Biological Psychiatry

Review

Neurobiology of Opioid Addiction: Opponent Process, Hyperkatifeia, and Negative Reinforcement

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ABSTRACT

Opioids are powerful drugs that usurp and overpower the reward function of endogenous opioids and engage dramatic tolerance and withdrawal via molecular and neurocircuitry neuroadaptations within the same reward system. However, they also engage the brain systems for stress and pain (somatic and emotional) while producing hyperalgesia and hyperkatifeia, which drive pronounced drug-seeking behavior via processes of negative reinforcement. Hyperkatifeia (derived from the Greek "katifeia" for dejection or negative emotional state) is defined as an increase in intensity of the constellation of negative emotional or motivational signs and symptoms of withdrawal from drugs of abuse. In animal models, repeated extended access to drugs or opioids results in negative emotion-like states, reflected by the elevation of reward thresholds, lower pain thresholds, anxiety-like behavior, and dysphoric-like responses. Such negative emotional states that drive negative reinforcement are hypothesized to derive from the within-system dysregulation of key neurochemical circuits that mediate incentive-salience and/or reward systems (dopamine, opioid peptides) in the ventral striatum and from the between-system recruitment of brain stress systems (corticotropin-releasing factor, dynorphin, norepinephrine, hypocretin, vasopressin, glucocorticoids, and neuroimmune factors) in the extended amygdala. Hyperkatifeia can extend into protracted abstinence and interact with learning processes in the form of conditioned withdrawal to facilitate relapse to compulsive-like drug seeking. Compelling evidence indicates that plasticity in the brain pain emotional systems is triggered by acute excessive drug intake and becomes sensitized during the development of compulsive drug taking with repeated withdrawal. It then persists into protracted abstinence and contributes to the development and persistence of compulsive opioid-seeking behavior.

Keywords: Addiction, Dysphoria, Hyperkatifeia, Negative reinforcement, Opioids, Stress

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OPIOID ADDICTION: HEURISTIC FRAMEWORK

A heuristic framework for opioid addiction consists of a 3-stage cycle—binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation—that represents dysregulation in 3 functional domains (incentive salience and/or habits, negative emotional states, and executive function, respectively) and is mediated by 3 major neurocircuitry elements (basal ganglia, extended amygdala, and prefrontal cortex, respectively). Opioids are a classic drug of addiction, in which an evolving pattern of use includes intense initial intoxication that is associated with intravenous or smoked drug taking, the development of profound tolerance, and the consequent escalation of intake. Abstinence results in profound dysphoria, physical discomfort, and somatic signs of withdrawal. Intense preoccupation with obtaining opioids (craving) then develops, often preceding somatic signs of withdrawal. This craving is linked to stimuli that are associated with obtaining the drug and stimuli that are associated with withdrawal and internal and external states of stress. A pattern develops in which the drug must be administered to avoid the severe dysphoria and discomfort of abstinence. Thus, opioid addiction can be defined as a compulsion to seek and take a drug, a loss of control in limiting intake, and the emergence of a negative emotional state when access to the drug is prevented.

From a conceptual framework, excessive drug taking in the binge/intoxication stage drives an allostatic-like process, in which the break with reward homeostasis triggers compensatory responses in the reward and stress systems of the brain to generate the withdrawal/negative affect stage and preoccupation/anticipation stage (1). The 3 stages feed into one another, becoming more intense and ultimately leading to the pathological state known as addiction (1) (Figure 1). Particularly with opioids, the termination of drug taking inevitably leads to negative emotional states of acute and protracted withdrawal in the withdrawal/negative affect stage, which generates a second motivational drive from negative reinforcement. Protracted abstinence incorporates residual elements of negative emotional states and cue and contextual craving to form the preoccupation/anticipation stage. Opioid use disorder is now considered a spectrum disorder as described by the DSM-5 (2), which provides a framework for the intensity of symptoms with regard to the number of symptoms that are

