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Drug Addiction: Hyperkatifeia/Negative Reinforcement as a Framework for Medications Development

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Abstract	164
Significance Statement.....	164
I. Introduction	164
II. Addiction: Definition and Theoretical Framework.....	165
A. Definition.....	165
B. Hyperkatifeia Versus Physical Withdrawal	167
C. Opponent Process	168
D. Validation of the Hyperkatifeia Construct in Humans.....	169
D. Validation of the Hyperkatifeia Construct in a Molecular-Neurocircuitry Study in an Animal Model.....	169
III. Within-System/Between-System Neurobiological Substrates for Hyperkatifeia Associated with Opioid and Alcohol Withdrawal	170
A. Within-System Neurocircuits	170
B. Between-System Neurocircuits	171
IV. Within-System Neurobiological Substrates for Hyperkatifeia Associated with Opioid and Alcohol Withdrawal.....	172
A. Within-System Neuroadaptations: Dopamine	172
B. Within-System Neuroadaptations: Enkephalin/Endorphin Opioid Peptides.....	173
C. Within-System Neuroadaptations: GABA and Glutamate	174
V. Between-System Neurobiological Substrates for Hyperkatifeia Associated with Opioid and Alcohol Withdrawal	175
A. Between-System Neuroadaptations: Corticotropin-Releasing Factor	175
B. Between-System Neuroadaptations: Norepinephrine	176
C. Between-System Neuroadaptations: Glucocorticoids.....	177
D. Between-System Neuroadaptations: Dynorphin/ κ -Opioid Receptors	177
E. Between-System Neuroadaptations: Vasopressin.....	178
F. Between-System Neuroadaptations: Hypocretin.....	179
G. Between-System Neuroadaptations: Neuroimmune Systems.....	180
VI. Antistress Neurotransmitters/Neuromodulators and Hyperkatifeia.....	181
A. Neuropeptide Y	181
B. Nociceptin	182
C. Endocannabinoids.....	182
D. Oxytocin	183
VII. Hyperkatifeia and Sex Differences	184
VIII. Pain, Hyperkatifeia, and Addiction.....	185
A. Opioids and Pain.....	185
B. Alcohol and Pain.....	186
C. Pain and Animal Models of Addiction.....	187
IX. Individual Differences in Hyperkatifeia.....	188

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A. Genetics	188
B. Development, Comorbidities, Epigenetics, and Hyperkatifeia	188
X. The Case for Hyperkatifeia as a Target for Medications Development	189
A. Reward Dysregulation, Stress Surfeit, Pain, and Negative Reinforcement	189
B. Negative Results	190
C. Construct Validity	190
D. Conditioning in Withdrawal and Protracted Abstinence	191
Acknowledgments	192
References	192

Abstract—Compulsive drug seeking that is associated with addiction is hypothesized to follow a heuristic framework that involves three stages (binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation) and three domains of dysfunction (incentive salience/pathologic habits, negative emotional states, and executive function, respectively) via changes in the basal ganglia, extended amygdala/habenula, and frontal cortex, respectively. This review focuses on neurochemical/neurocircuitry dysregulations that contribute to hyperkatifeia, defined as a greater intensity of negative emotional/motivational signs and symptoms during withdrawal from drugs of abuse in the withdrawal/negative affect stage of the addiction cycle. Hyperkatifeia provides an additional source of motivation for compulsive drug seeking via negative reinforcement. Negative reinforcement reflects an increase in the probability of a response to remove an aversive stimulus or drug seeking to remove hyperkatifeia that is augmented by genetic/epigenetic vulnerability, environmental trauma, and psychiatric comorbidity. Neurobiological targets for hyperkatifeia in addiction involve neurocircuitry of the extended amygdala and its connections via within-system neuroadaptations in dopamine, enkephalin/endorphin opioid peptide, and γ -aminobutyric acid/glutamate

systems and between-system neuroadaptations in prostress corticotropin-releasing factor, norepinephrine, glucocorticoid, dynorphin, hypocretin, and neuroimmune systems and antistress neuropeptide Y, nociceptin, endocannabinoid, and oxytocin systems. Such neurochemical/neurocircuitry dysregulations are hypothesized to mediate a negative hedonic set point that gradually gains allostatic load and shifts from a homeostatic hedonic state to an allostatic hedonic state. Based on preclinical studies and translational studies to date, medications and behavioral therapies that reset brain stress, antistress, and emotional pain systems and return them to homeostasis would be promising new targets for medication development.

Significance Statement—The focus of this review is on neurochemical/neurocircuitry dysregulations that contribute to hyperkatifeia, defined as a greater intensity of negative emotional/motivational signs and symptoms during withdrawal from drugs of abuse in the withdrawal/negative affect stage of the drug addiction cycle and a driving force for negative reinforcement in addiction. Medications and behavioral therapies that reverse hyperkatifeia by resetting brain stress, antistress, and emotional pain systems and returning them to homeostasis would be promising new targets for medication development.

I. Introduction

Addiction remains a worldwide problem and a significant burden to public health. Three prominent addictive drugs from a public health perspective are tobacco, alcohol, and opioids. The annual costs to society in the United States of tobacco, alcohol, and opioid addiction are estimated to be \$300 billion (<https://www.cdc.gov/drugoverdose/pdf/pubs/2019-cdc-drug-surveillance-report.pdf>), \$249 billion (<https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates>), and \$179.4 billion (Sacks et al., 2015), respectively.

The present review explores the neurobiology of hyperkatifeia, defined as the manifestation of a negative

emotional state during the withdrawal/negative affect stage of the addiction cycle, as a key driving force in addiction that overlaps with pathology that is associated with pain (Egli et al., 2012) and deaths of despair (Case and Deaton, 2015). The theoretical framework of addiction has generally been outlined previously in multiple reviews (Koob and Le Moal, 1997, 2005, 2008; Koob and Volkow, 2010). The focus of this review is on exploring the theoretical basis for hyperkatifeia, linking it to physical and emotional pain, and identifying key within-system and between-system neuroadaptations that mediate hyperkatifeia. With a focus on alcohol use disorder (AUD) and opioid use disorder (OUD), this knowledge of the neurobiology of hyperkatifeia is used as

ABBREVIATIONS: ACTH, adrenocorticotrophic hormone; AEA, *N*-arachidonylethanolamine; 2-AG, 2-arachidonoylglycerol; AUD, alcohol use disorder; BAL, blood alcohol level; BDNF, brain-derived neurotrophic factor; BNST, bed nucleus of the stria terminalis; CB, cannabinoid; CeA, central nucleus of the amygdala; CREB, cAMP response element binding protein; CRF, corticotropin-releasing factor; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; FAAH, fatty acid amid hydrolase; Hcrtr, hypocretin; HPA, hypothalamic-pituitary-adrenal; MAGL, monoacylglycerol lipase; msP, Marchigian Sardinian alcohol-preferring; NAc, nucleus accumbens; NMDA, *N*-methyl-D-aspartate; nor-BNI, nor-binaltorphimine; NPY, neuropeptide Y; OUD, opioid use disorder; P, alcohol-preferring; PKC, protein kinase C; PVN, paraventricular nucleus of the hypothalamus; SNP, single-nucleotide polymorphism; SRC, steroid receptor coactivator; TLR4, Toll-like receptor 4; TNF α , tumor necrosis factor α ; VTA, ventral tegmental area.

a framework for the development of promising new targets for medication development and behavioral therapies that can reset brain stress, anti-stress, and emotional pain systems and return them to homeostasis.

The United States remains in the grips of an opioid crisis that began with misuse and death from prescription opioids in the late 1990s, followed by a rise in deaths from heroin and synthetic opioids around 2010 (https://www.cdc.gov/tobacco/data_statistics/fact_sheets/economics/econ_facts/index.htm). Opioid-involved overdose deaths increased from 21,088 in 2010 to 46,802 in 2018 (<https://www.soa.org/globalassets/assets/files/resources/research-report/2019/econ-impact-non-medical-opioid-use.pdf>). As with opioids, deaths that involve alcohol have increased over the past two decades. The number of alcohol-involved deaths, based on death certificates, increased from 35,914 in 1999 to 72,558 in 2017 (White et al., 2020). Using a combination of death certificates and estimates of alcohol-related deaths not indicated on death certificates, the Centers for Disease Control and Prevention estimated that alcohol was involved in 88,424 deaths in 2010 (<https://www.cdc.gov/chronicdisease/resources/publications/factsheets/alcohol.htm>; Table 1). A steady increase in individuals with OUD has been seen, reaching 2.0 million in 2018 (https://www.cdc.gov/tobacco/data_statistics/fact_sheets/economics/econ_facts/index.htm; Table 1). Note that estimates of the prevalence of AUD in the United States are considerably higher (14.4 million in 2018; <https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHDetailedTabs2018R2/NSDUHDetTabsSect5pe2018.shtm#tab5-4a>; Table 1). Alcohol and opioids contribute in a major way to the three primary factors that drive “deaths of despair”: overdoses (alcohol and opioids), suicides (alcohol and opioids), and liver disease (alcohol; Case and Deaton, 2015). Opioids were involved in 67.8% of all drug overdose deaths in 2017 (https://www.cdc.gov/tobacco/data_statistics/fact_sheets/economics/econ_facts/index.htm). Alcohol contributed to roughly one in seven (14.7%) opioid overdose deaths in 2017 (Tori et al., 2020). The combination of alcohol and opioids is particularly dangerous. A dose of 20 mg oxycodone in healthy subjects reduced ventilation by 28%. Alcohol at a blood alcohol level (BAL) of 0.10% reduced ventilation by another 19% from baseline and increased apneic events (van der Schrier et al., 2017). There were 47,173 suicides in the United States in 2017, representing a 33% increase since 1999 (Ranade et al., 2020). Opioids are present in 20% of suicides, and 26% of suicide decedents who were tested for alcohol had intoxicating BALs (>0.08%) in their systems (Ertl et al., 2019). Alcohol causes roughly 50% of deaths from liver disease (<https://pubs.niaaa.nih.gov/publications/surveillance111/Cirr15.htm>). Between 1999 and 2017, the number of deaths from alcohol-associated liver disease increased from 11,947 to 22,245 (White et al., 2020).

TABLE 1

Relative scope of the problem: opioids vs. alcohol

Data for opioid misuse, alcohol use, OUD, and AUD are from Substance Abuse and Mental Health Services Administration (2019). Data for opioid- and alcohol-related emergency department visits are from the Nationwide Emergency Department Sample (NEDS), Healthcare Cost and Utilization Project (HCUP), of the Agency for Healthcare Research and Quality, Rockville, MD (www.hcup-us.ahrq.gov/nedsoverview.jsp) and White et al. (2018). Data for for opioid overdose deaths and combined alcohol + opioid overdose deaths are from Centers for Disease Control and Prevention (2020). Data for alcohol-related deaths are from Centers for Disease Control and Prevention (www.cdc.gov/ARDD).

Opioids	Alcohol
Misuse: 10,250,000 ^a % of population: 3.7%	Use: 179,289,000 % of population: 65.5%
Opioid use disorder: 2,028,000 % of population: 0.7%	Alcohol use disorder: 14,818,000 % of population: 5.4%
Emergency department visits Primary reason: 408,079 All opioid-related: 1,461,770	Emergency department visits Primary reason: 1,714,757 All alcohol-related: 4,936,690
Deaths Total overdoses: 46,802 Prescription opioids: 14,975 Fentanyl and similar: 31,335 Heroin: 14,996 Opioid + alcohol-related deaths: 7143 ^b	Deaths Total deaths: ~95,000 Acute overdose/injury: 44,080 Chronic liver/cancer: 51,078

^aAny past-year heroin use or prescription opioid use other than as prescribed.

^bOf all opioid overdose deaths in 2018, 15% involved alcohol.

II. Addiction: Definition and Theoretical Framework

A. Definition

Definitions of addiction vary but usually include compulsion to seek and take a drug and the loss of control in limiting intake. A third component is the emergence of a negative emotional state when access to the drug is prevented (Koob et al., 1998), setting the stage for the present thesis and review. The focus of this review is on this third component (emergence of a negative emotional state), termed hyperkatifeia (Shurman et al., 2010). 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.

A heuristic framework for addiction includes a three-stage cycle—binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation—that provides a starting point for exploring the relatively new construct of hyperkatifeia in the context of drug withdrawal (Koob and Le Moal, 1997; Koob, 2019). Under this addiction framework, stage-related dysregulation occurs in three functional domains (incentive salience/habits, negative emotional states, and executive function) that are mediated by three major neurocircuitry elements (basal ganglia, extended amygdala, and prefrontal cortex, respectively; Koob and Le Moal, 1997). These three stages feed into each other, become more intense, and ultimately lead to the pathologic state of addiction or substance use disorder (Koob and Le Moal, 1997; Fig. 1).

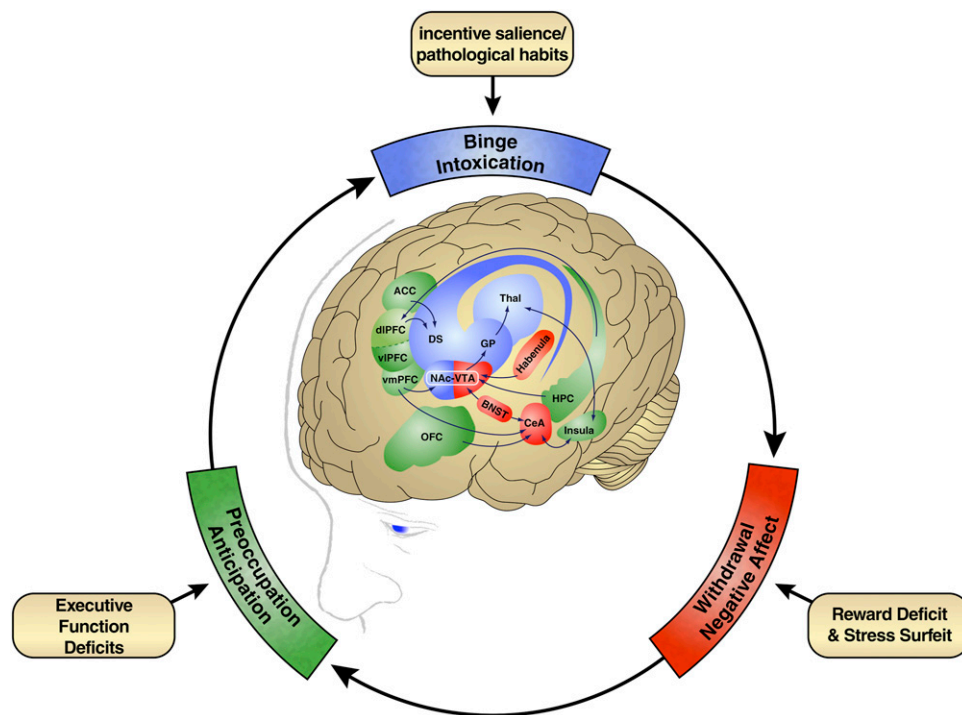


Fig. 1. Conceptual framework for the neurobiological basis of substance use disorders, involving a three-stage cycle—binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation. These three stages involve dysregulations in three functional domains (incentive salience/pathological habits, negative emotional states, and executive function) that are mediated by three major neurocircuitry elements (basal ganglia, extended amygdala, and prefrontal cortex, respectively). ACC, anterior cingulate cortex; dIPFC, dorsolateral prefrontal cortex; DS, dorsal striatum; GP, globus pallidus; HPC, hippocampus; OFC, orbitofrontal cortex; PAG, periaqueductal gray; Thal, thalamus; vIPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex. [Modified with permission from Koob and Volkow (2010)].

From a physiologic perspective, entrance into the three-stage cycle at any stage can engage neuroadaptations that lead to hyperkatifeia. The argument here is that such engagement ultimately triggers a break from hedonic homeostasis and subsequent compensatory responses in brain reward and stress systems to generate the withdrawal/negative affect stage (Koob and Le Moal, 1997). Although all drugs of abuse have positive reinforcing properties, 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. Negative reinforcement can be defined as an increase in the probability of a response that is produced by the removal of an aversive event. Here, negative reinforcement becomes the source of motivation for drug seeking as the individual works to reduce, terminate, or prevent the negative emotional state or hyperkatifeia of drug withdrawal.

From a nosology perspective, substance use disorders are now considered spectrum disorders as described by the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5; American Psychiatric Association, 2013), which provides a framework for the intensity of symptoms with regard to the number of symptoms that are presented by the individual. Consistent with the spectrum and allostatic framework,

an individual can enter the addiction cycle at different stages. Classically, with opioids and alcohol, individuals with a substance use disorder may start with recreational use of the drug during the binge/intoxication stage and progress to the withdrawal/negative affect stage as negative reinforcement evolves (Koob et al., 2019; Fig. 2). However, much of the misuse of opioids and alcohol also develops because negative reinforcement may be the initial starting point either via self-medication or chronic pain (Ballantyne et al., 2019).

The classic drugs of addiction are opioids and alcohol. The pattern of misuse for each encompasses most of the patterns that are observed with other drugs of abuse. For this reason and because elements of hyperkatifeia have been extensively studied in opioid and alcohol addiction, the focus of this review is on these two drugs. In opioid addiction or OUD, drug use includes intense initial intoxication that is associated with intravenous or smoked drug intake, followed by the development of profound tolerance and the consequent escalation of intake. An inability to obtain the drug and the resulting abstinence results in physical discomfort, somatic signs of withdrawal, and profound hyperkatifeia. Hyperkatifeia, which often precedes somatic signs of withdrawal, signals pronounced preoccupation with obtaining opioids (craving). Craving in OUD is linked to stimuli that are associated with obtaining the drug and stimuli that are associated with withdrawal and internal and

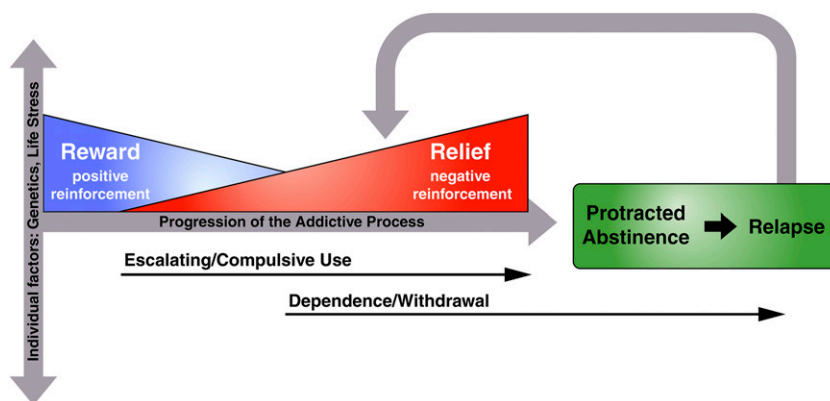


Fig. 2. Conceptual framework of sources of reinforcement in addiction. Positive reinforcement, in which the drug typically engenders positive hedonic effects, is defined as an increase in the probability of responding that is produced by the presentation of a drug. Positive reinforcement is associated with the early stages of addiction as part of the binge/intoxication stage but persists throughout the addiction cycle. Negative reinforcement is defined as an increase in the probability of responding for a drug to relieve hyperkatifeia or stress, in which drug withdrawal during the withdrawal/negative affect stage of the addiction cycle typically engenders hyperkatifeia and stress. Both sources of reinforcement can coexist and be perpetuated by protracted abstinence and cue-, drug-, and stress-induced reinstatement in the preoccupation/anticipation stage of the addiction cycle. [Figure modified from an original diagram from Dr. Loren Parsons].

external states of stress. A classic pattern evolves in which the individual must administer the drug to avoid the severe dysphoria and discomfort that are associated with abstinence (Koob et al., 2019).

