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Brain stress systems in the amygdala and addiction

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Abstract

Dysregulation of the brain emotional systems that mediate arousal and stress is a key component of the pathophysiology of drug addiction. Drug addiction is a chronically relapsing disorder characterized by a compulsion to seek and take drugs and the development of dependence and manifestation of a negative emotional state when the drug is removed. Activation of brain stress systems is hypothesized to be a key element of the negative emotional state produced by dependence that drives drug-seeking through negative reinforcement mechanisms. The focus of the present review is on the role of two key brain arousal/stress systems in the development of dependence. Emphasis is placed on the neuropharmacological actions of corticotropin-releasing factor (CRF) and norepinephrine in extrahypothalamic systems in the extended amygdala, including the central nucleus of the amygdala, bed nucleus of the stria terminalis, and a transition area in the shell of the nucleus accumbens. Compelling evidence argues that these brain stress systems, a heretofore largely neglected component of dependence and addiction, play a key role in engaging the transition to dependence and maintaining dependence once it is initiated. Understanding the role of the brain stress and anti-stress systems in addiction not only provides insight into the neurobiology of the “dark side” of addiction but also provides insight into the organization and function of basic brain emotional circuitry that guides motivated behavior.

Keywords

Addiction; Neurobiology; Stress; Corticotropin-releasing factor; Norepinephrine; Extended amygdala

1. Conceptual framework: addiction, stress, motivational withdrawal, and negative reinforcement

Drug addiction is a chronically relapsing disorder characterized by compulsion to seek and take the drug and loss of control in limiting intake. A third key element included by some and particularly relevant to the present review is the emergence of a negative emotional state (e.g., dysphoria, anxiety, irritability) when access to the drug is prevented (defined here as dependence) (Koob and Le Moal, 1997, 2008). *Addiction* is used interchangeably in the present treatise with the term *Substance Dependence* (currently defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; American Psychiatric Association, 1994), but “dependence” with a lower-case “d” will be used to define the manifestation of a withdrawal syndrome when chronic drug administration is stopped (Koob and Le Moal, 2006). The occasional but limited use of a drug with the *potential* for abuse or dependence is distinct from the emergence of a chronic drug-dependent state.

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Stress can be defined as responses to demands (usually noxious) upon the body (Selye, 1936) that historically have been defined by various physiological changes that include activation of the hypothalamic-pituitary-adrenal (HPA) axis. This activation is characterized by the release of adrenal steroids triggered by the release of adrenocorticotrophic hormone (ACTH) from the pituitary. Adrenocorticotrophic hormone release is controlled, in turn, by the liberation of hypothalamic corticotropin-releasing factor (CRF) into the pituitary portal system of the median eminence. A definition of stress more compatible with its many manifestations in the organism is any alteration in psychological homeostatic processes (Burchfield, 1979). The construct of stress subsequently has been linked to the construct of arousal and as such may represent the extreme pathological continuum of overactivation of the body's normal activational or emotional systems (Hennessy and Levine, 1979; Pfaff, 2006).

Drug addiction has been conceptualized as a disorder that involves elements of both impulsivity and compulsivity (Fig. 1). *Impulsivity* can be defined as an individual engaging in rapid, unplanned reactions to internal and external stimuli without regard for the negative consequences of these reactions to the individual or others. *Compulsivity* can be defined as perseveration in responding in the face of adverse consequences or perseveration in the face of incorrect responses in choice situations. Both of these elements reflect increased motivation to seek drug and have face validity with the symptoms of Substance Dependence as outlined by the American Psychiatric Association.

Collapsing the cycles of impulsivity and compulsivity yields a composite addiction cycle comprising three stages—*preoccupation/anticipation*, *binge/intoxication*, and *withdrawal/negative affect*—in which impulsivity often dominates at the early stages and compulsivity dominates at terminal stages. As an individual moves from impulsivity to compulsivity, a shift occurs from positive reinforcement driving the motivated behavior to negative reinforcement driving the motivated behavior (Koob, 2004). Negative reinforcement can be defined as the process by which removal of an aversive stimulus (e.g., negative emotional state of drug withdrawal) increases the probability of a response (e.g., dependence-induced drug intake). These three stages are conceptualized as interacting with each other, becoming more intense, and ultimately leading to the pathological state known as addiction (Koob and Le Moal, 1997).

The thesis of this review is that a key element of the addiction process involves a profound activation of stress systems in the brain that interacts but is independent of hormonal stress systems. Such brain stress systems are further hypothesized to be localized to the circuitry of the central nucleus of the amygdala and to produce the negative emotional state that becomes the powerful motivation for drug-seeking associated with compulsive use. The focus of this paper will be on the role of CRF and norepinephrine in addiction as a central element of a complex system that maintains emotional homeostasis.

