Published in final edited form as:
Pharmacopsychiatry. 2009 May ; 42(Suppl 1): S32–S41. doi:10.1055/s-0029-1216356.

Dynamics of Neuronal Circuits in Addiction: Reward, Antireward, and Emotional Memory

George F. Koob, Ph.D.
Committee on the Neurobiology of Addictive Disorders, The Scripps Research Institute, La Jolla California, USA

Abstract

Drug addiction is conceptualized as chronic, relapsing compulsive use of drugs with significant dysregulation of brain hedonic systems. Compulsive drug use is accompanied by decreased function of brain substrates for drug positive reinforcement and recruitment of brain substrates mediating the negative reinforcement of motivational withdrawal. The neural substrates for motivational withdrawal ("dark side" of addiction) involve recruitment of elements of the extended amygdala and the brain stress systems, including corticotropin-releasing factor and norepinephrine. These changes, combined with decreased reward function, are hypothesized to persist in the form of an allostatic state that forms a powerful motivational background for relapse. Relapse also involves a key role for the basolateral amygdala in mediating the motivational effects of stimuli previously paired with drug seeking and drug motivational withdrawal. The basolateral amygdala has a key role in mediating emotional memories in general. The hypothesis argued here is that brain stress systems activated by the motivational consequences of drug withdrawal can not only form the basis for negative reinforcement that drives drug seeking, but also potentiate associative mechanisms that perpetuate the emotional state and help drive the allostatic state of addiction.

Conceptual Framework

Drug addiction, also known as substance dependence, is a chronically relapsing disorder characterized by (1) compulsion to seek and take the drug, (2) loss of control in limiting intake, and (3) emergence of a negative emotional state (e.g., dysphoria, anxiety, irritability) when access to the drug is prevented (defined here as dependence). Although the emergence of a negative emotional state is not an established criterion of Substance Dependence defined by the *Diagnostic and Statistical Manual of Mental Disorder*, 4th edition (DSM-IV, [4]), it is a reflection of what has been termed motivational withdrawal. As such, it is one criterion in the DSM-IV and a widespread symptom of addiction [78]. Clinically, the occasional but limited use of an abusable drug is distinct from compulsive drug use and the emergence of chronic drug addiction. An important goal of current neurobiological research is to understand the neuropharmacological and neuroadaptive mechanisms within specific neurocircuits that mediate the transition from occasional, controlled drug use and the loss of behavioral control over drug seeking and drug taking that defines chronic addiction. Drug addiction has been conceptualized as a disorder that progresses from impulsivity to compulsivity in a collapsed cycle of addiction comprised of three stages: preoccupation/anticipation, binge intoxication, and withdrawal/negative affect [41,44,45].

Correspondence: George F. Koob, Ph.D., Committee on the Neurobiology of Addictive Disorders, The Scripps Research Institute, 10550 North Torrey Pines Road, SP30-2400, La Jolla, CA 92037, tel: 858-784-7062, fax: 858-784-7405, gkoob@scripps.edu.

Different theoretical perspectives, ranging from experimental and social psychology to neurobiology, can be superimposed on these three stages, which are conceptualized as feeding into each other, becoming more intense, and moving from positive to negative reinforcement. Positive reinforcement can be defined as a situation in which presentation of a stimulus increases the probability of a response, and negative reinforcement can be defined as a situation in which removal of a stimulus increases the probability of a response. Neural substrates for the positive reinforcing properties of drug taking and drug seeking have dominated the field of the neurobiology of addiction. However, more recent work has focused on the negative reinforcement mechanisms associated with removal of a negative emotional state associated with abstinence and protracted abstinence of the withdrawal/negative affect stage and the preoccupation/anticipation stage of the addiction cycle, respectively [34,37]. The conceptual framework is based on "motivational" aspects of addiction and an emphasis on the transition from drug use to addiction in which emergence of a negative emotional state (e.g., dysphoria, anxiety, irritability; termed the "dark side") emerges when access to the drug is prevented and provides a key motivational basis for the establishment of addiction and its perpetuation.

Two neurobiological circuits are proposed as key to the hedonic aspects of the motivation to seek drugs: the neurobiological circuitry involved in dysregulation of the positive-reinforcing properties of drugs of abuse (ventral striatal-pallidal-thalamic loops) and the neurobiological circuitry associated with recruitment of the negative-reinforcing properties of drugs of abuse (extended amygdala) (Figure 1). The present review will explore the neurobiological mechanisms of addiction that are involved in various stages of the addiction cycle, with a focus on the plasticity of neurocircuits associated with the transition from drug taking to drug addiction, the motivational effects of withdrawal and protracted abstinence, and the parallels with emotional memory that help sustain the addiction process.

Neurocircuitry of Positive Reinforcement that is Dysregulated with Drugs of Abuse

A brain reward system has long been hypothesized since the discovery of electrical brain stimulation reward or intracranial self-stimulation [64] and the discovery that animals will self-administer drugs without a history of dependence [81]. Brain stimulation reward involves widespread neurocircuitry in the brain, but the most sensitive sites defined by the lowest reward thresholds involve the trajectory of the medial forebrain bundle connecting the ventral tegmental area with the basal forebrain [64]. Although much emphasis was focused initially on the role of the ascending monoamine systems in the medial forebrain bundle, other nondopaminergic systems in the medial forebrain bundle clearly have a key role [27]. The interaction of drugs of abuse with the hypothesized reward system was emphasized by the observation that all drugs of abuse, when administered acutely, decrease brain stimulation reward thresholds [47].

The acute reinforcing effects of drugs of abuse are mediated by the activation of dopamine, serotonin, opioid peptides, and γ-aminobutyric acid (GABA) systems, either by direct actions in the basal forebrain (notably the nucleus accumbens and central nucleus of the amygdala) or by indirect actions in the ventral tegmental area [32,35,42,61]. Much evidence supports the hypothesis that the mesolimbic dopamine system is dramatically activated by psychostimulant drugs during limited-access self-administration. Although injections of all drugs of abuse increase extracellular dopamine levels in the nucleus accumbens measured by *in vivo* microdialysis [14], significantly less of an increase occurs in the nucleus accumbens for ethanol, nicotine, and opioids during self-administration [15,97]. Additionally, opioid and ethanol self-administration are unaffected by selective destruction of the mesolimbic dopamine system [16,60,66,69]. Serotonin systems, particularly those involving serotonin 5-HT_{1B} receptor activation in the nucleus accumbens, also have been implicated in the acute reinforcing

effects of psychostimulant drugs. Opioid peptide receptors in the ventral striatum, ventral tegmental area, and amygdala have been hypothesized to mediate the acute reinforcing effects of opioid and ethanol self-administration, largely based on the effects of opioid antagonists. Opioid antagonists injected into the nucleus accumbens and central nucleus of the amygdala are particularly effective in blocking opioid and ethanol self-administration [28,92]. GABAergic systems are activated pre- and postsynaptically in the amygdala by ethanol at intoxicating doses, and GABA antagonists injected into the amygdala block ethanol self-administration (for reviews, see [35,61]).

The neural substrates and neuropharmacological mechanisms for the negative motivational effects of drug withdrawal may involve disruption of the same neurochemical systems and neurocircuits implicated in the positive reinforcing effects of drugs of abuse, termed a within-system neuroadaptation. All drugs of abuse produce elevations in brain reward thresholds during acute withdrawal [43], and in animal models of the transition to addiction, increases in brain reward thresholds (i.e., decreased reward) temporally precede and highly correlate with the increase in drug intake with extended access [1,31] (Figure 2).

During such acute withdrawal, decreased activity of the mesocorticolimbic dopamine system occurs, as well as decreased functional activity in opioid peptide, GABA, and glutamate systems in the nucleus accumbens and amygdala. Repeated administration of psychostimulants produces an initial facilitation of dopamine and glutamate neurotransmission in the nucleus accumbens [91,96]. However, chronic administration leads to decreases in dopaminergic and glutamatergic neurotransmission in the nucleus accumbens during acute withdrawal [29,97], opposite responses of opioid receptor transduction mechanisms in the nucleus accumbens during opioid withdrawal [84], changes in GABAergic neurotransmission during alcohol withdrawal [25,71], and differential regional changes in nicotinic acetylcholine receptor function during nicotine withdrawal.

Human imaging studies of addicts during withdrawal or protracted abstinence have provided results that are consistent with animal studies. Dopamine D_2 receptors decrease (hypothesized to reflect hypodopaminergic functioning), and hypoactivity of the orbitofrontal-infralimbic cortex system occurs [95]. Decreases in reward neurotransmitter function have been hypothesized to contribute significantly to the negative motivational state associated with acute drug abstinence and may trigger long-term biochemical changes that contribute to the clinical syndrome of protracted abstinence and vulnerability to relapse.