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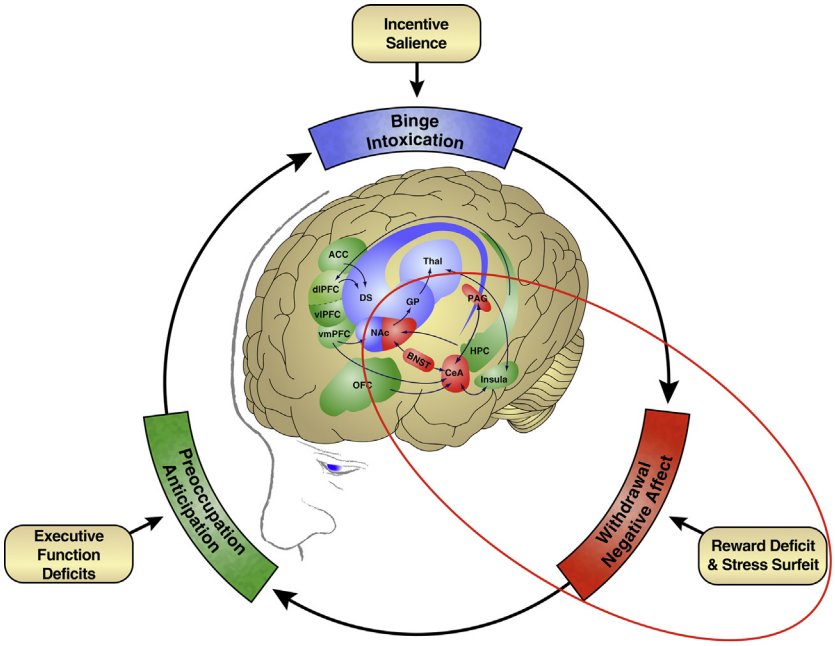

Figure 1. Conceptual framework for neurobiological bases of substance use disorders. ACC, anterior cingulate cortex; BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; DS, dorsal striatum; dlPFC, dorsolateral prefrontal cortex; GP, globus pallidus; HPC, hippocampus; NAC, nucleus accumbens; OFC, orbitofrontal cortex; PAG, periaqueductal gray; Thal, thalamus; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex. [Modified with permission from Koob and Volkow (105).]

presented, showing that an individual can enter the addiction cycle at different stages. For example, with opioid use disorder, much like with other substance use disorders, individuals may start opioid misuse with recreational use of the drug and progress to the withdrawal/negative affect stage as negative reinforcement evolves. However, opioids differ from many other addictive substances because negative reinforcement may be the starting point, via either self-medication or chronic pain. The focus of this review is on the withdrawal/negative affect stage, the relationship to emotional pain, and the neurobiological circuits that are engaged to produce the negative emotional states that drive negative reinforcement.

NEGATIVE REINFORCEMENT IN OPIOID ADDICTION

The negative reinforcement that is associated with compulsive opioid seeking derives from the well-established framework of opponent processes. Here, euphoria (a-process) that is produced by the opioid is followed by dysphoria (b-process) that grows with repeated administration and that can be equated with the development of withdrawal and dependence (see the Supplement for details of opponent process theory). Development of the b-process reflects the development of a negative emotional state in opposition to the hedonic effects (a-process) of the opioid, including malaise, irritability, alexithymia, anxiety, dysphoria, and subjective feelings of unease and simply not feeling "hedonically normal," all of which are also withdrawal symptoms. This hypernegative emotional state, termed hyperkatifeia (3), was proposed to worsen with repeated experience, and sensitized hyperkatifeia was hypothesized to be dissociable from somatic signs of withdrawal and major psychiatric disorders. Here, negative reinforcement becomes the source of motivation for drug seeking, in which the individual will work to reduce, terminate, or prevent this sensitized negative emotional state. As a result, a greater amount and more frequent use of the previously rewarding substance is needed to maintain or approach euthymia.

Thus, repeated opioid intoxication and withdrawal lead to repeated hypohedonia, hyperkatifeia, and hyperalgesia and more pronounced behavioral responses to stress that the individual misregulates by taking more drug (Figure 1, Supplemental Figure S1, and the Supplement). Under this framework, substance use is compulsively escalated or renewed (in relapse) via negative reinforcement mechanisms because it transiently prevents or relieves the negative emotional symptoms of withdrawal or hyperkatifeia, and this compulsive drug seeking defends a hedonic set point that gradually gains allostatic load and shifts from a homeostatic hedonic state to an allostatic hedonic state (4) (see the Supplement for a definition of allostasis).

Opponent process–like negative emotional states have been characterized in humans by acute and protracted abstinence from opioids (5–7), and similar results have been observed in animal models with opioids (8). Dysphoric-like responses in rodents, measured by elevations of brain stimulation reward thresholds, accompany acute opioid withdrawal (9,10). Perhaps a more compelling example of the allostatic-like dysregulation of drug taking that results in hypohedonia is the elevation of reward thresholds that is charted during the course of the escalation of heroin intake in rats during extended access to opioids (Supplemental Figure S2).

HYPERKATIFEIA: NEUROBIOLOGICAL BASES

Hyperalgesia and hyperkatifeia are well-documented symptoms of acute and protracted withdrawal from opioid drugs, and both directly reflect opponent processes that have motivational significance (see the Supplement). The motivational power of these painful and negative emotional states in driving

negative reinforcement requires further elucidation of the neurobiological mechanisms.