2. Hormonal stress systems: hypothalamic-pituitary-adrenal axis

The HPA axis is composed of three major structures: the paraventricular nucleus of the hypothalamus, the anterior lobe of the pituitary gland, and the adrenal gland (for review, see Smith and Vale, 2006). Neurosecretory neurons in the medial parvocellular subdivision of the paraventricular nucleus synthesize and release CRF into the portal blood vessels that enter the anterior pituitary gland. Binding of CRF to the CRF₁ receptor on pituitary corticotropes induces the release of ACTH into the systemic circulation. Adrenocorticotrophic hormone in turn stimulates glucocorticoid synthesis and secretion from the adrenal cortex. The HPA axis is finely tuned via negative feedback from circulating glucocorticoids that act on glucocorticoid receptors in two main brain areas: the paraventricular nucleus and the hippocampus. The hypophysiotropic neurons of the paraventricular nucleus of the hypothalamus are innervated

by numerous afferent projections, including from brainstem, other hypothalamic nuclei, and forebrain limbic structures.

3. Brain stress systems: corticotropin-releasing factor and norepinephrine

Corticotropin-releasing factor is a 41 amino acid polypeptide that controls hormonal, sympathetic, and behavioral responses to stressors. The discovery of other peptides with structural homology, notably the urocortin family (urocortins 1, 2, and 3), suggested broad neurotransmitter roles for the CRF systems in behavioral and autonomic responses to stress (Bale and Vale, 2004; Hauger et al., 2003). Substantial CRF-like immunoreactivity is present in the neocortex, extended amygdala, medial septum, hypothalamus, thalamus, cerebellum, and autonomic midbrain and hindbrain nuclei (Charlton et al., 1987; Swanson et al., 1983). The distribution of urocortin 1 projections overlaps with CRF but also has a different distribution, including visual, somatosensory, auditory, vestibular, motor, tegmental, parabrachial, pontine, median raphe, and cerebellar nuclei (Zorrilla and Koob, 2005). The CRF₁ receptor has abundant, widespread expression in the brain that overlaps significantly with the distribution of CRF and urocortin 1.

The endogenous selective CRF₂ agonists—the type 2 urocortins urocortin 2 (Reyes et al., 2001) and urocortin 3 (Lewis et al., 2001)—differ from urocortin 1 and CRF in their neuropharmacological profiles. Urocortins 2 and 3 show high functional selectivity for the CRF₂ receptor and have neuroanatomical distributions that are distinct from those of CRF and urocortin 1. Urocortins 2 and 3 are notably salient in hypothalamic nuclei that express the CRF₂ receptor, including the supraoptic nucleus, magnocellular neurons of the paraventricular nucleus, and forebrain, including the ventromedial hypothalamus, lateral septum, bed nucleus of the stria terminalis, and medial and cortical amygdala (Li et al., 2002). The CRF_{2(a)} receptor isoform is localized neuronally in brain areas distinct from those of the CRF/urocortin 1/CRF₁ receptor system, such as the ventromedial hypothalamic nucleus, paraventricular nucleus of the hypothalamus, supraoptic nucleus, nucleus tractus solitarius, area postrema, lateral septum, and bed nucleus of the stria terminalis.

Norepinephrine binds to three distinct families of receptors, α_1 , α_2 , and β -adrenergic, each of which has three receptor subtypes (Rohrer and Kobilka, 1998). The α_1 receptor family comprises α_{1a} , α_{1b} , and α_{1d} . Each subtype activates phospholipase C and is coupled to the inositol phosphate second messenger system via the G-protein G_q. A centrally active α_1 receptor antagonist used in drug dependence research is prazosin. The α_2 family comprises α_{2a} , α_{2b} , and α_{2c} . Each subtype inhibits adenylate cyclase via coupling to the inhibitory G-protein G_i. Two α_2 drugs commonly used in drug dependence research are the α_2 agonist clonidine and the α_2 antagonist yohimbine. The β -adrenergic receptor family comprises β_1 , β_2 , and β_3 . Each subtype activates adenylate cyclase via coupling to the G-protein G_s. Few β -adrenergic drugs have been explored in drug dependence research, with the exception of the β -adrenergic antagonist propranolol, presumably because of poor brain bioavailability.

Perhaps more intriguing is the pronounced interaction of central nervous system CRF systems and central nervous system norepinephrine systems. Conceptualized as a feed-forward system at multiple levels of the pons and basal forebrain, CRF activates norepinephrine, and norepinephrine in turn activates CRF (Koob, 1999). Much pharmacologic, physiologic, and anatomic evidence supports an important role for a CRF-norepinephrine interaction in the region of the locus coeruleus in response to stressors (Valentino et al., 1991, 1993; Van Bockstaele et al., 1998). However, norepinephrine also stimulates CRF release in the paraventricular nucleus of the hypothalamus (Alonso et al., 1986), bed nucleus of the stria terminalis, and central nucleus of the amygdala. Such feed-forward systems were hypothesized

to have powerful functional significance for mobilization of an organism for environmental challenge, but such a mechanism may be particularly vulnerable to pathology (Koob, 1999).

