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Review article

Addiction and stress: An allostatic view

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ABSTRACT

Allostasis, or stability through change, has most often been linked with challenges to homeostasis, in which repeated challenges or stressors produce sufficient allostatic load to generate an allostatic state that can ultimately lead to a disease state. The present review argues that the impact of stress on drug addiction fits with an allostatic model and represents a challenge to brain circuit regulatory mechanisms that underlie the emotional state of the animal. The central thesis is that stress leads to changes in corticotropin-releasing factor in the brain that impact addiction. Stress is further argued to impact all three stages of the addiction cycle—*binge/intoxication*, *withdrawal/negative affect*, and *preoccupation/anticipation*—exposing the animal to an emotional allostatic load and allostatic state that forms the growing motivational pathology of addiction. Viewing addiction as an allostatic mechanism provides key insights into the ways in which dysregulated neurocircuitry that is involved in basic motivational systems can transition to pathophysiology.

1. Introduction

Our overall hypothesis is that drug addiction fits with an allostatic model and represents a challenge to brain circuits that underlie regulatory mechanisms of the state of the animal. The central thesis is that stress leads to changes in corticotropin-releasing factor (CRF) in the brain that impact addiction. In the context of addiction, allostatic mechanisms have been hypothesized to be involved in maintaining a dysregulated emotional system in the face of the growing motivational pathology of addiction (Koob and Le Moal, 2001). As with other chronic physiological disorders, such as high blood pressure, drug addiction worsens over time, is subject to significant environmental influences, and leaves a residual neuroadaptive trace that allows rapid relapse even months and years after detoxification and abstinence. The present review provides a confluence of seemingly disparate reward and stress interactions that integrate the ways in which stress can jumpstart the allostatic process of addiction via the classic hypothalamic-pituitary-adrenal (HPA) axis and more importantly drive the brain pathways that mediate hyperkatifeia or hyperemotional pain. Finally, we argue that the dysregulation of brain-neuroendocrine feedback in the stress axis perpetuates addiction in protracted abstinence.

1.1. Drug addiction

Drug addiction can be defined as a compulsion to seek and take a drug, loss of control in limiting intake, and the emergence of a negative emotional state when access to the drug is prevented. A heuristic framework for addiction consists of a three-stage cycle—*binge/intoxication*, *withdrawal/negative affect*, and *preoccupation/anticipation*—that represents dysregulation in three functional domains (incentive salience/habits, negative emotional states, and executive function, respectively) and is mediated by three major neurocircuitry elements (basal ganglia, extended amygdala, and prefrontal cortex, respectively). Excessive drug intake in the *binge/intoxication* stage drives the allostatic process, with the three stages feeding into each other, becoming more intense, and ultimately leading to the pathological state known as addiction (Koob and Le Moal, 1997; Fig. 1). Subsequently, the termination of drug intake inevitably leads to the negative emotional states of acute and protracted withdrawal in the *withdrawal/negative* affect stage, which generates a second motivational drive from negative reinforcement. Negative reinforcement is defined as the process by which the removal of an aversive stimulus (or an aversive, negative emotional state of withdrawal in the case of addiction) increases the probability of a response. Protracted abstinence incorporates residual elements of negative emotional states and cue and contextual craving that forms the basis of the *preoccupation/anticipation* stage.

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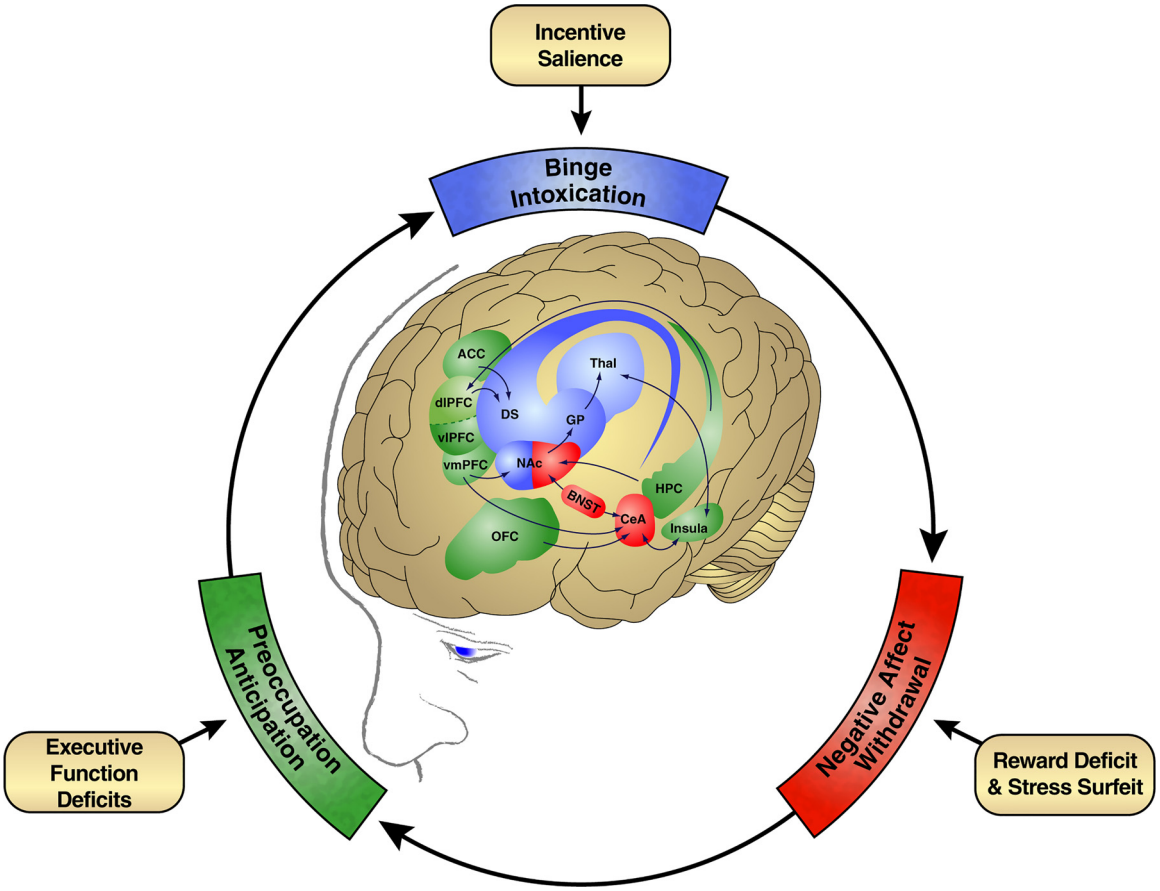

Fig. 1. Conceptual framework for the neurobiological basis of addiction. In the *binge/intoxication* stage, reinforcing effects of drugs may engage neurocircuits of the basal ganglia (blue structures). Reward neurotransmitter activation and associative mechanisms engage the nucleus accumbens shell and core and then stimulus-response habits engage the dorsal striatum. Two major neurotransmitters that mediate the rewarding effects of drugs of abuse are dopamine and opioid peptides. In the *withdrawal/negative affect* stage, the negative emotional state of withdrawal may engage activation of the extended amygdala (red structures). 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 a transition zone in the medial portion (or shell) of the nucleus accumbens. Major neurotransmitters in the extended amygdala that are hypothesized to function in negative reinforcement are corticotropin-releasing factor, norepinephrine, and dynorphin. There are major projections from the extended amygdala to the hypothalamus and brainstem. The *preoccupation/anticipation* (craving) stage involves neurocircuitry of the cortex and allocortex (green structures). The processing of conditioned reinforcement involves the basolateral amygdala, and the processing of contextual information involves the hippocampus. Executive control depends on the prefrontal cortex and includes the representation of contingencies, the representation of outcomes, and their value and subjective states (i.e., craving and, presumably, feelings) that are associated with drugs. The subjective effects, termed "drug craving" in humans, involve activation of the orbital and anterior cingulate cortices and temporal lobe, including the amygdala. A major neurotransmitter that is involved in the craving stage is glutamate that is localized in pathways from frontal regions and the basolateral amygdala that project to the ventral striatum. ACC, anterior cingulate cortex; BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; DS, dorsal striatum; dlPFC, dorsolateral prefrontal cortex; GP, globus pallidus; HPC, hippocampus; NAC, nucleus accumbens; OFC, orbitofrontal cortex; Thal, thalamus; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex. [Modified from Koob and Volkow, 2010].

1.2. Allostasis

The neurobiologist Peter Sterling and epidemiologist James Eyer hypothesized the physiological construct of allostasis to explain the basis of vulnerability in human mortality and pathophysiology (Sterling and Eyer, 1988). Allostasis can be defined as "the process by which a state of internal, physiological equilibrium is maintained by an organism in response to actual or perceived environmental and psychological stressors" (Webster's Ninth New Collegiate Dictionary, 1984). In contrast to homeostasis, allostasis involves a feed-forward mechanism instead of a negative feedback mechanism that characterizes homeostasis and has often been described as "stability through change" (Sterling and Eyer, 1988). The advantage of a feed-forward mechanism is that it allows the fine matching of resources to needs through the continuous reevaluation of needs and continuous readjustment of all parameters toward new set points.

However, when an organism is repeatedly challenged, the ability to quickly mobilize resources and use feed-forward mechanisms can lead to an allostatic state and an ultimate cost to the individual that is known as allostatic load (McEwen et al., 1998). An allostatic state can be defined as a state of chronic deviation of the regulatory system from its normal (homeostatic) operating level (Koob and Le Moal, 2001). Allostatic load can be defined as the long-term cost of allostasis that accumulates over time and reflects the accumulation of damage that can lead to pathological states. Allostatic load results from repeated deviations from homeostasis that take the form of changes in set points that require increasing amounts of energy to defend and ultimately reach the level of pathology (McEwen, 2000). The allostatic state can thus be considered an intermediate stage in the allostatic process (Koob and Le Moal, 2001), which may be a reflection of allostatic load but may also have some relevance to the ways in which psychiatric diseases develop a progressively pathological phenotype (i.e., allostatic state) as the allostatic load grows larger.