In alcohol addiction or AUD, a broader spectrum of drug misuse evolves that can range from binges of alcohol intake that can be daily episodes or prolonged days of heavy drinking to constant drinking for fear of withdrawal, similar to opioids. A binge can be defined as consuming five standard drinks for males and four standard drinks for females in a 2-hour period or obtaining a BAL of 0.08 g% (National Institute on Alcohol Abuse and Alcoholism, 2004). Many individuals with AUD continue with a binge/withdrawal pattern for extended periods; for others, the pattern evolves into an opioid-like substance use disorder, in which they must have alcohol available at all times to avoid the consequences of abstinence (Koob et al., 2019). Withdrawal from an alcohol binge or chronic high alcohol intake is characterized by a severe emotional and somatic withdrawal syndrome and intense craving for alcohol that is often driven by both negative emotional states and positive emotional states, similar to opioids. The hypothesis in this review is that neural substrates of hyperkatifeia are a driving force of addiction, are multidetermined components of key motivational neurocircuits, and have been largely neglected in the search for pharmacotherapies for addiction.

B. Hyperkatifeia Versus Physical Withdrawal

Historically, the terms withdrawal and dependence have been defined differently in different contexts and have led to significant confusion. Withdrawal can be defined simply as abstinence from or the removal of chronic drug use, usually characterized by signs and symptoms that are opposite to the acute effects of the drug (Koob et al., 2019). Withdrawal from drugs of

abuse is one symptom of what is defined symptomatically as substance use disorder in the DSM-5 and Drug Dependence in the *International Statistical Classification of Diseases and Related Health Problems*, 10th revision (World Health Organization, 1992). The word dependence, though, has multiple meanings. Dependence is defined as the manifestation of a withdrawal syndrome upon the cessation of drug use. Under this definition, any drug, even drugs without abuse potential, can produce dependence. However, the term dependence was also part of the diagnostic term “substance dependence” in the DSM-IV (American Psychiatric Association, 1994) and remains part of the *International Statistical Classification of Diseases and Related Health Problems* terminology for “drug dependence” (World Health Organization, 1992). Dependence was initially defined as “an arbitrary term used to denote the presence of an acquired abnormal state wherein the regular administration of adequate amount of a drug has, through previous prolonged use, become requisite to physiologic equilibrium. Since it is not yet possible to diagnose physical dependence objectively without withholding drugs, the sine qua non of physical dependence remains the demonstration of a physical abstinence syndrome” (Himmelsbach, 1943).

This authoritative definition evolved into the definition of physical dependence, an intense physical disturbance when drug use is discontinued. Psychologic dependence was later defined as a “condition in which a drug produces a feeling of satisfaction and a psychic drive that require periodic or continuous administration of the drug to produce pleasure or to avoid discomfort” (Eddy et al., 1965).

However, both somatic and psychologic symptoms are mediated by physiological changes in the body and brain, but the argument here is that the symptoms that are associated with hyperkatifeia have significantly

more motivational significance than somatic signs of withdrawal (Koob, 2019). Physical symptoms of withdrawal are reflected by signs and symptoms of a physical nature that are usually opposite to the acute effects of the drug itself. For example, with opioids, pupillary dilation is a telltale sign of opioid withdrawal, whereas pupillary constriction is a telltale sign of opioid intoxication. Similarly, for alcohol, sympathetic-like responses, such as hyperthermia, indicate withdrawal, whereas hypothermia characterizes acute intoxication. However, from the perspective of negative reinforcement, drug seeking and craving that are associated with acute and protracted abstinence are key to the thesis outlined herein, in which somatic measures of withdrawal can be an index of dependence but do not always reflect the more motivational measures of withdrawal or hyperkatifeia. Notably, however, hyperkatifeia-associated symptoms of withdrawal generally have an earlier onset and are manifested at lower doses of chronic drug intake.

Under this framework in the withdrawal/negative affect stage, the manifestation of a withdrawal syndrome after the cessation of chronic drug administration can be defined not only in terms of the classic “physical” signs of withdrawal but more importantly in terms of motivational aspects of dependence, such as the emergence of hyperkatifeia when access to the drug is prevented. The emphasis on motivational aspects of withdrawal has been largely ignored, but some theoreticians have actually argued that the development of such a negative affective state can define dependence as it relates to addiction: “The notion of dependence on a drug, object, role, activity or any other stimulus-source requires the crucial feature of negative affect experienced in its absence. The degree of dependence can be equated with the amount of this negative affect, which may range from mild discomfort to extreme distress, or it may be equated with the amount of difficulty or effort required to do without the drug, object, etc.” (Russell, 1976).

Thus, the conceptual framework herein focuses on hyperkatifeia in AUD and OUD (Koob, 2019). Several medications that target hyperkatifeia have been approved by the U.S. Food and Drug Administration for the treatment of AUD and OUD. For alcohol, these treatments are limited to acamprosate. For opioids, they are mostly drugs that are opioids themselves and substitute for opioids. The present review explores the rich neurobiology of hyperkatifeia in the context of animal models of opioid and alcohol addiction, with a focus on neuroadaptations that break with homeostasis and can possibly be reversed to facilitate recovery from addiction.

C. Opponent Process

The theoretical basis of hyperkatifeia as a driving force in negative reinforcement in addiction has its roots

in opponent process theory. Early theorists argued that counteradaptations can explain the physiological (physical, somatic) effects of opioid withdrawal in the domain of body temperature (Himmelsbach, 1943; Martin, 1968). Later, counteradaptations were invoked to explain how the initial acute hedonic effects of a drug are opposed or counteracted by homeostatic changes in systems that mediate the primary effects of the drug (Solomon and Corbit, 1974; Siegel, 1975; Poulos and Cappell, 1991). A key theory that was proposed was called opponent process theory (Solomon and Corbit, 1973, 1974; D’Amato, 1974; Hoffman and Solomon, 1974; Solomon, 1980; Koob and Bloom, 1988). In fact, opponent process theory was not only argued to be a counteraction to the hedonic actions of drugs of abuse; it was also argued to be a general phenomenon that is associated with hedonic breaks with homeostasis, including fear conditioning, tonic immobility, ulcer formation, eating disorders, jogging, peer separation, glucose preference, and even skydiving (Solomon and Corbit, 1973, 1974; Hoffman and Solomon, 1974; Solomon, 1980).

In opponent process theory, many affective control mechanisms in the brain are hypothesized to serve as an emotional stabilization system that counteracts or opposes departures from emotional neutrality or equilibrium, regardless of whether they are aversive or pleasant (Solomon and Corbit, 1974). A negative feedback control construct was theorized that keeps mood in homeostatic balance, even with strong perturbations. Under this framework, the first, initial use of a drug triggers a primary affective process (a positive hedonic process), termed the “a-process,” which has a short time constant. The signal from the a-process triggers an opposing “b-process,” which responds with a slow rise and slow decay. Here, the b-process presents as a negative emotional state and is described as intensely aversive (Solomon and Corbit, 1974). This opponent process reduces the hedonic intensity of the a-process (i.e., the state that the input initially activated). The two opposing responses are temporally linked (a triggers b), with the b-process subtracting the impact of the already existing a-process. With repeated stimulation (e.g., drug taking), the b-process is strengthened so that it has a faster onset and greater intensity and takes longer to decay (Solomon and Corbit, 1974). As discussed by Solomon and Corbit (1974), the quickest and possibly most effective way of removing the b-process is to produce the a-process by taking the drug again. However, this leads to further strengthening of the b-process and the necessity to increase the amount of drug that is needed to remove the b-process. Masking of the a-process results in what has been termed “apparent tolerance” (Colpaert, 1996; Laulin et al., 1999). This resulting tolerance produces more drug taking to remove the b-process and thus engages the addictive cycle (Solomon and Corbit, 1974).

Indeed, data indicate that if the development of the b-process is blocked, then tolerance does not develop.

Under this framework, development of the b-process reflects the development of hyperkatifeia (or a constellation of negative emotional withdrawal symptoms), masked at least initially by the hedonic properties of the drug. As the opponent b-process grows, such symptoms as dysphoria, anxiety, alexithymia, irritability, sleep disturbances, physical and emotional pain, subjective feelings of unease, and simply not feeling hedonically normal become manifest. This hypernegative emotional state, termed hyperkatifeia, is hypothesized to sensitize with repeated drug exposure and withdrawal. Hyperkatifeia can be considered an emotional parallel to hyperalgesia (i.e., greater sensitivity to physical pain) that is observed with repeated administration of chronic opioids and alcohol (Shurman et al., 2010; Koob, 2019). In terms of the motivation for drug seeking, a new source of acquired motivation is generated, termed negative reinforcement (Ahmed and Koob, 2005). As a result, a greater amount and more frequent use of the previously rewarding drug is needed to maintain or approach euthymia (i.e., tolerance).

D. Validation of the Hyperkatifeia Construct in Humans

Several lines of evidence, ranging from a factor analysis of responses on self-report measures and neuropsychological tests in humans with AUD to a connectome imaging study in mice, have validated the importance of the hyperkatifeia construct as a key stage in the development and maintenance of AUD and other substance use disorders. In an attempt to translate the research domain framework to a clinical framework, a study was performed with the goal of translating and reverse-translating knowledge that has been derived from animal models of AUD and substance use disorders to the human condition via measures of neurobiological processes that are orthologous in animals and humans and that are shared in AUD and substance use disorders (Kwako et al., 2016). Thus, the hypothesis was that measures of three neuroscience-based functional domains (incentive salience, negative emotionality, and executive function) could capture many of the effects of heritability and early exposure that lead to trait vulnerability that is shared across different addictive disorders. A further hypothesis was that measures of these domains in a general framework of an Addictions Neuroclinical Assessment have the possibility to transform the assessment and nosology of addictive disorders and can be informative for staging disease progression. A subhypothesis was that a focus on negative emotionality and stress may serve as a bridge to a reformulation of the addiction nosology to better capture individual differences in patients for whom the withdrawal/negative affect stage drives compulsive drug taking (Kwako and Koob, 2017). Using the Addictions Neuroclinical

Assessment, five subdomains of negative emotional states that can be operationally measured in human laboratory settings and paralleled by animal models were outlined (Kwako et al., 2016). In a subsequent study, the three neurofunctional domains that were proposed to be critical for the addiction cycle (incentive salience, negative emotionality, and executive function) were validated using a factor analysis of a deeply phenotyped clinical sample (Kwako et al., 2019; Fig. 3). Clinical, behavioral, and self-report measures of addiction, personality, cognition, behavior, and exposure to early life stress were collected as part of a screening and natural history study of AUD in 454 individuals who represented the spectrum of alcohol use and AUD. A three-factor model generally demonstrated a good fit with the assessment measures, and the factors closely aligned with the Addictions Neuroclinical Assessment domains of incentive salience, negative emotionality, and executive function.

Note that a similar theoretical framework has been proposed for compulsive eating, in which habitual overeating, overeating to relieve a negative emotional state, and overeating despite aversive consequences reflect the three functional domains that are outlined in drug addiction (Moore et al., 2017, 2019). Such a framework has generated significant evidence to suggest that powerful nondrug reinforcers, such as food, can also dysregulate the same motivational constructs and circuits that are outlined herein.

D. Validation of the Hyperkatifeia Construct in a Molecular-Neurocircuitry Study in an Animal Model

To delineate the neurocircuits that are involved in the role of μ -opioid receptor tone in controlling aversion/pain, key symptoms of hyperkatifeia, a connectome imaging study that used a hypothesis-free analysis of combined resting-state functional magnetic resonance imaging diffusion tractography was conducted. The authors showed that μ -opioid receptor gene (*Oprm1*) inactivation produced dramatic changes in aversion/pain-related connectivity and less so in reward connectivity (Mechling et al., 2016). Direct statistical intergroup comparisons and an analysis of changes in hub status indicated a reshaping of networks that are known to process information of negative valence. The negative valence network that evolved included such structures as the periaqueductal gray, hippocampus, amygdala, cingulate cortex, median raphe, and habenula (Mechling et al., 2016). Behavioral differences in *Oprm1* mutant mice compared with wild-type mice showed that pain and emotional-like and reward-related behaviors correlated predominantly with alterations within reward/aversion pathways (Kieffer and Gaveriaux-Ruff, 2002). The authors hypothesized that under resting-state conditions, the results may reflect stronger inhibitory μ -opioid receptor tone or a developmental influence on negative affect neurocircuits.

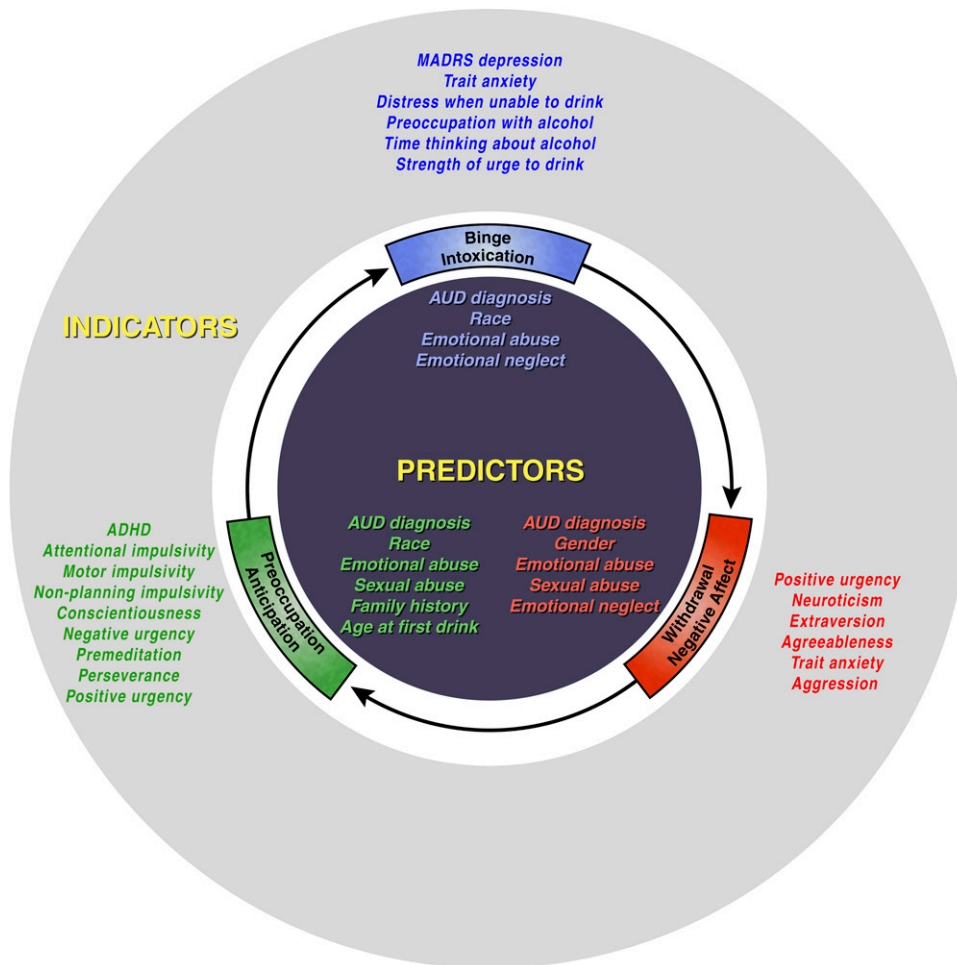


Fig. 3. Validation of three neurofunctional domains in AUD by deep behavioral phenotyping. These three domains of incentive salience, negative emotionality, and executive function correspond to the binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation stages, respectively. Three neurobiological domains that are hypothesized to be critical for the addiction cycle were identified through factor analysis in a large and diverse clinical sample that represented the spectrum of AUD. Measures of addiction, personality, cognition, behavior, and exposure to early life stress were collected in 454 patients in 2015 and 2016 at the clinical Center at the National Institutes of Health (Kwako et al., 2019). The study confirmed the relevance of the three neurofunctional domains to AUD. Using a multiple-indicators, multiple-causes (MIMIC) approach, early life stress and sociodemographic predictors were identified. ADHD, attention-deficit/hyperactivity disorder; MADRS, Montgomery-Asberg Depression Rating Scale. [Figure based on results of Kwako et al. (2019)].

III. Within-System/Between-System Neurobiological Substrates for Hyperkatifeia Associated with Opioid and Alcohol Withdrawal

A. Within-System Neurocircuits

From the perspective of self-regulation theory, opponent process-driven hyperkatifeia sets up misregulation in which subjects take more drug to alleviate hyperkatifeia, which paradoxically drives more hyperkatifeia. Under this framework, substance use is compulsively escalated or renewed (in relapse) via negative-reinforcement mechanisms because it transiently prevents or relieves negative emotional symptoms or hyperkatifeia (Koob and Le Moal, 1997).

Little work has explored the neurobiological basis of opponent processes. Solomon (1980) hypothesized possible roles for endogenous opioid peptides and the hypothalamic-pituitary-adrenal (HPA) axis. What follows is

what we know about the neurobiology of the b-process, taken from the neurobiology of motivational aspects of drug withdrawal, and how these neurocircuits form a rich substrate for pharmaceutical treatment of a neglected but key component of addiction. Thus, the argument in this review is that there are elements of drug withdrawal and repeated, chronic drug intake that are expressed in common elements across different drugs of abuse.