A connectome imaging study in mice revealed a major influence of μ opioid receptor gene (*Oprm1*) inactivation, showing a dramatic change in aversion- and/or pain-related connectivity rather than reward connectivity using a hypothesis-free analysis of combined resting-state functional magnetic resonance imaging diffusion tractography (11). These results may reflect stronger inhibitory μ opioid receptor tone or a developmental influence on negative affect neurocircuits, at least under resting-state conditions. Predominant alterations within reward/aversion pathways correlated with major behavioral modifications in *Oprm1* mutant mice with regard to pain-, emotion-, and reward-related behaviors (12). Examinations of alterations of hub status and direct statistical intergroup comparisons indicated a predominant reshaping of networks that are known to process information of negative valence. These networks included such structures as the periaqueductal gray (PAG), hippocampus, amygdala, cingulate cortex, median raphe, and habenula (11).

Consistent with the connectome results, neurochemistry and neurocircuitry studies have shown that neuroadaptations that mediate hyperkatifeia have a focal point in the extended amygdala. The extended amygdala comprises several basal forebrain structures, including the bed nucleus of the stria terminalis, the central nucleus of the amygdala, the sublenticular substantia innominata, and a transition zone in the medial part of the nucleus accumbens (e.g., shell) (13). Lesions of the central nucleus of the amygdala blocked the development of morphine withdrawal–induced conditioned place aversion but had less of an effect on somatic signs of withdrawal (14).

A conceptual framework that was adopted to explain the neural systems that are argued to mediate hyperkatifeia and drive the motivational component of opponent processes of excessive opioid use involved the within-system downregulation of brain reward circuitry and between-system recruitment of brain stress circuitry (15,16). A within-system neuroadaptation was defined as a process by which the primary cellular response element to the drug within a given neurochemical circuit itself adapts to neutralize the effects of the drug. In contrast, between-system neuroadaptation was defined as a circuitry change in which another circuit (i.e., stress or antireward circuit) is activated by a reward circuit. Persistence of the opposing effects after removal of the drug is reflected by the negative emotional withdrawal syndrome that is described above.

Within-System Neuroadaptations

One source of within-system neuroadaptations involves elements of opioid receptor function that mediate tolerance to opioids, and this tolerance would extend to the rewarding effects of the drug. G proteins that are activated through the μ opioid receptor modulate the activity of several second messengers and cellular effectors, which may generate both short-term and long-term neuroadaptations that are relevant to tolerance at the molecular and cellular levels. Other molecular and/or cellular events, in addition to G protein signaling cascades, contribute to μ opioid receptor signaling, including receptor desensitization, receptor internalization, transcriptional changes, and structural changes such as dendritic spine remodeling (17–19), and tolerance at the cellular level may be the sum of these multiple events (20).

At the neurocircuitry level, early studies showed that precipitated opioid withdrawal was associated with decreases in extracellular dopamine levels in the nucleus accumbens (21) and mesolimbic dopamine system, with decreases in dopamine neuron firing and extracellular dopamine levels during opioid withdrawal (22,23) (Figure 2A). Chronic morphine administration is also associated with a decrease in the size of dopamine neurons in the ventral tegmental area and an increase in the sensitivity to dopamine receptor antagonists. These cellular changes that occur during opioid withdrawal are accompanied by an increase in γ-aminobutyric acid activity and increase in metabotropic glutamate receptor sensitivity, both of which decrease glutamate release in the ventral tegmental area and lead to a decrease in dopamine cell firing (24).

Human positron emission tomography studies found lower baseline dopamine D_2 receptor availability in the dorsal striatum in opioid-dependent subjects compared with control subjects (25). In a study that showed a decrease in D_2 receptor availability in the left caudate nucleus, D_2 receptor availability in the putamen was negatively correlated with years of opioid use (26). One mechanism to explain the hypodopaminergic state is that opioids trigger a cascade of molecular events that involve cyclic adenosine monophosphate and ultimately activate dynorphin, particularly in the shell of the nucleus accumbens (27,28).

The lateral habenula is a brain structure with connections to the brain reward systems, and it plays a key role in mediating and encoding aversive states (29) (Figure 2A; also see the Supplement). Activation of the lateral habenula strongly inhibits dopamine neurons in the ventral tegmental area, and thus the regulation of dopamine activity in the ventral tegmental area by the lateral habenula has been hypothesized to underlie aversive effects of abused drugs (30) and, by extrapolation, aversive effects of drug withdrawal. Intralateral habenula administration of KN-62, a specific inhibitor of calcium/calmodulin-dependent protein kinase II, eliminated naloxone-precipitated conditioned place aversion in morphine-dependent mice, a finding that is consistent with the observation that chronic morphine use induced the overexpression of calcium/calmodulin-dependent protein kinase II in the lateral habenula (31). In humans, an increase in habenula–striatum connectivity was observed in opioid-using patients who exhibited withdrawal avoidance and aversion (32).