One advantage of an allostatic change rather than a homeostatic change in physiology is the existence of a feed-forward system that is in place for responses to rapid, anticipated challenges (Schulkin et al.,

1994; Schulkin, 2017). However, the same feed-forward system that allows rapid responses to environmental challenges becomes the driving force for allostatic states, allostatic load, and ultimately pathology if adequate time or resources are unavailable to shut off the response. Thus, for example, an acute elevation of blood pressure is "appropriate" in an allostasis model to meet the environmental demand of acute arousal, but chronic blood pressure elevations under conditions of chronic stress may address the chronic environmental demand but is certainly not healthy (Sterling and Eyer, 1988).

We argue below that engagement in excessive drug seeking and taking results in the repeated hyperactivation of reward function by drugs of abuse, facilitated by acute stress mechanisms, in turn leading to attempts of the brain via molecular, cellular, and neurocircuitry processes to maintain stability but at a cost (i.e., allostasis). Allostatic mechanisms have been hypothesized to be involved in maintaining a functional motivational system that has relevance to the pathology of addiction (Koob and Le Moal, 2001). The development of a negative emotional state that occurs during acute withdrawal and persists into protracted abstinence has been defined as an allostatic state (Koob and Le Moal, 2008). Such a state has been hypothesized to involve both decreases in reward function and increases in stress function, both of which can contribute to a negative emotional state in humans, defined as irritability, physical pain, emotional pain, malaise, dysphoria, alexithymia, and the loss of motivation for natural rewards (i.e., hyperkatifeia or a hypernegative emotional state; Shurman et al., 2010).

2. *Binge/Intoxication* stage: reward, glucocorticoids, and incentive salience

2.1. Hypothesis

The *binge/intoxication* stage of the addiction cycle is characterized by engagement in drug seeking, incentive salience, and drug taking that progresses to compulsive-like responding and major changes in corticostriatal-pallidal-thalamic circuits that encode pathological habits (Belin et al., 2013; Everitt and Robbins, 2005). Stress can be rewarding in small or intense doses (Wand et al., 2007; Robinson, 1985), possibly mediated by glucocorticoids that act on brain reward systems. Our hypothesis is that in the *binge/intoxication* stage, excessive drug use can initiate neuroadaptations that feed allostasis via activation of the HPA axis to facilitate reward and then subsequently via the sensitization of extrahypothalamic CRF systems in the extended amygdala to facililate incentive salience.

2.2. Reward and stress: the two faces of Janus

Reward and stress are intimately linked. Some levels of stress can actually be rewarding in the sense that they are sought and activate brain reward systems (Wand et al., 2007; Robinson, 1985), and excess reward can lead to stress (Carlezon et al., 2000). Janus was the god of doors, passages, and transitions, and his two faces look to the future and to the past. Reward and stress represent different components of transitions in our brain emotional systems that lead to and perpetuate addiction.

2.3. Glucocorticoids facilitate drug seeking

For example, many studies demonstrate that rats with higher levels of corticosterone and CRF are more likely to self-administer cocaine, heroin, and amphetamines (Piazza et al., 1989, 1993; Erb et al., 1996), and corticosterone is self-administered by rats (Deroche et al., 1993; Piazza et al., 1993; Fig. 2). Thus, an early allostatic change occurs in the activity of elements of the reward system to facilitate the function of the mesolimbic dopamine incentive salience system and promote excessive drug seeking.

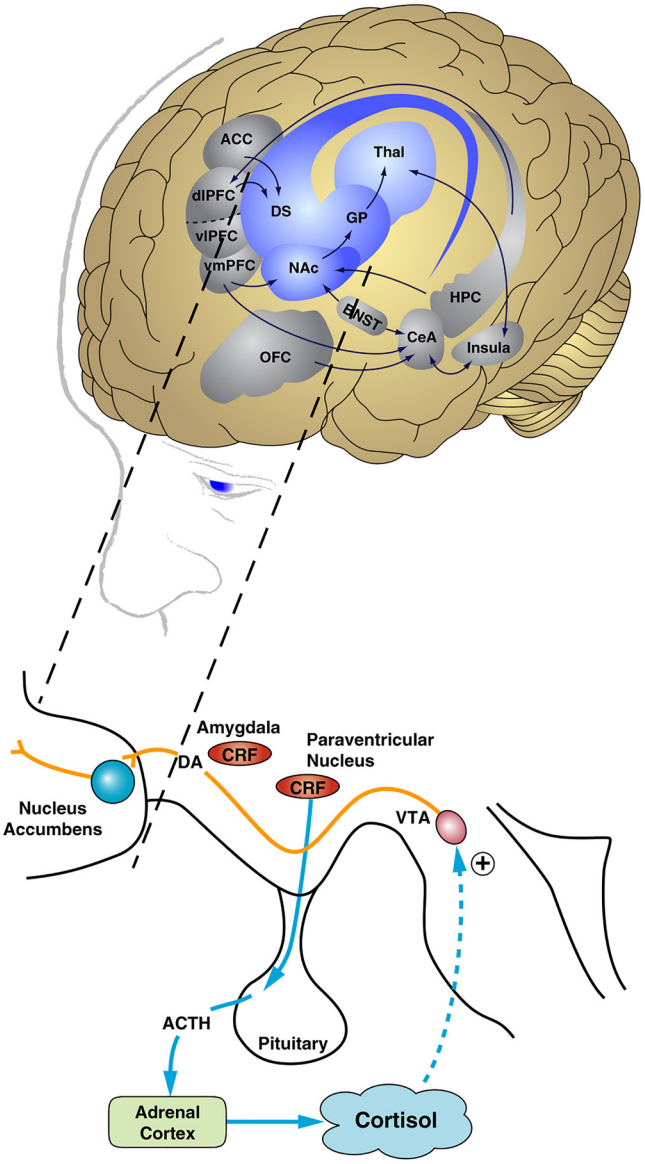

Fig. 2. Conceptual framework of the way in which dysregulation of the hypothalamic-pituitary-adrenal axis and extrahypothalamic CRF systems can influence the *binge/intoxication* stage of the addiction cycle to drive allostasis in addiction. Here, the activation of glucocorticoids (bottom) facilitates activity of the mesolimbic dopamine system to drive incentive salience. CRF in the nucleus accumbens can facilitate incentive salience. One hypothesis is that CRF neurons in the shell of the nucleus accumbens are sensitized with repeated administration of glucocorticoids, similar to those in the central nucleus of the amygdala and bed nucleus of the stria terminalis, but this hypothesis remains to be tested.

2.4. Glucocorticoids and CRF in the paraventricular nucleus of the hypothalamus, amygdala, bed nucleus of the stria terminalis, and prefrontal cortex

A classic physiological response to stress is activation of the HPA axis (Selye, 1976). Here, a variety of pathways, presumably conveying external or internal challenges to homeostasis, activate CRF-expressing neurons in the paraventricular nucleus of the hypothalamus, and CRF is released into the portal system and activates the release of ACTH from the pituitary, which in turn activates the release of glucocorticoids from the adrenal cortex. Even this initial activation of the HPA axis triggers neuroadaptations that initiate the allostatic process.

Perhaps most critically, CRF gene expression is differentially

regulated in the brain by glucocorticoid hormones (Swanson and Simmons, 1989; Imaki et al., 1991; Tanimura and Watts, 1998). In the parvocellular region of the paraventricular nucleus of the hypothalamus, glucocorticoid activation decreases CRF gene expression. Several studies have shown that corticosterone can facilitate the induction of CRF gene expression in several brain regions. These regions include the central nucleus of the amygdala, bed nucleus of the stria terminalis, and infralimbic cortex (Gray et al., 2016; Makino et al., 1994a,b; Watts and Sanchez-Watts, 1995; Swanson and Simmons, 1989; Shepard et al., 2000; Thompson et al., 2004; Kolber et al., 2008; Merali et al., 2008). Notably, although the overall effect of glucocorticoids is to inhibit the paraventricular nucleus of the hypothalamus, there are also neuronal populations within the paraventricular nucleus of the hypothalamus that project to the brainstem that are not inhibited by glucocorticoids, and some are actually enhanced (Swanson and Simmons, 1989; Watts and Sanchez-Watts, 1995; Makino et al., 1994a,b).

In an elegant demonstration of this differential interaction of glucocorticoids with hypothalamic and extrahypothalamic CRF, Cook (2004) found a significant relationship between cortisol and CRF in the amygdala in sheep in response to acute and repeated predator stress. With a single exposure to a dog, sheep exhibited a biphasic CRF response in the amygdala as measured by microdialysis. There was an initial rapid increase in CRF levels that decreased quickly and was a direct response to the dog. This was followed by a slower rising cortisol response that was paralleled by a second CRF peak, smaller and more prolonged than the first (Cook, 2004; Fig. 3). The first CRF response was cortisol-independent and part of the initial fear response to the stressor, whereas the second response was a cortisol-dependent elevation of CRF that perhaps sustained the fear state and related behavior during and after the presence of the threat. The second response was mimicked by cortisol administration in non-stressed animals. Furthermore, following repeated exposure to a dog, sensitization of the CRF system (i.e., an increase in CRF release) in the amygdala was found by giving a novel footshock stressor to the sheep (Cook, 2004).