Neurocircuitry of the Negative Reinforcement Associated with Chronic Use of Drugs of Abuse

The dark side of addiction [43] has been hypothesized to involve long-term, persistent plasticity in the activity of neural circuits mediating motivational systems that derive from recruitment of antireward systems that drive aversive states. The withdrawal/negative affect stage defined above consists of key motivational elements, such as chronic irritability, emotional pain, malaise, dysphoria, alexithymia, and loss of motivation for natural rewards, and is characterized in animals by increases in reward thresholds during withdrawal from all major drugs of abuse. Antireward is a concept based on the hypothesis that brain systems are in place to limit reward [41,45].

The neuroanatomical entity termed the extended amygdala may represent a neuroanatomical substrate for the negative effects on reward function defined as antireward. The extended amygdala is composed of the bed nucleus of the stria terminalis, the central nucleus of the amygdala, and a transition zone in the medial subregion of the nucleus accumbens (shell of the nucleus accumbens). Each of these regions has certain cytoarchitectural and circuitry

similarities. The central division of the extended amygdala receives numerous afferents from limbic structures, such as the basolateral amygdala and hippocampus, and sends efferents to the medial part of the ventral pallidum and the lateral hypothalamus, thus further defining the specific brain areas that interface classical limbic (emotional) structures with the extrapyramidal motor system [2].

The neurochemical systems within the extended amygdala that provide the neurochemical basis for antireward may be extensive and reflect a complex buffered system for maintaining hedonic homeostasis [41]. However, a neurochemical focal point for the antireward neurotransmitter systems are corticotropin-releasing factor (CRF), norepinephrine, and dynorphin. CRF, norepinephrine, and dynorphin are recruited during chronic drug exposure, producing aversive or stress-like states during withdrawal [36,45].

Different neurochemical systems involved in stress modulation may also be engaged within the neurocircuitry of the brain stress systems in an attempt to overcome the chronic presence of the perturbing drug and to restore normal function despite the presence of drug—termed a between-system neuroadaptation. The hypothalamic-pituitary-adrenal axis and the brain stress system, both mediated by CRF, are dysregulated by chronic administration of drugs of abuse, with a common response of elevated adrenocorticotropic hormone and corticosterone and extended amygdala CRF during acute withdrawal from all major drugs of abuse [43,48]. Acute withdrawal from drugs of abuse may also increase the release of norepinephrine in the bed nucleus of the stria terminalis and decrease functional levels of neuropeptide Y (NPY) in the amygdala [65,77].

For example, with alcohol, CRF may have a key role in mediating the neuroendocrine, autonomic, and behavioral responses to stress and anxiety that drive excessive drinking during dependence [40]. Regions of the extended amygdala (including the central nucleus of the amygdala) contain high amounts CRF terminals, cell bodies, and receptors and comprise part of the “extrahypothalamic” CRF-stress system [57]. Numerous studies have demonstrated the involvement of the extended amygdala CRF system in mediating the behavioral responses associated with fear and anxiety [40]. During ethanol withdrawal, extrahypothalamic CRF systems become hyperactive, with an increase in extracellular CRF within the central nucleus of the amygdala and bed nucleus of the stria terminalis of dependent rats [19,58,65,99], and this dysregulation of brain CRF systems is hypothesized to underlie both the enhanced anxiety-like behaviors and enhanced ethanol self-administration associated with ethanol withdrawal. Supporting this hypothesis, the subtype nonselective CRF receptor antagonists α-helical CRF_{9-41} and D-Phe CRF_{12-41} (intracerebroventricular administration) reduce both ethanol withdrawal-induced anxiety-like behavior and ethanol self-administration in dependent animals [5,93]. CRF receptor antagonists also attenuate anxiety-like behavior [68] as well as ethanol self-administration in ethanol-dependent rats [19]. Systemic administration of CRF_1 antagonists have similar actions on anxiety-like responses associated with acute and protracted abstinence and on ethanol self-administration during acute withdrawal and protracted abstinence [36]. These data suggest an important role for CRF, primarily within the central nucleus of the amygdala, in mediating the increased self-administration associated with dependence. Similar results have been observed with the increased intravenous self-administration associated with extended access to heroin [24], cocaine [85], and nicotine [21].

These results suggest not only a change in the function of neurotransmitters associated with the acute reinforcing effects of drugs of abuse during the development of dependence, such as decreases in dopamine, opioid peptides, serotonin, and GABA function, but also recruitment of the CRF system (Figure 3). Additional between-system neuroadaptations associated with motivational withdrawal include activation of the dynorphin/κ opioid system, activation of the

norepinephrine brain stress system, and dysregulation of the NPY brain antistress system [43]. Additionally, activation of the brain stress systems may contribute not only to the negative motivational state associated with acute abstinence, but also to the vulnerability to stressors observed during protracted abstinence in humans. Altogether these neurochemical studies (from addiction neurobiology) and neuroanatomical studies (from behavioral neuroscience) point to a rich substrate for the integration of emotional stimuli related to the "dark side of addiction," defined as the development of the aversive emotional state that drives the negative reinforcement of addiction.

Addiction and Antireward: Fear and Pain

Another compelling argument for the integration of the extended amygdala and emotional states comes from the extensive data from Le Doux and colleagues, whom have shown a convergence of the expression of the conditioned fear response in the central nucleus of the amygdala [50]. Studies on the neurocircuitry of fear conditioning show that auditory stimuli from the auditory cortex and pain from the somatosensory cortex converge on the lateral amygdala, which then projects to the central nucleus of the amygdala to elicit the various autonomic and behavioral responses to conditioned fear [50]. Perhaps even more intriguing is the hypothesis that the central nucleus of the amygdala is a key component of the neurocircuitry involved in emotional pain processing [67]. The spino (trigemino)-ponto-amygdaloid pathway that projects from the dorsal horn to the mesencephalic parabrachial area to the central nucleus of the amygdala has been hypothesized to be involved in emotional pain processing [7]. Under this framework, pain represents a break with homeostatic brain regulatory mechanisms that mediate nociception.

The conditions under which opioids block pain and restore homeostasis would be situations of pain in which the opioid relieves the pain and returns the subject to a homeostatic hedonic state; thus, opponent processes do not need to be engaged. However, if too much opioid is administered, either because of overdosing or pharmacokinetic variables, the body will react to that perturbation with the engagement of opponent processes. Hyperalgesia to opioids may occur in subjects in whom the opioid itself produces a break with homeostasis. Hyperalgesia is much less likely to occur when the opioid is in fact restoring homeostasis. Repeated engagement of opponent processes without time for the system to reestablish homeostasis will engage not only hyperalgesia but also the allostatic process described below. Such processes may be invoked by treating with too high a dose of an opioid, treating with an opioid when the dose overshoots the pain need because of pharmacokinetic issues, and/or treating a subject in whom in fact no pain exists (Koob GF, Shurman J, Gutstein H, unpublished results).

Withdrawal, Protracted Abstinence, and Allostasis

The development of the aversive emotional state that drives the negative reinforcement of addiction has been defined as the "dark side" of addiction [43,45] and is hypothesized to be the motivational withdrawal component of the hedonic dynamic known as opponent process when the initial drug effect is euphoria. The negative emotional state that comprises the withdrawal/negative affect stage defined above consists of key motivational elements, such as chronic irritability, emotional pain, malaise, dysphoria, alexithymia, and loss of motivation for natural rewards in humans, and is reflected in animal models by increases in anxiety-like behavior, dysphoric-like responses, and reward thresholds during withdrawal from all major drugs of abuse. As noted above, two processes are hypothesized to form the neurobiological basis for motivational withdrawal: loss of function in the reward systems (within-system neuroadaptation) and recruitment of the brain stress or antireward systems (between-system neuroadaptation) [38,41]. As dependence and withdrawal develop, brain stress systems such as CRF, norepinephrine, and dynorphin are recruited, producing aversive or stress-like states

[45]. At the same time, within the motivational circuits of the ventral striatum-extended amygdala, reward function decreases. The combination of decreases in reward neurotransmitter function and recruitment of antireward systems provides a powerful source of negative reinforcement that contributes to compulsive drug-seeking behavior and addiction.

The overall conceptual theme argued here is that drug addiction represents a break with homeostatic brain regulatory mechanisms that regulate the emotional state of the animal. However, the view that drug addiction represents a simple break with homeostasis is not sufficient to explain a number of key elements of addiction. Drug addiction, similar to other chronic physiological disorders such as high blood pressure, worsens over time, is subject to significant environmental influences, and leaves a residual neuroadaptive trace that allows rapid "re-addiction" even months and years after detoxification and abstinence. Relapse, or the return to drug abuse following periods of abstinence, is one of the principle characteristics of substance dependence on alcohol. The development of dependence has been suggested to play an important role in the maintenance of compulsive use and relapse following periods of abstinence.