Key components of hyperkatifeia are dysphoria and malaise, reflected by a decrease in brain reward function and an increase in brain and hormonal stress responses. Rapid acute tolerance and opponent process-like actions against the hedonic effects of psychostimulants have been reported in humans (Breiter et al., 1997). Indeed, in opponent process theory, tolerance and dependence are inextricably linked, in which the hedonic effects of the drug subside, and the b-process gets progressively larger over time, in effect contributing to or producing more

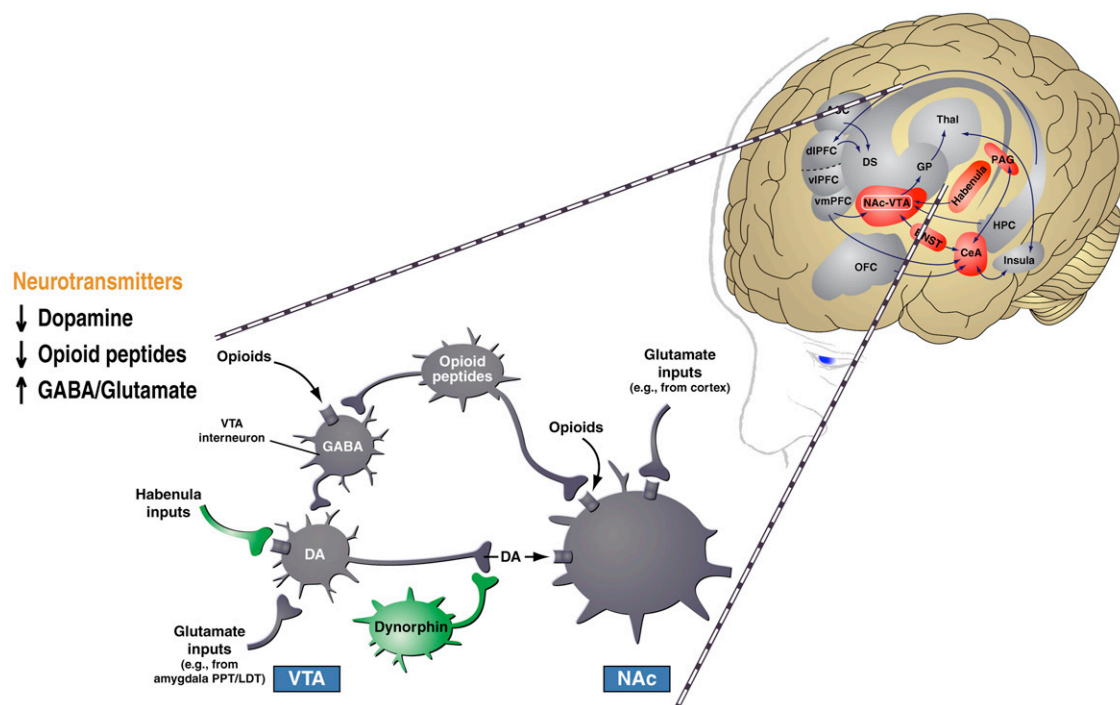


Fig. 4. Within-system neurocircuitry associated with hyperkatifeia in the withdrawal/negative affect stage. Note the loss of dopamine and opioid peptide function in ventral tegmental area-nucleus accumbens circuitry, with a hypothesized contribution of the habenula that suppresses neuron activity in the ventral tegmental area and dynorphin that suppresses dopamine release in the nucleus accumbens. 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; DA, dopamine; dIPFC, dorsolateral prefrontal cortex; DS, dorsal striatum; GP, globus pallidus; HPC, hippocampus; LDT, laterodorsal tegmentum; OFC, orbitofrontal cortex; PAG, periaqueductal gray; PPT, pedunculopontine tegmentum; Thal, thalamus; vIPFC, ventrolateral prefrontal cortex; VTA, ventral tegmental area. [Adapted with permission from Koob (2008); George and Koob (2013)].

complete tolerance to the initial euphoric effects of the drug.

Brain reward systems that involve connections between the medial forebrain bundle and such structures as the ventral tegmental area (VTA) and ventral striatum are compromised during withdrawal from drugs of abuse (Koob and Le Moal, 2005). All major drugs of abuse produce elevations of reward thresholds (measured by intracranial self-stimulation) during withdrawal from either chronic drug administration or in animal models of drug self-administration with extended access. Such elevations have been observed in studies of alcohol-dependent animals (Schulteis et al., 1995), extended access to cocaine self-administration (Ahmed et al., 2002), methamphetamine self-administration (Jang et al., 2013a), heroin self-administration (Kenny et al., 2006), and nicotine self-administration (Harris et al., 2011).

A conceptual framework that was adopted to explain the neural systems that mediate the long-hypothesized opponent process adaptation to excessive reward system engagement and drive negative reinforcement involved the within-system downregulation of brain reward circuitry and the between-system recruitment of brain stress circuitry (Koob and Bloom, 1988). Within-system neuroadaptations were defined as the process by which the primary cellular response to the drug within a given neurochemical circuit itself adapts to neutralize the effects

of the drug. Much of the work on within-system neuroadaptations has focused on the mesolimbic dopamine system that projects from the VTA to the nucleus accumbens (NAc; Fig. 4). Significant evidence has also emerged for a role for the lateral habenula-VTA circuit in driving aversive responses to the loss of reward and mediating and encoding aversive states (Hikosaka, 2010). The lateral habenula may play a role in modulating motivated behavior and addiction by modulating dopamine neurotransmission via actions on dopamine neurons in the VTA (Hikosaka, 2010; Velasquez et al., 2014; Boulos et al., 2017). Neurons in the lateral habenula fire in response to the presentation of unexpected aversive events (Matsumoto and Hikosaka, 2007). The unexpected delivery of rewards caused inhibition of the lateral habenula, consistent with an aversive role for activation of the habenula (Matsumoto and Hikosaka, 2007). Consistent with these observations, electrical stimulation of the lateral habenula output caused conditioned place aversions (Stamatakis and Stuber, 2012). Finally, a local dynorphin circuit in the NAc has been hypothesized to be activated and ultimately contribute to the hypodopaminergic state of opioid and alcohol withdrawal (Carlezon et al., 2000).

B. Between-System Neurocircuits

In contrast, between-system neuroadaptations were defined as circuitry changes in which other circuits

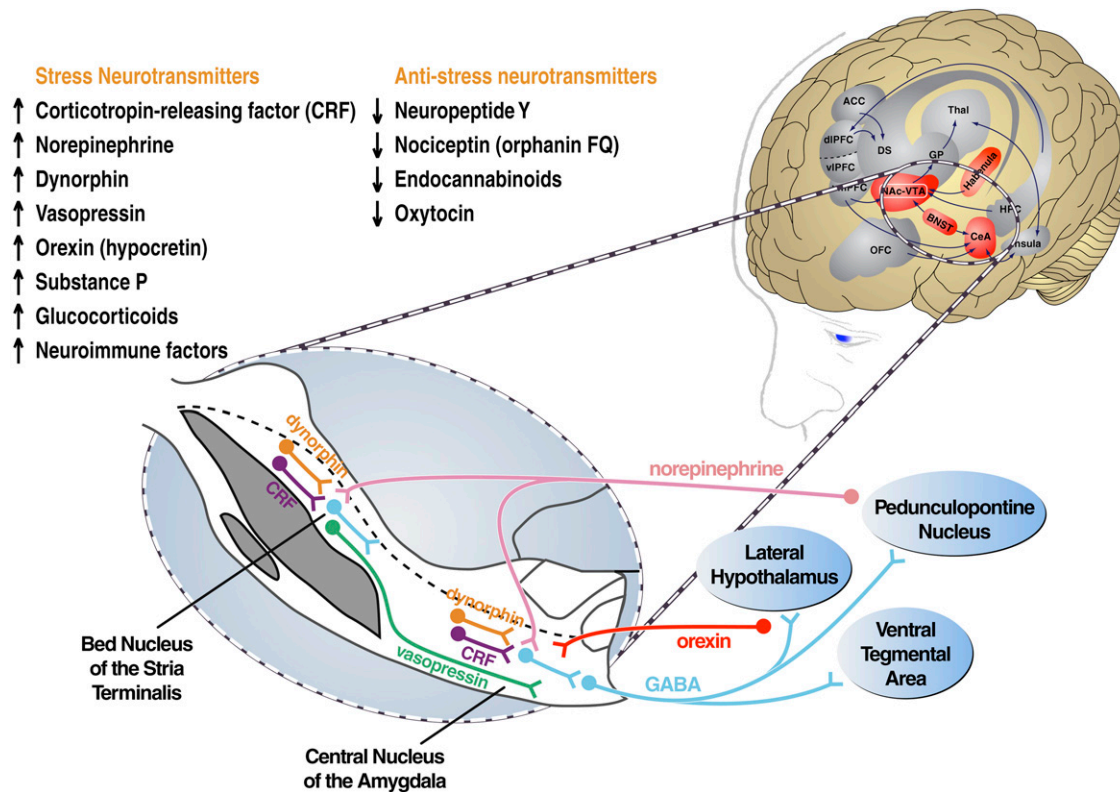


Fig. 5. Between-system extended amygdala circuitry associated with hyperkatifeia in the withdrawal/negative affect stage. Note the gain of stress neurotransmitter and neuromodulator function and the loss of antistress neurotransmitter and neuromodulator function throughout the neurocircuitry of the extended amygdala. 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; dIPFC, dorsolateral prefrontal cortex; DS, dorsal striatum; GP, globus pallidus; HPC, hippocampus; OFC, orbitofrontal cortex; Thal, thalamus; vIPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex; VTA, ventral tegmental area. [Taken with permission from George and Koob (2013)].

(i.e., stress or antireward circuits) are activated to oppose overactivity in reward circuits. Subsequently, the focus of between-system neuroadaptations fell on understanding neurocircuitry within the extended amygdala and its role in opponent process, more specifically hyperkatifeia (Koob and Bloom, 1988; Koob and Le Moal, 2008; Koob, 2019).

The extended amygdala comprises several basal forebrain structures, including the bed nucleus of the stria terminalis (BNST), central nucleus of the amygdala (CeA), subnucleus of the stria terminalis, and a transition zone in the shell of the NAc (Heimer and Alheid, 1991). The regions that comprise the extended amygdala have cytoarchitectural and circuitry similarities with each other (Heimer and Alheid, 1991). Afferents to the extended amygdala come from brain structures that are involved in emotion, such as the basolateral amygdala and hippocampus, and the extended amygdala sends efferents to the medial part of the ventral pallidum and a large projection to the lateral hypothalamus (Alheid et al., 1995; Fig. 5). The extended amygdala has long been hypothesized to play a key role in fear, anxiety, and stress (Le Doux, 2000; Shackman and Fox, 2016) and also in the emotional component of pain processing (Neugebauer et al., 2004). The extended

amygdala has been hypothesized to be a key link that defines specific brain areas that interface classic structures that are involved in emotion with classic structures that are involved in motor action and motivation, such as the extrapyramidal motor system (Alheid et al., 1995).

IV. Within-System Neurobiological Substrates for Hyperkatifeia Associated with Opioid and Alcohol Withdrawal

A. Within-System Neuroadaptations: Dopamine

The mesolimbic dopamine system has historically been hypothesized to mediate the reinforcing effects of drugs of abuse. As more studies evolved, however, it became clear that although the mesolimbic dopamine system is critical for the reinforcing actions of drugs, such as cocaine and amphetamines, other drugs of abuse, such as opioids and alcohol, can activate the mesolimbic dopamine system and exert actions on reward circuits independent of dopamine release (Wise and Koob, 2014). Nevertheless, what is also evident is that the mesolimbic dopamine system becomes compromised after the chronic administration of virtually all drugs of abuse, including opioids and alcohol (Koob and Volkow, 2010; Diana, 2011). Such within-system neuroadaptations

can take on many forms, including changes in receptors, transduction mechanisms, local circuits, and modulatory circuits, such as the habenula-VTA aversion circuit.

For opioids at the neurocircuitry level, a prominent neuroadaptation is the loss of dopaminergic function in the mesolimbic dopamine pathway, which is hypothesized to contribute to hedonic tolerance and the hypohedonia that is associated with opioid withdrawal (see Fig. 4). In animal models, early studies showed that precipitated opioid withdrawal decreases extracellular dopamine levels in the NAc and mesolimbic dopamine system (Pothos et al., 1991; Rossetti et al., 1992) and decreases dopamine neuron firing in the VTA (Diana, 2011). In humans, positron emission tomography imaging studies reported lower baseline dopamine D_2 receptor availability in the dorsal striatum in psychostimulant abusers and opioid-dependent subjects compared with control subjects (Wang et al., 1997; Ashok et al., 2017). In another study, the decrease in D_2 receptor availability in the striatum was negatively correlated with years of opioid use (Zijlstra et al., 2008).

For alcohol, both the mesocorticolimbic dopamine system and endogenous opioid system have been hypothesized to contribute to the mechanisms that mediate acute alcohol reinforcement (Lewis, 1996). In humans, consistent with animal studies, oral doses of alcohol increased extracellular dopamine concentrations during intoxication in healthy volunteers, based on positron emission tomography measures (Boileau et al., 2003; Urban et al., 2010).

Dopaminergic function is also compromised during acute alcohol withdrawal in animal models of chronic administration or compulsive-like drinking (Diana et al., 1993; Weiss et al., 1996). Animals that were subjected to alcohol withdrawal after the intragastric delivery of a dose of 2–5 g/kg every 6 hours for six consecutive days, based on the method of Majchrowicz (1975), exhibited a dramatic decrease in extracellular dopamine, measured by microdialysis, that correlated with withdrawal scores (Diana et al., 1993). In a study in which animals were sustained on an alcohol liquid diet that was sufficient to produce dependence, a decrease in extracellular dopamine levels was observed in the NAc during withdrawal (Weiss et al., 1996). When the animals were allowed to self-administer alcohol during acute withdrawal, they self-administered just enough alcohol to return extracellular dopamine levels in the NAc back to predependence baseline levels (Weiss et al., 1996). Substantial electrophysiological data suggest profound neuroadaptations in both the origins and terminals of the mesocorticolimbic dopamine system with chronic alcohol that drive these changes (Diana et al., 1993, 2003; Bailey et al., 2001).

In humans, dopamine dysfunction has also been repeatedly observed in detoxified alcohol-dependent

subjects using brain imaging (Volkow et al., 1996, 2002, 2007; Kuikka et al., 2000). Similar to other drugs of abuse, studies that employed positron emission tomography and single-photon emission computed tomography using D_2 or D_2/D_3 receptor ligands showed that D_2 receptor expression was lower in the temporal cortex and striatum in subjects with AUD (Volkow et al., 1996; Kuikka et al., 2000). When detoxified individuals with AUD were tested using positron emission tomography combined with [^{11}C]raclopride, a D_2/D_3 receptor ligand with binding that is sensitive to endogenous dopamine in the basal ganglia, challenges with the stimulant drug methylphenidate failed to produce the increases in endogenous dopamine levels that were associated with the stimulant effects of methylphenidate (Volkow et al., 2007).

Another mechanism to explain the hypodopaminergic state is that opioids, psychostimulants, and alcohol activate dynorphin, particularly in the shell of the NAc, triggered by a cascade of molecular events that involve cAMP-to-dynorphin activation (Carlezon et al., 2000; Chavkin and Koob, 2016).

B. Within-System Neuroadaptations: Enkephalin / Endorphin Opioid Peptides

For the acute effects of opioid drugs, G proteins are activated through the μ -opioid receptor and modulate the activity of several second messengers and cellular effectors that generate both short-term and long-term neuroadaptations that are relevant to a blunted hedonic response to the drug (i.e., tolerance; Cahill et al., 2016). Other molecular/cellular events, in addition to G protein signaling cascades, contribute to decreases in μ -opioid receptor signaling, including receptor desensitization, receptor internalization, transcriptional changes, and structural changes, such as dendritic spine remodeling (Sugiura et al., 2009; Al-Hasani and Bruchas, 2011; Williams et al., 2013). Within-system neuroadaptations that produce both hyperkatifeia and consequently apparent tolerance at the cellular level may be the sum of these multiple events (Cahill et al., 2016).

From a medication development perspective, accumulating evidence suggested that different effects of μ -opioid receptor agonists may be mediated by different transduction pathways that are linked to the μ -opioid receptor (Raehal and Bohn, 2014). Mutant mice that lacked arrestin 3 (β -arrestin 2) exhibited greater analgesia but significantly less antinociceptive tolerance, physical dependence, constipation, and respiratory suppression in response to morphine (Raehal and Bohn, 2014). These observations led to the hypothesis that drugs could be developed that activate μ -opioid receptors without activating the arrestin 3 signal transduction cascade and by extrapolation result in less receptor internalization and desensitization, higher analgesic potential, and lower respiratory depression (Raehal and Bohn, 2014). Moreover, the effects on fentanyl tolerance

and dependence, a high receptor-internalizing agonist, were unaltered in mice that lacked arrestin 3 (β -arrestin 2; Raehal and Bohn, 2014). Non-arrestin-activating drugs produced more potent analgesia and less tolerance, but they produced more gastrointestinal side effects (e.g., constipation; Altarifi et al., 2017). Thus, data to date suggest that such non-arrestin 3-signaling drugs retain undesirable constipating and abuse-related effects with repeated exposure, despite their bias for G protein signaling (Altarifi et al., 2017).

For alcohol, endogenous enkephalin/endorphin opioid peptide systems have long been hypothesized to play a role in their reinforcing effects (Nutt, 2014), but there is some evidence of a direct role for within-system changes in μ -opioid receptor transduction mechanisms. Indeed, molecular changes in the cAMP system are classically opposite to changes that are associated with opioids but nevertheless provide an example of within-system changes of motivational significance, albeit in other structures, such as the extended amygdala. Acute alcohol potentiates receptor-activated cAMP production, but chronic exposure to alcohol decreases cAMP-protein kinase A activity and a decrease in cAMP response element binding protein (CREB) phosphorylation (Gordon et al., 1986). Lower phosphorylated CREB in the CeA and medial nucleus of the amygdala is associated with anxiety-like responses during withdrawal and an increase in alcohol self-administration. Alcohol-preferring Indiana P rats have lower levels of phosphorylated CREB in the CeA and medial nucleus of the amygdala (Pandey et al., 2003, 2004; Pandey, 2004). These decreases in CREB activity have been associated with a decrease in neuropeptide Y (NPY; see below), linking within-system molecular changes with between-system neurotransmitter circuit changes.

C. Within-System Neuroadaptations: GABA and Glutamate

GABA and glutamate are ubiquitous neurotransmitter systems throughout the neuraxis that have long been associated with neuroadaptations that are associated with the chronic use of opioids and alcohol (Hwa et al., 2017; Roberto and Varodayan, 2017). For opioids, a transient increase in GABA neuronal activity in the VTA may explain the loss of dopaminergic function with chronic opioids. A prominent observation is a chronic opioid-induced cAMP-dependent increase in the probability of GABA release in the VTA, which would inhibit dopamine neurons (Bonci and Williams, 1997). Notably, however, GABA tone returns during protracted abstinence (Bonci and Williams, 1996). Consistent with these preclinical results is a human positron emission tomography imaging study that showed that in recently abstinent male opioid-dependent subjects, a decrease in D_2 receptor binding and anhedonia were observed, but higher dopamine release was found in the striatum after cue exposure (Zijlstra et al., 2008), suggesting that

craving that is produced by hypohedonia and craving that is produced by cues can coexist, albeit at different time points of opioid addiction.