Between-System Neuroadaptations

For between-system neuroadaptations, the recruitment of brain stress systems, including corticotropin-releasing factor (CRF), norepinephrine, and dynorphin, is a major key substrate that is responsible for the aversive stimulus effects of opioid withdrawal that drive compulsive-like opioid seeking (15) (Figure 2B). Early work showed that the antagonism of CRF receptors and noradrenergic receptors in the extended amygdala blocked the aversive stimulus effects of opioid withdrawal (33–35). The administration of a CRF_1/CRF_2

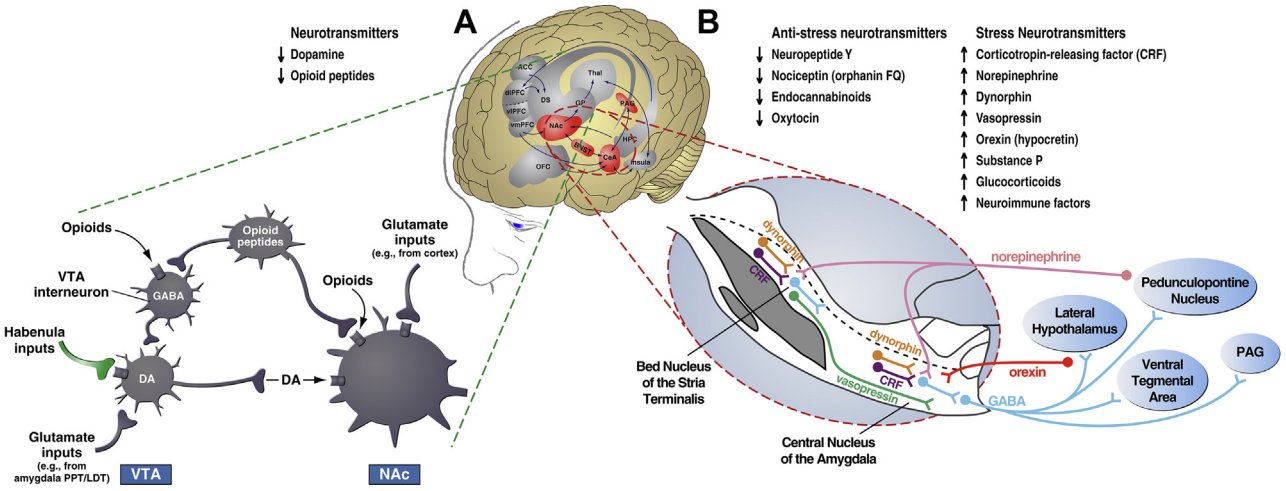

Figure 2. Neural circuitry associated with the negative emotional state of the withdrawal/negative affect stage. **(A)** Extended amygdala and within-system neuroadaptations. Note the loss of dopamine and opioid peptide function in ventral tegmental area–nucleus accumbens circuitry, with a hypothesized contribution of the habenula that suppresses neuron activity in the ventral tegmental area (inset panel). **(B)** Extended amygdala and between-system neuroadaptations. Note the gain of stress neurotransmitter and neuromodulator function and loss of antistress neurotransmitter and neuromodulator function throughout the neurocircuitry of the extended amygdala (inset panel). The extended amygdala is composed of several basal forebrain structures, including the bed nucleus of the stria terminalis, the central nucleus of the amygdala, and possibly a transition area in the medial portion (shell) of the nucleus accumbens. ACC, anterior cingulate cortex; BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; DA, dopamine; DS, dorsal striatum; dlPFC, dorsolateral prefrontal cortex; GABA, γ-aminobutyric acid; GP, globus pallidus; HPC, hippocampus; LDT, laterodorsal tegmentum; NAC, nucleus accumbens; OFC, orbitofrontal cortex; PAG, periaqueductal gray; PPT, pedunculopontine tegmentum; Thal, thalamus; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex; VTA, ventral tegmental area. [Adapted with permission from Koob (106) and George and Koob (107).]

peptide receptor antagonist in the central nucleus of the amygdala blocked precipitated conditioned place aversion that was produced by opioid withdrawal (33). The blockade of noradrenergic function in the bed nucleus of the stria terminalis also blocked opioid withdrawal–induced place aversions (34,35). These same neuropharmacological systems that are implicated in the aversive effects of opioid withdrawal are also implicated in compulsive drug taking and seeking that are associated with extended-access intravenous self-administration in animal models. Both CRF receptor antagonists and α_1-adrenergic receptor antagonists dose-dependently decreased compulsive-like drug intake in rats with extended access to opioids (36–38).

To date, no clinical studies have found efficacy of CRF_1 receptor antagonists for the treatment of stress-related psychiatric disorders, such as major depression, generalized anxiety, social anxiety, or posttraumatic stress disorder (39,40). The findings of a few limited human laboratory studies of alcohol use disorder have also been negative (41). No double-blinded treatment study for addiction has been conducted. An in-depth discussion of the reason for such treatment failures is beyond the scope of this review, but a possibility is that the efficacy of CRF_1 receptor antagonists for particular psychiatric disorders or symptoms, patient subgroups, or circumstances in which pro–stress-like CRF-CRF_1 circuits are dynamically activated may need to be tested (40,42).