4. Extended amygdala: interface of stress and addiction

Recent neuroanatomical data and new functional observations have provided support for the hypothesis that the neuroanatomical substrates for many of the motivational effects of drug addiction may involve a common neural circuitry that forms a separate entity within the basal forebrain, termed the “extended amygdala” (Alheid and Heimer, 1988). The extended amygdala represents a macro-structure composed of several basal forebrain structures: the bed nucleus of the stria terminalis, central medial amygdala, and a transition zone in the posterior part of the medial nucleus accumbens (i.e., posterior shell) (Johnston, 1923; Heimer and Alheid, 1991). These structures have similarities in morphology, immunohistochemistry, and connectivity (Alheid and Heimer, 1988), and they receive afferent connections from limbic cortices, the hippocampus, basolateral amygdala, midbrain, and lateral hypothalamus. The efferent connections from this complex include the posterior medial (sublenticular) ventral pallidum, ventral tegmental area, various brainstem projections, and perhaps most intriguing from a functional point of view, a considerable projection to the lateral hypothalamus (Heimer and Alheid, 1991). Key elements of the extended amygdala include not only neurotransmitters associated with the positive reinforcing effects of drugs of abuse, but also major components of the brain stress systems associated with the negative reinforcement of dependence (Koob and Le Moal, 2005).

5. Pharmacological evidence for a role of CRF and norepinephrine in negative emotional states associated with drug withdrawal

A common response to acute withdrawal and protracted abstinence from all major drugs of abuse is the manifestation of anxiety-like or aversive-like responses. Animal models have revealed anxiety-like responses to all major drugs of abuse during acute withdrawal (Fig. 2). The dependent variable is often a passive response to a novel and/or aversive stimulus, such as the open field or elevated plus maze, or an active response to an aversive stimulus, such as defensive burying of an electrified metal probe. Withdrawal from repeated administration of cocaine produces an anxiogenic-like response in the elevated plus maze and defensive burying test, both of which are reversed by administration of CRF antagonists (Sarnyai et al., 1995; Basso et al., 1999). Precipitated withdrawal in opioid dependence also produces anxiety-like effects (Schulteis et al., 1998; Harris and Aston-Jones, 1993). Precipitated withdrawal from opioids also produces place aversions (Stinus et al., 1990). Here, in contrast to conditioned place preference, rats exposed to a particular environment while undergoing precipitated withdrawal to opioids spend less time in the withdrawal-paired environment when subsequently presented with a choice between that environment and an unpaired environment. Systemic administration of a CRF₁ receptor antagonist and direct intracerebral administration of a peptide CRF₁/CRF₂ antagonist also decreased opioid withdrawal-induced place aversions (Stinus et al., 2005; Heinrichs et al., 1995). Functional noradrenergic antagonists (i.e., β_1 antagonist and α_2 agonist) blocked opioid withdrawal-induced place aversion (Delfs et al., 2000).

Ethanol withdrawal produces anxiety-like behavior that is reversed by intracerebroventricular administration of CRF₁/CRF₂ peptidergic antagonists (Baldwin et al., 1991), intracerebral administration of a peptidergic CRF₁/CRF₂ antagonist into the amygdala (Rassnick et al., 1993), and systemic injections of small molecule CRF₁ antagonists (Knapp et al., 2004; Overstreet et al., 2004; Funk et al., 2007). CRF antagonists injected intracerebroventricularly or systemically also blocked the potentiated anxiety-like responses to stressors observed during protracted abstinence from chronic ethanol (Breese et al., 2005; Valdez et al., 2003).

Precipitated withdrawal from nicotine produces anxiety-like responses that are also reversed by CRF antagonists (Tucci et al., 2003; George et al., 2007). These effects of CRF antagonists have been localized to the central nucleus of the amygdala (Rassnick et al., 1993).

6. Neurochemical evidence for a role of CRF and norepinephrine in motivational effects of acute drug withdrawal

Chronic administration of drugs of abuse either via self-administration or passive administration increases extracellular CRF from the extended amygdala measured by *in vivo* microdialysis (Fig. 3). Continuous access to intravenous self-administration of cocaine for 12 h increased extracellular CRF in dialysates of the central nucleus of the amygdala (Richter and Weiss, 1999). Opioid withdrawal induced after chronic morphine pellet implantation in rats increased extracellular CRF in the central nucleus of the amygdala (Weiss et al., 2001). Acute nicotine administration and withdrawal from chronic nicotine elevated CRF extrahypothalamically in the basal forebrain (Matta et al., 1997). Increased CRF-like immunoreactivity has been observed in adult rats exposed to nicotine during adolescence and has been linked to an anxiety-like phenotype (Slawecki et al., 2005). Extracellular CRF has been shown to be increased in the central nucleus of the amygdala during precipitated withdrawal from chronic nicotine administered via minipump (George et al., 2007). 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 during acute withdrawal (2–12 h) (Funk et al., 2006; Merlo-Pich et al., 1995; Olive et al., 2002). Precipitated withdrawal from chronic cannabinoid exposure also increased CRF in the central nucleus of the amygdala (Rodriguez de Fonseca et al., 1997). Altogether these results show that all major drugs of abuse produce a dramatic increase in extracellular levels of CRF measured by *in vivo* microdialysis during acute withdrawal after chronic drug administration.