For opioids, the noncompetitive glutamate receptor antagonist MK-801 blocked the expression of withdrawal signs that were precipitated by naloxone in opioid-dependent animals (Tanganelli et al., 1991; Tokuyama et al., 1996), suggesting a hyperglutamatergic contribution to opioid withdrawal. In an animal model of long-lasting hyperalgesia after exposure to heroin, a noncompetitive glutamate receptor antagonist reversed hyperalgesia (Laulin et al., 1998). A noncompetitive glutamate receptor antagonist also prevented the long-lasting heroin-induced enhancement of pain sensitivity and naloxone-precipitated hyperalgesia in humans (Koppert et al., 2003).

For alcohol, both GABA and glutamate modulate its acute intoxicating effects, with GABA function being enhanced and glutamatergic function being suppressed (Roberto and Varodayan, 2017). However, chronic alcohol decreases GABA receptor function, with multiple effects on GABA receptor subunits, including downregulation of the $\alpha 1$ subunit and upregulation of the $\alpha 4$ subunit (Mhatre et al., 1993; Devaud et al., 1997). Nevertheless, subsequent work on the action of alcohol on GABA in local circuits demonstrated that alcohol-exposed neurons in the VTA showed electrophysiological evidence of a higher probability of action potential-independent GABA release after alcohol exposure, consistent with actions that would drive a hypodopaminergic state, similar to opioids (Melis et al., 2002). Similarly, in the extended amygdala, chronic alcohol exposure increased GABAergic tone in dependent animals, which was hypothesized to drive compulsive-like drinking (Roberto et al., 2008).

In contrast, alcohol withdrawal is characterized by a hyperglutamatergic state that is opposite to the acute effects of alcohol (Hwa et al., 2017). Chronic alcohol is well known to upregulate *N*-methyl-D-aspartate (NMDA) receptor function in the brain (Chandler et al., 1993; Snell et al., 1993; Roberto et al., 2004), including the upregulation of different NMDA receptor subunits with chronic alcohol and withdrawal in some brain regions (Trevisan et al., 1994; Follesa and Ticku, 1995). Competitive glutamate receptor antagonists can partially reverse the anxiogenic-like effects of alcohol withdrawal (Gatch et al., 1999).

One hypothesis is that glutamate plays a key role in sensitization or hyperexcitability that is elicited by repeated alcohol withdrawal (McCown and Breese, 1990; Stephens, 1995). Chronic acamprosate, a glutamate modulator and Food and Drug Administration-approved treatment of AUD, blocked the alcohol deprivation effect-induced increase in drinking in rodents (Heyser et al., 1998) and blocked increases in glutamate in the brain in rats (Dahchour et al., 1998) and humans (Umhau et al., 2010; Hermann et al., 2012).

V. Between-System Neurobiological Substrates for Hyperkatifeia Associated with Opioid and Alcohol Withdrawal

In addition to the above within-system neuroadaptations, other neurocircuits appear to be activated by excessive drug intake that act in hedonic opposition to reward neurotransmitter circuits [corticotropin-releasing factor (CRF), norepinephrine, glucocorticoids, dynorphin, hypocretin, and neuroimmune factors] or act to protect against the development of hyperkatifeia (NPY, nociceptin, endocannabinoids, and oxytocin; Koob and Bloom, 1988; Koob and Le Moal, 1997; Koob, 2008). The location of the circuits that mediate hyperkatifeia to a large extent involves elements of the extended amygdala or its connections (see above and Fig. 5).

Consistent with the connectome study described above, a substantial number of neurochemical/neurocircuitry studies implicate brain stress systems in between-system neuroadaptations that contribute to hyperkatifeia, with the extended amygdala as a focal point. Much of the data show the recruitment of brain stress systems, including CRF, norepinephrine, hypocretin, dynorphin, and glucocorticoids, as major key substrates that are responsible for hyperkatifeia that is associated with drug withdrawal and thus compulsive-like drug seeking via negative reinforcement (Koob and Bloom, 1988; Koob, 2019).

A. Between-System Neuroadaptations: Corticotropin-Releasing Factor

Corticotropin-releasing factor has long been known to mediate behavioral responses to stress in addition to its role in driving the sympathetic nervous system response to stress (Koob, 1999). Corticotropin-releasing factor is a 41-amino-acid neuropeptide that mediates neuroendocrine and behavioral responses to stress (Bale and Vale, 2004). It interacts with two G_s protein-coupled receptors: CRF₁ and CRF₂ (Bale and Vale, 2004). Corticotropin-releasing factor neurons are highly expressed in the extended amygdala and project throughout the midbrain and pons (Swanson et al., 1983).

For opioids, CRF has been implicated in hyperkatifeia that is associated with opioid withdrawal in animal models. Precipitated opioid withdrawal increases the release of CRF in the CeA (Weiss et al., 2001). The antagonism of CRF receptors in the extended amygdala blocked the aversive stimulus effects of drug withdrawal (Koob, 2015). Systemic CRF receptor antagonist and functional noradrenergic receptor antagonist administration blocked naloxone-precipitated conditioned place aversion in opioid-dependent rats (Schulteis et al., 1998; Stinus et al., 2005). Excitotoxic lesions of the basolateral amygdala abolished the robust conditioned suppression of response rates in an operant task after

the presentation of a withdrawal-associated conditioned stimulus that was observed in sham-operated rats (Schulteis et al., 2000). Excitotoxic lesions of the CeA blocked the development of morphine withdrawal-induced conditioned place aversion but had less of an effect on somatic signs of withdrawal (Watanabe et al., 2002). CRF is aversive to animals and produces place aversions and elevations of reward thresholds, both of which are reversed by intracerebroventricular administration of a CRF₁/CRF₂ peptide receptor antagonist (Cador et al., 1992; Macey et al., 2000). Conditioned place aversion that was produced by precipitated opioid withdrawal was also blocked by the administration of a CRF₁/CRF₂ peptide receptor antagonist in the CeA (Heinrichs et al., 1995). CRF₁ receptor antagonists selectively decreased heroin self-administration in long-access but not short-access rats in an animal model of extended access (Greenwell et al., 2009a). Chronic systemic administration of a CRF receptor antagonist also attenuated the escalation of heroin self-administration that was associated with extended access (Park et al., 2015).

For alcohol, early work reported that CRF was involved in hyperkatifeia that was associated with alcohol withdrawal. Alcohol withdrawal is associated with increases in the release of CRF in the CeA (Merlo-Pich et al., 1995) and BNST (Olive et al., 2002). Systemic CRF₁ receptor antagonist administration blocked anxiety-like responses to alcohol withdrawal (Knapp et al., 2004; Overstreet et al., 2004b; Breese et al., 2005). Microinjections of a peptide CRF₁/CRF₂ antagonist in the CeA blocked the anxiogenic-like effects of alcohol withdrawal in rats (Rassnick et al., 1993). Intracerebroventricular or systemic CRF receptor antagonist administration also blocked the potentiation of anxiety-like responses to stressors that were observed during protracted abstinence from chronic alcohol (Valdez et al., 2003; Breese et al., 2005; Sommer et al., 2008). A CRF₁ receptor antagonist prevented the sensitization of withdrawal-induced anxiety, supporting a between-system neuroadaptation (Overstreet et al., 2004a). Additionally, systemic CRF₁ receptor antagonist administration blunted the hyperalgesic response to alcohol withdrawal (Edwards et al., 2012b).

Rats drink alcohol excessively during acute and protracted abstinence from intermittent, high, sustained alcohol via a liquid diet or vapor exposure. Systemic injections of small-molecule CRF₁ receptor antagonists blocked the increase in alcohol intake that was associated with acute withdrawal (Knapp et al., 2004; Overstreet et al., 2004a; Funk et al., 2007) and protracted abstinence (Gehlert et al., 2007). Corticotropin-releasing factor receptor antagonists also reduced binge-like, excessive drinking and stress-induced increases in alcohol intake (Lowery et al., 2008; Cippitelli et al., 2012; Lowery-Gionta et al., 2012; Simms et al., 2014).

The increase in alcohol self-administration that was observed in alcohol-dependent rats was also blocked by a peptide CRF₁/CRF₂ receptor antagonist that was

directly administered in the CeA (Funk et al., 2006). Cellular studies have identified the actions of CRF on GABAergic interneurons in the CeA (Roberto et al., 2010) and CRF projections from the BNST to midbrain and hypothalamus (Vranjkovic et al., 2017; Pati et al., 2020). An optogenetic study showed that activation of CRF neurons in the CeA during alcohol withdrawal that projected to the BNST may mediate dependence-induced excessive alcohol intake (de Guglielmo et al., 2016, 2019).

B. Between-System Neuroadaptations: Norepinephrine

Norepinephrine is a key member of the sympathetic nervous system. Ascending noradrenergic projections from the brainstem have long been implicated in stress responsivity (Koob, 2008). Norepinephrine binds to three receptor families, α_1 -, α_2 -, and β -adrenergic, and each of these has three receptor subtypes (Rohrer and Kobilka, 1998). Norepinephrine activation has long been hypothesized to be involved in opioid withdrawal in animals, based on neurobiological measures and the pharmacology of withdrawal (Maldonado, 1997), and in humans, based largely on pharmacological studies of opioid withdrawal (Gold et al., 1978; Harris and Gewirtz, 2005). Noradrenergic function is well documented to be activated during alcohol withdrawal in humans (Hawley et al., 1981). Signs and symptoms of alcohol withdrawal in humans are blocked by postsynaptic β -adrenergic receptor blockade (Romach and Sellers, 1991).

For opioids, norepinephrine has also been implicated in hyperkatifeia that is associated with opioid withdrawal in animal models. Norepinephrine inhibition with an α_2 -adrenergic receptor agonist blocked naloxone-precipitated conditioned place aversion in opioid-dependent rats (Kosten, 1994; Nader and Van der Kooy, 1996). An *in vivo* microdialysis study reported an elevation of norepinephrine release in the CeA during naloxone-precipitated morphine withdrawal (Watanabe et al., 2003). Opioid withdrawal-induced conditioned place aversion was blocked by the inhibition of noradrenergic function with an α_2 -adrenergic receptor agonist or β -adrenergic receptor antagonist in the BNST (Delfs et al., 2000) and by the administration of β_1 - and β_2 -adrenergic receptor antagonists in the CeA (Watanabe et al., 2003). The α_1 -adrenergic receptor antagonist prazosin dose-dependently reduced intravenous heroin self-administration in long-access rats but not in short-access rats in an animal model of extended access to opioid self-administration that produces dependence (Greenwell et al., 2009b).

For alcohol, the norepinephrine metabolite 3-Methoxy-4-hydroxyphenylglycol was elevated during acute withdrawal in alcohol-dependent rats (Karoum et al., 1976), and alcohol withdrawal signs were blocked in animals by

α_1 -adrenergic receptor antagonists and β -adrenergic receptor antagonists and the selective blockade of norepinephrine synthesis (Trzaskowska and Kostowski, 1983). In dependent rats, the α_1 -adrenergic receptor antagonist prazosin selectively blocked the increase in drinking that was associated with acute withdrawal (Walker et al., 2008), and the β -adrenergic receptor antagonist propranolol blocked the increase in drinking that was associated with acute withdrawal in dependent rats at doses that did not block nondependent drinking (Gilpin and Koob, 2010).

Consistent with these results, a subsensitivity of α_2 -adrenergic receptors by α_2 -adrenergic receptor agonists has also been shown to be effective in blocking somatic alcohol withdrawal signs, reducing anxiogenic-like withdrawal responses and reducing alcohol intake in alcohol-preferring rodents. In an early rat study in which alcohol dependence was induced by repeated intragastric alcohol administration, clonidine suppressed withdrawal signs, whereas yohimbine, which increases norepinephrine levels, exacerbated withdrawal (Trzaskowska and Kostowski, 1983). Subsequent studies have shown that α_2 -adrenergic agonists decrease somatic signs of alcohol withdrawal in animal models (Parale and Kulkarni, 1986; Riihioja et al., 1997), including responses that are associated with hyperkatifeia, such as the clonidine-induced blockade of anxiogenic-like effects of alcohol withdrawal in mice (Arora and Vohora, 2016). The α_2 -adrenergic agonists decreased alcohol intake in Finnish Alko alcohol rats that had free-choice access to 10% alcohol and drinking water (Opitz, 1990). Clonidine also decreased voluntary alcohol drinking in Indiana alcohol-preferring (P) rats, but it also affected saccharin intake (Rasmussen et al., 2014).

Additionally, the subsensitivity of α_2 -adrenergic receptors has been hypothesized to be a marker of alcohol dependence in humans (Balldin et al., 1992; Berggren et al., 2000). For example, postsynaptic α_2 -adrenergic receptor function was downregulated in patients not only during acute withdrawal but also during late withdrawal after heavy alcohol intake, measured by the growth hormone response to clonidine (Berggren et al., 2000). In an animal study, prolonged treatment with alcohol (5 g/kg per day, orally) produced subsensitivity to clonidine's actions on protein kinase activity as measured by the inhibition of an endogenous inhibitor of protein kinase in the hippocampus, NAc, and hypothalamus in rats (Szmigielski et al., 1977, 1989).

Altogether, converging data from studies of CRF and norepinephrine suggest that both CRF and noradrenergic neurotransmission are enhanced during opioid and alcohol withdrawal, and CRF and noradrenergic functional receptor antagonists can block motivational aspects of opioid and alcohol withdrawal. A feed-forward system of CRF-norepinephrine interactions at

multiple levels of the pons and basal forebrain has been conceptualized in which CRF activates norepinephrine, and norepinephrine in turn activates CRF (Koob, 1999). Such an interaction may play a key role in the vulnerability and maintenance of hyperkatifeia.

C. Between-System Neuroadaptations: Glucocorticoids

Given that opioid withdrawal is a severely dysphoric and emotionally painful state, there is significant activation of the HPA axis stress response during opioid withdrawal (Koob and Kreek, 2007). Whereas, acutely, opioid receptor agonists inhibit the HPA axis, opioid withdrawal potentially activates it (Culpepper-Morgan and Kreek, 1997; Bearn et al., 2001). Upon activation, the paraventricular nucleus of the hypothalamus (PVN) releases CRF that in turn stimulates the release of adrenocorticotrophic hormone (ACTH) in the anterior pituitary. Adrenocorticotrophic hormone stimulates the cortex of the adrenal gland to synthesize the release of corticosteroids (corticosterone in rats). Corticosteroids bind to both mineralocorticoid receptors and glucocorticoid receptors, but given that glucocorticoid receptors are low-affinity receptors for corticosteroids, they are activated only at high circulating levels of corticosteroid, such as those that are produced by intense stress. Negative feedback mechanisms inhibit HPA axis activity to terminate the acute stress response and maintain homeostasis, but intense and repeated activation of the HPA axis produces cumulative corticosteroid-dependent changes in brain stress circuits (Koob and Schulkin, 2019; McEwen and Akil, 2020).

One hypothesis is that although activation of the HPA axis can feed back and shut off the HPA axis, this same activation of the HPA axis can drive neuroadaptive changes in extrahypothalamic CRF systems in the extended amygdala (Makino et al., 1994a,b; Richardson et al., 2008; Koob and Schulkin, 2019). High corticosterone decreases CRF mRNA in the PVN but increases CRF mRNA in the CeA and lateral BNST (Makino et al., 1994a,b; Albeck et al., 1997; Schulkin et al., 1998; Shepard et al., 2000).

For opioids, individuals with OUD, when subjected to acute withdrawal from heroin and methadone, exhibited persistent elevations of cortisol levels (Culpepper-Morgan and Kreek, 1997; Bearn et al., 2001), and cortisol levels correlated with withdrawal severity (Bearn et al., 2001). However, subjects with OUD while under methadone maintenance therapy exhibited lower levels of craving, withdrawal, anxiety, ACTH, and cortisol, suggesting a return of the HPA axis to homeostasis (Walter et al., 2013). In parallel and linked directly to HPA axis overactivity, opioid withdrawal activates central extrahypothalamic CRF signaling, even long into protracted abstinence, which contributes to negative emotional symptoms that are associated with opioid withdrawal, such as dysphoria and pain. Altogether, these results suggest that HPA axis activity is central to the persistence

of negative emotional states during abstinence (Koob and Schulkin, 2019).

The chronic or acute blockade of glucocorticoid receptor with mifepristone prevented or reversed the escalation of heroin intake that was associated with extended access in rats, similar to the effect of a CRF receptor antagonist (see above; Carmack et al., unpublished results). The glucocorticoid receptor antagonist also blocked the opioid-induced enhancement of CRF neurotransmission in the amygdala (Carmack et al., unpublished results), consistent with the hypothesis that high glucocorticoids drive CRF circuitry in the CeA.

For alcohol, high comorbidity is seen between AUD and stress-associated disorders, reflected by dysregulation of the HPA axis (Boden and Fergusson, 2011; Haass-Koffler et al., 2014; Lijffijt et al., 2014). Indeed, a blunted cortisol response is commonly reported in individuals with AUD. A condition known as pseudo-Cushing's syndrome, manifested by high levels of corticosterone, can be observed in individuals with AUD (Kirkman and Nelson, 1988; Besemer et al., 2011).

Similar effects have been observed in animal models in which rats that are made dependent using the chronic intermittent alcohol vapor model exhibit a blunted corticosterone response (Richardson et al., 2008). In the same paradigm, these animals exhibit an increase in CRF mRNA in the CeA (Roberto et al., 2010). Consistent with the hypothesis of blunted glucocorticoids in the HPA and sensitized CRF in the CeA, chronic glucocorticoid receptor blockade with mifepristone, when administered systemically during the course of alcohol vapor exposure, prevented the escalation of alcohol intake and blocked the increase in progressive-ratio responding for alcohol in dependent animals (Vendruscolo et al., 2012). Chronic, systemic glucocorticoid receptor antagonist treatment blocked escalated and compulsive alcohol drinking during protracted abstinence in rats with a history of alcohol dependence, suggesting the persistence of such stress axis dysregulation in animals with a history of alcohol dependence.

One hypothesis for the differential control of CRF transcription by corticosteroids in the PVN versus CeA is that tissue-specific differences in steroid receptor coactivators, such as SRC-1, might play a role in the neuron-specific action of glucocorticoids on CRF transcription (Kovacs, 2013). The SRC1 α isoform is highly expressed in the PVN, whereas the SRC1 ϵ isoform is enriched in the CeA, and the expression of both was shown to correlate with the differential effect of corticosterone in these areas (Meijer et al., 2000).

D. Between-System Neuroadaptations: Dynorphin/ κ -Opioid Receptors

Dynorphin is an opioid peptide that binds κ -opioid receptors. It has long been known to be activated by chronic psychostimulant and opioid administration and

self-administration (Nestler, 2004; Koob, 2008) and alcohol self-administration (Karkhanis and Al-Hasani, 2020). κ -Opioid receptor agonists (administered systemically) and dynorphins (administered intracerebrally) produce aversive-like effects in both animals and humans (Shippenberg et al., 2007) and have been hypothesized to mediate negative emotional states that are associated with drug withdrawal (Chavkin and Koob, 2016), pain, and more specifically pain that is associated with acute withdrawal (see also the *Pain, Hyperkatifeia, and Addiction* section).