Dynorphin is released by stressors, and blockade of the dynorphin–κ opioid receptor system blocks the aversive effects of stress (43,44) and produces antidepressant-like effects in animal models of depression (44). The dynorphin-induced activation of κ opioid receptors decreases dopamine release in the nucleus accumbens and produces conditioned place aversions (45). Perhaps more compelling, behavioral studies have consistently demonstrated that κ opioid receptor antagonists do not block the acute rewarding ("euphoric-like") effects of opioids but do block the stress-induced potentiation of opioid reward, the stress-induced reinstatement of opioid-seeking behavior, and the escalation of drug consumption in long-access models (46) (Supplemental Figure S3).

The activation of neuropeptide Y, oxytocin, and endocannabinoid systems in the extended amygdala may buffer the increase in stress reactivity that is associated with opioid withdrawal (47–50). Thus, chronic opioid administration dysregulates the neuropharmacological systems that interface with the reward and stress systems in the nucleus accumbens and extended amygdala to lower reward function and increase stress and pain. Prostress systems can drive hyperkatifeia, and antistress systems can reverse hyperkatifeia.

A human imaging study of individuals who were dependent on prescription opioids found striking alterations of amygdala structure and connectivity (51). This study included a subgroup of matched prescription opioid–dependent subjects who underwent structural magnetic resonance imaging, diffusion tensor imaging, and resting-state functional magnetic resonance imaging. Compared with healthy control subjects, the opioid-dependent subjects exhibited bilateral volumetric loss in the amygdala, a significant decrease in anisotropy in efferent and afferent pathways of the amygdala, and decreases in functional connectivity in brain networks that involved the amygdala, insula, and nucleus accumbens, including a decrease in functional connectivity between the amygdala and PAG (51).

One prominent output of the extended amygdala is the PAG (52). The PAG is also well known to play a key role in

processing pain via both the classic spinothalamic pain pathway and the emotional parabrachial pain pathway via its connections to the amygdala (53). Pain can drive motivated behavior, in which pain and other aversive processes drive avoidance and escape. The PAG also has long been associated with the classic precipitated morphine withdrawal syndrome that is produced in animals that are chronically treated with morphine. The local administration of enkephalinase inhibitors in the PAG blocked naloxone-precipitated withdrawal (54,55). One mechanism that may drive some of these neuroadaptations in the PAG involves neuroinflammatory responses. The development of tolerance to morphine is paralleled by increases in the gene expression of several proinflammatory factors in the PAG, such as toll-like receptor-4, tumor necrosis factor α, and interleukin-1β (56–58). The increase in proinflammatory activity results in a significant increase in excitatory neurotransmission that is mediated by increases in glutamatergic tone, which is hypothesized to actively oppose the analgesic effect of morphine (57). Similarly, opioid withdrawal is mediated by the activation of proinflammatory systems in the PAG. Induction of the interleukin-4 gene (*Il4*) with a recombinant vector blunted the morphine withdrawal syndrome in mice (59). Microinjection of a herpes simplex virus vector in the PAG to decrease tumor necrosis factor α before the start of morphine treatment significantly reduced naloxone-precipitated withdrawal in mice (60). Thus, the PAG mediates hyperkatifeia and has been implicated in mediating aversive prediction errors that are associated with fear (52) (Supplement). In aversive learning, an aversive prediction error occurs when the discrepancy between the predicted value and the experienced value of the aversive state is worse than expected. Whether the PAG is involved in aversive prediction errors that are associated with hyperkatifeia in opioid withdrawal remains to be determined.

NEUROCIRCUITRY INTERSECTION OF OPIOIDS, PAIN, AND ADDICTION

A behavioral mechanism of action for opioids that is a unifying common theme is their relief of pain and suffering, including relief of negative emotional states (61). Opioids are recognized as the most powerful and effective drugs for the relief of acute pain in humans. However, opioids are significantly less effective against chronic pain, such as neuropathic pain, fibromyalgia, or low-back pain. Tolerance to the analgesic effects of opioids requires increasingly higher doses to sustain analgesia (62,63). More importantly for the present thesis, opioids can also relieve emotional pain, and this is one of the behavioral mechanisms that is strongly implicated in driving the withdrawal/negative affect stage of the addiction cycle. Individuals who experienced or expressed physical abuse and violent behavior described the ways in which opioids helped them feel normal, calm, mellow, soothed, and relaxed (64).