In human alcoholics, numerous symptoms that can be characterized by negative emotional states persist long after acute physical withdrawal from ethanol. These symptoms, post-acute withdrawal, tend to be affective in nature and subacute and often precede relapse. Negative affective states, including negative emotions such as elements of anger, frustration, sadness, anxiety, and guilt, are the leading precipitants of relapse [53]. This state has been termed "protracted abstinence" and has been defined in humans who exhibit a Hamilton Depression rating ≥8 with the following three items consistently noted by subjects: depressed mood, anxiety, and guilt [53]. For example, fatigue and tension have been reported to persist up to 5 weeks post-withdrawal [3]. Anxiety has been shown to persist up to 9 months [73], and anxiety and depression have been shown to persist in up to 20-25% of alcoholics for up to 2 years post-withdrawal.

Animal work with alcohol dependence has shown that prior dependence can lower the "dependence threshold" such that previously dependent animals made dependent again display more severe physical withdrawal and anxiety-like symptoms than groups receiving alcohol for the first time [6,8]. This supports the hypothesis that alcohol experience and the development of dependence in particular can lead to relatively permanent alterations in responsiveness to alcohol. However, relapse often occurs even after acute withdrawal signs have subsided, suggesting that the neuropharmacological changes that occur during the development of dependence can persist beyond the final overt signs of withdrawal ("protracted motivational withdrawal syndrome"). Such protracted withdrawal has motivational significance. A history of dependence in rats and mice can produce a prolonged elevation in ethanol self-administration in daily 30 min sessions long after acute withdrawal and detoxification [70,72]. The increase in self-administration is also accompanied by increased behavioral responsivity to stressors and increased responsivity to CRF receptor antagonists [46]. These persistent alterations in ethanol self-administration and residual sensitivity to stressors can be arbitrarily defined as a state of "protracted abstinence." Protracted abstinence in the rat spans a period after acute physical withdrawal has disappeared when elevations in ethanol intake over baseline and increased behavioral responsivity to stress persist (2-8 weeks post-withdrawal from chronic ethanol). The persistent increase in drug self-administration during protracted abstinence has been hypothesized to involve an allostatic-like adjustment such that the set point for drug reward is elevated (hedonic tolerance) [42]. These characteristics of drug addiction imply more than simply homeostatic dysregulation of hedonic function and executive function, but rather a dynamic break with homeostasis of these systems that has been termed allostasis.

Allostasis, originally conceptualized to explain persistent morbidity of arousal and autonomic function, is defined as "stability through change" [86]. Allostasis involves a feed-forward mechanism rather than the negative feedback mechanisms of homeostasis, with continuous re-evaluation of need and continuous readjustment of all parameters toward new set points. Thus, the very physiological mechanism that allows rapid responses to environmental challenges becomes the engine of pathology if adequate time or resources are not available to shut off the response (e.g., the interaction between CRF, norepinephrine, and dynorphin in the basal forebrain that could lead to pathological anxiety and dysphoria) [33]. Allostatic mechanisms also have been hypothesized to be involved in maintaining a functioning brain emotional system that has relevance for the pathology of addiction [42]. Two components that are hypothesized to account for the negative emotional state associated with addiction are decreased function of brain reward transmitters and circuits and recruitment of the brain antireward or stress systems (Figure 3). Repeated challenges, such is the case with drugs of abuse, lead to attempts of the brain via molecular, cellular, and neurocircuitry changes to maintain stability but at a cost. The cost is a worsening of the negative emotional state during acute and protracted withdrawal and fits the definition of allostatic load [54]. For the drug addiction framework elaborated here, the residual negative emotional state is considered an *allostatic state* [42]. An intriguing hypothesis to be elaborated below is that the same emotional systems engaged for the "fight or flight" response may also participate in consolidation of addiction-related memories.

Addiction, Antireward, and Emotional Memory

Much evidence indicates that drugs, and more specifically psychostimulant drugs, can enhance cognitive performance. Such effects may include actions on perception, attention, arousal, and motivation, as well as on learning and memory. However, possibly more important for the neurobiology of addiction, drugs of abuse may alter the memory of the positive and negative reinforcing effects of drug actions. Even more intriguing is whether the memory of drug actions has any unique neural substrate that conveys a particular additional salience to such memories. The hypothesis to be considered here is that the neural substrates for the dark side of addiction overlap signficantly with the neural substrates of "emotional" memory.

Much evidence from both human and animal studies supports the hypothesis that drugs of abuse can convey conditioned positive reinforcing properties and conditioned negative reinforcing properties. Animal models of drug craving and relapse continue to be developed and refined, but to date have largely reflected secondary sources of reinforcement such as conditioned reinforcement [52,87]. A conditioned reinforcer can be defined as any neutral stimulus that acquires reinforcing properties through associations with a primary reinforcer. In a conditioned reinforcement paradigm involving drug self-administration, subjects are trained in an operant box containing two levers in which responses on one lever result in presentation of a brief stimulus followed by a drug injection (active lever), and responses on the other lever have no consequences throughout the experiment (inactive lever; [12,82]). Subsequently, the ability of the previously neutral, drug-paired stimulus to maintain responding in the absence of drug injections provides a measure of the reinforcing value of the stimulus. Second-order schedules of reinforcement can also be used as a measure of the conditioned reinforcing properties of drugs [22]. Work in primates and rats suggests that reliable responding for cocaine can be established with a second-order schedule [79]. Noncontingent drug administration or previously neutral stimuli paired with drug delivery can also can elicit drug seeking following extinction (reinstatement). Drugs or cues that have been paired with drug self-administration or predict drug self-administration can serve as discriminative stimuli when applied noncontingently after extinction and will induce reinstatement of drug seeking behavior [13,82,88]. The conditioned place preference paradigm also provides a measure of conditioned reinforcement, which is conceptually similar to the measures provided by the operant

paradigms. Several extensive reviews have been written on the place preference paradigm [10,89,90,94].

The neural substrates for such conditioned positive reinforcing effects of drugs of abuse, particularly the neural substrates of reinstatement, involve activation of glutamatergic pathways from the frontal cortex to the nucleus accumbens and from the basolateral amygdala to the central nucleus of the amygdala and nucleus accumbens (for reviews, see [17,30,83].

Conditioned opiate withdrawal has been observed clinically. Former opioid addicts often report symptoms similar to opioid abstinence when returning to environments associated with drug experiences [62]. In an experimental study of former heroin addicts maintained on methadone, opioid antagonist injections were repeatedly paired with a tone and peppermint smell [63]. Subsequent presentation of only the tone and odor elicited both the subjective effects of discomfort as well as the objective physical signs of withdrawal. Similar effects have been observed in both primate and rodent models. Primates and rodents that were allowed to self-administer opioids intravenously 23-24 h per day were challenged with an opioid antagonist and a previously neutral stimulus. The opioid antagonist elicited a compensatory-like increase in responding for the opioid. After repeated pairings, presentation of the conditioned stimulus alone resulted in a conditioned increase in responding for the opioid, similar to what was observed with the opioid antagonist alone [23,31]. The conditioned negative reinforcing effects of drugs of abuse have only been studied in the context of opioid drugs in animal models but involve the basolateral amygdala [80] and possibly associative mechanisms similar to the conditioned positive reinforcing properties of drugs of abuse. However, an emotional component to conditioned withdrawal may also recruit the brain stress circuitry implicated in the negative reinforcing properties of drug withdrawal and protracted abstinence. Indeed this “emotional memory” may contribute to the allostatic state hypothesized to perpetuate protracted withdrawal.

The neural substrates for emotional memory have been explored extensively and overlap with some of the neural substrates for conditioned positive and negative reinforcement associated with drugs of abuse. The neural substrates for emotional memory also form an intriguing neuropharmacological parallel with the neural substrates associated with the negative emotional states associated with abstinence in drug dependence. Emotional experiences are often associated with lasting and vivid memories that have also been described as “flashbulb memories” [11]. A key brain region that mediates the consolidation of such emotional memories is the basolateral amygdala and the convergence of stress hormones and other neuromodulatory noradrenergic systems systems contained therein [55,56]. In a series of elegant studies by McGaugh, Roosendal, and colleagues, the basolateral amygdala was shown to mediate the memory-modulating effects of adrenal stress hormones, with a key role for noradrenergic activation. The basolateral system modulates consolidation of many different kinds of information. In human studies, the degree of activation of the amgydala by emotional arousal correlates highly with subsequent recall [9]. Additionally, as noted above, the basolateral amygdala has a key role in mediating conditioned positive and conditioned negative reinforcement associated with drugs of abuse.

The role of noradrenergic mechanisms in enhancing memory consolidation was established in a series of studies with injections of noradrenergic agonists and antagonists into the basolateral amygdala. Norepinephrine or noradrenergic agonists injected directly into the basolateral amygdala immediately post-training facilitated the memory of emotionally arousing training tasks such as inhibitory avoidance [18], contextual fear conditioning [49], a water maze spatial task [26], and an object recognition task [74]. Post-training injections of β-noradrenergic antagonists had the opposite effect of impairing consolidation of memory of emotionally arousing tasks [20,26,59]. Adrenal hormones also facilitated consolidation of emotionally

arousing tasks via interactions with noradrenergic mechanisms in the basolateral amygdala [75]. Particularly germane to the present thesis, activation of CRF in the basolateral amygdala via inhibition of the CRF-binding protein produced noradrenergic-dependent facilitation of memory consolidation [76]. These results suggest that CRF may play a selective role in consolidation of long-lasting memories of emotionally arousing experiences [76].