Norepinephrine has long been hypothesized to be activated during withdrawal from drugs of abuse. Opioids decreased firing of noradrenergic neurons in the locus coeruleus, and the locus coeruleus was activated during opioid withdrawal (Nestler et al., 1994). The chronic opioid effects on the locus coeruleus noradrenergic system have been shown in an extensive series of studies to involve upregulation of the cyclic adenosine monophosphate (cAMP) signaling pathway and increased expression of tyrosine hydroxylase (Nestler et al., 1994). Recent studies suggest that neurotrophic factors (e.g., brain-derived neurotrophic factor and neurotrophin-3 originating from non-noradrenergic neurons) may be essential for opiate-induced molecular neuroadaptations in the locus coeruleus noradrenergic pathway (Akbarian et al., 2001, 2002). Substantial evidence also suggests that in animals and humans, central noradrenergic systems are activated during acute withdrawal from ethanol and may have motivational significance. Alcohol withdrawal in humans is associated with activation of noradrenergic function in cerebrospinal fluid (Borg et al., 1981, 1985; Fujimoto et al., 1983). Chronic nicotine self-administration (23 h access) increased norepinephrine release in the paraventricular nucleus of the hypothalamus (Sharp and Matta, 1993; Fu et al., 2001) and the amygdala (Fu et al., 2003). However, during the late maintenance phase of 23 h access to nicotine, norepinephrine levels were no longer elevated in the amygdala, suggesting some desensitization/tolerance-like effect (Fu et al., 2003).

7. Pharmacological evidence of a role for CRF and norepinephrine in increased motivation for drug-seeking in withdrawal

The ability of neuropharmacological agents to block the anxiogenic-like and aversive-like motivational effects of drug withdrawal would predict motivational effects of these agents in

animal models of extended access to drugs. Animal models of extended access involve exposure of the animals to extended sessions of intravenous self-administration of drugs (cocaine, 6 h; heroin, 12 h; nicotine, 23 h) and passive vapor exposure (14 h on/12 h off) for ethanol. Animals are then tested for self-administration at various times into withdrawal, ranging from 2–6 h for ethanol to days with nicotine. CRF antagonists selectively blocked the increased self-administration of drugs associated with extended access to intravenous self-administration of cocaine (Specio et al., 2008), nicotine (George et al., 2007), and heroin (Greenwell et al., 2009a). CRF antagonists also blocked the increased self-administration of ethanol in dependent rats (Funk et al., 2007) (Table 1, Fig. 4).

Evidence for specific sites in the brain mediating these CRF antagonistic actions have centered on the central nucleus of the amygdala. Injections of CRF antagonists injected directly into the central nucleus of the amygdala blocked the aversive effects of precipitated opioid withdrawal (Heinrichs et al., 1995) and blocked the anxiogenic-like effects of ethanol withdrawal (Rassnick et al., 1993). Intracerebroventricular administration of the CRF₁/CRF₂ antagonist D-Phe CRF_{12–41} blocked the dependence-induced increase in ethanol self-administration during both acute withdrawal and protracted abstinence (Valdez et al., 2004; Rimondini et al., 2002). When administered directly into the central nucleus of the amygdala, lower doses of D-Phe CRF_{12–41} blocked ethanol self-administration in ethanol-dependent rats (Funk et al., 2006). A CRF₂ agonist, urocortin 3, injected into the central nucleus of the amygdala also blocked ethanol self-administration in ethanol-dependent rats (Funk et al., 2007), suggesting a reciprocal CRF₁/CRF₂ action in the central nucleus of the amygdala contributing to the mediation of withdrawal-induced drinking in the rat (Bale and Vale, 2004).

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 and suggest that CRF in the basal forebrain also may have an important role in the development of the aversive motivational effects that drive the increased drug-seeking associated with cocaine, heroin, and nicotine dependence.

Support also exists for a role of norepinephrine systems in ethanol self-administration and in the increased self-administration associated with dependence. Significant evidence supports an interaction between central nervous system norepinephrine and ethanol reinforcement and dependence. In a series of early studies, Amit and colleagues showed that voluntary ethanol consumption was decreased by both selective pharmacological and neurotoxin-specific disruption of noradrenergic function (Amit et al., 1977; Brown and Amit, 1977). Administration of selective dopamine β -hydroxylase inhibitors produced a marked suppression of alcohol intake in previously alcohol-preferring rats (Amit et al., 1977). Central administration of the neurotoxin 6-hydroxydopamine at doses that massively depleted norepinephrine neurons also blocked ethanol consumption in rats (Brown and Amit, 1977; Mason et al., 1979). Intragastric self-administration of ethanol also was blocked by dopamine β -hydroxylase inhibition (Davis et al., 1979). Selective depletion of norepinephrine in the medial prefrontal cortex of high ethanol-consuming C57BL/6J mice decreased ethanol consumption (Ventura et al., 2006). Mice with knockout of brain norepinephrine via knockout of the dopamine β -hydroxylase gene have a reduced preference for ethanol (Weinshenker et al., 2000).

In more recent studies, the α_1 noradrenergic receptor antagonist prazosin blocked the increased drug intake associated with ethanol dependence (Walker et al., 2008), extended access to cocaine (Wee et al., 2008), and extended access to opioids (Greenwell et al., 2009b) (Table 2, Fig. 5). Thus, converging data suggest that disruption of noradrenergic function blocks ethanol reinforcement, that noradrenergic neurotransmission is enhanced during drug withdrawal, and

that noradrenergic functional antagonists can block the increased drug self-administration associated with acute withdrawal.