For opioids, animal studies have demonstrated region-specific increases in the levels of dynorphin after the passive administration of morphine (Nylander et al., 1995) and heroin (Weissman and Zamir, 1987). Expression of the dynorphin precursor prodynorphin is also increased during the anticipation of heroin (Cappendijk et al., 1999) and after heroin self-administration (Solecki et al., 2009). The selective blockade of κ -opioid receptor by 20 mg/kg nor-binaltorphimine (nor-BNI) administration (i.p.) 5 hours before naltrexone-precipitated withdrawal in morphine-dependent rats decreased some signs of opioid withdrawal during a 30-minute withdrawal session and, more relevant for the present thesis, decreased the subsequent conditioned place aversion for the withdrawal chamber 2 days later (Kelsey et al., 2015).

One hypothesized mechanism by which dynorphin alters the aversive/rewarding aspects of drug intake is through a decrease in dopamine release in the NAc shell (Carlezon et al., 2000). The κ -opioid receptor agonist U50,488H suppressed dopamine release in the NAc in rats that self-administered heroin, resulting in an increase in immediate heroin intake (Xi et al., 1998). κ -Opioid receptor antagonists do not block the acute rewarding (“euphoric-like”) effects of opioids but 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 (Schlosburg et al., 2013; Zhou et al., 2013b).

For alcohol, an increase in prodynorphin mRNA expression is observed in the CeA during acute withdrawal (Kissler et al., 2014) and in the NAc during withdrawal after 1 month of voluntary alcohol consumption (Przewłocka et al., 1997). There is also an increase in the expression of dynorphin mRNA in the CeA and hypothalamus in alcohol-preferring rats compared with nonpreferring rats after voluntary consumption (Zhou et al., 2013a). Acute withdrawal and extended withdrawal (72 hours) from exposure to chronic intermittent exposure to alcohol in mice increased anxiety-like responses, which were reversed by a κ -opioid receptor antagonist (Rose et al., 2016). In this study, the κ -opioid receptor activation-induced inhibition of dopamine release, measured by fast-scan voltammetry, was produced by a κ -opioid receptor agonist, and these effects were

exacerbated in mice that were exposed to chronic intermittent alcohol (Rose et al., 2016). In mice that were exposed to chronic intermittent alcohol, an acute alcohol challenge decreased extracellular dopamine levels in the NAc, measured by microdialysis, which was reversed by the blockade of κ -opioid receptors, suggesting that an increase in dynorphin/ κ -opioid receptor system activity drives the reduction of stimulated (by electrical stimulation and alcohol) dopamine release in the NAc (Karkhanis et al., 2016; Karkhanis and Al-Hasani, 2020).

Both systemic and intracerebral κ -opioid receptor antagonist administration blocked high compulsive-like drug intake that was associated with extended access to and dependence on alcohol (Hölter et al., 2000; Walker and Koob, 2008). The stress-induced escalation of intake in mice that were exposed to chronic intermittent alcohol (Anderson et al., 2016a) was blocked by a κ -opioid receptor antagonist (Anderson et al., 2016b). These effects may be mediated by the extended amygdala, including the CeA and shell of the NAc (Nealey et al., 2011). The CeA may mediate the effects of κ -opioid receptor blockade on binge-like drinking in mice (Anderson et al., 2019).

E. Between-System Neuroadaptations: Vasopressin

Vasopressin is a neurohormone that is synthesized in the hypothalamus and transported to the posterior pituitary (Brownstein et al., 1980), where it is released into the bloodstream during dehydration to act via vasopressin V_2 receptors on the kidneys to produce water retention (Kaufmann et al., 2000). Arginine vasopressin also exerts synergistic effects with CRF to release ACTH (Antoni, 1993). Vasopressin has a neurotropic action by being centrally localized and originating in the PVN, BNST, medial amygdala, and suprachiasmatic nucleus and projecting extensively throughout the basal forebrain (Veinante and Freund-Mercier, 1997; De Vries and Buijs, 1983). Early studies hypothesized a role for central vasopressin in aversive learning and memory mechanisms (de Wied and Versteeg, 1979; Le Moal et al., 1984; Engelmann et al., 1996).

For opioids, vasopressin has some parallels to CRF in its role in opioid addiction. Brattleboro rats, which are genetically vasopressin-deficient, exhibited attenuation of the increase in ACTH and corticosterone during spontaneous withdrawal from chronic morphine (Domokos et al., 2008). Vasopressin mRNA levels increased selectively in the amygdala only during early spontaneous withdrawal from chronic heroin exposure and not during late withdrawal (Zhou et al., 2008). The vasopressin V_{1B} receptor antagonist SSR149415 blocked the heroin- and foot shock-induced reinstatement of heroin-seeking behavior, suggesting that vasopressin systems in the amygdala may be a key component of the aversive emotional consequences of opioid withdrawal (Zhou et al., 2008).

For alcohol, vasopressin administration in animals potentiated the long-term maintenance of tolerance to the hypothermic and sedative effects of alcohol (Hoffman et al., 1978, 1990; Lê et al., 1982), and this effect was linked to a central vasopressin V_1 receptor subtype (Szabó et al., 1988). Later studies implicated vasopressin more in regulating various affective-like behaviors (Caldwell et al., 2008). A small-molecule V_{1b} receptor antagonist exerted anxiolytic- and antidepressant-like effects (Griebel et al., 2002), with a focus on sites of action in the basolateral amygdala, CeA, medial amygdala (Salomé et al., 2006), lateral septum (Stemmelin et al., 2005), and dorsal hippocampus (Engin and Treit, 2008). The V_{1b} receptor antagonist SSR149415 dose-dependently reduced the higher levels of alcohol self-administration that were observed in dependent animals, without affecting alcohol drinking in nondependent animals (Edwards et al., 2012a). The V_{1b} receptor antagonist also significantly reduced alcohol intake in Sardinian alcohol-preferring rats (Zhou et al., 2011).

In a 12-week, multisite, randomized clinical trial in 150 alcohol-dependent individuals, the selective V_{1b} receptor antagonist ABT-436 significantly increased the percentage of days abstinent compared with placebo (Ryan et al., 2017). Altogether, these results suggest that elevations of vasopressin release during withdrawal can promote a negative emotional state that in turn facilitates the escalation of drinking to alleviate that aversive state. Indeed, individuals who reported higher baseline levels of stress responded better to ABT-436 treatment than to placebo on drinking outcomes in an analysis of moderators (Ryan et al., 2017).

F. Between-System Neuroadaptations: Hypocretin

The neuropeptides hypocretin (Hcrt)-1 (also called orexin A) and Hcrt-2 (also called orexin B) have been associated with sleep-wake regulation, arousal, stress, and drug-seeking behavior (Sutcliffe and de Lecea, 2002; Johnson et al., 2012; Mahler et al., 2012). Hypocretin-containing neurons are found in restricted regions of the dorsal hypothalamus, including the lateral hypothalamus proper, adjacent perifornical area, and dorsomedial hypothalamus (de Lecea et al., 1998; Sakurai et al., 1998), and project widely throughout the brain (Peyron et al., 1998). Hypocretin neurons target two G protein-coupled receptors: Hcrt-1 and Hcrt-2. Hypocretin neuron projections also include reciprocal connections to the extended amygdala and other basal forebrain regions (Peyron et al., 1998; Baldo et al., 2003), thus providing a neuroanatomical basis for the hypothesis that hypocretin neurotransmission plays an important role in negative reinforcement that is thought to contribute to the motivation for compulsive-like intake during dependence (for review, see Koob, 2008; Koob et al., 2014).

Consistent with this hypothesis, immunohistochemical studies indicate the stress-induced activation of

Hcrt neurons through CRF_1 receptor activation (Winsky-Sommerer et al., 2004, 2005). Additional studies demonstrate that intraventricular Hcrt-1 elevates intracranial self-stimulation thresholds, suggesting an aversive effect of excessive activation of the Hcrt system (Boutrel et al., 2005). Intra-VTA infusions of Hcrt-1 also elevated reward thresholds via the activation of CRF in the CeA (Hata et al., 2011). Altogether, these results support the hypothesis that Hcrt may have antireward/brain stress actions possibly via the CRF system in the extended amygdala.

For opioids, the negative affective state that is associated with opioid withdrawal is also associated with greater Hcrt neuron activation. Using a chronic-morphine, intermittent, escalating-dose procedure, Hcrt mRNA levels in the lateral hypothalamus increased during the aversive state of acute morphine withdrawal (Zhou et al., 2010). Naloxone-precipitated morphine withdrawal in rats that were chronically treated with morphine increased Hcrt-1 gene expression and Hcrt neuron activation in the lateral hypothalamus, and an Hcrt-1 receptor antagonist attenuated the somatic expression of naloxone-precipitated morphine withdrawal (Laorden et al., 2012). The Hcrt-1 receptor antagonist also partially reduced withdrawal-induced Fos expression in the extended amygdala in morphine-withdrawn rats (Laorden et al., 2012). Others have observed a decrease in opioid withdrawal in Hcrt knockout mice (Georgescu et al., 2003). An Hcrt-1 receptor antagonist blocked naloxone-precipitated withdrawal in morphine-dependent mice (Sharf et al., 2008). The systemic administration of an Hcrt-2 receptor antagonist dose-dependently decreased heroin self-administration in long-access but not in short-access animals in an extended-access procedure (Schmeichel et al., 2015). Additionally, an increase in Hcrt-2 receptor mRNA levels in the CeA in long-access rats was observed by quantitative polymerase chain reaction.

For alcohol, prepro-Hcrt mRNA increased in the lateral hypothalamus in inbred alcohol-preferring rats after chronic alcohol consumption (Lawrence et al., 2006) but decreased in the perifornical area in Sprague-Dawley rats (Morganstern et al., 2010). Both Hcrt-1 and Hcrt-2 receptor blockade decreased alcohol self-administration in alcohol-preferring rats (Lawrence et al., 2006; Brown et al., 2013). Another study tested the effect of an Hcrt-1 receptor-specific antagonist on responding for alcohol in dependent mice that were exposed to chronic intermittent alcohol vapor compared with mice that were nondependent. The Hcrt-1 receptor antagonist dose-dependently decreased alcohol intake, particularly in alcohol-dependent mice (Lopez et al., 2016). An Hcrt-1 receptor antagonist also blocked the stress (yohimbine)-induced reinstatement of alcohol seeking (Richards et al., 2008). Altogether, Hcrt likely exerts both direct and indirect modulatory actions on brain stress systems to

contribute to opioid and alcohol withdrawal-induced hyperkatifeia.

G. Between-System Neuroadaptations: Neuroimmune Systems

Neuroinflammatory signaling pathways in the central nervous system are also hypothesized to contribute to neuroadaptive processes that mediate the dysregulation of hyperkatifeia that is associated with the withdrawal/negative affect stage of the addiction cycle (Koob and Volkow, 2010; Crews and Vetreno, 2016). Repeated cycles of withdrawal have a particularly pronounced effect on neuroimmune function. Here, withdrawal from chronic drug exposure amplifies neuroimmune gene expression, impacting stress and fear circuits, and as a result is hypothesized to contribute to hyperkatifeia.

Interactions between the immune system and stress system that are associated with the withdrawal/negative affect stage involve both microglia and astrocytes (Crews et al., 2017). Microglia are the primary neuroimmune cells in the brain and act as resident macrophages of the brain. Microglia normally exist in a “resting” state but can become activated in response to insults (Kettenmann et al., 2013). Astrocytes are also an important component of the brain immune system but are also involved in the metabolic support of neurons and modulation of synaptic transmission (Farina et al., 2007; Khakh and Sofroniew, 2015). In response to insults, astrocytes undergo a process of activation; like microglia, they are capable of adopting proinflammatory and anti-inflammatory states (Jang et al., 2013b). Repeated cycles of stress and excessive drug use are hypothesized to result in increasingly sensitized/activated microglia, contributing to signs and symptoms that are associated with the withdrawal/negative affect stage of the addiction cycle (Crews et al., 2017). With repeated episodes of drug administration or stress, as observed with hyperkatifeia, immune danger signals and glial activation are amplified within glia and across other brain cells. Such activation persists for long periods of time. Both stress and chronic pain activate microglia, increase Toll-like receptor 4 (TLR4) danger signals, increase the expression of nuclear factor κ B target genes, and increase tumor necrosis factor α (TNF α ; Watkins et al., 2007; Graeber, 2010).

For opioids, glia and proinflammatory cytokines may also play a role in the development of opioid-induced hyperalgesia during withdrawal (DeLeo et al., 2004) and other physical and motivational measures of opioid withdrawal (Wieseler-Frank et al., 2005; Hao et al., 2011; Taylor et al., 2016). The acute administration of opioids exerts anti-inflammatory effects (Eisenstein, 2019), whereas chronic opioid exposure activates microglia and astrocytes in the spinal cord (Watkins et al., 2009; Cahill et al., 2016) and central nervous system, including

the VTA, NAc, frontal cortex, and periaqueductal gray (Hao et al., 2011; Taylor et al., 2016).

Glial activation may also contribute to hyperkatifeia-like responses that are observed during opioid withdrawal. The blockade of glial cell activation restored mesolimbic dopamine function using minocycline (Taylor et al., 2016), prevented withdrawal using various inhibitors of glial cell activation (Watkins et al., 2009), prevented the relapse of morphine-seeking behavior via the epigenetic reprogramming of interleukin-10 overexpression (Schwarz et al., 2011), and prevented incubation-induced heroin seeking in rats after prolonged abstinence using the TLR4 antagonist (+)-naloxone (Theberge et al., 2013). For example, chronic opioid treatment caused the dysregulation of transmembrane Cl⁻ homeostasis in GABAergic neurons in the VTA, driven by brain-derived neurotrophic factor (BDNF) and activated microglia (Taylor et al., 2016). Here, microglia via a BDNF-potassium-chloride transporter member 5 mechanism are hypothesized to be activated during opioid withdrawal and increase VTA GABAergic tone, which inhibits dopaminergic neurons (Cahill et al., 2016). The resulting blunting of VTA-dependent reward suggests opponent process-like changes that are driven by nonneuronal modulators (Cahill et al., 2016).

In parallel, neuroimmune activation contributes to opioid withdrawal and tolerance. Intra-periaqueductal gray microinjections of a herpes simplex virus vector that expressed the soluble TNF receptor, which downregulates the expression of glial fibrillary acidic protein and TNF α in astrocytes, significantly attenuated behavioral manifestations of naloxone-precipitated withdrawal (Hao et al., 2011). Microinjections of the soluble TNF receptor-expressing herpes simplex virus vector in the periaqueductal gray also significantly reduced the phosphorylation of both extracellular signal-regulated kinase 1/2 and CREB and reduced Fos immunoreactivity in periaqueductal gray neurons after naloxone-precipitated withdrawal. These findings support the hypothesis that proinflammatory cytokines that are expressed in astrocytes in the periaqueductal gray may play an important role in the pathogenesis of the morphine withdrawal response (Hao et al., 2011). An alternate hypothesis to explain proinflammatory actions of opioids after administration and withdrawal is that lipopolysaccharide may be released into the circulation from the escape of Gram negative flora from the gastrointestinal tract, which would be proinflammatory (Eisenstein, 2019). The inhibition of glial activation and inhibition of many of the resulting downstream signaling components (e.g., chemokines, cytokines, fractalkine, nitric oxide, and connexin 43) can reverse analgesic tolerance after chronic morphine administration (Song and Zhao, 2001; DeLeo et al., 2004; Johnston et al., 2004; Watkins et al., 2009; Horvath et al., 2010; Muscoli et al., 2010; Wen et al., 2011; Shen et al., 2014; Hua et al., 2016).

For alcohol, chronic alcohol treatment in mice induced proinflammatory gene expression in the brain that persisted for at least 1 week of abstinence (Qin et al., 2007). Mice that lacked TLR4 were protected from alcohol-induced glial activation, anxiety-like behavior, and cognitive impairments (Pascual et al., 2011). Similarly, mice that lacked CD14, a key TLR4 accessory signaling protein, drank significantly less alcohol than normal mice (Blednov et al., 2012). The amygdala may be one site for the action of neuroimmune cytokines. Mice that lacked CD14 had significantly lower GABA interneuron firing in the CeA in response to alcohol (Bajo et al., 2014). Injections of TNF α in the amygdala in rats increased anxiety-like behavior and mimicked the amplification of anxiety-like behavior that was observed with repeated cycles of alcohol drinking (Breese et al., 2008). Injections of cytokines in the amygdala increased withdrawal-induced hyperkatifeia-like responses, similar to exposure to stress or alcohol (Knapp et al., 2011). Furthermore, TLR4 knockdown in the amygdala reduced responding for alcohol in alcohol-dependent rats (Liu et al., 2011), consistent with the hypothesis that the activation of innate immune danger signals within the amygdala may contribute to hyperkatifeia that drives dependence-induced alcohol drinking. Phosphodiesterase-4 inhibitors, which hydrolyze cAMP within immune cells and have anti-inflammatory actions, reduced alcohol drinking and relapse in alcohol-preferring P rats, high-alcohol drinking (HAD1) rats, and mice that were made dependent on alcohol by repeated cycles of alcohol vapor exposure, with no effect in nondependent mice (Bell et al., 2015; Franklin et al., 2015).

Additionally, CRF receptor antagonists that blocked alcohol dependence-induced excessive drinking also blocked the induction of withdrawal/negative affect and anxiety by cytokines (Knapp et al., 2011). These studies support the hypothesis that the amplification of danger signals and glial activation in the amygdala and other components of brain fear/anxiety/stress neurocircuitry contribute to the progression and persistence of the withdrawal/negative affect stage, possibly by interacting with brain stress systems.

Another link between alcohol abuse and innate immunity is hypothesized to involve the gut. Alcoholic liver disease involves inflammation, in part through an alcohol-induced increase in the permeability of the gut to endotoxins, such as lipopolysaccharide, that activate innate immune cells in the liver (Szabo et al., 2011). Lipopolysaccharide is a large molecule that does not cross the blood-brain barrier, but cytokines that are induced by lipopolysaccharide may be transported into the brain and result in neuroinflammation and microglial activation (Qin et al., 2007; Banks and Erickson, 2010). Indeed, high levels of lipopolysaccharide cause a “sickness-like” response, characterized by decreases in food and water intake, loss of weight, lethargy, and hypohedonia (Dantzer et al., 2008). Thus, the hypothesis

is that repeated cycles of binge/withdrawal sensitize neuroimmune systems that interact with brain stress systems to facilitate negative emotional states during withdrawal and drive compulsive-like drinking under a negative-reinforcement framework.