The integration of brain stress systems at two levels of the amygdala may provide a compelling basis for an overwhelming drive to seek drugs in dependent individuals. The basolateral amygdala has a major projection to the central nucleus of the amygala. Classically, in fear conditioning, associative processes have been localized to the basolateral amygdala, and the expression of fear has been localized to the output of the amygdala: the central nucleus of the amygdala. Thus, activation of CRF and norepinephrine systems in both the central nucleus of the amygdala and basolateral amygdala may influence two separate domains that may combine to potentiate each domain: the negative emotional state of acute withdrawal and protracted abstinence and the consolidation of memories of emotionally arousing experiences (Figure 4). For example, the central nucleus of the amygdala is well documented to output to brain regions implicated in emotional expression, such as the hypothalamus and brain stem. Conversely, the basolateral amygdala is hypothesized to mediate consolidation of memories of emotionally arousing experiences via the nucleus accumbens, caudate nucleus, hippocampus, and entorhinal cortex [56]. In fear conditioning, two competing models of information processing within the amygdala have been hypothesized to be engaged during learning. In the serial model, information about the conditioned stimulus and unconditioned stimulus enters and is associated with the BLA, and this information is then transmitted to the central nucleus of the amygdala for the fear expression. Alternatively, a parallel model proposes that the basolateral amygdala and central nucleus of the amygdala both perform associative functions [98]. Thus, hormonal, noradrenergic, and CRF systems may be hypothesized to be activated by the aversive consequences of drug withdrawal to form the basis for negative reinforcement that drives drug seeking and potentiate associative mechanisms that perpetuate the emotional state that helps drive the allostatic state of addiction.

Acknowledgments

The author would like to thank Michael Arends for his assistance with the preparation of this manuscript. Research was supported by National Institutes of Health grants AA06420 and AA08459 from the National Institute on Alcohol Abuse and Alcoholism, DA10072, DA04043, and DA04398 from the National Institute on Drug Abuse, and DK26741 from the National Institute of Diabetes and Digestive and Kidney Diseases. Research was also supported by the Pearson Center for Alcoholism and Addiction Research. This is publication number 19965 from The Scripps Research Institute.

References

1. Ahmed SH, Kenny PJ, Koob GF, Markou A. Neurobiological evidence for hedonic allostasis associated with escalating cocaine use. Nat Neurosci 2002;5:625–626. [PubMed: 12055635]
2. Alheid, GF.; De Olmos, JS.; Beltramino, CA. Amygdala and extended amygdala. In: Paxinos, G., editor. The rat nervous system. San Diego: Academic Press; 1995. p. 495-578.
3. Alling C, Balldin J, Bokstrom K, Gottfries CG, Karlsson I, Langstrom G. Studies on duration of a late recovery period after chronic abuse of ethanol: a cross-sectional study of biochemical and psychiatric indicators. Acta Psychiatr Scand 1982;66:384–397. [PubMed: 6129776]
4. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Vol. 4. Washington DC: American Psychiatric Press; 2000. text revision
5. Baldwin HA, Rassnick S, Rivier J, Koob GF, Britton KT. CRF antagonist reverses the “anxiogenic” response to ethanol withdrawal in the rat. Psychopharmacology 1991;103:227–232. [PubMed: 2027923]

6. Becker HC. Positive relationship between the number of prior ethanol withdrawal episodes and the severity of subsequent withdrawal seizures. Psychopharmacology 1994;116:26–32. [PubMed: 7862927]
7. Bester H, Menendez L, Besson JM, Bernard JF. Spino (trigemino) parabrachiohypothalamic pathway: electrophysiological evidence for an involvement in pain processes. J Neurophysiol 1995;73:568–585. [PubMed: 7760119]
8. Breese GR, Overstreet DH, Knapp DJ, Navarro M. Prior multiple ethanol withdrawals enhance stress-induced anxiety-like behavior: inhibition by CRF_1- and benzodiazepine-receptor antagonists and a 5-HT_{1a}-receptor agonist. Neuropsychopharmacology 2005;30:1662–1669. [PubMed: 15726114]
9. Cahill L, Haier RJ, Fallon J, Alkire MT, Tang C, Keator D, Wu J, McGaugh JL. Amygdala activity at encoding correlated with long-term, free recall of emotional information. Proc Natl Acad Sci USA 1996;93:8016–8021. [PubMed: 8755595]
10. Carr, GD.; Fibiger, HC.; Phillips, AG. Conditioned place preference as a measure of drug reward. In: Liebman, JM.; Cooper, SJ., editors. The neuropharmacological basis of reward. Vol. 1. New York: Oxford University Press; 1989. p. 264-319.series title: Topics in experimental psychopharmacology
11. Conway, MA. Flashbulb memories. Hillsdale NJ: Lawrence Erlbaum; 1995.
12. Davis WM, Smith SG. Role of conditioned reinforcers in the initiation, maintenance and extinction of drug-seeking behavior. Pavlovian J Biol Sci 1976;11:222–236.
13. Davis, WM.; Smith, SG. Conditioned reinforcement as a measure of the rewarding properties of drugs. In: Bozarth, MA., editor. Methods of assessing the reinforcing properties of abused drugs. New York: Springer-Verlag; 1987. p. 199-210.
14. Di Chiara G, Bassareo V, Fenu S, De Luca MA, Spina L, Cadoni C, Acquas E, Carboni E, Valentini V, Lecca D. Dopamine and drug addiction: the nucleus accumbens shell connection. Neuropharmacology 2004;47(suppl 1):227–241. [PubMed: 15464140]
15. Doyon WM, York JL, Diaz LM, Samson HH, Czachowski CL, Gonzales RA. Dopamine activity in the nucleus accumbens during consummatory phases of oral ethanol self-administration. Alcohol Clin Exp Res 2003;27:1573–1582. [PubMed: 14574227]
16. Dworkin SI, Guerin GF, Co C, Goeders NE, Smith JE. Lack of an effect of 6-hydroxydopamine lesions of the nucleus accumbens on intravenous morphine self-administration. Pharmacol Biochem Behav 1988;30:1051–1057. [PubMed: 3147458]
17. Everitt BJ, Wolf ME. Psychomotor stimulant addiction: a neural systems perspective. J Neurosci 2002;22:3312–3320. [PubMed: 11978805]erratum: 22(16): 1a
18. Ferry B, Roozendaal B, McGaugh JL. Involvement of alpha1-adrenoceptors in the basolateral amygdala in modulation of memory storage. Eur J Pharmacol 1999;372:9–16. [PubMed: 10374709]
19. Funk CK, O'Dell LE, Crawford EF, Koob GF. Corticotropin-releasing factor within the central nucleus of the amygdala mediates enhanced ethanol self-administration in withdrawn, ethanol-dependent rats. J Neurosci 2006;26:11324–11332. [PubMed: 17079660]
20. Gallagher M, Kapp BS, Musty RE, Driscoll PA. Memory formation: evidence for a specific neurochemical system in the amygdala. Science 1977;198:423–425. [PubMed: 20664]
21. George O, Ghozland S, Azar MR, Cottone P, Zorrilla EP, Parsons LH, O'Dell LE, Richardson HN, Koob GF. CRF-CRF1 system activation mediates withdrawal-induced increases in nicotine self-administration in nicotine-dependent rats. Proc Natl Acad Sci USA 2007;104:17198–17203. [PubMed: 17921249]
22. Goldberg, SR.; Gardner, ML. Second-order schedules: extended sequences of behavior controlled by brief environmental stimuli associated with drug self-administration. In: Thompson, T.; Johanson, CE., editors. Behavioral pharmacology of human drug dependence. Vol. 37. Rockville MD: National Institute on Drug Abuse; 1981. p. 241-270.series title: NIDA research monograph
23. Goldberg SR, Kelleher RT. Behavior controlled by scheduled injections of cocaine in squirrel and rhesus monkeys. J Exp Anal Behav 1976;25:93–104. [PubMed: 814192]
24. Greenwell TN, Funk CK, Cottone P, Richardson HN, Chen SA, Rice K, Lee MJ, Zorrilla EP, Koob GF. Corticotropin-releasing factor-1 receptor antagonists decrease heroin self-administration in long-, but not short-access rats. Addict Biol. 2009in press
25. Grobin AC, Matthews DB, Devaud LL, Morrow AL. The role of $GABA_A$ receptors in the acute and chronic effects of ethanol. Psychopharmacology 1998;139:2–19. [PubMed: 9768538]