Withdrawal from chronic opioid self-administration produces hyperalgesia (i.e., lower pain thresholds) (65,66). Patients who receive long-term opioid therapy for weeks to years can develop unexpectedly abnormal pain and hyperalgesia on withdrawal from opioid treatment (67). In humans, opioid withdrawal can lower pain thresholds and exacerbate pain, and heightened pain perception has long been observed in individuals with a history of opioid addiction (68,69). Patients who are on methadone maintenance have low pain tolerance (70), and pain is one of the main triggers of relapse to addiction in such individuals (71). In a study of the interaction between negative emotional states and withdrawal hyperalgesia, subjects who were in either acute withdrawal (24–72 hours) or protracted abstinence (average of 30 months) from opioids exhibited decreases in pain thresholds and pain tolerance, measured by the ischemic pain submaximal tourniquet procedure, and these effects were exacerbated by negative emotional states (72). Individuals in all groups (i.e., nonusers, ex-users, and withdrawn users) exhibited lower pain tolerance after viewing negative pictures compared with tolerance latencies that were observed after viewing positive and neutral pictures (72). Acute opioid administration can produce hyperalgesia. Men who were not dependent on opioids and who underwent an acute opioid physical dependence challenge paradigm by receiving naloxone exhibited the presence of hyperalgesia in response to experimental cold-pressor pain (73).

In animal models, when the opioid is administered repeatedly (e.g., once daily for 2 weeks), a gradual and dose-dependent decrease in nociceptive threshold is observed that lasts for several weeks after drug administration (74,75). A small dose of heroin that was otherwise ineffective in triggering delayed hyperalgesia in non–heroin-treated rats enhanced pain sensitivity for several days after a series of heroin injections, suggesting the occurrence of pain sensitization. Thus, a neuronal memory that is characterized by a vulnerable state may remain long after complete washout of the drug and when apparent equilibrium near the predrug state has been reestablished. Such hyperalgesia has also been observed with a single injection of heroin in rats (76).

Neurobiological mechanisms for opioid-induced hyperalgesia include the activation of glutamatergic systems and the same brain stress systems (e.g., CRF and dynorphin) that are implicated in hyperkatifeia (see above). In an animal model of long-lasting hyperalgesia after exposure to heroin, a noncompetitive glutamate receptor antagonist reversed hyperalgesia (76). A noncompetitive glutamate receptor antagonist also prevented the long-lasting heroin-induced enhancement of pain sensitivity and naloxone-precipitated hyperalgesia in humans (77). Hyperalgesia in the tail flick test that was associated with morphine withdrawal was blocked by microinjections of a CRF_1/CRF_2 peptide receptor antagonist in the central nucleus of the amygdala, without affecting plasma corticosterone responses (78). Consistent with this observation, hyperalgesia during withdrawal in animals that developed compulsive-like responding with extended access to heroin was blocked by the systemic administration of a CRF_1 receptor antagonist (38,79). Dynorphin knockout mice exhibited a facilitated return to normal nociceptive baselines after a peripheral nerve lesion (80), suggesting a pronociceptive role for dynorphin in chronic pain, in contrast to the antinociceptive effects of acute administration of κ opioid receptor agonist.

A link between hyperalgesia and hyperkatifeia can be found, with a focus on CRF and dynorphin in the extended amygdala. CRF in the amygdala, particularly in the central nucleus of the amygdala, plays an important role in pain modulation and