VI. Antistress Neurotransmitters/ Neuromodulators and Hyperkatifeia

The vulnerability to hyperkatifeia in driving AUD and substance use disorders may derive not only from the activation of prostress neurotransmitter systems but also from antistress neurotransmitter systems (see Fig. 5). Antistress neurotransmitter systems can be defined as neuroadaptive buffers to prostress actions that are described above, in which neurotransmitter systems are hypothesized to act either in opposition to stress neurotransmitters (Heilig, 2004; Pleil et al., 2015) or in response to the excess activation of prostress neural systems or even in anticipation of the activation of stress (Heilig and Koob, 2007). Neurotransmitter/neuromodulatory systems that are implicated in antistress actions include NPY, nociceptin, endocannabinoids, and oxytocin.

A. Neuropeptide Y

Neuropeptide Y has powerful orexigenic and anxiolytic-like effects in animal models and has been hypothesized to act in opposition to the actions of CRF in AUD and substance use disorders (Heilig and Koob, 2007).

For opioids, NPY can potentiate their acute rewarding effects (Robinson and Thiele, 2017). For example, one study showed that in nondependent rats (3 hours of access per day), intracerebroventricular NPY injections increased ongoing heroin self-administration and induced the reinstatement of extinguished heroin-seeking behavior (Maric et al., 2008). However, NPY administration attenuated somatic withdrawal symptoms that were produced during naloxone-precipitated withdrawal from chronic opioids (Woldbye et al., 1998; Clausen et al., 2001). *Npy* gene expression decreased in rats at both 1 and 14 days of withdrawal from 3 hours of heroin self-administration, with an increase in the Y₅ receptor (Kuntz-Melcavage et al., 2009). Little work has been done on the effects of NPY on opioid self-administration in dependent animals. These studies suggest that NPY may facilitate the initial rewarding effects of opioids but may also play a role in withdrawal, although little research has been done in the domain of hyperkatifeia.

For alcohol, NPY administration directly in the brain blocked the increase in self-administration in alcohol-preferring rats and in alcohol dependence, blocked the transition to excessive drinking with the development of dependence, and blocked the increase in GABA release in the CeA that was produced by alcohol

(Gilpin et al., 2003, 2008, 2011; Thorsell et al., 2005a,b, 2007). Similar effects on dependence-induced drinking in rats and binge-like drinking in mice were observed with injections of NPY in the amygdala, BNST, and NAc shell but not in the hypothalamus, suggesting a focus of the effects of NPY on alcohol drinking on the extended amygdala (Kelley et al., 2001; Gilpin et al., 2008; Pleil et al., 2015). Viral vector-induced NPY overexpression in the amygdala reversed the increase in alcohol intake that was caused by repeated deprivations in Wistar rats (Thorsell et al., 2007). Given that the activation of NPY in the CeA has opposite effects to CRF, one hypothesis is that NPY may act as a buffer to the stress-driving effects of CRF; by extrapolation, low functional activity of NPY may contribute to the etiology and vulnerability to hyperkatifeia.

B. Nociceptin

Nociceptin has antistress-like effects in animals (Ciccocioppo et al., 2003; Martin-Fardon et al., 2010). High numbers of nociceptin-containing neurons are found in the extended amygdala, cortex, and midbrain (Mollereau and Mouledous, 2000). Nociceptin can block both opioid and alcohol withdrawal and attenuate the increase in alcohol and opioid self-administration in dependent animals.

For opioids, intraventricular injections of nociceptin inhibited naloxone-precipitated withdrawal signs in morphine-dependent rats (Kotlinska et al., 2000, Kotlińska et al., 2004), and conditioned withdrawal (measured by place aversion) increased nociceptin levels (measured by a radioimmunoassay) in the frontal cortex (Walker et al., 2002). Intracerebroventricular nociceptin administration did not block heroin self-administration in nondependent rats, but a nociceptin receptor agonist decreased intravenous remifentanyl self-administration in rats and rhesus monkeys (Podlesnik et al., 2011; Sukhtankar et al., 2014). Perhaps more compelling for the present thesis, direct injections of nociceptin in the CeA attenuated the escalation of intravenous oxycodone self-administration in a high addiction index subset of outbred rats (Kallupi et al., 2020). The same high-addiction subgroup had lower levels of nociceptin in the CeA, and nociceptin normalized GABAergic transmission in the CeA, suggesting that the downregulation of nociceptin levels in the CeA may be responsible for the hyper-GABAergic tone in the CeA that is observed in individuals who develop addiction-like behaviors.

For alcohol, intracerebroventricular nociceptin administration significantly reduced the expression of somatic withdrawal signs and reversed anxiety-like behaviors that were associated with both chronic and acute alcohol intoxication in Wistar rats (Economidou et al., 2011). Synthetic nociceptin receptor agonists blocked high alcohol consumption in Marchigian Sardinian alcohol-preferring

(msP) rats, a genetically selected line of rats that is known to be hypersensitive to stressors (Economidou et al., 2008). Nociceptin receptor agonists exerted effects on GABA synaptic activity in the CeA that were similar to NPY (Economidou et al., 2008). msP rats exhibited increases in nociceptin and nociceptin receptor mRNA expression in most of the brain but a decrease in nociceptin signaling, which was measured by [³⁵S]GTP γ S binding in the CeA (Economidou et al., 2008). Intra-amygdala administration of nociceptin also blunted alcohol self-administration in msP rats (Economidou et al., 2008). In postmortem brains of humans with AUD, nociceptin mRNA decreased in the amygdala (Kuzmin et al., 2009). Altogether, one hypothesis is that repeated alcohol intake may downregulate the endogenous nociceptin system, resulting in the activation of alcohol consumption through the release of stress modulation.

Notably, however, nociceptin receptor antagonists also decreased high levels of drinking in msP rats (Rorick-Kehn et al., 2016), leading to the hypothesis by these authors that the previously reported agonist effects that are mentioned above may reflect receptor desensitization with agonist administration, in effect producing the antagonist-like functional blockade of subchronic agonist dosing (Rorick-Kehn et al., 2016; Toll et al., 2016). Another hypothesis to explain the efficacy of both nociceptin agonists and antagonists in animal models of high alcohol consumption is that such agonists and antagonists of nociceptin receptors may produce different patterns of activation or inhibition in different brain areas that are relevant to reward and addiction (Rorick-Kehn et al., 2016). Future studies are needed to elucidate the exact nature of the neuromodulatory role of nociceptin.

C. Endocannabinoids

Endocannabinoids are hypothesized to have stress-buffering actions that may be involved not only in the response to repeated withdrawal from alcohol but also in the vulnerability to negative emotional dysregulation that drives excessive drinking. Reductions of endocannabinoid signaling produce anxiogenic-like behavioral effects. Increasing endogenous endocannabinoid levels through the inhibition of endocannabinoid clearance mechanisms produces anxiolytic-like effects in various animal models of anxiety, particularly under stressful or aversive conditions (Serrano and Parsons, 2011).

Opioids and cannabinoids have a long history of interactions, including crosstolerance and crosswithdrawal precipitation with antagonists (Scavone et al., 2013). These interactions may involve alterations in the level of endogenous opioids or their receptors or via changes in G protein-mediated signaling through opioid receptors or μ -opioid receptor-cannabinoid CB₁ receptor complexes (Scavone et al., 2013). The administration of an opioid or cannabinoid CB₁ receptor

antagonist in morphine-dependent individuals precipitated withdrawal symptoms with somatic and affective components (Navarro et al., 1998; Kosten and George, 2002). Less work has explored the role of endocannabinoids in opioid withdrawal and withdrawal-induced self-administration (Scavone et al., 2013).

With regard to the hyperkatifeia-buffering role of endogenous cannabinoids, the administration of 2-arachidonoylglycerol (2-AG) and anandamide blunted physical symptoms of morphine withdrawal (Vela et al., 1995; Yamaguchi et al., 2001). The blockade of fatty acid amide hydrolase (FAAH) blocked somatic signs of precipitated opioid withdrawal and facilitated the extinction of naloxone-precipitated withdrawal-induced place aversion in rats (Manwell et al., 2009), and systemic pretreatment with the monoacylglycerol lipase (MAGL) inhibitor MJN110 blocked place aversion that was produced by naloxone-precipitated acute withdrawal after a single large dose of morphine through a cannabinoid CB₁ receptor-dependent mechanism in rats (Wills et al., 2016). Neutral CB₁ receptor antagonists also blocked place aversion that was produced by naloxone-precipitated acute withdrawal after a single large dose of morphine in rats (Wills et al., 2014). Additionally, intracerebral administration of the MAGL inhibitor directly in the basolateral amygdala blocked acute withdrawal-induced place aversion in rats, and CB₁ receptor antagonist administration in the CeA blocked acute withdrawal-induced place aversion in rats (Wills et al., 2016). These authors suggested that CB₁ receptor antagonists decrease the inhibition of GABA release in the basolateral amygdala, and MAGL inhibitors inhibit GABA release in the CeA, returning the amygdala to normal levels of function in both cases (Wills et al., 2016). Intraperitoneal administration of a dual FAAH/MAGL inhibitor also decreased heroin seeking in mice, which was measured as a decrease in nose poking for heroin during the escalation of intake and a decrease in progressive-ratio responding after escalation (Wilkerson et al., 2017). This same dual FAAH/MAGL inhibitor dose-dependently reversed mechanical allodynia in a sciatic nerve constriction injury model of neuropathic pain and in a model of carrageenan-induced inflammatory pain (Wilkerson et al., 2017). However, in mice, an FAAH inhibitor and an MAGL inhibitor blocked somatic signs of precipitated opioid withdrawal in mice (Gamage et al., 2015), but they failed to block naloxone-precipitated withdrawal-induced place aversion. Altogether, the data suggest that, at least in rats, the modulation of endogenous endocannabinoids can reverse hyperkatifeia that is associated with opioid withdrawal, but the nature of such modulation may be circuit-specific.

For alcohol, chronic alcohol exposure increases brain 2-AG (Caillé et al., 2007; Alvarez-Jaimes et al., 2009) and *N*-arachidonylethanolamine (AEA), particularly

in basal forebrain areas, in rodents (González et al., 2004; Vinod et al., 2006), but decreases in both 2-AG and AEA were observed in the CeA during withdrawal (Serrano et al., 2018). Both FAAH inhibitors and MAGL inhibitors, which functionally increase endocannabinoids, decreased withdrawal-induced anxiety-like behavior and decreased alcohol consumption in alcohol-dependent rats (Serrano et al., 2018). Alcohol-preferring rats that exhibited high alcohol drinking and preference showed high anxiety-like responses, with higher FAAH activity in the CeA and lower AEA levels in the CeA, measured by in vivo microdialysis (Natividad et al., 2017). Consistent with these results, microinjections of the selective FAAH inhibitor URB597 in the CeA in alcohol-preferring rats significantly reduced alcohol self-administration (Stoppioni et al., 2018).

D. Oxytocin

Oxytocin has been hypothesized to play a role in such diverse functions as memory, learning, social behavior, fear, and anxiety (Stoop, 2012). It has also been hypothesized to normalize stress function and attenuate hyperkatifeia in the context of addiction (Lee and Weerts, 2016). Oxytocin has been detected in the brain after both intraperitoneal and intranasal administration in mice, rats, and rhesus monkeys (Neumann et al., 2013; Bustion et al., 2016; Lee et al., 2018, 2020; Tanaka et al., 2018).

For opioids, early studies showed that systemic, intracerebroventricular, and intracerebral injections of oxytocin and oxytocin analogs in the dorsal hippocampus and NAc attenuated morphine tolerance and dependence (Kovacs et al., 1984). Both systemic and central routes of administration have been used in preclinical studies to evaluate the effects of oxytocin on drug self-administration. Systemic injections of oxytocin and oxytocin analogs blocked intravenous heroin self-administration in heroin-tolerant rats (Kovács and Van Ree, 1985; Kovács et al., 1985). Naloxone-precipitated morphine withdrawal after chronic exposure to morphine produced the hyperexcitation of oxytocin neurons and gene expression and increased Fos expression in the rat supraoptic nucleus (Murphy et al., 1997; Johnstone et al., 2000). Increases in oxytocin content in the PVN and median eminence were observed during naloxone-precipitated morphine withdrawal (Laorden et al., 1998). These effects on central oxytocin neurons led some authors to suggest that hypothalamic oxytocin neurons develop morphine dependence, and despite the requirement of afferent inputs for the expression of morphine withdrawal-induced excitation, “the underlying mechanisms appear to reside within the oxytocin neurons themselves and probably involve changes in the intrinsic membrane properties of these neurons” (Brown and Russell, 2004; Brown et al., 2005). Systemic injections of an oxytocin analog also blunted anxiety-like responses that were associated with opioid withdrawal

in mice and prevented opioid-induced reinstatement in the place preference test (Zanos et al., 2014). Particularly interesting from a translational perspective, in human clinical studies of individuals with opioid addiction, higher withdrawal-related levels of stress were associated with higher plasma oxytocin levels and early treatment discharge (Nikolaou et al., 2017). In heroin users during abstinence in a double-blind placebo-controlled study, acute intranasal oxytocin administration reduced craving and withdrawal scores and decreased cortisol levels but did not significantly change anxiety (Moeini et al., 2019).

For alcohol, early studies showed that oxytocin or oxytocin analogs inhibited the development of tolerance to its hypnotic and hypothermic effects (Pucilowski et al., 1985; Szabó et al., 1987; Jodogne et al., 1991). Systemic oxytocin administration suppressed the opposite compensatory response that was conditioned to alcohol-paired cues that were hypothesized to cause tolerance (Tirelli et al., 1992). Oxytocin significantly decreased withdrawal signs in alcohol-dependent mice (Szabó et al., 1987; Kovacs et al., 1998).

Oxytocin receptors are found in many brain regions that are relevant to alcohol dependence, such as the frontal cortex and extended amygdala, in rats and humans (Knobloch et al., 2012; Boccia et al., 2013). Oxytocin and oxytocin analogs can blunt alcohol reward (Bahi, 2015) and decrease alcohol drinking (MacFadyen et al., 2016; King et al., 2017). Oxytocin also attenuated the increase in drinking that was associated with dependence in animal models after both systemic and central administration. Oxytocin administration intranasally or directly in the brain blocked the increase in drinking in alcohol-dependent rats (Tunstall et al., 2019). Oxytocin blocked this increase in alcohol drinking at doses that did not alter non-alcohol-related behaviors or alcohol drinking in nondependent rats, suggesting that the effect was specific to alcohol drinking in dependence. These effects were hypothesized to be centrally rather than peripherally mediated. *Ex vivo* electrophysiological recordings in the CeA indicated that oxytocin blocked the facilitatory effects of alcohol on GABA release in the CeA in dependent rats but not in nondependent rats (Tunstall et al., 2019). Intraperitoneal oxytocin administration also blocked the stress-induced reinstatement of alcohol seeking in mice (King and Becker, 2019). Oxytocin also reduced cue-induced reinstatement in dependent rats but not in nondependent rats (Hansson et al., 2018).

In a postmortem study of males with AUD, oxytocin peptide mRNA was significantly elevated in the prefrontal cortex in subjects with AUD compared with controls (Lee et al., 2017). A small study showed that intranasal oxytocin blocked alcohol withdrawal in humans, based on such measures as the Alcohol Withdrawal Symptom Checklist of the Clinical Institute Withdrawal Assessment for Alcohol, and reduced

the amount of benzodiazepines that were required for treatment (Pedersen et al., 2013). Another study failed to observe such a reduction of the amount of benzodiazepines that were required for alcohol withdrawal treatment (Melby et al., 2019). In a double-blind crossover study of non-treatment-seeking individuals with alcohol abuse, oxytocin did not produce an overall decrease in craving, but further analysis revealed that the effects on craving were moderated by attachment anxiety, with oxytocin reducing craving in more anxiously attached individuals and increasing craving in less anxiously attached individuals (Mitchell et al., 2016).

VII. Hyperkatifeia and Sex Differences

More men use and are addicted to opioids and alcohol (National Survey on Drug Use and Health Substance Abuse and Mental Health Services Administration, 2007). However, for alcohol, the gaps between women and men are narrowing with regard to the prevalence, frequency, and intensity of drinking, early onset drinking, having AUD, drunk driving, and self-reported consequences (White et al., 2015; Slade et al., 2016).

For opioids, 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 (Brady and Randall, 1999). In animal models, female rodents generally acquire morphine and heroin self-administration faster than males and exhibit higher motivation to self-administer opioids (Lynch and Carroll, 1999; Cicero et al., 2003; Becker and Koob, 2016). Female rodents are also less sensitive to the analgesic effects of μ -opioid receptor agonists (Barrett et al., 2002; Negus et al., 2002), and some physical signs of opioid withdrawal are more pronounced in male mice than in female mice (Diaz et al., 2005).

To date, little work has focused on preclinical studies of gender differences in animal models of hyperkatifeia and negative reinforcement with opioids (Becker and Koob, 2016).

For alcohol, women are more likely to experience blackouts, liver inflammation, brain atrophy, cognitive deficits, certain cancers, negative affect during withdrawal, and stress- or anxiety-induced relapse (Becker and Koob, 2016). Female rodents also drink more alcohol than males (Eriksson and Pikkarainen, 1968; Becker and Koob, 2016). Selectively bred lines exhibited the faster acquisition of self-administration (Li and Lumeng, 1984; Moore and Lynch, 2015).

For alcohol, males generally exhibit a greater withdrawal response and slower recovery from acute alcohol withdrawal (Becker and Koob, 2016). Male rats also exhibit greater physical signs of withdrawal, such as greater seizure susceptibility, compared with female rats (Devaud and Chadda, 2001). However, male rats

also exhibit greater motivational signs of withdrawal, such as anxiety-like responses in the social interaction test (Varlinskaya and Spear, 2004) and elevated plus maze after one cycle of exposure to an alcohol liquid diet (Overstreet et al., 2004a), and greater increases in acoustic startle responses than female rats (Reilly et al., 2009). Male rats also exhibit greater hangover-like anxiety-like responses (acute alcohol withdrawal; Varlinskaya and Spear, 2004). Chronic alcohol exposure and withdrawal result in modest elevations of alcohol intake in male High Alcohol Preferring 2 mice. In contrast, female High Alcohol Preferring 2 mice did not show changes in alcohol intake (Lopez et al., 2011).

VIII. Pain, Hyperkatifeia, and Addiction

A. Opioids and Pain

Opioids are recognized as the most powerful and effective drugs for the relief of acute pain in humans, and a unifying common theme is their relief of pain and suffering, including negative emotional states (Lutz and Kieffer, 2013). Particularly important for the present thesis, opioids also relieve emotional pain, which is a key component of hyperkatifeia, as noted above, and the driving force for 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 (Khantjian, 1985).

However, opioids are significantly less effective against chronic pain, such as neuropathic pain, fibromyalgia, and low-back pain, and tolerance develops to the analgesic effects of opioids, thus necessitating the need for increasingly higher doses to sustain analgesia (McQuay, 1988; Dowell et al., 2016). Interwoven into this framework is that chronic opioids lose their effectiveness for chronic emotional pain. One could argue that chronic opioids actually drive chronic emotional pain via withdrawal.