26. Hatfield T, McGaugh JL. Norepinephrine infused into the basolateral amygdala posttraining enhances retention in a spatial water maze task. Neurobiol Learn Mem 1999;71:232–239. [PubMed: 10082642]
27. Hernandez G, Hamdani S, Rajabi H, Conover K, Stewart J, Arvanitogiannis A, Shizgal P. Prolonged rewarding stimulation of the rat medial forebrain bundle: neurochemical and behavioral consequences. Behav Neurosci 2006;120:888–904. [PubMed: 16893295]
28. Heyser CJ, Roberts AJ, Schulteis G, Koob GF. Central administration of an opiate antagonist decreases oral ethanol self-administration in rats. Alcohol Clin Exp Res 1999;23:1468–1476. [PubMed: 10512312]
29. Kalivas, PW.; McFarland, K.; Bowers, S.; Szumlinski, K.; Xi, ZX.; Baker, D. Glutamate transmission and addiction to cocaine. In: Moghaddam, B.; Wolf, ME., editors. Glutamate and disorders of cognition and motivation. Vol. 1003. New York: New York Academy of Sciences; 2003. p. 169-175.series title: Annals of the New York Academy of Sciences
30. Kalivas PW, O'Brien C. Drug addiction as a pathology of staged neuroplasticity. Neuropsychopharmacology 2008;33:166–180. [PubMed: 17805308]
31. Kenny PJ, Chen SA, Kitamura O, Markou A, Koob GF. Conditioned withdrawal drives heroin consumption and decreases reward sensitivity. J Neurosci 2006;26:5894–5900. [PubMed: 16738231]
32. Koob GF. Drugs of abuse: anatomy, pharmacology, and function of reward pathways. Trends Pharmacol Sci 1992;13:177–184. [PubMed: 1604710]
33. Koob GF. Corticotropin-releasing factor, norepinephrine and stress. Biol Psychiatry 1999;46:1167–1180. [PubMed: 10560023]
34. Koob, GF. Allostatic view of motivation: implications for psychopathology. In: Bevins, RA.; Bardo, MT., editors. Motivational factors in the etiology of drug abuse. Vol. 50. Lincoln NE: University of Nebraska Press; 2004. p. 1-18.series title: Nebraska Symposium on Motivation
35. Koob GF. The neurobiology of addiction: a neuroadaptational view relevant for diagnosis. Addiction 2006;101(suppl 1):23–30. [PubMed: 16930158]
36. Koob GF. A role for brain stress systems in addiction. Neuron 2008;59:11–34. [PubMed: 18614026]
37. Koob GF. Neurobiological substrates for the dark side of compulsivity in addiction. Neuropharmacology 2009;56(suppl 1):18–31. [PubMed: 18725236]
38. Koob GF, Bloom FE. Cellular and molecular mechanisms of drug dependence. Science 1988;242:715–723. [PubMed: 2903550]
39. Koob, GF.; Everitt, BJ.; Robbins, TW. Reward, motivation, and addiction. In: Squire, LG.; Berg, D.; Bloom, FE.; Du Lac, S.; Ghosh, A.; Spitzer, N., editors. Fundamental neuroscience. Vol. 3. Amsterdam: Academic Press; 2008. p. 987-1016.
40. Koob GF, Heinrichs SC. A role for corticotropin-releasing factor and urocortin in behavioral responses to stressors. Brain Res 1999;848:141–152. [PubMed: 10612706]
41. Koob GF, Le Moal M. Drug abuse: Hedonic homeostatic dysregulation. Science 1997;278:52–58. [PubMed: 9311926]
42. Koob GF, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology 2001;24:97–129. [PubMed: 11120394]
43. Koob GF, Le Moal M. Plasticity of reward neurocircuitry and the 'dark side' of drug addiction. Nat Neurosci 2005;8:1442–1444. [PubMed: 16251985]
44. Koob GF, Le Moal M. Neurobiological mechanisms for opponent motivational processes in addiction. Phil Trans Royal Society B Biol Sci 2008a;363:3113–3123.
45. Koob GF, Le Moal M. Addiction and the brain antireward system. Ann Rev Psychol 2008b;59:29–53. [PubMed: 18154498]
46. Koob GF, Zorrilla EP. Corticotropin-releasing factor-1 antagonists. Drug Discov Today Ther Strat. 2009submitted
47. Kornetsky C, Esposito RU. Euphorigenic drugs: Effects on the reward pathways of the brain. Fed Proc 1979;38:2473–2476. [PubMed: 488370]
48. Kreek MJ, Koob GF. Drug dependence: Stress and dysregulation of brain reward pathways. Drug Alcohol Depend 1998;51:23–47. [PubMed: 9716928]

49. LaLumiere RT, Buen TV, McGaugh JL. Post-training intra-basolateral amygdala infusions of norepinephrine enhance consolidation of memory for contextual fear conditioning. J Neurosci 2003;23:6754–6758. [PubMed: 12890768]
50. Le Doux JE, Iwata J, Cicchetti P, Reis DJ. Different projections of the central amygdaloid nucleus mediate autonomic and behavioral correlates of conditioned fear. J Neurosci 1988;8:2517–2529. [PubMed: 2854842]
51. Markou, A.; Koob, GF. Intracranial self-stimulation thresholds as a measure of reward. In: Sahgal, A., editor. Behavioural neuroscience: a practical approach. Vol. 2. Oxford: IRL Press; 1993. p. 93-115.
52. Markou A, Weiss F, Gold LH, Caine SB, Schulteis G, Koob GF. Animal models of drug craving. Psychopharmacology 1993;112:163–182. [PubMed: 7871016]
53. Mason BJ, Light JM, Escher T, Drobes DJ. Effect of positive and negative affective stimuli and beverage cues on measures of craving in non treatment-seeking alcoholics. Psychopharmacology 2008;200:141–150. [PubMed: 18604601]
54. McEwen BS. Allostasis and allostatic load: Implications for neuropsychopharmacology. Neuropsychopharmacology 2000;22:108–124. [PubMed: 10649824]
55. McGaugh JL. Memory consolidation and the amygdala: a systems perspective. Trends Neurosci 2002;25:456. [PubMed: 12183206]
56. McGaugh JL. The amygdala modulates the consolidation of memories of emotionally arousing experiences. Ann Rev Neurosci 2004;27:1–28. [PubMed: 15217324]
57. Merchenthaler I, Vigh S, Petrusz P, Schally AV. Immunocytochemical localization of corticotropin-releasing factor (CRF) in the rat brain. Am J Anat 1982;165:385–396. [PubMed: 6760710]
58. Merlo-Pich E, Lorang M, Yeganeh M, Rodriguez de Fonseca F, Raber J, Koob GF, Weiss F. Increase of extracellular corticotropin-releasing factor-like immunoreactivity levels in the amygdala of awake rats during restraint stress and ethanol withdrawal as measured by microdialysis. J Neurosci 1995;15:5439–5447. [PubMed: 7643193]
59. Miranda MI, LaLumiere RT, Buen TV, Bermudez-Rattoni F, McGaugh JL. Blockade of noradrenergic receptors in the basolateral amygdala impairs taste memory. Eur J Neurosci 2003;18:2605–2610. [PubMed: 14622162]
60. Myers RD. Anatomical “circuitry” in the brain mediating alcohol drinking revealed by THP-reactive sites in the limbic system. Alcohol 1990;7:449–459. [PubMed: 2222848]
61. Nestler EJ. Is there a common molecular pathway for addiction? Nat Neurosci 2005;8:1445–1449. [PubMed: 16251986]
62. O’Brien CP. Experimental analysis of conditioning factors in human narcotic addiction. Pharmacol Rev 1975;27:533–543. [PubMed: 1223916]
63. O’Brien CP, Testa J, O’Brien TJ, Brady JP, Wells B. Conditioned narcotic withdrawal in humans. Science 1977;195:1000–1002. [PubMed: 841320]
64. Olds J, Milner P. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. J Comp Physiol Psychol 1954;47:419–427. [PubMed: 13233369]
65. Olive MF, Koenig HN, Nannini MA, Hodge CW. Elevated extracellular CRF levels in the bed nucleus of the stria terminalis during ethanol withdrawal and reduction by subsequent ethanol intake. Pharmacol Biochem Behav 2002;72:213–220. [PubMed: 11900791]
66. Pettit HO, Ettenberg A, Bloom FE, Koob GF. Destruction of dopamine in the nucleus accumbens selectively attenuates cocaine but not heroin self-administration in rats. Psychopharmacology 1984;84:167–173. [PubMed: 6438676]
67. Price DD. Central neural mechanisms that interrelate sensory and affective dimensions of pain. Mol Interv 2002;2:392–403. [PubMed: 14993415]
68. Rassnick S, Heinrichs SC, Britton KT, Koob GF. Microinjection of a corticotropin-releasing factor antagonist into the central nucleus of the amygdala reverses anxiogenic-like effects of ethanol withdrawal. Brain Res 1993a;605:25–32. [PubMed: 8467387]
69. Rassnick S, Stinus L, Koob GF. The effects of 6-hydroxydopamine lesions of the nucleus accumbens and the mesolimbic dopamine system on oral self-administration of ethanol in the rat. Brain Res 1993b;623:16–24. [PubMed: 8221085]