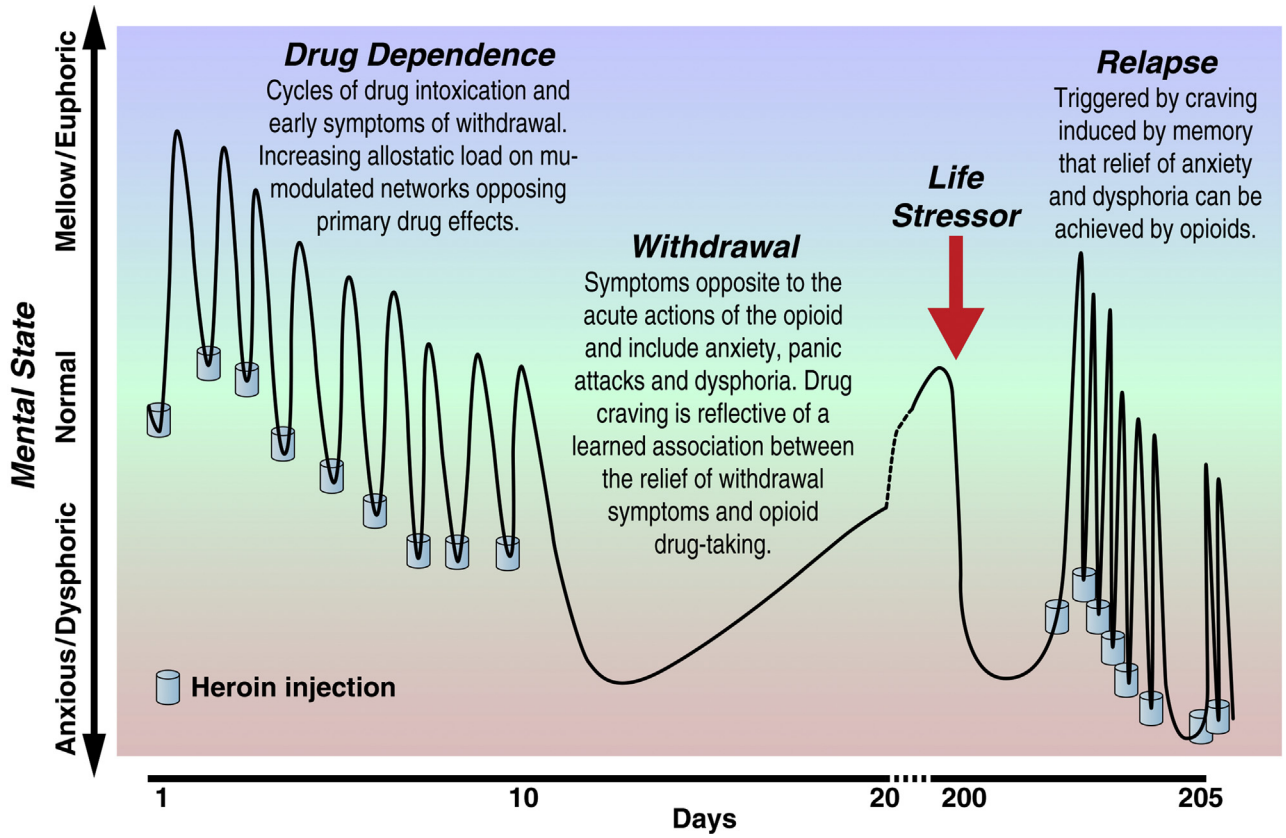

Figure 3. Allostatic framework for addiction to and withdrawal from opioid drugs, and relapse to opioid drug use. The diagram is based on "Laura's pathway to heroin addiction" from Evans and Cahill (103). A hypothetical scenario is provided about how the learned association of the relief of aversive states can lead to the development of addiction and the key role of opioid dependence therein. [Modified with permission from Evans and Cahill (103).]

pain-related affect (81). The blockade of CRF_1 receptors in the central nucleus of the amygdala inhibited pain- and anxiety-like behaviors in an animal model of arthritic pain (82,83).

The dynorphin–κ opioid receptor system is also engaged in negative emotional states that are associated with chronic pain (84–86). Evidence that supports this hypothesis includes findings from studies of knockout mice, the neurocircuitry-specific engagement of dynorphin neurons, and the neuropharmacological blockade of κ opioid receptors. The stimulation of specifically dynorphin-containing neurons in the ventral nucleus accumbens shell by selectively expressing channelrhodopsin-2 in dynorphin-Cre+ mice decreased the motivation to self-administer sucrose. The local infusion of microgram amounts of the κ opioid receptor antagonist norbinaltorphimine in the ventral nucleus accumbens shell blocked the place aversion that was produced by inflammation combined with the activation of ventral nucleus accumbens shell dynorphin neurons (85,86). The authors of these two reports argued that the in vivo recruitment of nucleus accumbens shell dynorphin neurons that act through κ opioid receptors can drive pain-induced negative affect (85,86). Thus, there is a clear role for the dynorphin–κ opioid receptor system in modulating the interplay of pain, stress, and reward processing. The high comorbidity between chronic pain, addiction, depression, and suicide provides a compelling rationale for further study in this domain.

CONDITIONED WITHDRAWAL

The break with emotional homoeostasis, defined as hyperkatifeia, does not end with acute withdrawal and can extend into prolonged abstinence, such as with hypersensitivity to pain as described above. Support for such a framework comes from several sources: allostasis theory, negative affective networks, and learned associations. Indeed, perturbations to the brain reward and stress systems can engage learning systems to leave a residual neuroadaptive trace that allows rapid relapse even months and years after detoxification and abstinence. Although craving in addiction is often linked to cues and contexts that are paired with the positive hedonic effects of the drug, craving and drug seeking can also be elicited by cues and contexts that are linked to withdrawal via conditioned withdrawal (87). In a classic study, a previously neutral peppermint smell (conditioned stimulus) that was paired with withdrawal reactions (unconditioned response) elicited subjective and physiological manifestations of the narcotic withdrawal syndrome (conditioned response). After numerous pairings of the peppermint smell with precipitated withdrawal that was

produced by naloxone in methadone-maintained individuals, the peppermint smell alone precipitated withdrawal (87).