Thus, the induction of CRF gene expression in the amygdala and bed nucleus of the stria terminalis by glucocorticoid hormones may drive early involvement in drug-seeking behaviors. For example, CRF infusions in the lateral ventricle facilitated amphetamine-induced self-administration (Sarnyai et al., 1993). Corticosterone levels are known to influence the expression of amphetamine self-administration (Piazza et al., 1991; Cador et al., 1993). Systemic injections of corticosterone and stressful events increase the likelihood of amphetamine self-administration (Maccari et al., 1991) via the activation of glucocorticoid receptor sites (Steckler and Holsboer, 2001), which increase both corticosterone and central CRF (Heinrichs et al., 1995). In fact, amphetamine increases CRF in such regions as the nucleus accumbens (Cadet et al., 2014).

2.5. Corticotropin-releasing factor and incentive salience

Neuropeptides, such as CRF, can increase incentive salience (Pecina et al., 2006; Merali et al., 2001, 2003, 2008; Dallman and Bhatnagar, 2000; Dallman et al., 2003), consistent with the involvement of CRF in attentional responses to both external and internal events (Pecina et al., 2006; Dallman et al., 2003). Indeed, rats can be trained to associate a sound with the availability of sucrose pellets if they press a lever (Pecina et al., 2006; Berridge and Robinson, 1998). In these studies, an injection of CRF in the nucleus accumbens increased cue-triggered lever pressing for sucrose pellets (Pecina et al., 2006; Fig. 4). This can be interpreted as an ability of CRF to increase the salience of external cues and the motivation of the rats to respond (or diminished motivation when overly expressed; e.g., Bryce and Floresco, 2016).

Regions of the nucleus accumbens are critical in appetitive behaviors (Berridge, 2004). These regions contain both glucocorticoid and CRF receptors (e.g., Lim et al., 2005). An intracranial infusion of CRF in the nucleus accumbens shell can be visualized with a Fos plume map

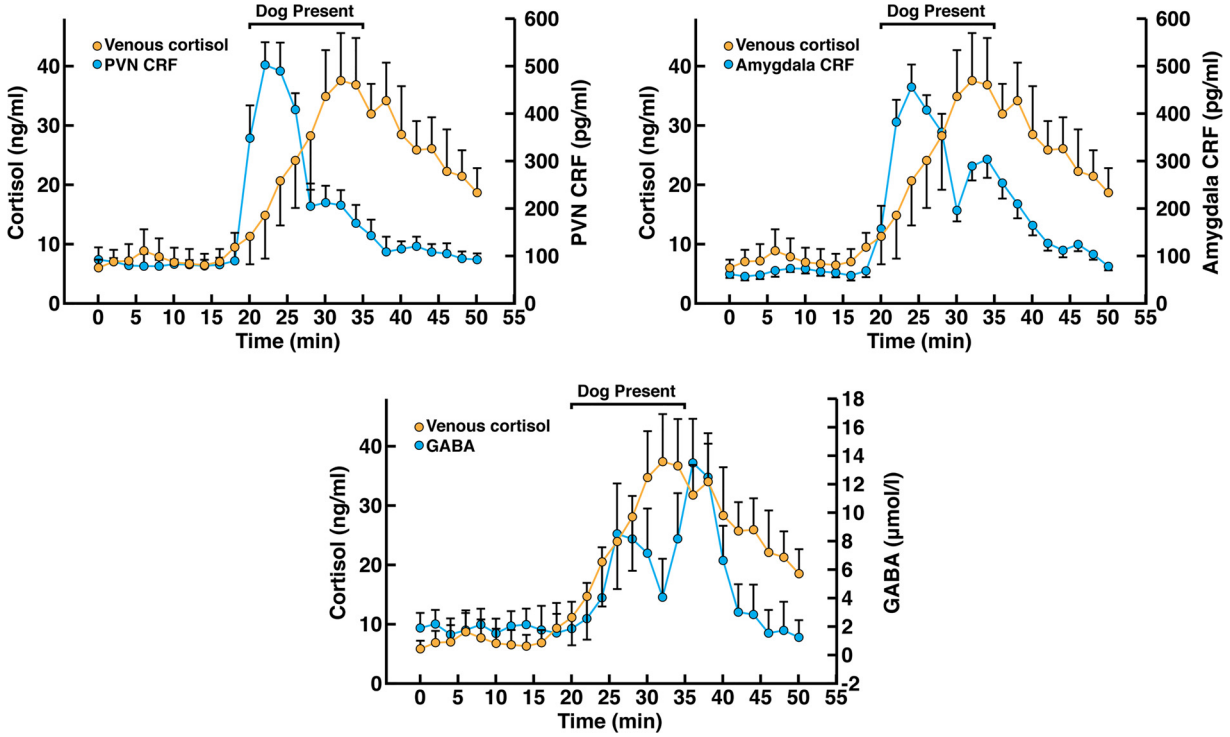

Fig. 3. Stress induces CRF release in the paraventricular nucleus of the hypothalamus (PVN) and both CRF and γ-aminobutyric acid (GABA) release in the amygdala. With and without saline microinjections, CRF (top left) showed a single peak in response to predator stress in the PVN and (top right) two peaks in the amygdala, whereas venous cortisol changes showed a single large peak following the stress application. (Bottom) GABA showed two peaks that were similar in time to the changes in CRF in the amygdala. Data were obtained from animals that were either untreated in the first stressor exposure (n = 15) or saline-treated in the first stress exposure (n = 5). The data are expressed as mean ± SEM. [Modified with permission from Cook, 2004].

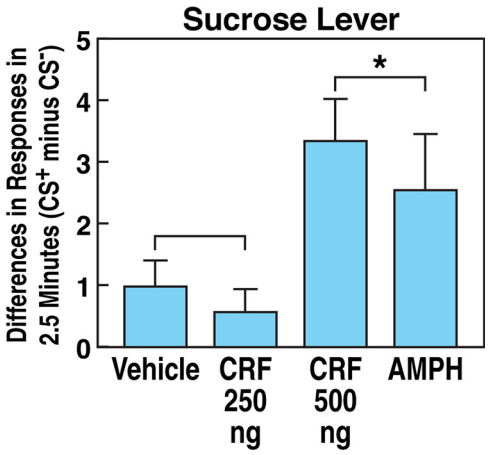

Fig. 4. Enhancement of incentive motivation by CRF, showing effects on cue-triggered lever pressing during extinction testing caused by CRF (500 ng) and amphetamine (20 μg) microinjections in the caudal medial nucleus accumbens shell. Transform scores showed a direct contrast between CS^+ and CS– effects on lever pressing. CS^+ effects on cue-triggered lever pressing were amplified by CRF (500 ng) and amphetamine (20 μg) microinjections. [Taken with permission from Pecina et al., 2006].

that localizes the magnification effect of the CRF microinjection (Pecina et al., 2006). One way to understand appetitive behaviors is that one function of glucocorticoids is to magnify the effects of CRF with regard to increases in attention to objects and their potential value. This may be a particularly important aspect of the release of CRF when an object is unfamiliar or uncertain, as well as if it is dangerous (Habib et al., 2000; Kalin et al., 1998).

3. *Withdrawal/negative affect* stage: opponent process and negative reinforcement

3.1. Hypothesis

Repeated withdrawal from drugs of abuse in humans in the *withdrawal/negative affect* stage is defined by the presence of both physical signs and motivational signs of withdrawal, such as chronic irritability, physical pain, emotional pain (i.e., hyperkatifeia; Shurman et al., 2010), malaise, dysphoria, alexithymia, sleep disturbances, and the loss of motivation for natural rewards. The hypothesis here is that allostatic changes in the stress axis, notably activation of the HPA axis, with subsequent blunting of the HPA axis and sensitization of extra-hypothalamic CRF, are further exaggerated by repeated binge-withdrawal cycles of drug taking, such that progressively greater negative emotional states are generated that drive negative reinforcement.

3.2. Opponent process and negative reinforcement

Addiction can be considered the pathophysiology of motivation or the "hijacking" of motivational systems. Motivation is a construct that can be defined as "a state that varies with arousal and guides behavior in relationship to changes in the environment. The environment can be external (incentives) or internal (central motive states or drives), and such motivation or motivational states are not constants and vary over time" (Koob et al., 2010). The construct of motivation in addiction was intimately linked with temporal changes in hedonic, affective, or emotional states by the opponent-process theory of motivation by Solomon and Corbit (1974). Here, the rewarding effects of drugs, possibly facilitated by initial activation of the HPA axis (see Fig. 2) are followed by a dysphoric-like state that drives negative reinforcement, in which the motivation for drug seeking involves an attempt to relieve or remove the negative emotional state of withdrawal (Koob and Le Moal, 1997; see above). Relevant to the allostatic perspective that is discussed herein, the affective dynamics of opponent-process theory generate new sources of motivation for energizing behavior.

Key evidence of negative reinforcement mechanisms that are involved in the transition from drug use to compulsive-like drug use can be found in studies of animal models of prolonged access to intravenous drug self-administration, combined with measures of brain stimulation reward. Prolonged exposure to cocaine self-administration produced an elevation of reward thresholds (decrease in reward or hypohedonia) that was not observed in rats with short access to the drug across successive self-administration sessions (Ahmed et al., 2002). Elevations of baseline reward thresholds temporally preceded and were highly correlated with the escalation of cocaine intake (Fig. 5). Showing an allostatic-like phenotype, post-session elevations of reward thresholds failed to return to baseline levels before the onset of each subsequent self-administration session, thereby progressively deviating from control levels and paralleling a robust escalation of cocaine consumption. Similar results have been observed with extended access to heroin (Kenny et al., 2006) and methamphetamine (Jang et al., 2013).

Thus, the process of developing an allostatic negative emotional state with increasing allostatic load may begin with the first challenge to homeostasis, the massive release of reward neurotransmitters, and (as the drug wears off) drug-opposite responses (i.e., opponent processes). This negative emotional state, reflected by elevations of reward thresholds, has been hypothesized to provide the driving force for an additional source of motivation, namely negative reinforcement (Koob and Le Moal, 1997).