70. Rimondini R, Arlinde C, Sommer W, Heilig M. Long-lasting increase in voluntary ethanol consumption and transcriptional regulation in the rat brain after intermittent exposure to alcohol. FASEB J 2002;16:27–35. [PubMed: 11772933]
71. Roberto M, Madamba SG, Stouffer DG, Parsons LH, Siggins GR. Increased GABA release in the central amygdala of ethanol-dependent rats. J Neurosci 2004;24:10159–10166. [PubMed: 15537886]
72. Roberts AJ, Heyser CJ, Cole M, Griffin P, Koob GF. Excessive ethanol drinking following a history of dependence: animal model of allostasis. Neuropsychopharmacology 2000;22:581–594. [PubMed: 10788758]
73. Roelofs SM. Hyperventilation, anxiety, craving for alcohol: a subacute alcohol withdrawal syndrome. Alcohol 1985;2:501–505. [PubMed: 4026971]
74. Roozendaal B, Castello NA, Vedana G, Barsegyan A, McGaugh JL. Noradrenergic activation of the basolateral amygdala modulates consolidation of object recognition memory. Neurobiol Learn Mem 2008a;90:576–579. [PubMed: 18657626]
75. Roozendaal B, Quirarte GL, McGaugh JL. Glucocorticoids interact with the basolateral amygdala β-adrenoceptor-cAMP/cAMP/PKA system in influencing memory consolidation. Eur J Neurosci 2002;15:553–560. [PubMed: 11876783]
76. Roozendaal B, Schelling G, McGaugh JL. Corticotropin-releasing factor in the basolateral amygdala enhances memory consolidation via an interaction with the β-adrenoceptor-cAMP pathway: dependence on glucocorticoid receptor activation. J Neurosci 2008b;28:6642–6651. [PubMed: 18579737]
77. Roy A, Pandey SC. The decreased cellular expression of neuropeptide Y protein in rat brain structures during ethanol withdrawal after chronic ethanol exposure. Alcohol Clin Exp Res 2002;26:796–803. [PubMed: 12068247]
78. Russell, MAH. What is dependence?. In: Edwards, G., editor. Drugs and drug dependence. Lexington MA: Lexington Books; 1976. p. 182-187.
79. Schindler CW, Panlilio LV, Goldberg SR. Second-order schedules of drug self-administration in animals. Psychopharmacology 2002;163:327–344. [PubMed: 12373434]
80. Schulteis G, Ahmed SH, Morse AC, Koob GF, Everitt BJ. Conditioning and opiate withdrawal: The amygdala links neutral stimuli with the agony of overcoming drug addiction. Nature 2000;405:1013–1014. [PubMed: 10890431]
81. Schuster CR, Thompson T. Self administration and behavioral dependence on drugs. Ann Rev Pharmacol Toxicol 1969;9:483–502.
82. Schuster CR, Woods JH. The conditioned reinforcing effects of stimuli associated with morphine reinforcement. Int JAddict 1968;3:223–230.
83. See, RE.; Fuchs, RA.; Ledford, CC.; McLaughlin, J. Drug addiction, relapse, and the amygdala. In: Shinnick-Gallagher, P.; Pitkanen, A.; Shekhar, A.; Cahill, L., editors. The amygdala in brain function: basic and clinical approaches. Vol. 985. New York: New York Academy of Sciences; 2003. p. 294-307.series title: Annals of the New York Academy of Sciences
84. Shaw-Lutchman TZ, Barrot M, Wallace T, Gilden L, Zachariou V, Impey S, Duman RS, Storm D, Nestler EJ. Regional and cellular mapping of cAMP response element-mediated transcription during naltrexone-precipitated morphine withdrawal. J Neurosci 2002;22:3663–3672. [PubMed: 11978842]
85. Specio SE, Wee S, O'Dell LE, Boutrel B, Zorrilla EP, Koob GF. CRF_1 receptor antagonists attenuate escalated cocaine self-administration in rats. Psychopharmacology 2008;196:473–482. [PubMed: 17965976]
86. Sterling, P.; Eyer, J. Allostasis: a new paradigm to explain arousal pathology. In: Fisher, S.; Reason, J., editors. Handbook of life stress, cognition and health. Chichester: John Wiley; 1988. p. 629-649.
87. Stewart, J. Conditioned stimulus control of the expression of sensitization of the behavioral activating effects of opiate and stimulant drugs. In: Gormezano, I.; Wasserman, EA., editors. Learning and memory: the behavioral and biological substrates. Hillsdale NJ: Lawrence Erlbaum; 1992. p. 129-151.
88. Stewart, J.; de Wit, H. Reinstatement of drug-taking behavior as a method of assessing incentive motivational properties of drugs. In: Bozarth, MA., editor. Methods of assessing the reinforcing properties of abused drugs. New York: Springer-Verlag; 1987. p. 211-227.

89. Stewart, J.; Eikelboom, R. Conditioned drug effects. In: Iversen, LI.; Iversen, SD.; Snyder, SH., editors. New directions in behavioral pharmacology. Vol. 19. New York: Plenum Press; 1987. p. 1-57.series title: Handbook of psychopharmacology

90. Swerdlow, NR.; Gilbert, D.; Koob, GF. Conditioned drug effects on spatial preference: critical evaluation. In: Boulton, AA.; Baker, GB.; Greenshaw, AJ., editors. Psychopharmacology. Vol. 13. Clifton NJ: Humana Press; 1989. p. 399-446.series title: Neuromethods

91. Ungless MA, Whistler JL, Malenka RC, Bonci A. Single cocaine exposure in vivo induces long-term potentiation in dopamine neurons. Nature 2001;411:583–387. [PubMed: 11385572]

92. Vaccarino FJ, Bloom FE, Koob GF. Blockade of nucleus accumbens opiate receptors attenuates intravenous heroin reward in the rat. Psychopharmacology 1985;86:37–42. [PubMed: 2991967]

93. Valdez GR, Koob GF. Allostasis and dysregulation of corticotropin-releasing factor and neuropeptide Y systems: implications for the development of alcoholism. Pharmacol Biochem Behav 2004;79:671–689. [PubMed: 15582675]

94. van der Kooy, D. Place conditioning: a simple and effective method for assessing the motivational properties of drugs. In: Bozarth, MA., editor. Methods of assessing the reinforcing properties of abused drugs. New York: Springer-Verlag; 1987. p. 229-240.

95. Volkow ND, Fowler JS, Wang GJ. The addicted human brain: insights from imaging studies. J Clin Invest 2003;111:1444–1451. [PubMed: 12750391]

96. Vorel SR, Ashby CR Jr, Paul M, Liu X, Hayes R, Hagan JJ, Middlemiss DN, Stemp G, Gardner EL. Dopamine D3 receptor antagonism inhibits cocaine-seeking and cocaine-enhanced brain reward in rats. J Neurosci 2002;22:9595–9603. [PubMed: 12417684]

97. Weiss F, Markou A, Lorang MT, Koob GF. Basal extracellular dopamine levels in the nucleus accumbens are decreased during cocaine withdrawal after unlimited-access self-administration. Brain Res 1992;593:314–318. [PubMed: 1450939]

98. Zimmerman JM, Rabinak CA, McLachlan IG, Maren S. The central nucleus of the amygdala is essential for acquiring and expressing conditional fear after overtraining. Learn Mem 2007;14:634–644. [PubMed: 17848503]

99. Zorrilla EP, Koob GF. The therapeutic potential of CRF_1 antagonists for anxiety. Expert Opin Investig Drugs 2004;13:799–828.