In humans and animal models, withdrawal from chronic opioid self-administration produces hyperalgesia (i.e., lower pain thresholds; Tilson et al., 1973; Angst and Clark, 2006). In humans, heightened pain perception has long been observed in individuals with a history of opioid addiction (Ho and Dole, 1979; Ren et al., 2009). Methadone-maintained patients have low pain tolerance (Doverty et al., 2001). In these individuals, pain is one of the main triggers of relapse to addiction (Compton et al., 2001). Particularly important is an interaction between negative emotional states and withdrawal-related hyperalgesia. Individuals who were in acute withdrawal (24–72 hours) from opioids or protracted abstinence (average of 30 months) exhibited lower pain thresholds and pain tolerance, measured by the ischemic pain submaximal tourniquet procedure, and these decreases in pain thresholds were exacerbated

by negative emotional states (Carcoba et al., 2011). Non-opioid-dependent individuals who underwent an acute opioid physical dependence challenge with naloxone exhibited the presence of hyperalgesia in response to experimental cold-pressor pain, thus showing that even acute opioid administration can produce hyperalgesia (Compton et al., 2003).

In animal models, repeated opioid administration (e.g., once daily for 2 weeks) produces a gradual and dose-dependent decrease in nociceptive thresholds that lasts for several weeks after drug administration (Célèrier et al., 2001; Simonnet and Rivat, 2003). Such hyperalgesia has also been observed with a single injection of heroin in rats (Laulin et al., 1998). Some have argued that a neuronal memory of pain sensitization may remain long after complete washout of the drug and when apparent equilibrium near the predrug state has been reestablished (Laulin et al., 1998).

Neurobiological mechanisms for opioid-induced hyperalgesia have long been hypothesized to be mediated by glutamatergic mechanisms and involve alterations of the function of NMDA glutamate receptors. Behavioral studies in rodents have shown that the activation of NMDA pronociceptive processes by opioids may be involved in the development of hyperalgesia that is classically observed after chronic opioid treatment (Célèrier et al., 1999; Laulin et al., 2002; see the *Within-System Neuroadaptations* section above). Given that protein kinase C (PKC) regulates NMDA receptors, opioid-induced hyperalgesia was also reduced in PKC γ gene knockout mice (Célèrier et al., 2004). NMDA receptor antagonists, such as ketamine, blocked hyperalgesia in animal models (Célèrier et al., 2000).

Opioid withdrawal-induced hyperalgesia also includes the activation of the same brain stress systems (e.g., CRF and dynorphin) that are implicated in hyperkatifeia in general. Hyperalgesia in the tail flick test that was associated with morphine withdrawal was blocked by microinjections of a CRF₁/CRF₂ peptide receptor antagonist in the CeA, without affecting plasma corticosterone responses (McNally and Akil, 2002). 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 CRF₁ receptor antagonist (Edwards et al., 2012b; Park et al., 2015). Dynorphin knockout mice exhibited a facilitated return to normal nociceptive baselines after a peripheral nerve lesion (Wang et al., 2001), suggesting a pronociceptive role for dynorphin in chronic pain, in contrast to the antinociceptive effects of acute κ -opioid receptor agonist administration.

The dynorphin/ κ -opioid receptor system may also be engaged in negative emotional states that are associated with chronic pain (Cahill et al., 2014; Massaly et al., 2016, 2019). Evidence that supports this hypothesis includes studies of the neuropharmacological

blockade of κ -opioid receptors and neurocircuitry-specific engagement of dynorphin neurons. Increases in the GTP γ s binding of κ -opioid receptor-specific ligands in the amygdala were associated with anxiety that was produced by Complete Freund's Adjuvant-induced chronic pain or sciatic nerve ligation-induced neuropathic pain (Narita et al., 2006). The pain-induced attenuation of conditioned place preference can be reversed by the systemic or local NAc blockade of κ -opioid receptors using nor-BNI (Narita et al., 2005), and nor-BNI significantly prevented loss of the diffuse noxious inhibitory control response (i.e., a pain-inhibiting pain response) in the rat hindpaw after morphine-primed stress (Nation et al., 2018).

At the microcircuitry level, the stimulation of specifically dynorphin-containing neurons in the ventral NAc 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 nor-BNI into the ventral NAc shell blocked conditioned place aversion and the lower motivation to self-administer sucrose that was produced by inflammation (Massaly et al., 2019). These authors hypothesized that the in vivo recruitment of NAc shell dynorphin neurons that act through κ -opioid receptors can drive pain-induced negative affect (Massaly et al., 2016, 2019). Much evidence shows that the activation of κ -opioid receptor agonists elevates intracranial self-stimulation reward thresholds and decreases the function of the mesolimbic dopamine system (Todtenkopf et al., 2004; Chefer et al., 2013). However, systemic doses of the κ -opioid receptor antagonist (3R)-7-hydroxy-N-((2S)-1-[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]-3-methylbutan-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (JDtic) failed to block conditioned place aversion that was produced by visceral and acid-induced pain in mice (Bagdas et al., 2016). Moreover, the κ -opioid receptor antagonist nor-BNI failed to block lactic acid-induced elevations of brain reward thresholds and the decrease in NAc dopamine in rats (Leitl et al., 2014). The type of pain is likely important, as well as the dependent variable that is used to measure negative affective effects of pain, the time course of dynorphin mediation, and the opposing actions of dynorphin neuron subcircuits (Cahill et al., 2014; Massaly et al., 2016). Furthermore, burgeoning interest in animal models of the affective/motivational component of pain will help elucidate specific interactions with pain and hyperkatifeia in addiction (Edwards et al., 2020). Nevertheless, a role for the dynorphin/ κ -opioid receptor system in negative affective effects of chronic pain remains "an engaging hypothesis" (Cahill et al., 2014).

Melanocortin receptors also modulate nociceptin, opioid-induced analgesia, the development of tolerance to this effect, and opioid withdrawal-induced hyperalgesia (Kalange et al., 2007). Thus, there appears to be some role

for glutamate, CRF, the dynorphin/ κ -opioid receptor system, and the melanocortin system in modulating the interplay between pain, stress, and reward processing. The high comorbidity between chronic pain, addiction, depression, and suicide provides a compelling rationale for further studies in this domain.

B. Alcohol and Pain

An association between pain and alcohol use and misuse is supported by clinical studies and meta-analyses. A meta-analysis of 18 controlled studies that compared pain in people who were given alcohol versus no alcohol provided support for the analgesic effects of alcohol (Thompson et al., 2017). The threshold appeared to be a mean BAL of \sim 0.08% (i.e., the legal driving limit) for producing a small elevation of pain thresholds, and a significant reduction of pain intensity with a higher BAL was associated with greater pain insensitivity. Additionally, individuals with chronic pain had significantly greater odds of also meeting DSM-IV criteria for alcohol abuse/dependence (Demyttenaere et al., 2007). Indeed, there is a positive association between pain severity and a higher risk for AUD (Lawton and Simpson, 2009; Eklund et al., 2013). Perhaps more compelling, physical pain appears to be a significant predictor of alcohol use and heavy alcohol use and relapse to drinking after a period of abstinence (Larson et al., 2007; Caldeiro et al., 2008; Witkiewitz et al., 2015).

Theorists have long hypothesized that a negative-reinforcement model of drug use assumes that individuals frequently consume alcohol (or opioids) to alleviate aversive physical or emotional states (Cappell and Herman, 1972; Sher and Levenson, 1982; Khantzian, 1985; Koob and Bloom, 1988; Baker et al., 2004; Ahmed and Koob, 2005). One model hypothesizes that there are effects of alcohol on pain and effects of pain on alcohol use (Zale et al., 2015). Here, pain serves as a situational motivator of alcohol consumption, partly as a function of pain-induced negative affect (Zale et al., 2015). Moderate alcohol use was associated with positive pain-related outcomes (e.g., greater quality of life), but excessive drinking and AUD were associated with deleterious pain-related outcomes (e.g., greater pain severity; Zale et al., 2015). As noted above, alcohol produces analgesic effects (Thompson et al., 2017). Individuals often report consuming alcohol to self-medicate physical and emotional pain (Holahan et al., 2001; Brennan et al., 2005; Aira et al., 2008; Riley and King, 2009; Zale et al., 2015). Indeed, negative affect, measured by the Beck Depression Inventory, increased thermal and electrical sensation pain sensitivity in alcohol withdrawal, and depressed mood in patients was associated with lower pain tolerance (Jochum et al., 2010). In a secondary analysis of two large clinical trials of AUD, negative affect significantly mediated the association between pain and drinking

outcomes (Witkiewitz et al., 2010). In a study that tested the effects of experimentally induced pain on proximal antecedents of alcohol consumption as proxies for ad libitum alcohol consumption and investigated pain-induced negative affect as a mechanism of action, participants in the pain condition subsequently endorsed a greater urge and intention to drink, and these effects were mediated by pain-induced negative affect (Moskal et al., 2018). Thus, individuals with comorbid pain and AUD may drink to alleviate pain-related negative affect, and behavioral treatments that improve pain-coping skills may enhance pain-management abilities, subsequently reducing coping-motivated drinking (Moskal et al., 2018). These effects could explain alcohol misuse in individuals with persistent pain despite high-dose alcohol having significant potential negative consequences for long-term health. These findings also suggest that medications that address both physical and emotional pain may be useful for treating alcohol and drug addiction.

As with opioids, although acute alcohol administration in animal studies may confer analgesic effects, abstinence from chronic alcohol consumption produces hyperalgesia (Gatch et al., 1999; Gatch, 2009; Egli et al., 2012). For example, rodent models of alcohol withdrawal have reliably observed hyperalgesia in multiple pain assays (Gatch et al., 1999; Gatch, 2009; Egli et al., 2012). The neurobiological substrates for alcohol withdrawal-induced hyperalgesia have to date focused on a hyperkatifeia neurocircuitry interaction. Corticotropin-releasing factor in the amygdala, particularly in the CeA, is hypothesized to play an important role in affect-like responses that are associated with pain and pain modulation (Ji et al., 2013). In a model of arthritic pain, the blockade of CRF₁ receptors in the CeA inhibited both pain- and anxiety-like behaviors (Ji et al., 2007; Fu and Neugebauer, 2008). Hyperalgesia that is associated with alcohol withdrawal can be blunted by the blockade of CRF₁ receptors (Edwards et al., 2012b), and CRF receptor antagonists can blunt nociceptive hypersensitivity in a wide variety of pain assays in animals (Hummel et al., 2010).

Intraventricular and intranasal administration of melanocortin-4 receptor antagonists reduced thermal hyperalgesia in alcohol-dependent rats during withdrawal (Roltsch Hellard et al., 2017), and this effect appeared to be mediated by melanocortin-4 receptor signaling in the CeA (Avegno et al., 2018). Other molecular targets include PKC ϵ , in which the administration of an antisense oligodeoxynucleotide to PKC ϵ blocked alcohol withdrawal-induced hyperalgesia (Shumilla et al., 2005; Dina et al., 2006). Alcohol withdrawal-induced hyperalgesia was also attenuated by a histone deacetylase inhibitor, suggesting possible epigenetic mechanisms (Pradhan et al., 2019).

Another structure that impacts the mesolimbic dopamine circuit and is implicated in alcohol withdrawal-

induced hyperalgesia is the habenula (Zuo et al., 2019; see the *Within-System Neuroadaptations* section above). The lateral habenula projects to the VTA, and its activation is known to decrease activity in VTA dopamine neurons (Hikosaka, 2010; see the *Within-System Neuroadaptations* section above). Alcohol withdrawal-induced hyperalgesia and relapse-like alcohol consumption were reversed by the chemogenetic inhibition of lateral habenula neurons, the pharmacological activation of M-channels, and the overexpression of the M-channel subunit potassium voltage-gated channel subfamily KQT member 3 (Kang et al., 2019). Intralateral habenula infusion of serotonin 5-hydroxytryptamine-2 receptor antagonists or a serotonin reuptake blocker decreased nociceptive sensitivity and alcohol intake in alcohol-withdrawn rats (Zuo et al., 2019).

C. Pain and Animal Models of Addiction

Given the widespread use of drug self-administration techniques to assess the neurobiological substrates of addiction, some have argued that drug self-administration could be used in combination with chronic pain models as a tool to develop novel therapies with less abuse liability and potential for producing physical dependence (Martin and Ewan, 2008). However, although a few mouse studies have shown some increase in drinking with chronic pain in a neuropathic model of pain (González-Sepúlveda et al., 2016) and osteoarthritis model of pain (Butler et al., 2017), the data to date that show increases in the rewarding effects of opioids or increases in opioid self-administration after chronic pain have been limited (Ozaki et al., 2002; Narita et al., 2005; Martin et al., 2007; Hipólito et al., 2015). One possibility is that rodents must learn the association between the removal of withdrawal and drug taking, as has been demonstrated in studies of alcohol self-administration during withdrawal using chronic intermittent exposure to alcohol vapor (Roberts et al., 1996). This may be particularly difficult in an animal model, although clonidine was shown to maintain self-administration intrathecally in spinal nerve-ligated rats only over a range of doses that reversed tactile hypersensitivity in these animals (Martin et al., 2006).

Future studies of drug self-administration in laboratory animals in the presence of chronic pain may need to focus more on chronic emotional-like pain rather than physical pain (Edwards et al., 2020). Indeed, in a study of chronic inflammatory pain that was induced by a hind-paw injection of Complete Freund's Adjuvant, dynorphin expression increased in dynorphin-containing neurons in a discrete subregion of the NAc shell through a disinhibition mechanism, and pain increased κ -opioid receptor function (Massaly et al., 2019). Even more compelling, using a series of pharmacological, optogenetic, and chemogenetic approaches, the authors showed that both dynorphin-containing neurons and κ -opioid receptor

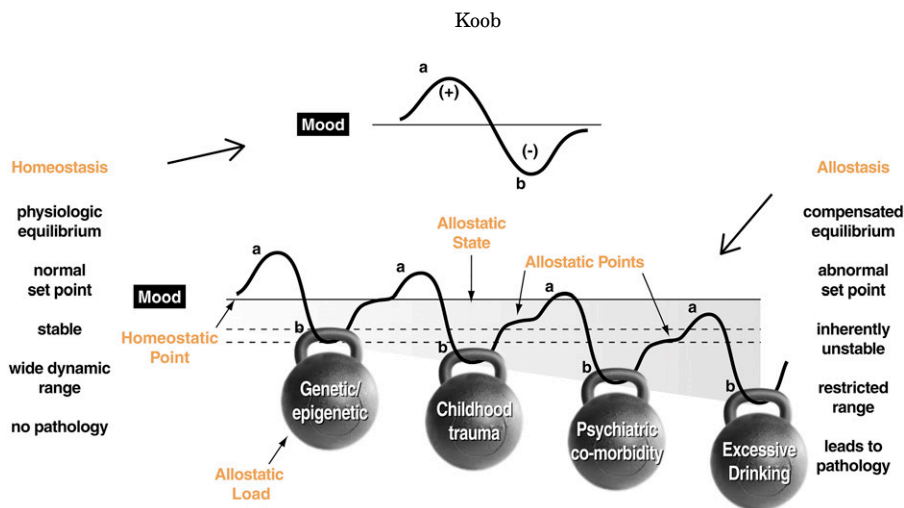


Fig. 6. Allostatic change in emotional state associated with the transition to addiction, illustrating the progression of dependence over time and the shift in underlying motivational mechanisms. From initial, positive-reinforcing, pleasurable effects of the drug, the addictive process progresses to a point at which it is maintained by negative-reinforcing relief from a negative emotional state. The figure shows a schematic description of the opponent process from an allostatic perspective. The a-process (a) represents a positive hedonic or positive mood state, and the b-process (b) represents the negative hedonic or negative mood state. The affective stimulus (state) has been argued to be the sum of both the a-process and b-process. An individual who experiences a positive hedonic mood state from a drug of abuse with sufficient time between readministering the drug is hypothesized to retain the normal set point. An appropriate counteradaptive opponent process (b-process) that balances the activational process (a-process) does not lead to an allostatic state. Changes in the affective stimulus (state) in an individual with repeated frequent drug use may represent a transition to an allostatic state in brain reward systems and, by extrapolation, a transition to addiction. Notice that the apparent b-process never returns to the original homeostatic level before drug taking begins again, thus creating a progressively greater allostatic state in the brain reward system. The counteradaptive opponent process (b-process) does not balance the activational process (a-process) but in fact shows residual hysteresis. Although these changes that are illustrated in the figure are exaggerated and condensed over time, the hypothesis is that even during post-detoxification (a period of protracted abstinence), the reward system still bears allostatic changes. Notice the allostatic loads to the system as described in the text include genetics/epigenetics, childhood trauma, psychiatric comorbidity, and excessive drug taking. The following definitions apply: allostasis, the process of achieving stability through change; allostatic state, a state of chronic deviation of the regulatory system from its normal (homeostatic) operating level; allostatic load, the cost to the brain and body of the deviation that accumulate over time, reflecting in many cases pathological states and the accumulation of damage. [Modified with permission from Koob and Le Moal (2001)].

activity in the NAc shell were necessary and sufficient to drive pain-induced negative affective states (Massaly et al., 2019).

IX. Individual Differences in Hyperkatifeia

A. Genetics

Finally, individual differences beg the question of selective vulnerability in individuals who enter the addiction cycle via the withdrawal/negative affect stage (Fig. 6). From a nosology perspective, the Addictions Neuroclinical Assessment framework allows the identification of individuals with phenotypes that signal dysregulation in this domain (Kwako et al., 2016). Genetic association studies that have focused on neurobiological substrates for hyperkatifeia (CRF and other brain stress system) are limited, but some are listed below.

An association was found between binge drinking and single-nucleotide polymorphisms (SNPs) of the CRF₁ receptor gene in adolescents and alcohol-dependent adults (Treutlein et al., 2006), one of which, rs1876831, is located on an intron that could potentially influence CRF₁ receptor gene transcription. In adolescents who were homozygous for the C allele of the rs1876831 SNP of the CRF₁ receptor gene, a history of stress was associated with greater increases in future alcohol intake (Blomeyer et al., 2008; Schmid et al., 2010) and an earlier onset of drinking (Schmid et al., 2010). In individuals who were

already dependent, CRF₁ SNPs also predicted greater alcohol consumption (Treutlein et al., 2006). Polymorphisms of the CRF binding protein (CRHBP) gene have also been associated with the risk of both heroin addiction in African Americans (Levrant et al., 2014) and a higher risk of drinking and/or anxiety in subjects with AUD (Haass-Koffler et al., 2016). Polymorphisms of the genes that encode the human κ -opioid receptor (Yuferov et al., 2004; Gerra et al., 2007) and prodynorphin (Clarke et al., 2012) have also been associated with a higher risk for opioid addiction.