Such opponent processes have long been hypothesized to occur even with a single injection of a drug and contribute to tolerance (Siegel, 1975). In human laboratory studies, intravenous cocaine administration produced patterns of a rapid "rush," followed by a greater "low" (Breiter et al., 1997; Van Dyke and Byck, 1982). Early-onset allostatic-like elevations of reward thresholds (i.e., hypohedonia) have been observed in animal models of intravenous cocaine self-administration. Within a single session of self-administration, elevations of reward thresholds begin rapidly and increase as cocaine exposure (i.e., self-administration) increases (Kenny et al., 2003; Fig. 6). Similar dysphoria-like responses have been observed for acute opioid and alcohol withdrawal (Liu and Schulteis, 2004; Schulteis and Liu, 2006). Both precipitated opioid withdrawal (Liu and Schulteis, 2004) and repeated acute spontaneous alcohol withdrawal elevated brain stimulation reward thresholds, and these elevations of thresholds further increased with repeated withdrawal experience. These findings demonstrate that elevations of brain reward thresholds can occur even within a single session. If cocaine self-administration persists, then the elevation of reward thresholds never returns to baseline levels (i.e., residual hysteresis), thus creating a progressively greater elevation of "baseline" reward thresholds and supporting a hedonic allostasis model of the development of compulsive-like drug seeking that is associated with addiction.

3.3. Neurobiological bases for negative emotional states

The observation of the development of a negative emotional state with excessive drug use led to investigations of the neurobiological bases for counteradaptive hedonic states. Such counteradaptive mechanisms were hypothesized to be mediated by two processes: within-system neuroadaptations and between-system neuroadaptations (Koob and Bloom, 1988). A key part of the neurocircuitry that mediates such negative emotional states is a neuroanatomical construct termed the "extended amygdala." The extended amygdala is composed of the bed nucleus of the stria terminalis, central nucleus of the amygdala, and a transition zone in the medial subregion (shell) of the nucleus accumbens, regions that have cytoarchitectural similarities and similar neuroanatomical connections. The extended amygdala, as an entity, receives numerous afferents from structures that have long been

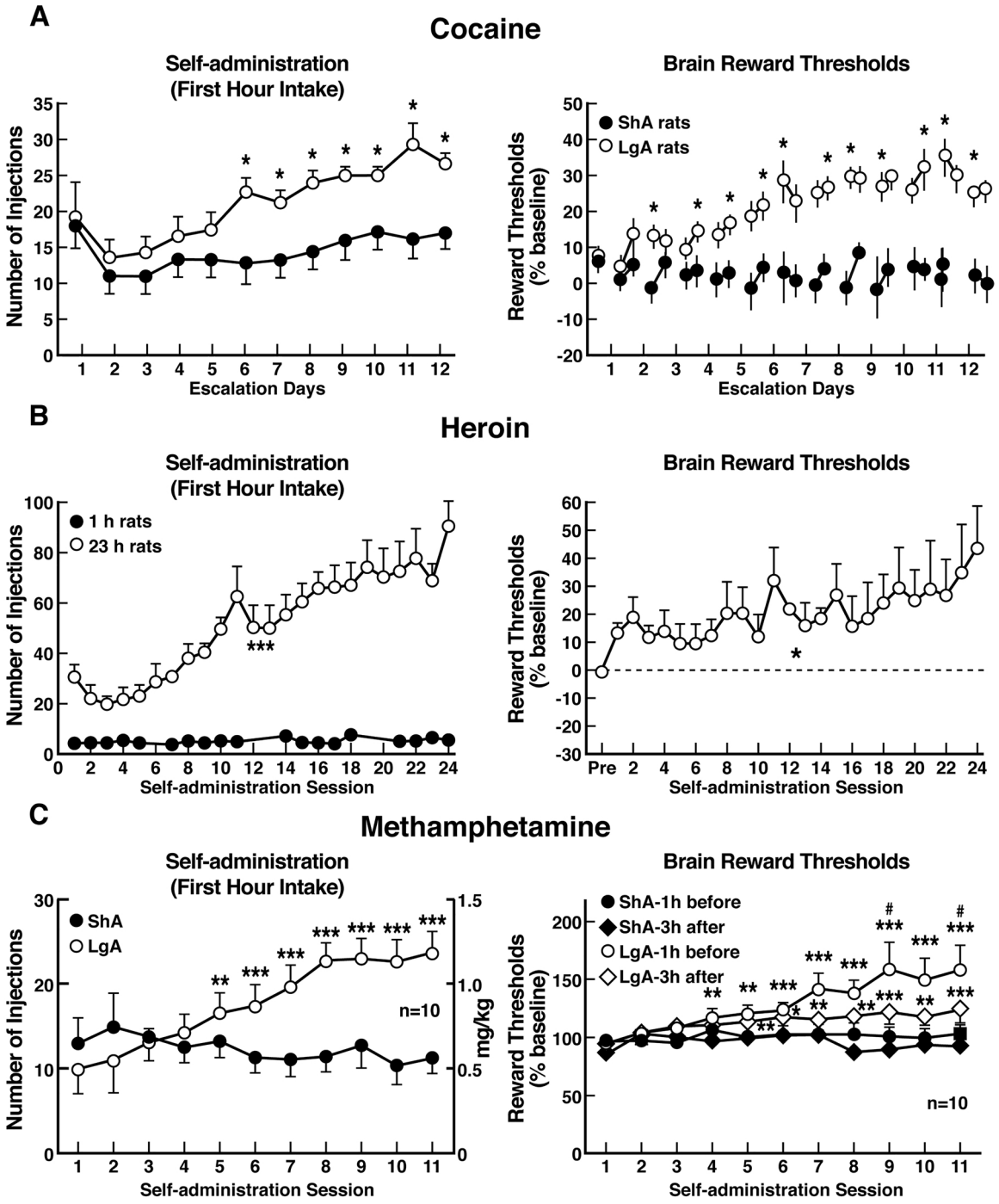

Fig. 5. The escalation of drug intake parallels elevations of reward thresholds (decreases in reward) for cocaine, heroin, and methamphetamine. (A) Relationship between elevation of intracranial self-stimulation (ICSS) reward thresholds and cocaine intake escalation. (*Left*) Percent change from baseline response latencies (3 h and 17–22 h after each self-administration session; first data point indicates 1 h before the first session). (*Right*) Percent change from baseline ICSS thresholds. $^{*}p < 0.05$, compared with drug-naive and/or short-access rats (tests for simple main effects). [Taken with permission from Ahmed et al., 2002]. (B) Unlimited daily access to heroin escalated heroin intake and decreased the excitability of brain reward systems. (*Left*) Heroin intake (± SEM; 20 μg 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). (*Right*) Percent change from baseline ICSS 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. [Taken with permission from Kenny et al., 2006]. (C) Escalation of methamphetamine self-administration and ICSS in rats. Rats were daily allowed to receive ICSS in the lateral hypothalamus 1 h before and 3 h after intravenous methamphetamine self-administration with either 1- or 6-h access. (*Left*) Methamphetamine self-administration during the first hour of each session. (*Right*) ICSS measured 1 h before and 3 h after methamphetamine self-administration. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, compared with session 1; $^{\#}p < 0.05$, compared with LgA 3 h after. [Taken with permission from Jang et al., 2013].

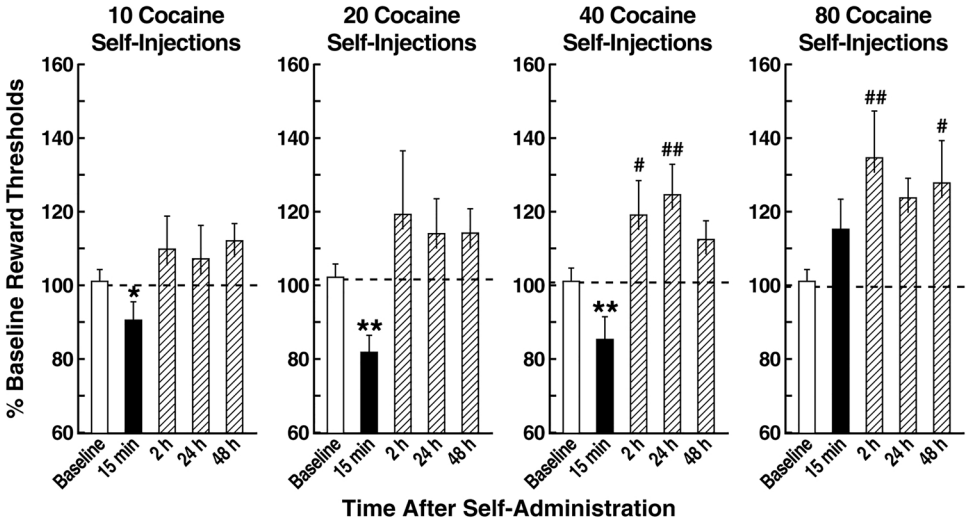

Fig. 6. Effects of increasing exposure to cocaine on reward thresholds during a single session. Rats ($n = 11$) were allowed to self-administer 10, 20, 40, and 80 injections of cocaine (0.25 mg per injection), and intracranial self-stimulation reward thresholds were measured 15 min and 2, 24, and 48 h after the end of each intravenous cocaine self-administration session. The horizontal dotted line in each plot represents 100% of baseline levels. The data are expressed as the mean + SEM percentage of baseline reward thresholds. $^{*}p < 0.05$, $^{**}p < 0.01$, compared with baseline (paired *t*-test); $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, compared with baseline (repeated-measures analysis of variance followed by Fisher's Least Significant Difference test). [Taken with permission from Kenny et al., 2003].

associated with emotion, such as the basolateral amygdala and hippocampus, and sends efferents to the medial part of the ventral pallidum (part of the extrapyramidal motor system), lateral hypothalamus (part of motivational circuitry and the expression of emotion circuitry), and periaqueductal gray (part of fight or flight, freezing, and pain circuitry), thus further defining the specific brain areas that interface classic emotion-related structures with the extrapyramidal motor system (Alheid et al., 1995). The medial part the nucleus accumbens is also a key part of the ventral striatum and as such part of the key reward motivational circuit that consists of cortical-striatal, pallidal, and thalamic-cortical loops that are implicated in the incentive salience-habit component of compulsive-like behavior (Haber et al., 2000; Everitt and Robbins, 2005).