8. Cellular basis in the central nucleus of the amygdala for motivational effects of CRF and norepinephrine interactions in dependence

Cellular studies using electrophysiological techniques have shown that γ -aminobutyric acid (GABA) activity within interneurons of the extended amygdala may reflect the negative emotional state of motivational significance for drug-seeking in dependence (Koob, 2008). CRF itself enhances GABA_A inhibitory postsynaptic potentials (IPSCs) in whole-cell recordings of the central nucleus of the amygdala and bed nucleus of the stria terminalis in brain slice preparations, and this effect is blocked by CRF₁ antagonists and is blocked in CRF₁ knockout mice (Nie et al., 2004; Kash and Winder, 2006). In the amygdala, CRF is localized within a subpopulation of GABAergic neurons in the bed nucleus of the stria terminalis and central nucleus of the amygdala different from those that colocalize enkephalin (Day et al., 1999).

For norepinephrine, evidence suggests a similar mechanism in the bed nucleus of the stria terminalis in which whole-cell recordings from slice preparations demonstrated that norepinephrine enhanced GABAergic neurotransmission. The noradrenergic effect appeared to be via the α_1 receptor (Dumont and Williams, 2004). If the data from the central nucleus of the amygdala and the bed nucleus of the stria terminalis are combined, then certain consistencies are evident: CRF and norepinephrine increase GABAergic activity, actions at the cellular level that are parallel to the behavioral effects described above with neuropharmacological studies.

Because GABAergic drugs are typically robust anxiolytics, the fact that anxiogenic-like neurotransmitters would activate GABAergic neurotransmission and anxiolytic-like neurotransmitters would depress GABAergic transmission in a brain region known to be involved in stress-related behavior may seem paradoxical. However, local GABAergic activity within the central nucleus of the amygdala may functionally influence neuronal responsivity of inhibitory central nucleus of the amygdala gating that regulates information flow through local intra-amygdaloidal circuits (i.e., by disinhibition of the central nucleus of the amygdala), leading to increased inhibition in downstream regions that mediate the behavioral response (Fig. 6).

Changes in neurotransmission in the brain stress systems with the development of dependence may reflect GABAergic neuron sensitization to the actions of the brain stress/anti-stress systems. The augmented GABA release produced by ethanol in the central nucleus of the amygdala increased even further in dependent animals, demonstrated both by electrophysiological and *in vivo* microdialysis measures (Roberto et al., 2004). The ethanol-induced enhancement of GABAergic IPSCs was blocked by CRF₁ antagonists (Nie et al., 2004; Roberto et al., 2004) and was not observed in CRF₁ knockout mice (Nie et al., 2004). Thus, chronic ethanol-induced changes in neuronal activity of GABA interneurons in the central nucleus of the amygdala can be linked at the cellular level to actions of CRF that reflect behavioral results in animal models of excessive drinking.

Given that most neurons in the central nucleus of the amygdala are GABAergic (Sun and Cassell, 1993), the mechanism mediating downstream targets associated with emotional states may reflect either inhibitory neurons with recurrent or feed-forward connections or inhibitory projection neurons to brainstem or downstream regions (e.g., bed nucleus of the stria terminalis). Thus, the central nucleus of the amygdala may be hypothesized to be a “gate” that regulates the flow of information through intra-amygdaloidal circuits. Moreover, the fine-

tuning of the GABAergic inhibitory system in the central nucleus of the amygdala may be a prerequisite for controlling both local and output neurons to downstream nuclei (Fig. 6).

9. Brain stress systems and addiction

Drug addiction, similar to other chronic physiological and psychological disorders such as high blood pressure, worsens over time, is subject to significant environmental influences (e.g., external stressors), and leaves a residual neural trace that allows rapid “re-addiction” even months and years after detoxification and abstinence. These characteristics of drug addiction have led to a reconsideration of drug addiction as more than simply a homeostatic dysregulation of emotional function, but rather as a dynamic break with homeostasis of these systems termed *allostasis* (Koob and Le Moal, 2001; Koob and Le Moal, 2008). The hypothesis outlined here is that drug addiction represents a break with homeostatic brain regulatory mechanisms that regulate the emotional state of the animal. *Allostasis* is defined as stability through change with an altered set point (Sterling and Eyer, 1988) and involves a feed-forward mechanism rather than the negative feedback mechanisms of homeostasis. A feed-forward mechanism has many advantages for meeting environmental demands. For example, in homeostasis, when increased need produces a signal, negative feedback can correct the need, but the time required may be long and the resources may not be available. Continuous reevaluation of need and continuous readjustment of all parameters toward new set points is hypothesized to occur in *allostasis*. This ability to mobilize resources quickly and to use feed-forward mechanisms may lead to an *allostatic state* if the systems do not have sufficient time to reestablish homeostasis. An *allostatic state* can be defined as a state of chronic deviation of the regulatory system from its normal (homeostatic) operating level.