Studies have also linked NPY or NPY receptor polymorphisms to addiction. Associations were found between SNPs of the NPY Y2 receptor (NPY2R) gene and alcohol dependence, alcohol withdrawal symptoms, tobacco addiction, comorbid alcohol and cocaine dependence, and cocaine dependence (Wetherill et al., 2008; Okahisa et al., 2009; Mutschler et al., 2012; Bhaskar et al., 2013). A polymorphism of the oxytocin gene, rs6133010, was associated with alcohol dependence in a northern Chinese Han population (Yang et al., 2017). For further details of these polymorphisms and their associations with hyperkatifeia, see Koob and Mason (2016) and Spierling and Zorrilla (2017).

B. Development, Comorbidities, Epigenetics, and Hyperkatifeia

Adult AUD and substance use disorders are linked not only to genetics but also to life experiences, such as

adverse childhood events (Khoury et al., 2010; Mingione et al., 2012). For example, there is a cumulative effect of childhood trauma on the risk of substance dependence, in which for every unit increase in the number of types of violent crime/abuse experiences, the odds of a person developing dependence on alcohol, cocaine, and/or opioids almost doubled (Douglas et al., 2010; Fig. 6). Exposure to childhood trauma is a major risk factor for the development and maintenance of AUD (De Bellis, 2002) and predicts an earlier onset of heavy drinking (Waldrop et al., 2007; Enoch, 2011). Thus, adverse childhood events are associated with an increase in alcohol and substance misuse, and repeated adverse events may potentiate such effects. Early-onset adolescent exposure to alcohol, tobacco, and drugs of abuse also predicts later AUD and substance use disorder and alcohol- and drug-related problems (Grant et al., 2001; Englund et al., 2008; Enoch, 2011). When the prevalence of lifetime illicit or nonmedical drug use and dependence was estimated for each year of onset of drug use from the ages of 13 and <21 years, the early onset of drug use was a significant predictor of the subsequent development of drug abuse (Hingson et al., 2003). The lifetime prevalence of DSM-IV substance dependence among people who began using drugs under the age of 14 was 34% and dropped to 14% for those who began using at age 21 or older (Grant and Dawson, 1998).

There is also substantial comorbidity between substance use and other psychiatric disorders. A recent epidemiological study showed particularly high comorbidity between AUD and major depressive disorder and bipolar disorder and comorbidity with personality disorders and anxiety disorders (Grant et al., 2015). Alcohol misuse correlates with poor mental health and often precedes diagnoses of mental health conditions. Alcohol is commonly used in an effort to cope with symptoms, but in the end, it makes the prognosis worse, and comorbid mental health conditions complicate treatments for AUD (Mäkelä et al., 2015). Such comorbidity has been particularly linked to the neural substrates of the extended amygdala that mediate common elements of negative affect and hyperkatifeia (Centanni et al., 2019).

The role of environmental factors begs the question of mechanism and inevitably leads to epigenetics—namely, the way in which environmental factors or other mechanisms of the expression of heritable traits are modified without a change in the DNA sequence. One example of epigenetic modifications in the extended amygdala provides a molecular basis of how hyperkatifeia that is engaged by repeated alcohol use, genetic vulnerability, and alcohol exposure during crucial developmental periods interact. Acute alcohol exposure in rodents produces an anxiolytic-like response that is mediated at least partially by the inhibition of histone deacetylase, an increase in histone

acetylation, and an increase in the opening of chromatin (Pandey et al., 2008a). Such an opening of chromatin results in an increase in synaptic plasticity-related genes, such as BDNF, and an increase in activity-related cytoskeleton-associated protein and NPY in the CeA (Pandey et al., 2008a,b). However, with chronic alcohol exposure and subsequent withdrawal, all of these epigenetic activities are reversed, with decreases in histone acetylation through an increase in histone deacetylase activity and decreases in the expression of BDNF, activity-related cytoskeleton-associated protein, and NPY in CeA circuitry that produce anxiety-like responses (Pandey et al., 2008a,b). Adolescent exposure to alcohol also leads to a deficit in global and gene-specific histone acetylation in the amygdala that is associated with a decrease in the expression of several synaptic plasticity-associated genes and contributes to heightened anxiety-like responses and excessive alcohol intake (Pandey et al., 2015). Thus, one can envision that ongoing and future epigenetic studies may help us understand risk factors for addiction that are biologically embedded and identify windows of vulnerability, such as childhood adverse events, adolescent exposure, and genetics. Ultimately, such approaches will capitalize on existing neurocircuitry of addiction for prevention or intervention, the identification of epigenetic biomarkers of addiction risk, and the development of personalized approaches to treatment (Cecil et al., 2016).

X. The Case for Hyperkatifeia as a Target for Medications Development

A. Reward Dysregulation, Stress Surfeit, Pain, and Negative Reinforcement

The thesis outlined herein is that the knowledge of neuroadaptations that occur within the framework of the hyperkatifeia construct of the addiction cycle withdrawal/negative affect stage provides fertile ground for developing new treatments for AUD and OUD and, by extrapolation, other drugs of addiction. Significant hyperkatifeia is also associated with psychostimulant, tobacco, and cannabinoid addiction from the perspectives of phenotypes and neurocircuitry/neurotransmitter systems (Baker et al., 1987, 2004; Diana, 2011; Cook et al., 2015; Koob, 2015; Ashok et al., 2017). Acute withdrawal-induced hyperkatifeia that results from chronic and excessive opioid and alcohol 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. Alcohol and opioids act directly on neurotransmitter systems that are associated with incentive salience and reward pathways and indirectly via GABA and glutamate systems to activate reward pathways. With excessive use, these systems undergo neuroadaptations with

chronic drug exposure that lower reward function, increase stress function, and increase the negative affect component of pain, all of which contribute to the construct of 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 hyperkatifeia and hyperalgesia (Shurman et al., 2010; Koob, 2019).

From a negative-reinforcement perspective, in a study cited above, rats showed avoidance of the cues that were paired with a hypothesized negative emotional state of precipitated opioid withdrawal, and this conditioned avoidance was blocked by a direct intracerebral injection of a peptide CRF antagonist in the CeA (Heinrichs et al., 1995). More recently, also as noted above, optogenetically shutting off CRF neurons in the CeA selectively suppressed alcohol-dependent drinking, but only in dependent animals (de Guglielmo et al., 2019). Thus, CRF in the extended amygdala may play an important role in the development of hyperkatifeia that drives compulsive-like drug seeking that is associated with opioids and alcohol via a negative-reinforcement process (Koob, 2019). Medications that have been developed to reverse the neurochemical changes outlined above would be hypothesized to be effective subjects when hyperkatifeia motivates drug seeking.

B. Negative Results

Despite the overwhelming evidence that CRF₁ receptor antagonists block hyperkatifeia-like responses in rodents, there are limited data on the effects of CRF₁ receptor antagonists on addiction in humans. One study reported negative results with one dose of a CRF₁ receptor small-molecule antagonist in a human laboratory study in reversing stress-induced craving but some efficacy in reversing HPA axis dysregulation (Schwandt et al., 2016). This study had a small sample size, was limited to only female subjects, and explored only one dose (Schwandt et al., 2016). However, the data on HPA axis endpoints confirmed target engagement by the tested dose and imply a dissociation between observation of the predicted endocrine effect without the predicted behavioral effect. Additionally, no clinical studies to date have found efficacy of CRF₁ receptor antagonists for the treatment of other stress-related psychiatric disorders, such as major depression, generalized anxiety disorder, social anxiety, or post-traumatic stress disorder (Griebel and Holsboer, 2012; Dunlop et al., 2017). No double-blind treatment study of alcohol or opioid addiction has been conducted. The reason for such treatment failures is largely unknown, but several possibilities include issues about the brain penetrance and receptor occupancy of small nonpeptide CRF₁ receptor antagonists and the need for circumstances in which prostress-like CRF-CRF₁ circuits are dynamically activated, which would mean evaluating

the efficacy of CRF₁ receptor antagonists with regard to particular symptoms of psychiatric disorders, specific patient subgroups, or specific genetic vulnerabilities (Griebel and Holsboer, 2012; Spierling and Zorrilla, 2017).

Other negative results for the hyperkatifeia hypothesis have been reported based on behavioral procedures that reflect elements of compulsive-like responding for drugs. Studies did show that changes in choice responding in rhesus monkeys during extended opioid exposure and subsequent opioid withdrawal reflected an increase in the reinforcing strength of heroin in a manner that supports the hypothesis that negative reinforcement is a source of motivation (Negus and Banks, 2018). However, using this choice model, a study in rhesus monkeys failed to show positive effects with a CRF₁ receptor antagonist (although one of three monkeys did respond) and a κ -opioid receptor antagonist, but it did show positive results with opioid substitution drugs (Negus and Rice, 2009). Obviously, species differences may be an important factor. In rodent studies, choice procedures are notoriously resistant to disruption, and a large proportion of rats continue to select a sweet solution (e.g., saccharin) rather than the drug even after the clear establishment of dependence (Lenoir et al., 2013; Ahmed, 2018). Altogether, these observations suggest that some measures of hyperkatifeia, such as the expression of stress-like responses in specific contexts and the escalation of drug taking in rodents, are sensitive to treatment with anti-hyperkatifeia agents, whereas other measures, such as choice procedures, may not be sensitive. Given that no single animal model is predictive of all aspects of the human condition, future studies might engage human laboratory studies that capture the phenotype that is exhibited by the activation of negative-reinforcement circuits, and any positive results could be back-translated to animal models.

C. Construct Validity

Construct validity refers to the explanatory power of a model but can also be defined in terms of the construct of functional equivalence, defined as “assessing how controlling variables influence outcome in the model and the target disorders” (Katz and Higgins, 2003). A validation of the present thesis may be derived not only from such observations as a compromised dopamine system or sensitized HPA system in animal models and humans but also from construct validity, in which the observations that treatments for hyperkatifeia in animal models are effective in OUD and AUD in the clinical setting. For OUD, all medically assisted treatments that interact with the μ -opioid receptor system (e.g., methadone and buprenorphine) reverse opioid withdrawal-induced hyperkatifeia in animal models and have established efficacy in treating opioid addiction (Mello and Mendelson, 1980). The opioid

substitution drug methadone transiently blocks opioid self-administration in rats and dogs but not in monkeys (Jones and Prada, 1977; Mello et al., 1983; Leri et al., 2004; Alizadeh et al., 2018), and buprenorphine decreases opioid self-administration in dependent rats and monkeys (Mello et al., 1983; Chen et al., 2006). However, one would expect a full agonist treatment to be transient because each subsequent treatment would contribute to future hyperkatifeia, which would consequently drive further tolerance and drug seeking (Masten et al., 1978). Methadone, buprenorphine, and other opioids are, however, substitution treatments, so they only transiently prevent hyperkatifeia while the drug is on board, but they do not reverse it. Several studies have shown that methadone and levo- α -acetyl-methadol substitute for morphine self-administration (Jones and Prada, 1977; Moreton et al., 1976; Young et al., 1978). Clearly, the opioid medication-assisted treatment of opioid addiction blocks hyperkatifeia in humans, but only while the drug is on board. Moreover, in the domain of stress dysregulation, the pioneering work of Kreek and colleagues showed that methadone-maintained individuals reestablish a homeostatic-like level of HPA activity (Kreek, 1973; Kreek and Koob, 1998).

For alcohol in animal models, alcohol self-administration in dependent rats prevented the manifestation of a withdrawal syndrome (Roberts et al., 1996) and reversed the hypodopaminergic effects of alcohol withdrawal (Weiss et al., 1996). With regard to non-alcohol-like drugs, acamprosate is one of three Food and Drug Administration-approved medications for the treatment of AUD that is widely prescribed worldwide, and it has an effect size (Mason, 2003; Maisel et al., 2013; Jonas et al., 2014) that is similar to selective serotonin reuptake inhibitors for depression (Schalkwijk et al., 2014). Acamprosate was developed from animal models of dependence-induced drinking (Le Magnen et al., 1987) and also blocked hyperkatifeia that was associated with alcohol withdrawal in rodent models (Cole et al., 2000). Acamprosate also blocked sleep disturbances that were associated with protracted abstinence in humans (Perney et al., 2012), again linking its therapeutic actions to the reversal of hyperkatifeia.

Gabapentin is an anticonvulsant Ca^{2+} channel blocker that increases GABAergic neurotransmission in the brain. Gabapentin decreased GABA inhibitory postsynaptic current amplitudes in the CeA in alcohol-dependent rats, suggesting the “normalization” of dependence-induced GABA dysregulation in the CeA. It also blocked hyperkatifeia-like responses in alcohol-dependent rats and blocked dependence-induced drinking in rodents (Roberto et al., 2008). In human studies, gabapentin blocked craving in a human laboratory study in non-treatment-seeking AUD subjects (Mason et al., 2009) and was shown to be an effective treatment

of AUD in a double-blind placebo-controlled clinical trial (Mason et al., 2014). Notably, gabapentin reversed sleep disturbances in AUD (Mason et al., 2014). A recent overall-negative study with a gabapentin prodrug has been reported, but the consensus was that the dose was low, and secondary analyses showed some efficacy in some subgroups of subjects in the study (Falk et al., 2019; Laska et al., 2020). Gabapentin is a widely used off-label drug for AUD and is currently on the Veterans Administration formulary for the treatment of AUD (https://www.veteranshealthlibrary.va.gov/Encyclopedia/142,41564_VA; accessed August 10, 2020).

Similarly, the chronic administration of mifepristone, a glucocorticoid and progesterone receptor antagonist, when administered systemically in rats during the course of alcohol vapor exposure, blocked the escalation of drinking during withdrawal that developed during dependence induction (Vendruscolo et al., 2012). In a human laboratory study of non-treatment-seeking subjects with AUD, mifepristone decreased alcohol-cued craving in the laboratory and reduced alcohol consumption during the 1-week treatment phase and 1-week post-treatment phase (Vendruscolo et al., 2015).

Additionally, α_2 -adrenergic receptor agonists block both somatic signs of withdrawal and anxiogenic-like responses to withdrawal in rodents. In humans, the α_2 -adrenergic receptor agonists clonidine and dexmedetomidine have been used extensively to treat acute alcohol withdrawal. It has been argued that α_2 -adrenergic receptor agonists safely and effectively reduce symptoms of sympathetic overdrive and concomitant medication use during the treatment of alcohol withdrawal (Muzyk et al., 2011).

D. Conditioning in Withdrawal and Protracted Abstinence

As discussed above, AUD and OUD are hypothesized to move to compulsive drug seeking via negative-reinforcement mechanisms because the use of these drugs 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 (Koob and Le Moal, 2001; Fig. 6). Negative affect networks have been hypothesized to be activated not only during withdrawal but also by conditioned predictors of withdrawal (e.g., drug cues) and unappetitive consequences (e.g., punishment and frustrative nonreward) or their conditioned cues (Baker et al., 1987). Here, as hypothesized by opponent process and allostatic theories, escape from and the avoidance of negative affect are powerful motives for compulsive drug use (Solomon, 1980; Koob and Le Moal, 2001; Baker et al., 2004; Evans and Cahill, 2016). Indeed, opioid addiction has been hypothesized to be sustained by a learned association between opioids

TABLE 2
Molecular and neurocircuitry targets for medications development to reverse hyperkatifeia of the withdrawal/negative affect stage for OUD and AUD

Target	Manipulation	Opioids	Alcohol
Within-system			
Dopamine	Dopamine receptor partial agonists	✓	✓
Opioid peptides	G protein modulators	✓	—
	CREB	✓	—
GABA/glutamate	cAMP/PKA modulators	—	✓
	CREB	—	✓
	GABA subunit receptor agonists	✓	✓
	Glutamate receptor antagonists	✓	✓
Between-system			
CRF	CRF ₁ receptor antagonists	✓	✓
Dynorphin	κ-Opioid receptor antagonists	✓	✓
Vasopressin	V _{1b} receptor antagonists	✓	✓
Norepinephrine	α ₁ -Adrenergic receptor antagonists	✓	✓
	α ₂ -Adrenergic receptor agonists	✓	✓
	β-Adrenergic receptor antagonists	✓	✓
Hypocretin	Hcrt-1 receptor antagonists	✓	✓
	Hcrt-2 receptor antagonists	✓	✓
Neuroimmune system	Neuroimmune modulators	✓	✓
	Tumor necrosis factor	✓	✓
Antistress modulators	Phosphodiesterase inhibitors	—	✓
	NPY	Y ₁ receptor agonists	✓
Nociceptin	Y ₂ receptor antagonists	✓	✓
	Nociceptin receptor agonists	✓	✓
Endocannabinoids	FAAH inhibitors	✓	✓
	MAGL inhibitors	✓	✓
Oxytocin	Oxytocin receptor agonists	✓	✓
Hyperalgesia/pain			
Glutamate	NMDA receptor antagonists	✓	✓
CRF	CRF ₁ receptor antagonists	✓	✓
Dynorphin	κ-Opioid receptor antagonists	✓	—
Melanocortin	Melanocortin receptor 4 antagonists	✓	✓
PKC	PKC _ε inhibitor	—	✓
	PKC _γ inhibitor	✓	—
Serotonin	5-HT _{2A} receptor antagonist	—	✓

PKA, protein kinase A; —, no data available; 5-HT_{2A}, 5-hydroxytryptamine-2A.

and relief from an existing dysphoric state, and this learned association is formed through negative reinforcement (Evans and Cahill, 2016). As noted above, the neurocircuitry that is activated during conditioned withdrawal shows a remarkable similarity to neurocircuitry that is associated with acute withdrawal (Carmack et al., 2019), consistent with the argument that stressful events during protracted abstinence can generalize to such a dysphoric state and produce recall that opioid drugs can relieve such a negative state (Koob, 2008; Evans and Cahill, 2016).

A neglected area in the domain of the development of medications and behavioral strategies is the identification of specific targets of the hyperkatifeia component of protracted abstinence. Studies have reported hypersensitivity to pain and discomfort with opioids that can last for over 1 year post-detoxification, and hypersensitivity to pain is linked to the misregulation of alcohol consumption as a coping response. Based on preclinical studies, medications and behavioral therapies that reset the HPA axis/CRF brain system and return other brain stress neurotransmitters and neuromodulators to homeostasis may be promising new targets for medication development. Table 2 outlines neurotransmitter and molecular targets for hyperkatifeia based on the neuropharmacological/neurocircuitry framework that

is outlined above. Although not exhaustive, this list may serve as a starting point to explore a relatively unexplored domain of treatment. Much of the clinical world recognizes the role of hyperkatifeia in driving addiction (Marlatt and Gordon, 1980; Khantzian, 1997, 2012, 2013), but most preclinical medication development efforts to date have focused on blocking or modulating drug reward. Medication development for the treatment of addiction must consider the dysregulation of pain and stress systems during acute withdrawal and long into recovery.

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