Significant evidence from both animal and human studies suggests that the hypoactivity of reward function and increases in stress function can occur following acute and protracted withdrawal from drugs of abuse. For example, withdrawal from all major drugs of abuse can produce acute elevations of reward thresholds, decreases in reward neurotransmitter function, elevations of glucocorticoid levels, and increases in the release of CRF in the central nucleus of the amygdala (Fig. 7**A**,**B**).

Within incentive-salience/reward neurocircuitry, neurochemical mechanisms for hypohedonic-like effects that are associated with within-system adaptations include decreases in dopaminergic transmission in the ventral striatum (nucleus accumbens) during drug withdrawal. Withdrawal from excessive administration of most major drugs of abuse decreases the firing of dopaminergic neurons in the ventral tegmental area (Diana et al., 1993, 1995; Tan et al., 2009; Grieder et al., 2012) and decreases dopamine release in the nucleus accumbens (measured by in vivo microdialysis; Parsons and Justice, 1993; Weiss et al., 1992). Human imaging studies of individuals with addiction during withdrawal or protracted abstinence indicate decreases in dopamine D_2 receptors (hypothesized to reflect hypodopaminergic functioning), hyporesponsiveness to dopamine challenge (Volkow et al., 2003), and hypoactivity of the orbitofrontal-infralimbic cortex system (Volkow et al., 2003).

Multiple molecular mechanisms can be hypothesized to be engaged to account for these within-system neuroadaptations in dopaminergic activity within the circuitry of the incentive/reward systems and may not directly involve activation of the brain stress systems. Such molecular changes include the perturbation of intracellular signal transduction pathways, including changes in G-protein functioning and protein kinase A activity in the nucleus accumbens during the development of compulsive drug seeking (Edwards and Koob, 2010). Such changes in signal transduction can trigger longer-term molecular neuroadaptations via such transcription factors as cyclic adenosine monophosphate response element binding protein and downstream ΔFosB, nuclear factor κB, and CDK5, which can modify gene expression and initiate long-term plasticity (Nestler, 2005) or even structural changes in the cytoskeleton of neurons via actions on actin (Russo et al., 2010). Thus, within-system molecular changes may form a critical juncture for genetic/epigenetic factors to sustain allostatic changes in the perpetuation of negative emotional states that are hypothesized to drive excessive drug seeking.

For the domain of between-system neuroadaptations, neurobiological systems that are involved in arousal and stress have been hypothesized to be the basis for what was originally described as "between-system neuroadaptations" (Koob and Bloom, 1988) and contribute to negative emotional states that are associated with acute withdrawal and protracted abstinence. The hypothesis is that these between-system neuroadaptations are engaged to overcome the chronic presence of the perturbing drug in an attempt to restore homeostasis but in the process helps generate an allostatic negative emotion state. Additionally, accumulating evidence suggests that activation of the brain stress systems via between-system changes that are triggered by overactivation of the brain reward systems can also feedback and decrease reward system function (Carlezon et al., 2000; Koob, 2015).

The neurobiological systems in the brain that constitute the brain stress systems that are engaged in between-system neuroadaptations during the *withdrawal/negative affect* stage include CRF, dynorphin, norepinephrine, hypocretin, vasopressin, glucocorticoids, and neuroinflammatory factors (Fig. 7**A**,**B**). CRF plays a key role via both the HPA axis and extrahypothalamic CRF stress systems, with a common response of elevated ACTH, corticosterone, and amygdala CRF during acute withdrawal (Rivier et al., 1984; Merlo-Pich et al., 1995; Koob et al., 1994; Rasmussen et al., 2000; Olive et al., 2002; Delfs et al., 2000; Koob, 2009; Roberto et al., 2010).

3.4. Sensitization of the HPA axis in addiction

Activation of the HPA axis may be an early dysregulation that is associated with excessive drug taking and ultimately produces a "kindling" or sensitization of extrahypothalamic CRF systems (Koob and Kreek, 2007; Vendruscolo et al., 2012; Fig. 7**A**). Data that support a role for CRF in mediating the negative emotional responses that are associated with acute and protracted abstinence have largely been generated by preclinical studies with animal models. The negative emotional-like states that are associated with acute withdrawal and protracted abstinence from all major drugs of abuse in animal models can be reversed by CRF receptor antagonists (Koob, 2015).

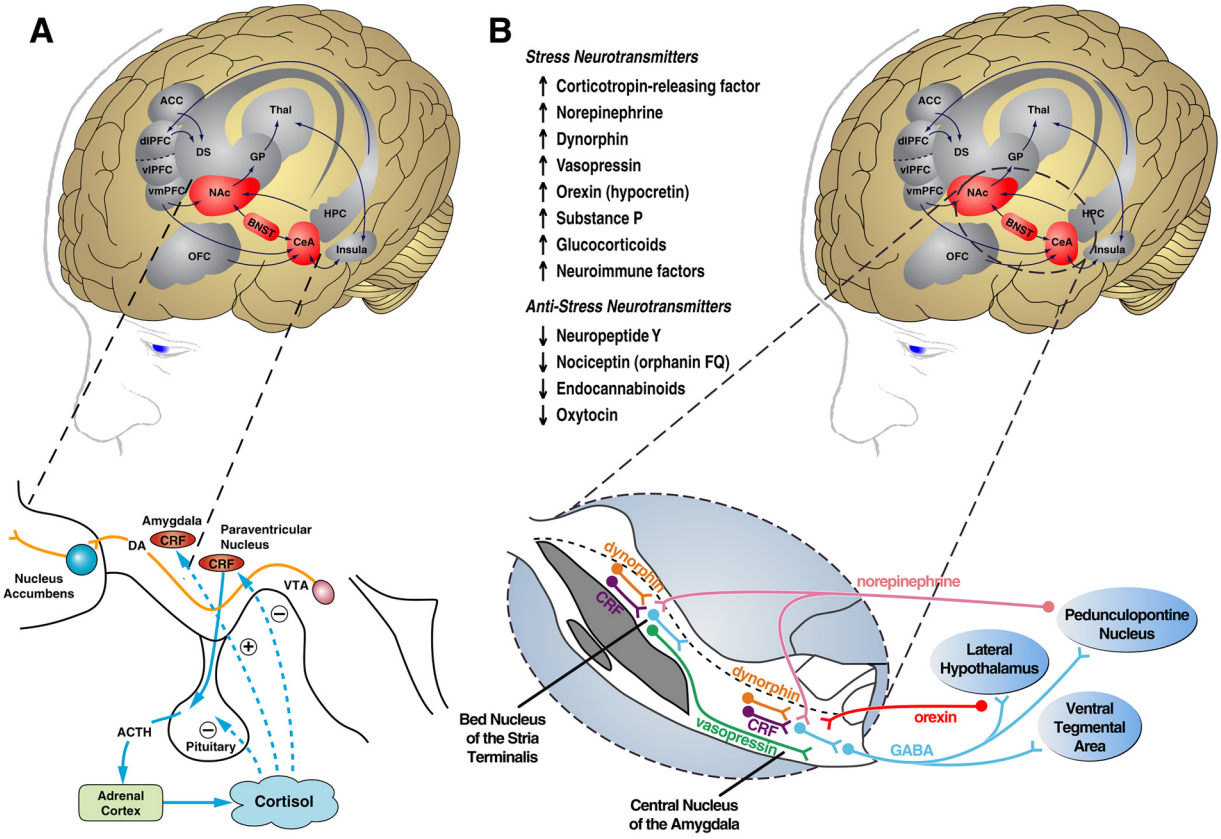

Fig. 7. (A) Conceptual framework of the way in which dysregulation of the hypothalamic-pituitary-adrenal axis and extrahypothalamic CRF systems can influence the *withdrawal/negative affect* stage of the addiction cycle to drive allostasis in addiction. Here, the activation of glucocorticoids (bottom) inhibits the paraventricular nucleus but drives CRF in the extended amygdala, triggering hyperkatifeia via extrahypothalamic stress systems. The activation of CRF in the central nucleus of the amygdala and bed nucleus of the stria terminalis produces increases in hyperkatifeia-like responses in animals during acute and protracted withdrawal. **(B)** Neurocircuitry relevant to allostatic changes in the extended amygdala associated with the *withdrawal/negative affect* stage of the addiction cycle. Neurotransmitters/neuromodulators are listed on the left. *Withdrawal/negative affect* stage (*red*): The negative emotional state of withdrawal engages 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 (shell) of the nucleus accumbens. Neurotransmitter systems that are engaged in the neurocircuitry of the extended amygdala that convey negative emotional states are indicated by upward arrows, and neurotransmitter systems that may buffer negative emotional states are indicated by downward arrows. The magnified section (*blue oval*) illustrates the extended amygdala in detail. A major neurotransmitter in the extended amygdala is CRF, which projects to the brainstem where noradrenergic neurons provide a major projection reciprocally to the extended amygdala. Green/blue arrows indicate glutamatergic projections. Acb, nucleus accumbens; ACC, anterior cingulate cortex; BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; CRF, corticotropin-releasing factor; DGP, dorsal globus pallidus; dlPFC, dorsolateral prefrontal cortex; NE, norepinephrine; OFC, orbitofrontal cortex; SNc, substantia nigra pars compacta; VGP, ventral globus pallidus; vlPFC and vmPFC, ventral prefrontal cortex; VTA, ventral tegmental area. *Binge/intoxication* stage (*blue*). *Preoccupation/anticipation* (craving) stage (*green*). [Modified with permission from Koob, 2008].