The hypothesis outlined here is that brain stress systems respond rapidly to anticipated challenges to homeostasis (excessive drug taking) but are slow to habituate or do not readily shut off once engaged (Koob, 1999). Thus, the very physiological mechanism that allows a rapid and sustained response to environmental challenge becomes the engine of pathology if adequate time or resources are not available to shut off the response. The interaction between CRF and norepinephrine in the brainstem and basal forebrain, with contributions from other brain stress systems, could lead to the chronic negative emotional-like states associated with addiction (Koob and Le Moal, 2001).

Such negative emotional states are dramatically engaged during acute withdrawal from chronic drugs of abuse but are also chronically “sensitized” in two domains associated with relapse to drug-seeking. The first domain is the construct of protracted abstinence. Numerous symptoms characterized by negative emotional states persist long after acute withdrawal from drugs of abuse. Protracted alcohol abstinence, for example, has been extensively characterized in humans, in which fatigue, tension, and anxiety have been reported to persist from 5 weeks post-withdrawal to up to 9 months (Roelofs, 1985; Alling et al., 1982). These symptoms, post-acute withdrawal, tend to be affective in nature and subacute and often precede relapse (Hershon, 1977; Annis et al., 1998). A leading precipitant of relapse is negative affect (Zywiak et al., 1996; Lowman et al., 1996). In a secondary analyses of patients in a 12 week clinical trial with alcohol dependence and not meeting criteria for any other DSM-IV mood disorder, the association with relapse and a subclinical negative affective state was particularly strong (Mason et al., 1994). Animal work has shown that prior dependence lowers the “dependence threshold” such that previously dependent animals made dependent again display more severe physical withdrawal symptoms than groups receiving alcohol for the first time (Branchey et al., 1971; Baker and Cannon, 1979; Becker and Hale, 1989; Becker, 1994). A history of dependence in male Wistar rats can produce a prolonged elevation in ethanol self-administration after acute withdrawal and detoxification (Roberts et al., 2000; Rimondini et al., 2002, 2008; Sommer et al., 2008). The increase in self-administration is also accompanied

by increased behavioral responsivity to stressors and increased responsivity to antagonists of the brain CRF systems (Valdez et al., 2003, 2004; Gehlert et al., 2007; Sommer et al., 2008).

The second domain is the increased sensitivity to reinstatement of drug-seeking behavior shown in stress-induced reinstatement. A variety of stressors, both in humans and animals, will reinstate drug-seeking. In animals, typically the drug-seeking is extinguished by repeated exposure to the drug-seeking environment without drug and in operant situations repeated exposure to the operant response without drug. A stressor, such as footshock, social stress, or pharmacological stress (e.g., yohimbine), reinstates drug-seeking behavior. The neural circuitry of stress-induced reinstatement has significant overlap with that of acute motivational withdrawal described above (Shaham et al., 2003). A history of dependence increases stress-induced reinstatement (Liu and Weiss, 2002).

Repeated challenges (e.g., excessive use of drugs of abuse) lead to attempts of the brain via molecular, cellular, and neurocircuitry changes to maintain stability but at a cost. For the drug addiction framework elaborated here, the residual deviation from normal brain emotional regulation (i.e., the *allostatic state*) is fueled by numerous neurobiological changes, including decreased function of reward circuits, loss of executive control, facilitation of stimulus–response associations, and notably recruitment of the brain stress systems described above. The compromised brain stress systems are further hypothesized to contribute to the compulsivity of drug-seeking and drug-taking and relapse to drug-seeking and drug-taking known as addiction (Koob, 2009).

10. Summary and conclusions

Acute withdrawal from all major drugs of abuse increases reward thresholds, anxiety-like responses, and CRF in the amygdala, each of which have motivational significance. Compulsive drug use associated with dependence is mediated by not only loss of function of reward systems but also recruitment of brain stress systems such as CRF and norepinephrine in the extended amygdala. Brain arousal/stress systems in the extended amygdala may be key components of the negative emotional states that drive dependence on drugs of abuse and may overlap with the negative emotional components of other psychopathologies.

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Fig. 1. Schematic for the progression of alcohol dependence over time, illustrating the shift in underlying motivational mechanisms. From initial, positively reinforcing, pleasurable drug effects, the addictive process progresses over time to being maintained by negatively reinforcing relief from a negative emotional state. Data presented in this paper suggest that neuroadaptations encompassing a recruitment of extrahypothalamic CRF systems are key to this shift. [Modified with permission from Heilig and Koob, 2007.]

