, or reinstatement of opioid seeking/taking after withdrawal is not included. CRF, Corticotropin Releasing Factor; CPP, conditioned place preference; DOR KO, delta opioid receptor knockout; DRN, dorsal raphe Nucleus; EA, extended amygdala; EPM, elevated-plus maze; FST, forced swim test; KOR KO, kappa opioid receptor knockout; NAc, nucleus accumbens; norBNI, norbinaltorphimine; NTS, nucleus tractus solitarius; OPF, open field; THC, D9-tetrahydrocannabinol; TST, tail suspension test; SI, direct social interaction; vlBNST, ventrolateral bed nucleus of the stria terminalis; 5-HT, serotonin; 5HT1R, 5HT1 receptor.

Opioid Treatment	Duration withdrawal (Species)	Behavioral Deficit (Test)	Neurotransmitter /Brain region	Reference
Morphine i.p. injection for 14 days, twice a day (escalating dose 20–300mg/kg)	6 days (Rats)	• Increased despair-like behavior (FST)		(46)
Morphine s.c. daily injection for 10 days (10mg/kg)	7 days (Rats)	• Increased anxiety-like behavior (OPF) • Social deficit and increased self-grooming (SI)	CRF modulates withdrawal-induced anxiety in social test	(48) (60)
Morphine i.p. injection for 7 days, twice a day (escalating-dose 20–100 mg/kg)	7 days (Mice)	• Increased anxiety-like behaviour (OPF and EPM) • Increased despair-like behaviour (FST) • Social Deficit	Oxytocin and mGluR5 antagonist reduce emotional impairment	(49) (61)
Morphine s.c. injections for 7 days, twice a day (intermittent escalating-dose)	3 and 9 days (Mice)	• Adult: increased despair-like behaviour (FST) on day 9 • Adolescent: decreased despair-like behaviour (FST) on day 3		(50)
Morphine i.p. injection for 10 days, twice a day (escalating dose 5–50mg/kg)	10 days (Rats)	• Anhedonia (sucrose self-administration)		(47)
Morphine s.c. implanted tablets implanted for 14 days (75 mg tablet)	5 days, 2 and 5 weeks (Rats)	5 days: • Increased morphine preference (CPP) and anxiety (defensive burying) 2 weeks • No food preference (CPP) 5 weeks • Altered hedonic processing (decreased food CPP & increased morphine CPP)	5 days: • Systemic fluoxetine reduces morphine preference and anxiety • Fluoxetine in NAc reduces morphine CPP 5 weeks: • c-fos increased in EA	(62) (51) (52) (106)

Opioid Treatment	Duration withdrawal (*Species*)	Behavioral Deficit (*Test*)	Neurotransmitter /Brain region	Reference
Morphine i.p. injection for 6 days, twice a day *(escalating dose 20–100 mg/kg)*	1 and 4 weeks *(Mice)*	1 week: • No significant emotional deficit 4 weeks: • Increased despair-like behaviour *(TST)* • Social deficit and increased self-grooming *(SI)*	• c-fos in vlBNST, EA & NTS correlates with behavior 1 week: • Decreased 5HT1R function 4 weeks: • Altered DRN 5HT levels • Chronic fluoxetine during 4 weeks abstinence prevents emotional deficits	(53) (107)
Heroin i.p. injection for 6 days, twice a day *(escalating dose 10–50 mg/kg)*	1,4 and 7 weeks *(Mice)*	4 & 7 weeks: • Increased despair-like behaviour *(TST)* • Social deficit and increased self-grooming *(SI)* • Reduced spatial memory *(Y-maze)*	4 weeks: • Sucre anhedonia enhanced in DOR KO mice • Social deficits reduced in KOR KO mice • Chronic fluoxetine and norBNI during/after 4 weeks abstinence prevent/reverse emotional deficits	(54) (7)
Morphine i.p. injection for 6 days, twice a day *(escalating dose 20–100 mg/kg)*	4 weeks *(Mice)*	• Increased anxiety-like behaviour *(marble burying, novelty suppressed feeding)* • Social deficit and increased self-grooming *(SI)*	• 14 genes identified in EA • Genes regulated by morphine, THC, alcohol, nicotine but not cocaine	(55, 72)
Morphine i.p. injection for 6 days, twice a day *(escalating dose 20–100mg/kg)*	4 weeks *(Mice)*	• Increased anxiety-like behavior *(EPM, OPF)*	Wnt7a knockdown in insular cortex reduces emotional impairment	(56)