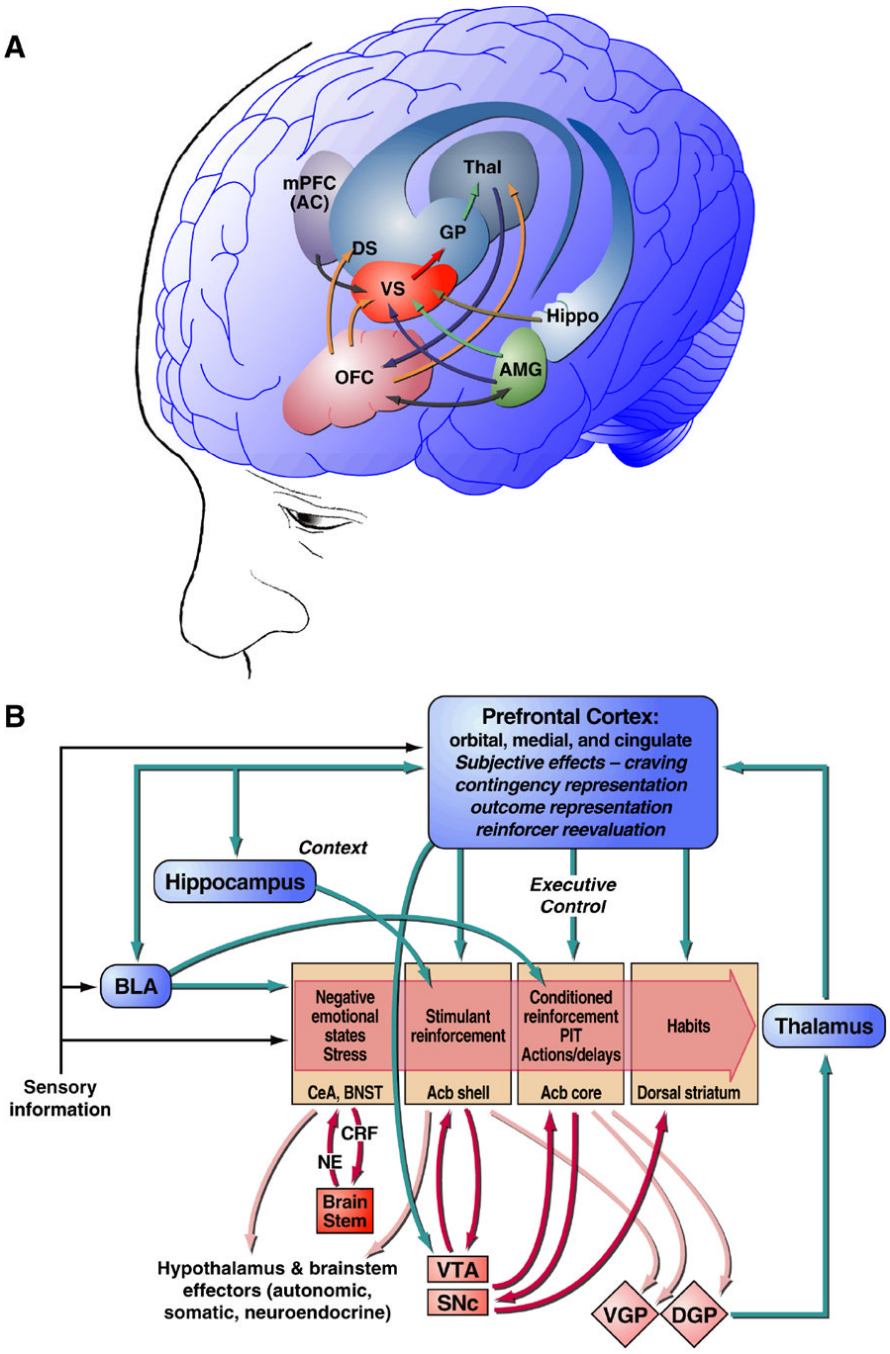

Figure 1.

Neural circuitry associated with the three stages of the addiction cycle, the drugs that are currently in use for the treatment focused on these stages, and the targets identified in this review relevant to these stages. *Binge/intoxication* stage: Reinforcing effects of drugs may engage associative mechanisms and reward neurotransmitters in the nucleus accumbens shell and core and then engage stimulus-response habits that depend on the dorsal striatum. *Withdrawal/negative affect* stage: The negative emotional state of withdrawal may engage the activation of the extended amygdala. The extended amygdala is composed of several basal forebrain structures, including the bed nucleus of the stria terminalis, central nucleus of the amygdala, and possibly the medial portion (or shell) of the nucleus accumbens. A major

neurotransmitter in the extended amygdala is corticotropin-releasing factor, projecting to the brainstem where noradrenergic neurons provide a major projection reciprocally to the extended amygdala. *Preoccupation/anticipation* ("craving") stage: This stage involves the processing of conditioned reinforcement in the basolateral amygdala and the processing of contextual information by the hippocampus. Executive control depends on the prefrontal cortex and includes representation of contingencies, representation of outcomes, and their value and subjective states (i.e., craving and, presumably, feelings) associated with drugs. The subjective effects, called drug craving in humans, involves activation of the orbital and anterior cingulate cortex and temporal lobe, including the amygdala, in functional imaging studies. For each stage of the addiction process, also shown in the diagram are the existing medications and future targets for addiction treatment particularly relevant to that stage. Green/blue arrows, glutamatergic projections; Orange arrows, dopaminergic projections; Pink arrows, GABAergic projections; Acb, nucleus accumbens; BLA, basolateral amygdala; VTA, ventral tegmental area; SNc, substantia nigra pars compacta. VGP, ventral globus pallidus; DGP, dorsal globus pallidus; BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; NE, norepinephrine; CRF, corticotropin-releasing factor; PIT, Pavlovian instrumental transfer. Modified with permission from [39].

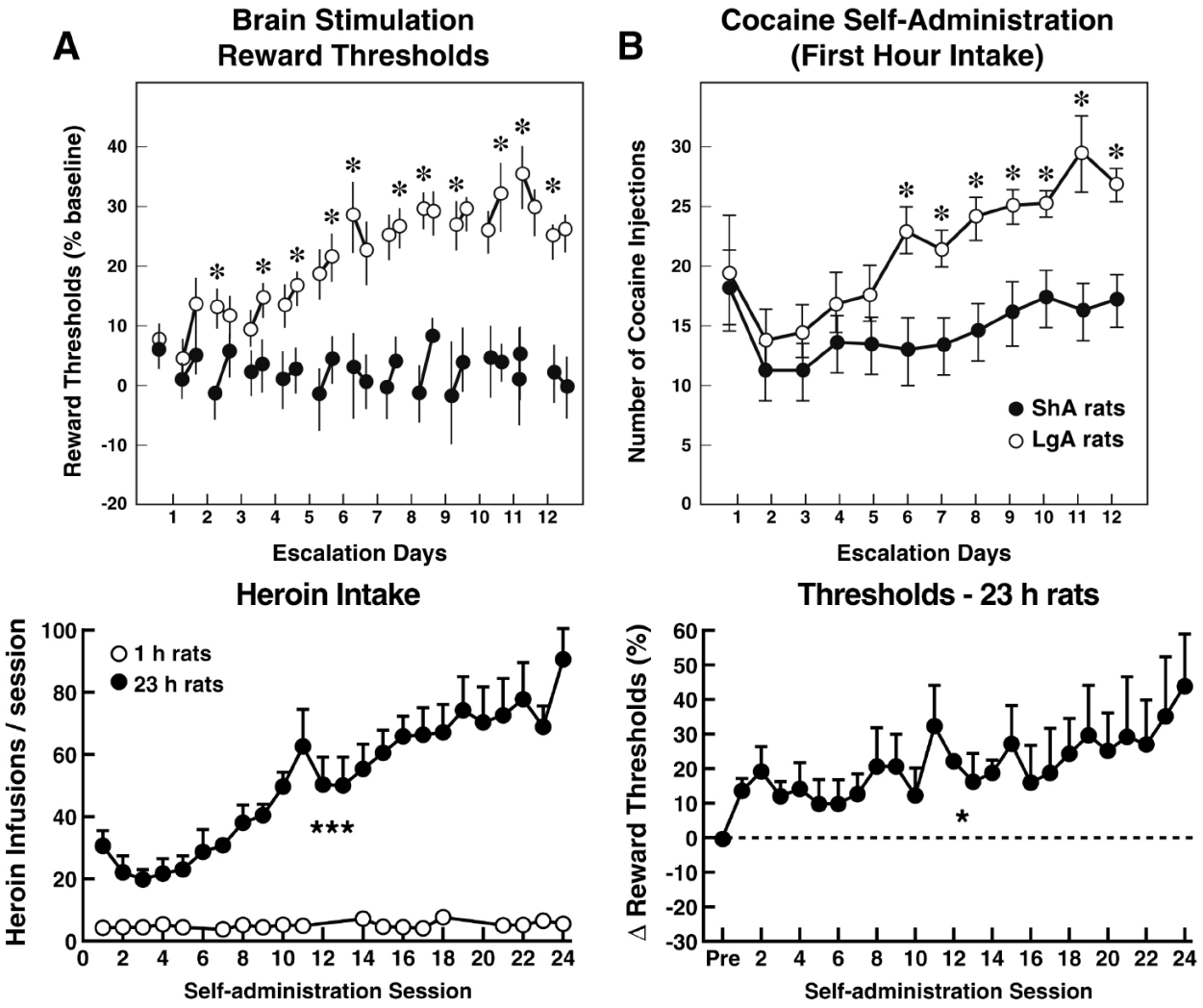

Figure 2.