Fig. 2. Effects of a CRF antagonist on ethanol, nicotine, cocaine, and opioid motivational withdrawal. (A) Effect of intracerebroventricular administration of the CRF peptide antagonist α -helical CRF₉₋₄₁ in rats tested in the elevated plus maze after ethanol withdrawal. The black bar contains data from rats tested 8 h after withdrawal from control diet and 30 min after intracerebroventricular vehicle administration (control). The three hashed bars contain data from rats tested 8 h after withdrawal from ethanol diet and 30 min after intracerebroventricular α -helical CRF₉₋₄₁ administration (0, 5, and 25 μ g). * p <0.05, difference from control. † p <0.05, difference from group receiving intracerebroventricular vehicle after ethanol withdrawal. [Taken with permission from Baldwin et al., 1991.] (B) Effect of intracerebroventricular administration of the CRF antagonist D-Phe CRF₁₂₋₄₁ on the anxiogenic-like effect following chronic cocaine administration. Rats received chronic cocaine (20 mg/kg, i.p., for 14 days) or saline (1 ml/kg, i.p.). Animals then were tested in the defensive burying paradigm 48 h after the last injection. D-Phe CRF₁₂₋₄₁ (0, 0.04, 0.2, and 1.0 μ g/5 μ l) was administered intracerebroventricularly immediately after the animal touched the electrified probe and received the shock and 5 min before the testing session. Each group contained 10–14 animals. Data represent the total duration of burying behavior (mean $\pm$ SEM) expressed in seconds for all experimental groups. * p <0.05, compared with chronically saline-treated groups. ** p <0.01, compared with cocaine/vehicle group. [Taken with permission from Basso et al., 1999.] (C) Effects of the CRF₁ small molecule antagonist antalarmin on naloxone-precipitated place aversion conditioning in morphine-dependent rats. Antalarmin significantly reduced naloxone-

precipitated place aversion conditioning in morphine-dependent rats. Within each dose group treatment, Wilcoxon signed ranks test (D vs. D0), $*p<0.05$; NS, no significant place preference or place aversion with the Wilcoxon signed ranks test; between-group comparison, Mann–Whitney test (Delta D), $^{##}p<0.01$, compared with Morph-Nal 15 group.[Taken with permission from Stinus et al., 2005.] (D) Effects of a CRF₁ antagonist MPZP on precipitated nicotine withdrawal-induced anxiety-like behavior in nicotine-dependent rats. The CRF₁ antagonist blocked precipitated nicotine withdrawal-induced anxiety-like behavior in rats using the defensive burying test. Mecamylamine (1.5 mg/kg, i.p.) injection in nicotine-dependent rats increased the time spent burying ($*p<0.05$, compared with vehicle), an effect blocked by pretreatment with the CRF₁ antagonist (4 mg/kg, s.c., 1 h pretreatment). $n=7-9$ per group. $^{#}p<0.05$, compared with mecamylamine. [Taken with permission from George et al., 2007.]

Fig. 3.

(A) Effects of ethanol withdrawal on CRF-like immunoreactivity (CRF-L-IR) in the rat amygdala determined by microdialysis. Dialysate was collected over four 2 h periods regularly alternated with nonsampling 2 h periods. The four sampling periods corresponded to the basal collection (before removal of ethanol liquid diet), and 2–4 h, 6–8 h, and 10–12 h after withdrawal. Fractions were collected every 20 min. Data are expressed as mean $\pm$ SEM ($n=5$ per group). Analysis of variance confirmed significant differences between the two groups over time ($p<0.05$). [Taken with permission from Merlo-Pich et al., 1995.] (B) Mean ($\pm$ SEM) dialysate CRF concentrations collected from the central nucleus of the amygdala of rats during baseline, 12 h cocaine self-administration, and a subsequent 12 h withdrawal period (cocaine

group, $n=5$). The control group consisted of rats with the same history of cocaine self-administration training and drug exposure but not given access to cocaine on the test day ($n=6$). Data are expressed as percentages of basal CRF concentrations. Dialysates were collected over 2 h periods alternating with 1 h nonsampling periods shown by the timeline at the top. During cocaine self-administration, dialysate CRF concentrations in the cocaine group were decreased by about 25% compared with control animals. In contrast, termination of access to cocaine significantly increased CRF efflux that began approximately 5 h post-cocaine and reached about 400% of pre-session baseline levels at the end of the withdrawal session. $*p<0.05$, $**p<0.01$, $***p<0.001$, simple main effects after overall mixed-factorial analysis of variance. [Taken with permission from Richter and Weiss, 1999.] (C) Effects of cannabinoid CB₁ receptor antagonist SR 141716A (3 mg/kg) on CRF release from the central nucleus of the amygdala in rats pretreated for 14 days with the CB₁ receptor agonist HU-210 (100 mg/kg). Cannabinoid withdrawal induced by SR 141716A was associated with increased CRF release ($*p<0.005$, $n=5-8$). Vehicle injections did not alter CRF efflux ($n=5-7$). Data were standardized by transforming dialysate CRF concentrations into percentages of baseline values based on averages of the first four fractions. [Taken with permission from Rodriguez de Fonseca et al., 1997.] (D) Effects of morphine withdrawal on extracellular CRF in the central nucleus of the amygdala. Withdrawal was precipitated by administration of naltrexone (0.1 mg/kg) in rats prepared with chronic morphine pellet implants. [Taken with permission from Weiss et al., 2001.] (E) Effect of mecamylamine-precipitated (1.5 mg/kg, i.p.) nicotine withdrawal on extracellular levels of CRF-like immunoreactivity in the central nucleus of the amygdala measured by in vivo microdialysis in chronic nicotine pump-treated (nicotine-dependent, $n=7$) and chronic saline pump-treated (nondependent, $n=6$) rats. $*p<0.05$, compared with nondependent. [Taken with permission from George et al., 2007.]

Fig. 4.