Specifically, in animal models of alcohol dependence, in which rats drink alcohol excessively during acute and protracted abstinence, systemic injections of small-molecule CRF_1 receptor antagonists blocked the increase in alcohol intake that was associated with acute withdrawal (Funk et al., 2007) and protracted abstinence (Gehlert et al., 2007). A CRF receptor antagonist that was administered chronically during the development of dependence blocked the development of compulsive-like responding for alcohol (Roberto et al., 2010). A peptide CRF_1/CRF_2 receptor antagonist, when administered directly in the central nucleus of the amygdala, blocked alcohol self-administration in alcohol-dependent rats (Funk et al., 2006). Cellular studies have identified the actions of CRF on γ-aminobutyric acid (GABA)ergic interneurons within the central nucleus of the amygdala (Roberto et al., 2010). CRF in the basal forebrain may also play an important role in the development of negative emotional states that drive compulsive-like drug seeking that is associated with cocaine, heroin, marijuana, and nicotine.

Drug addiction, particularly alcohol use disorder, has long been associated with dysregulation of the HPA axis, and high comorbidity is found between alcohol use disorder and stress-associated disorders (Boden and Fergusson, 2011; Haass-Koffler et al., 2014; Lijffijt et al., 2014). Clinical studies have reported impairments in stress responsivity in alcohol use disorder (Lovallo et al., 2000; O'Malley et al., 2002; Adinoff et al., 2005). A condition known as pseudo-Cushing's syndrome, manifested by high levels of corticosterone, can be observed in individuals with alcohol use disorder (Kirkman and Nelson, 1988), but more commonly reported is a blunted cortisol response in individuals with alcohol use disorder. Indeed, anti-craving drugs that are used to prevent relapse, such as opioid receptor antagonists, activate the HPA axis, and the sensitivity to this activation is most prominent in subjects with a strong family history of alcohol use disorder (O'Malley et al., 2002; Wand et al., 1999; Kiefer et al., 2006).

Animal models have shown similar effects, with a blunted corticosterone response in rats that are made dependent using the chronic intermittent alcohol vapor model (Richardson et al., 2008). Oral alcohol self-administration stimulated the HPA axis to release ACTH and corticosterone. One hypothesis is that activation of the HPA axis can drive neuroadaptive changes in extrahypothalamic CRF systems in the extended amygdala, as described above (see Fig. 3). High corticosterone increases CRF mRNA in the central nucleus of the amygdala and lateral

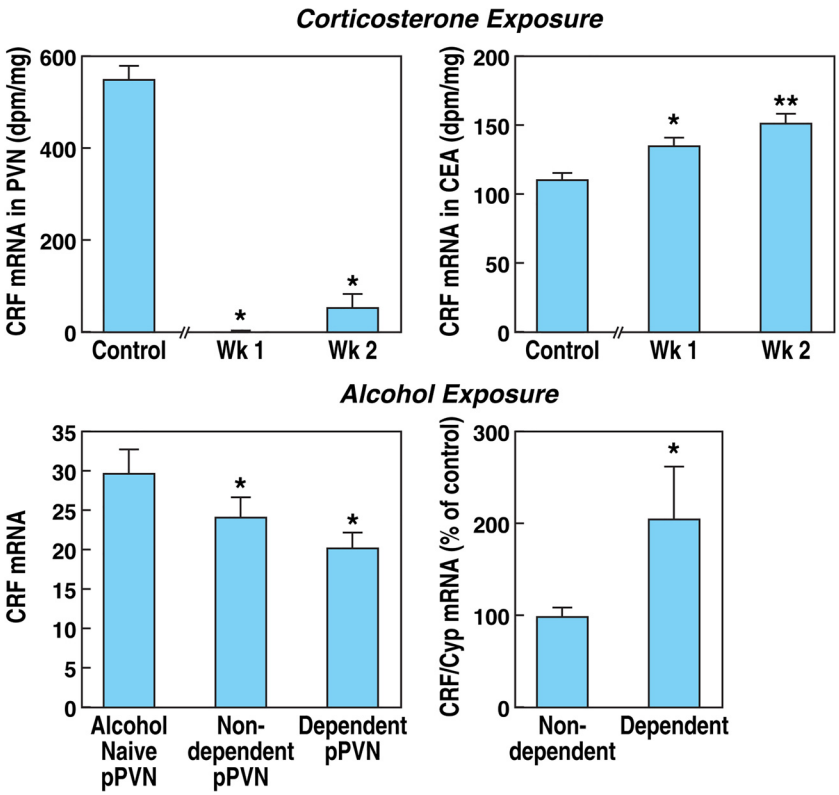

Fig. 8. Neuroplasticity of glucocorticoid expression in hypothalamic and extrahypothalamic stress systems during stress and alcohol dependence. (Top left) CRF mRNA hybridization levels in the paraventricular nucleus of the hypothalamus induced by corticosterone pellet (200 mg) implantation. Control rats ($n = 12$) were obtained from the pool of rats that were sacrificed at the same time points as the experimental group ($n = 7$ for each time point). The data are expressed as mean + SEM. $^{*}p <$ 0.001, vs. control. (Top right) CRF mRNA hybridization levels in the central nucleus of the amygdala induced by corticosterone pellet implantation over 2 weeks. Control rats ($n = 12$) were obtained from the pool of rats that were sacrificed at the same time points as the experimental groups ($n = 7$ for each time point). The data are expressed as mean + SEM. $^{*}p <$ 0.01, $^{**}p <$ 0.001, vs. control. (Bottom left) CRF mRNA signal in the paraventricular nucleus of the hypothalamus (PVN) and group means of transcript optical density (OD; arbitrary units of signal intensity corrected for background) in the parvocellular portion of the PVN (pPVN) in alcohol-naive ($n = 6$), nondependent ($n = 10$), and dependent ($n = 13$) animals 6–8 h into withdrawal from alcohol vapors (2–4 PM). CRF mRNA significantly decreased in the pPVN in dependent animals compared with alcohol-naive controls ($^{*}p =$ 0.01) but not compared with nondependent animals. The groups did not differ in CRF mRNA levels in the magnocellular division of the PVN (mPVN; data not shown). The data are expressed as mean + SEM. (Bottom right) In alcohol-dependent rats ($n = 8$), the levels of CRF mRNA, normalized to cyclophilin A, were significantly increased in punches of the central nucleus of the amygdala ($^{*}p <$ 0.05) compared with naive controls ($n = 11$), measured by quantitative real-time polymerase chain reaction. Top left and right reproduced from Makino et al., 1994a. Bottom left reproduced from Richardson et al., 2008. Bottom right reproduced from Roberto et al., 2010.

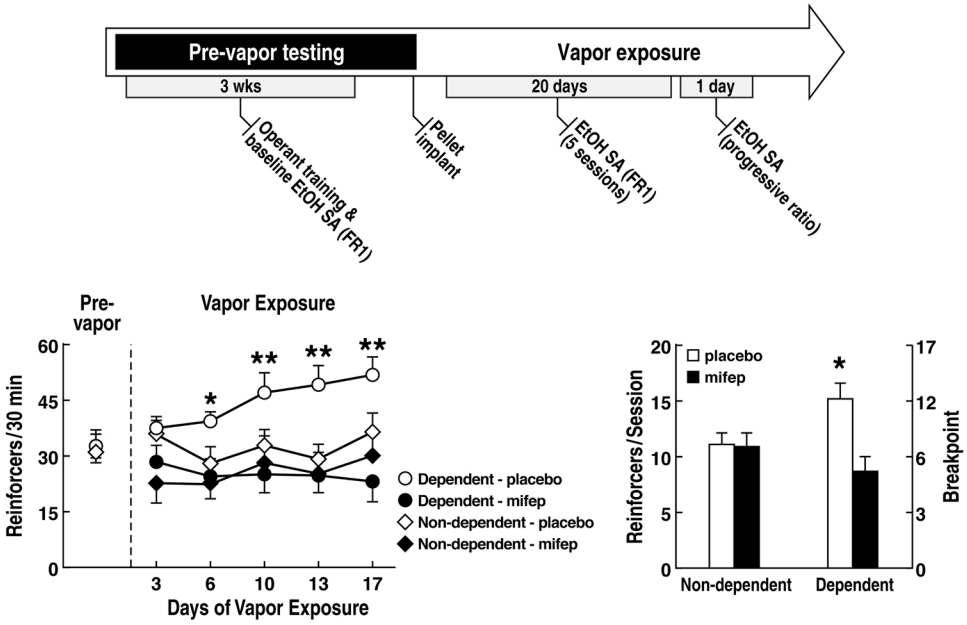

Fig. 9. Chronic glucocorticoid receptor blockade by mifepristone prevented the escalation of alcohol intake and motivation for alcohol in vapor-exposed animals. (Top) Timeline of the experiment. Dependent and nondependent rats were implanted with pellets for the chronic release of the glucocorticoid receptor antagonist mifepristone (150 mg for 21 days) or placebo before exposure to alcohol vapor. Mifepristone-treated vapor-exposed rats did not exhibit an escalation of alcohol intake (bottom left) or an increase in progressive-ratio responding (bottom right) compared with placebo-treated vapor-exposed rats. Mifepristone did not influence alcohol intake in nondependent rats. The data are expressed as mean ± SEM. $^{*}p <$ 0.05, significant difference from mifepristone-treated vapor-exposed rats; $^{+}p <$ 0.05, significant difference from placebo-treated nondependent rats. $n = 9$–10 per group. [Taken with permission from Vendruscolo et al., 2012].