(**A**) Relationship between elevations in intracranial self-stimulation (ICSS) reward thresholds and cocaine intake escalation. (**Left**) Percent change from baseline ICSS thresholds. (**Right**) Number of cocaine injections earned during the first hour of each session. Rats were first prepared with bipolar electrodes in either the right or left posterior lateral hypothalamus. One week post-surgery, they were trained to respond for electrical brain stimulation. Reward thresholds measured in microamps were assessed according to a modified discrete-trial current-threshold procedure [51]. During the screening phase, the 22 rats that were tested for self-administration were allowed to self-administer cocaine during only 1 h on a fixed-ratio 1 schedule of reinforcement, after which two balanced groups with the same weight, cocaine intake, and reward thresholds were formed. During the escalation phase, one group had access to cocaine self-administration for only 1 h per day (short-access, ShA) and the other group for 6 h per day (long-access, LgA). The remaining eight rats were exposed to the same experimental manipulations as the other rats, with the exception that they were not exposed to cocaine (not shown). Reward thresholds were measured in all rats two times per day, 3 h and 17-22 h after each daily self-administration session (ShA and LgA rats) or the control procedure (drug-naive rats; data not shown). Each reward threshold session lasted about 30 min. *$p < 0.05$, compared with drug-naive and/or ShA rats (tests of simple main effects). Taken with permission from [1]. (**B**) Unlimited daily access to heroin escalated heroin intake and decreased the excitability

of brain reward systems. Heroin intake (± SEM; 20 mg per infusion) in rats during limited (1 h) or unlimited (23 h) self-administration sessions. ***$p < 0.001$, main effect of access (1 or 23 h), two-way repeated-measures analysis of variance. Also presented is the percent change from baseline reward thresholds (± SEM) in 23 h rats. Reward thresholds, assessed immediately after each daily 23 h self-administration session, became progressively more elevated as exposure to self-administered heroin increased across sessions. *$p < 0.05$, main effect of heroin on reward thresholds (two-way repeated-measures analysis of variance). Taken with permission from [31].

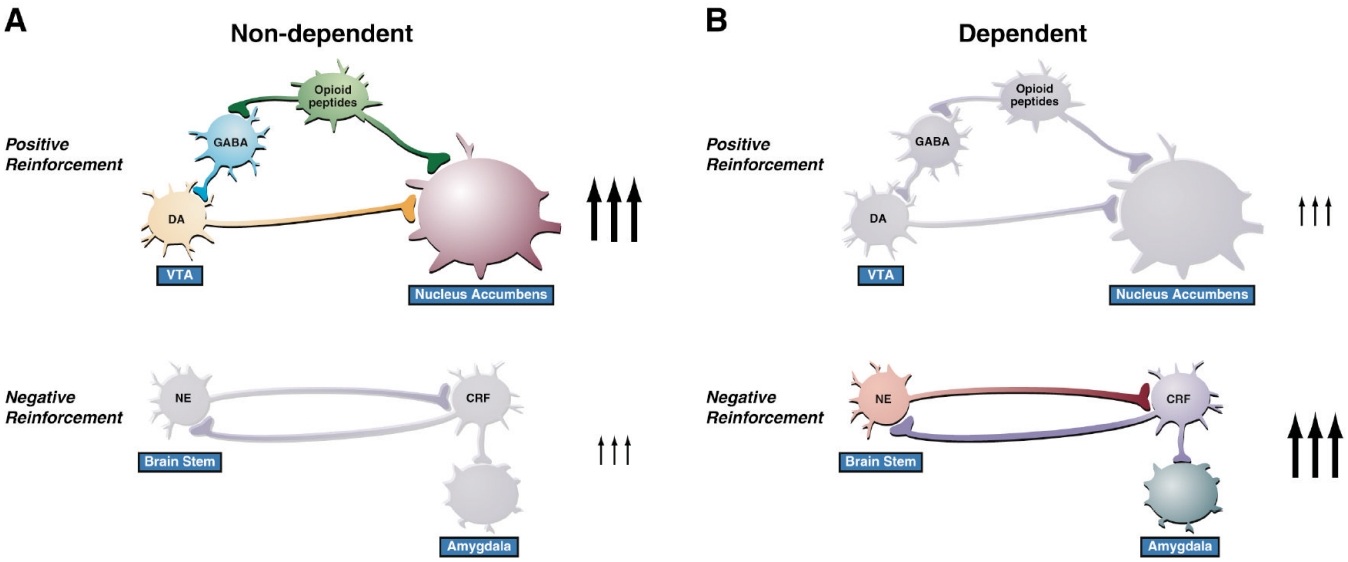

Figure 3.

Neurocircuitry associated with the acute positive reinforcing effects of drugs of abuse and the negative reinforcement of dependence and how it changes in the transition from nondependent drug taking to dependent drug taking. Key elements of the reward circuit are dopamine (DA) and opioid peptide neurons that intersect at both the ventral tegmental area (VTA) and nucleus accumbens and are activated during initial use and the early binge/intoxication stage. Key elements of the stress circuit are corticotropin-releasing factor (CRF) and noradrenergic (norepinephrine, NE) neurons that converge on γ-aminobutyric acid (GABA) interneurons in the central nucleus of the amygdala that are activated during the development of dependence. Taken with permission from [45].

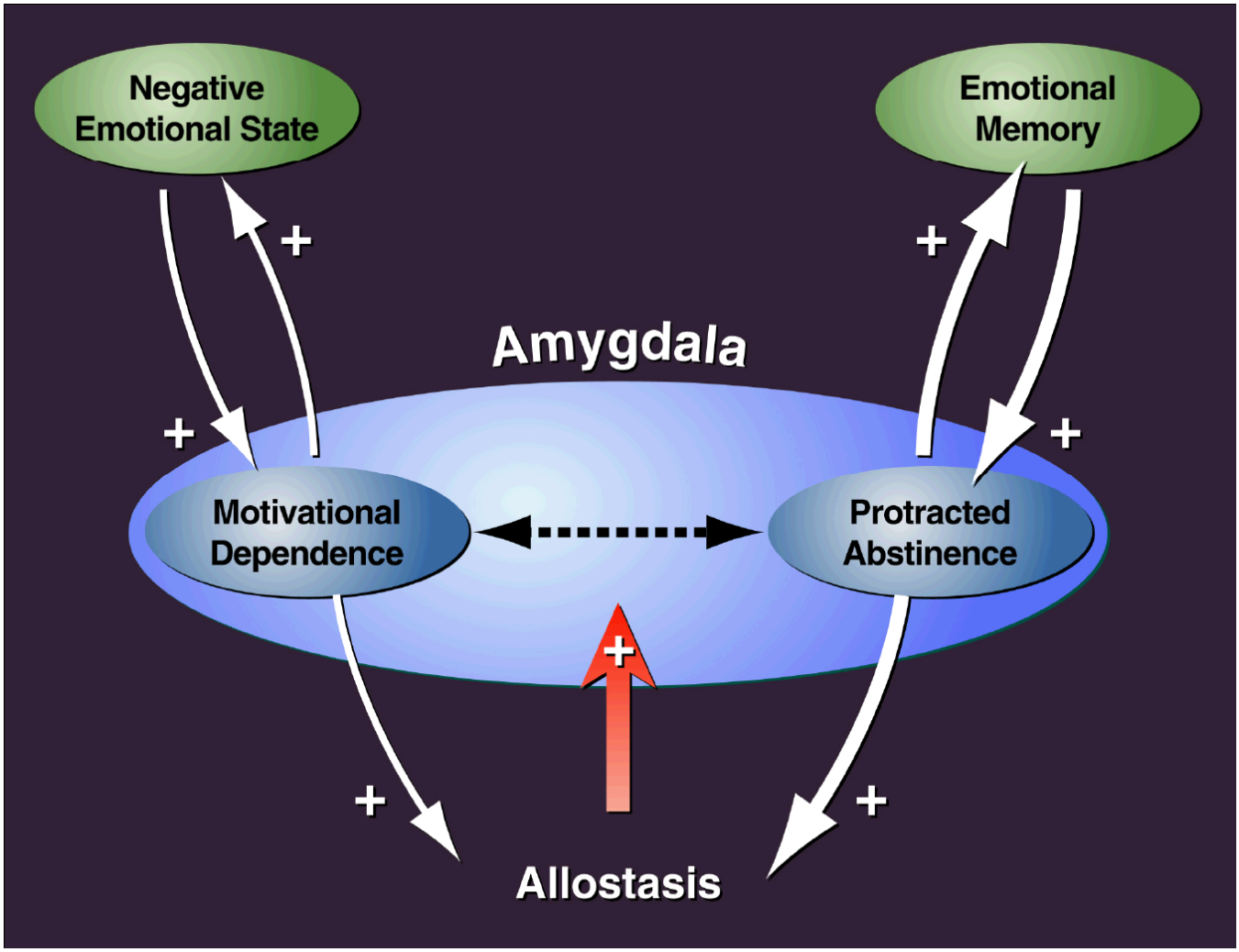

Figure 4.
Schematic diagram summarizing the hypothesized relationship between motivational dependence and emotional memory. Emotional states are well known to trigger relapse, and a mechanism may be a parallel action in which the negative emotional state of drug withdrawal and the emotional memories of protracted abstinence are hypothesized to combine to exacerbate relapse and the addiction process. The conceptual framework for such changes involves a break from emotional homeostasis, termed allostasis (stability through change), in neurobiological mechanisms in the extended amygdala.