Effects of small molecule CRF₁ receptor antagonists on drug self-administration in dependent rats (A) Effect of small molecule CRF₁ receptor antagonist MPZP on operant self-administration of alcohol (g/kg) in dependent and nondependent rats. Testing was conducted when dependent animals were in acute withdrawal (6–8 h after removal from ethanol vapor chambers). Dependent animals self-administered significantly more alcohol than nondependent animals. MPZP significantly reduced alcohol self-administration only in dependent animals. MPZP had no effect on alcohol self-administration in nondependent animals. * $p < 0.05$, compared with nondependent controls. # $p < 0.05$, compared with vehicle (0 mg/kg MPZP). Data are expressed as mean $\pm$ SEM ($n = 8$ per vapor treatment group). [Taken with permission from Richardson et al., 2008.] (B) Effect of MPZP on nicotine self-administration during the active period in rats given extended access to nicotine (* $p < 0.05$ vs. baseline, # $p < 0.05$ vs. post abstinence vehicle treatment, $n = 8$). [Taken with permission from George et al., 2007.] (C) Effect of MPZP on cocaine intake in short-access (ShA) and long-access (LgA) rats. MPZP dose-dependently reduced cocaine intake, achieving a maximal reduction of ~20%, with a greater effect in LgA compared with ShA rats. A main effect of Access (* $p < 0.05$), a main effect of MPZP dose ($p < 0.001$), and a significant access $\times$ MPZP dose interaction (+ $p < 0.05$) were observed. Data are expressed as mean $\pm$ SEM cocaine intake (mg/kg). [Taken with permission from Specio et al., 2008.] (D) The CRF₁ antagonist R121919 reduced total heroin responses in long-access rats. Mean $\pm$ SEM of heroin self-administration responses during R121919 treatment in long-access rats ($n = 7$). The 10 and 20 mg/kg doses

were effective at significantly reducing heroin self-administration in long-access rats ($p<0.05$).
[Taken with permission from Greenwell et al., 2009a.]

Fig. 5.

Effects of the α_1 adrenergic receptor antagonist prazosin on drug self-administration in dependent rats. (A) Mean ($\pm$ SEM) responses for ethanol during 30 min sessions in nondependent and ethanol-dependent animals following 0.0 and 1.5 mg/kg prazosin. Prazosin (1.5 mg/kg) attenuated ethanol self-administration in ethanol-dependent animals ($***p < 0.001$), leaving nondependent self-administration intact. [Taken with permission from Walker et al., 2008.] (B) Effect of prazosin on the break-point for 0.5 mg/kg/injection of cocaine under a progressive-ratio schedule of reinforcement. Prazosin was intraperitoneally injected 10 min before a session. Data are expressed as the number of injections/session on the left axis and the ratio per injection on the right axis. Error bars represent SEM values. The upper panel represents data from long-access (LgA) rats, and the lower panel represents data from short-access (ShA) rats. $*p < 0.05$, compared with vehicle treatment. $^{\#}p < 0.05$, compared with ShA rats. [Taken with permission from Wee et al., 2008.] (C) Prazosin decreased first hour heroin responding in long-access (12 h) rats but not in short-access (1 h) rats. Prazosin at a dose of 2 mg/kg significantly ($*p < 0.05$) reduced heroin intake (mean $\pm$ SEM) in the first hour in 12 h access rats (long-access, $n = 7$, left panel). No effect was observed in short-access rats ($n = 7$, right panel) at any of the doses tested. $*p < 0.05$, overall effect of dose and a specific effect at the 2 mg/kg dose compared with vehicle. [Taken with permission from Greenwell et al., 2009b.]

Fig. 6.

Neurocircuitry in the central nucleus of the amygdala relating CRF and norepinephrine in motivational withdrawal. CRF is hypothesized not only to drive GABAergic interneurons that engage hypothalamic and midbrain emotional systems, but also to directly engage norepinephrine systems in the brain stem which in turn reciprocally activate CRF. Such interactions provide a neurocircuitry basis for the allostatic recruitment of brain stress systems in addiction. [Modified with permission from Koob, 2008.]

Table 1
Role of CRF in dependence

Drug	CRF antagonist effects on withdrawal-induced anxiety-like responses	Withdrawal-induced changes in extracellular CRF in CeA	CRF antagonist effects on dependence-induced increases in self-administration	CRF antagonist reversal of stress-induced reinstatement
Cocaine	↓	↑	↓	↓
Opioids	↓ ^a	↑	↓	↓
Ethanol	↓	↑	↓	↓
Nicotine	↓	↑	↓	↓
Δ ⁹ -tetrahydrocannabinol	↓	↑	nt	nt

nt, not tested. CeA, central nucleus of the amygdala.

^a Aversive effects with place conditioning.

[Taken with permission from Koob, 2008.]

Table 2

Role of norepinephrine in dependence

Drug	Withdrawal-induced changes in extracellular norepinephrine in CeA	Noradrenergic antagonist effects		
		Withdrawal-induced anxiety- like or aversive responses	Baseline self-administration or place preference	Dependence-induced increases in self-administration
Cocaine		↓		↓
Opioids		↓		↓
Ethanol	↑	↓	↓	↓
Nicotine		↓	↑	↓

Blank entries indicate not tested. CeA, central nucleus of the amygdala. [Taken with permission from Koob, 2008.]