Conditioned withdrawal has also been observed in animal models using the conditioned place aversion paradigm (8) and intravenous operant self-administration of opioids or other rewards (88,89). In rats that were allowed 23-hour access to heroin (Supplemental Figure S2), previously neutral stimuli (odor and cue light) that were repeatedly paired with naloxone-precipitated withdrawal produced conditioned withdrawal, reflected by elevations of intracranial self-stimulation thresholds and an increase in heroin consumption (89) (Supplemental Figure S4). Fos activation in the extended amygdala paralleled the conditioned place aversion response (90). Additionally, bilateral inactivation of the basolateral amygdala (i.e., a major input to the extended amygdala) blocked the development of conditioned opioid withdrawal (91). The ability of a tone-light stimulus that had been paired with precipitated opioid withdrawal (conditioned stimulus) to suppress responding for food was blocked by bilateral quinolinic acid–induced lesions of the basolateral amygdala (91). Altogether, these results suggest a key pathway from the basolateral amygdala to the extended amygdala in mediating negative valence-induced craving.

SEX DIFFERENCES

More men use and are addicted to opioids (92) and other drugs of abuse (93). Nonetheless, clinical reports indicate that women who become addicted to opioids progress through the stages of addiction, from initial use to dependence, at a faster rate than men (94). In animal models, female rodents generally acquire morphine and heroin self-administration faster than male rodents, and they exhibit higher motivation to self-administer opioids (95–97). However, female subjects are less sensitive to the analgesic effects of μ opioid receptor agonists (98,99). The physical signs of opioid withdrawal are more pronounced in male mice than in female mice (100), although little or no work has focused on preclinical studies of sex differences in animal models of hyperkatifeia and negative reinforcement (97).

IMPLICATIONS FOR THE ETIOLOGY AND TREATMENT OF OPIOID USE DISORDER

The thesis outlined herein is that knowledge of the neuroadaptations that occur within the framework of the withdrawal/negative affect stage provides fertile ground for developing new treatments for opioid use disorder. Chronic opioid administration has numerous effects on neuropharmacological systems that interface with the extended amygdala, a key pathway that is associated with the withdrawal/negative affect stage of the addiction cycle. Opioids act directly and indirectly via γ-aminobutyric acid and glutamate systems to activate reward pathways. With excessive use, these same systems undergo neuroadaptations with chronic opioid exposure that lower reward function, increase stress function, and increase the negative affect component of pain, all of which contribute to hyperkatifeia. The argument is that these specific neurocircuitry dysregulations contribute to the links that have been hypothesized to exist between the neural mechanisms that are responsible for a hypersensitive negative emotional state (hyperkatifeia) and opioid-induced hyperalgesia (3).

As discussed above, opioid addiction is hypothesized to move to compulsive drug seeking via negative reinforcement mechanisms because opioid use transiently prevents or relieves negative emotional symptoms or hyperkatifeia. This compulsive drug seeking defends a hedonic set point that gradually gains allostatic load and shifts from a homeostatic hedonic state to an allostatic hedonic state (4). Others have argued that one of two main determinants of drug "urges" is a "negative affect" network (101). Such a negative affect network is activated not only during withdrawal but also by conditioned predictors of withdrawal (e.g., drug cues) and unappetitive consequences (e.g., punishment, frustrative nonreward) or their conditioned cues. In this model, escape from and the avoidance of negative affect are powerful motives for compulsive drug use (102). Evans and Cahill (103) argued that opioid addiction is sustained by a learned association between opioids and relief from an existing dysphoric state, a learned association that is formed by negative reinforcement. They further argued that later stressful events during protracted abstinence can generalize to such a dysphoric state and produce recall that opioid drugs can relieve such a negative state (103) (Figure 3).

A neglected area in the hyperkatifeia domain is the development of medications and behavioral strategies that target specifically the affective component of protracted abstinence from opioids. As noted above, studies have reported hypersensitivity to pain and discomfort with opioids that can last for more than a year after detoxification. Treatment must consider the dysregulation of pain and stress systems during acute withdrawal and long into recovery. Based on preclinical studies, medications and behavioral therapies that reset the hypothalamic-pituitary-adrenal axis and/or CRF brain systems and return the dynorphin–κ opioid receptor system to homeostasis would be promising new targets for medication development.

Additionally, cues that are paired with withdrawal can have significant motivational power in driving craving and relapse. Cues that were associated with conditioned withdrawal activated the extended amygdala and hypothalamic circuits in a preclinical imaging study (104). Very little work has focused on the neurobiology of conditioned withdrawal and the ways in which it may be applied to the sustained treatment of opioid use disorder. The focus on understanding the reward deficit and/or stress surfeit component of the withdrawal/negative affect stage of opioid use disorder can also inform which behavioral treatments may be more effective in moderate to severe opioid use disorder. For example, versions of cognitive behavioral therapy that address coping mechanisms for stress and pain (physical and affective) may be more important than refinements in contingency management.

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