bed nucleus of the stria terminalis and decreases CRF mRNA in the paraventricular nucleus of the hypothalamus. Thus, an initial exposure to high corticosterone, stimulated by moderate to heavy drinking, may stimulate CRF expression in the central nucleus of the amygdala and lateral bed nucleus of the stria terminalis, eventually leading to neuroadaptive changes, including the further sensitization of CRF activation in the extended amygdala and lower HPA function (Richardson et al., 2008; Makino et al., 1994a, b; Fig. 8). Consistent with this hypothesis, rats that were made dependent on alcohol by chronic intermittent alcohol vapor exposure exhibited glucocorticoid receptor mRNA downregulation in several stress/reward-related brain areas during acute withdrawal. Glucocorticoid receptor upregulation was observed during protracted alcohol abstinence. Chronic glucocorticoid receptor blockade with mifepristone, when administered systemically during the course of alcohol vapor exposure, prevented the escalation of alcohol intake and blocked the increase in progressive-ratio responding for alcohol in dependent animals (Vendruscolo et al., 2012; Fig. 9). Chronic, systemic glucocorticoid receptor antagonist treatment also blocked escalated and compulsive alcohol drinking during protracted abstinence in rats with a history of alcohol dependence. These results

suggest a critical role for glucocorticoid receptors in the development and maintenance of alcohol dependence.

The mechanisms for the differential control of CRF transcription by corticosteroids in the paraventricular nucleus of the hypothalamus vs. central nucleus of the amygdala are not yet fully known. One hypothesis is that tissue-specific differences in steroid receptor coactivators, such as SRC-1, might play a role in the neuron-specific action of glucocorticoids on CRF transcription (Kovacs, 2013). The SRC1α isoform is highly expressed in the paraventricular nucleus of the hypothalamus, whereas the central nucleus of the amygdala is enriched with SRC1ε. This differential expression was shown to correlate with the differential effect of corticosterone in these areas (Meijer et al., 2000).

Brain stress systems are not limited to CRF (Koob, 2015). Our hypothesis is that multiple neurotransmitter systems converge on the extended amygdala to address the needs of an organism to respond to an acute stressor but also to sustain a response to a chronic stressor (e.g., the cycle of repeated binge-withdrawal in addiction). In this vein, other modulatory brain neurotransmitter systems that have pro-stress actions also converge on the extended amygdala and include norepinephrine, vasopressin, substance P, hypocretin (orexin), and dynorphin, all of which may contribute to negative emotional states that are associated with drug withdrawal or protracted abstinence (Koob, 2008). κ-Opioid receptor agonists (administered systemically) and dynorphins (administered intracerebrally) produce aversive-like effects in both animals and humans (Shippenberg et al., 2007; Wee and Koob, 2010; Mucha and Herz, 1985; Pfeiffer et al., 1986) and have been hypothesized to mediate negative emotional states that are associated with drug withdrawal (Chartoff et al., 2012; Schindler et al., 2010; Land et al., 2009; McLaughlin et al., 2003; Redila and Chavkin, 2008; Land et al., 2008; McLaughlin et al., 2006; Knoll et al., 2007; Mague et al., 2003). High compulsive-like drug intake that is associated with extended access to and dependence on methamphetamine, heroin, and alcohol is blocked by both systemic and intracerebral κ-opioid receptor antagonist administration (Walker et al., 2010; Wee et al., 2009; Schlosburg et al., 2013; Whitfield et al., 2015). Two sites for these actions are the shell of the nucleus accumbens and amygdala (Nealey et al., 2011; Schlosburg et al., 2013; Kallupi et al., 2013), suggesting a κ-opioid receptor–dynorphin contribution within the extended amygdala to negative emotional states (Chavkin and Koob, 2016). High compulsive-like alcohol drinking in dependent rats during withdrawal can also be blocked by a β-adrenergic receptor antagonist, α_1 adrenergic receptor antagonist, κ-opioid receptor antagonist, vasopressin 1b receptor antagonist, glucocorticoid receptor antagonist, and neuroimmune system antagonist (Koob, 2008, 2017). High compulsive-like heroin intake in the model of extended-access self-administration was blocked by a substance P antagonist and hypocretin-2 antagonist (Barbier et al., 2013; Schmeichel et al., 2015; Fig. 7**B**).

Similarly, one may hypothesize that the vulnerability to drive an allostatic state may derive not only from the activation of pro-stress neurotransmitter systems but also from anti-stress neurotransmitter systems. Anti-stress neurotransmitter systems may serve as neuroadaptive buffers to the pro-stress actions that are described above. Neurotransmitter/neuromodulator systems that are implicated in anti-stress actions include neuropeptide Y (NPY), nociceptin, and endocannabinoids. Neuropeptide Y has powerful orexigenic and anxiolytic effects and has been hypothesized to act in opposition to the actions of CRF in addiction (Heilig and Koob, 2007). The activation of NPY in the central nucleus of the amygdala has opposite effects to CRF, in which NPY, injected into the brain, blocks the increase in GABA release in the central nucleus of the amygdala that is produced by alcohol, blocks high compulsive-like alcohol administration, and blocks the transition to excessive drinking with the development of dependence (Gilpin et al., 2003,2008,2011; Thorsell et al., 2005a,b, 2007). Nociceptin (also known as orphanin FQ) has anti-stress-like effects in animals (Ciccocioppo et al., 2003; Martin-Fardon et al., 2010). Nociceptin and synthetic NOP receptor agonists have effects on GABA synaptic activity in the central nucleus of the amygdala that are similar to NPY and can block high alcohol consumption in a genetically selected line of rats that is known to be hypersensitive to stressors (Economidou et al., 2008). Evidence also implicates endocannabinoids in the regulation of affective states, in which reductions of cannabinoid CB_1 receptor signaling produce anxiogenic-like behavioral effects (Serrano and Parsons, 2011). Blocking endocannabinoid clearance can also block some drug-seeking behaviors (Scherma et al., 2008; Adamczyk et al., 2009; Forget et al., 2009). Thus, endocannabinoids may play a protective role in preventing drug dependence by buffering the stress activation that is associated with withdrawal (see Fig. 7**B**).

Neuropharmacological studies that systemically administered neurotransmitter-modulating agents found that drugs that have either anti-stress or antidepressant-like activity in other animal models blocked the withdrawal-induced elevations of reward thresholds for most major drugs of abuse (Koob, 2017). Using nicotine as an example, a nicotinic receptor partial agonist, CRF_1 receptor antagonist (Bruijnzeel et al., 2007, 2009, 2012; Marcinkiewcz et al., 2009), vasopressin 1b receptor antagonist (Qi et al., 2015), and α_1 noradrenergic receptor antagonist (Bruijnzeel et al., 2010) blocked the elevations of reward thresholds that were produced by withdrawal from chronic high-dose nicotine exposure. A CRF_1 receptor antagonist, injected systemically, also reversed the elevations of reward thresholds that were produced by alcohol withdrawal (Bruijnzeel et al., 2010).

In summary, a multi-determined neurocircuitry promotes the activation of pro-stress neuromodulators and, combined with a weakening or inadequate anti-stress response, leads to negative emotional states that set up an allostatic hedonic load that drives negative reinforcement. Under this framework, a strong multi-determined buffer, if activated and sufficient to allow the pro-stress systems to recover, may help return the organism to homeostasis.

3.5. The pain of addiction: hyperkatifeia

In humans, withdrawal from opioids and alcohol can lower pain thresholds and exacerbate pain. Heightened pain perception has long been observed in individuals with addiction to opioids (Ho and Dole, 1979). Patients who are on methadone maintenance have low pain tolerance (Doverty et al., 2001), and pain is one of the main triggers of relapse to addiction in methadone-maintained individuals. Former opioid-addicted individuals who were maintained on either methadone or the opioid receptor partial agonist buprenorphine presented an increase in sensitivity to cold pressor pain (Compton et al., 2001). Others have found that a hyperalgesic state can persist for up to 5 months in abstinent individuals with opioid addiction, and addicted individuals with more pain sensitivity also exhibited greater cue-induced craving at this time point (Ren et al., 2009). Subjects who were in acute withdrawal (24–72 h) from opioids or protracted abstinence (average of 30 months) exhibited decreases in pain thresholds and pain tolerance in the ischemic pain submaximal tourniquet procedure, and these effects were exacerbated by negative emotional states. Individuals in all groups (i.e., nonusers, ex-users, and withdrawn users) exhibited lower pain tolerance after viewing negative pictures compared with tolerance latencies that were observed after viewing positive and neutral pictures. Indeed, even acute opioid administration can produce hyperalgesia in humans (Compton et al., 2003). Here, healthy non-opioid-dependent men who were tested in an acute opioid physical dependence paradigm exhibited the presence of hyperalgesia in response to experimental cold-pressor pain using three different pretreatment opioid administration protocols whereby acute physical dependence was precipitated by naloxone (Compton et al., 2003).

Heighted pain perception has also been observed during alcohol withdrawal. Patients who were undergoing acute withdrawal from alcohol exhibited greater heat pain sensitivity to a noxious thermal stimulus (Jochum et al., 2010). Again, the perceived painful thermal sensation was more intense in patients who were experiencing negative

affective states, in which pain tolerance correlated with their scores on the Beck Depression Inventory (Jochum et al., 2010).

In animal models, withdrawal from chronic self-administration of opioids and alcohol produced hyperalgesia (i.e., lowered pain thresholds; Egli et al., 2012). With opioids, hyperalgesia has been observed in numerous studies (Martin et al., 1987: Tilson et al., 1973). Animals that were allowed extended access to intravenous heroin self-administration developed dependence and compulsive-like responding and exhibited hyperalgesia during withdrawal (Edwards et al., 2012). Hyperalgesia was partially blocked by systemic administration of a CRF_1 receptor antagonist (Edwards et al., 2012). More compelling, every-other-day administration of a CRF receptor antagonist blocked the development of escalation of heroin intake and the development of hyperalgesia (Park et al., 2015). CRF_1 receptors mediate the pronociceptive effects of this peptide, and this relationship is mediated at least partially by the central nucleus of the amygdala (Ji and Neugebauer, 2007; Fu and Neugebauer, 2008). CRF_1 receptors also mediate pain-related anxiety-like behavior (Ji et al., 2007). The antinociceptive effects of CRF_1 receptor antagonists have been demonstrated across several pain models, although this class of drugs does not alter various pain-related indices (e.g., audible or ultrasonic vocalizations or paw withdrawal thresholds) in non-injured animals (e.g., Fu and Neugebauer, 2008).

In animal models of excessive alcohol intake and alcohol dependence, early work showed that hyperalgesia was produced when an alcohol (6.5%)-containing diet was fed continuously to male rats, and hyperalgesia took 4 weeks to develop (Dina et al., 2000). In another, more binge-like paradigm, feeding an alcohol diet (6.5%) in repeated cycles of 4 days of alcohol followed by 3 days without alcohol resulted in withdrawal-induced hyperalgesia that began at the end of one weekly cycle and reached a maximum during the fourth cycle. This withdrawal-induced hyperalgesia, similar to the hyperalgesia that is induced by continuous, chronic alcohol intake, was reversibly inhibited by intrathecal administration of an antisense oligodeoxynucleotide to protein kinase Cε (Dina et al., 2006). Using an operant oral self-administration model, animals that were trained to self-administer alcohol and were made dependent escalated their intake and exhibited hyperalgesia during withdrawal (Edwards et al., 2012). This hyperalgesia was partially blocked by systemic administration of a CRF_1 receptor antagonist, consistent with the results that were observed with opioid-dependent rats (see above). These results are consistent with the studies by Neugebauer and colleagues with regard to the role of the extrahypothalamic CRF stress system in pain modulation.

As described above, the neural substrates that underlie allostatic emotional changes that are seen in addiction include decreases in reward function that are mediated by neurochemical changes in the ventral striatum (molecular neuroadaptations in medium spiny neurons and loss of function of the dopamine system) and increases in brain stress system function that are mediated by neurochemical changes in the extended amygdala (recruitment of CRF, dynorphin, and norepinephrine; Koob, 2015). From a conceptual perspective of emotion, links have been hypothesized to exist between the neural mechanisms that are responsible for a hypersensitive negative emotional state (termed “hyperkatifeia”) and opioid-induced hyperalgesia (Shurman et al., 2010). Hyperkatifeia was defined as a greater intensity of the constellation of negative emotional/motivational symptoms and signs that are observed during withdrawal from drugs of abuse (derived from the Greek “katifeia” for dejection or negative emotional state). The hypothesis was that hyperkatifeia is more likely to occur in subjects in whom excessive opioid use produces a break with homeostasis and less likely to occur when the opioid is restoring homeostasis, such as in effective pain treatment (Shurman et al., 2010).

For example, evidence suggests that the neural substrates of stress system neuroadaptations that are associated with addiction may overlap with substrates of emotional aspects of pain processing in such areas as the amygdala (Neugebauer, 2007). The spino (trigemino)-ponto-amygdaloid pathway projects from the dorsal horn of the spinal cord to the mesencephalic parabrachial area and then to the central nucleus of the amygdala. This pathway has been implicated in processing emotional components of pain perception (Price, 2000; Bester et al., 1995; Fig. 10).

Pain-responsive neurons are also abundant in the lateral part of the central nucleus of the amygdala (Neugebauer and Li, 2002), an area that may also be responsible for negative emotional responses to abused drugs (Funk et al., 2006). As noted above, opioid withdrawal and alcohol withdrawal in animal models of compulsive-like self-administration produce greater anxiety-like responses and hyperalgesia, both of which are blocked by CRF receptor antagonists (Edwards et al., 2012).

Thus, one hypothesis to explain the crosstalk between opioid addiction and chronic pain syndromes is that some patients may be more prone to the development of hyperkatifeia during withdrawal. An allostatic view would suggest that opioid-induced hyperalgesia and hyperkatifeia would be much more likely to occur during chronic opioid administration if excessive opioids are administered. One could argue that because of overdosing, rapid escalation (overshooting), pharmacokinetic variables, or genetic sensitivity, the body will react to that perturbation with the engagement of the opponent processes of hyperalgesia and hyperkatifeia that are mediated by significant crosstalk in such brain structures as the central nucleus of the amygdala. The repeated engagement of opponent processes without time for the system to reestablish homeostasis will engage the allostatic mechanisms that are described above. Such a framework suggests that the manifestation of opioid-induced hyperalgesia has important clinical implications: (*i*) the opioid has exceeded the amount that is effective for pain control, and (*ii*) susceptible individuals are at risk for developing hyperkatifeia, the unstable emotional and behavioral state that underlies addiction (Shurman et al., 2010). One test of subhypothesis (*i*) above would be to chart hyperalgesic responses during postoperative pain management and then follow up by longitudinally charting opioid misuse postoperatively over time in a cohort of individuals who receive opioid medications for acute postoperative pain. One could then observe whether carefully limiting opioids that are sufficient to manage pain, by possibly utilizing a method such as patient-controlled analgesia (MacIntyre, 2001), would minimize subsequent abuse.

Between-system changes in brain stress systems also have a genetic, genetic-environment, even possibly epigenetic overlay. For example, at least two single-nucleotide polymorphisms (SNPs) of the CRF_1 receptor gene (*Crhr1*) have been associated with binge drinking in adolescents and excessive drinking in adult humans (Treutlein et al., 2006), suggesting a mechanism for genetic and epigenetic interactions. One possibility is that such an SNP might alter gene regulation through epigenetic processes that are related to differences in genetic sequence. For example, specific SNP-containing intergenic transcript alleles regulate numerous chromatin modifier genes, thus directly linking SNPs and epigenetic regulation (Zaina et al., 2010). Here, epigenetics can be defined as the study of mechanisms of gene regulation that are dependent on chromatin architecture (Zaina et al., 2010). Several polymorphisms of human CRF system molecules have also been associated with excessive alcohol use phenotypes, often in interactions with a history of stress. One of these SNPs, rs1876831 (C allele), that showed homozygosity was associated with heavy drinking relative to stressful life events in adolescents (Blomeyer et al., 2008). *Crhr1* SNPs also predicted greater alcohol consumption in individuals who were already dependent (Treutlein et al., 2006), and significant associations were found between P3 amplitude and alcohol dependence and multiple SNPs of the *Crhr1* gene (Chen et al., 2010). The rs1876831 SNP is located in an intron region that can potentially influence transcription of the CRF_1 receptor gene in response to stress (Schmid et al., 2010; but see Blomeyer et al., 2008). Finally, a history of stress was shown to produce greater increases in future alcohol intake (Blomeyer et al., 2008; Schmid et al., 2010) and an earlier onset of drinking (Schmid et al., 2010) in adolescents who were homozygous for the C allele of the rs1876831 SNP of the *Crhr1* gene. Adolescent carriers of the A allele of

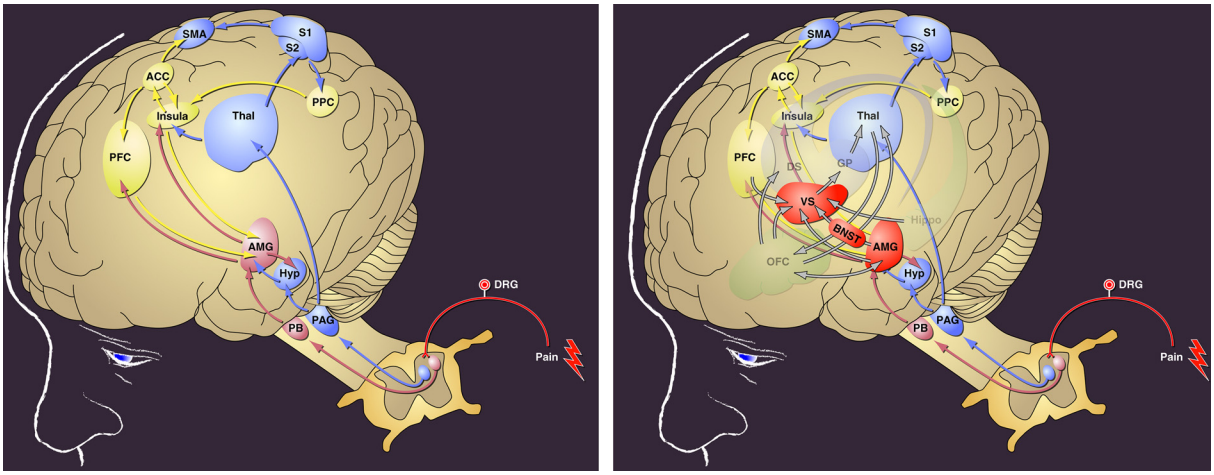

Fig. 10. Pathways for the supraspinal processing of pain superimposed on key elements of addiction circuitry that are implicated in negative emotional states. Blue structures are involved in the "fast" processing of pain via the spinothalamic tract and arrive indirectly at the amygdala. Pink structures are involved in the "fast" processing of pain via the spinal-parabrachial-amygdala pathway and arrive directly at the amygdala. Yellow structures are involved in the "slower" cognitive processing of pain. Addiction circuitry is composed of structures that are involved in the three stages of the addiction cycle: *binge/intoxication* (ventral striatum, dorsal striatum, thalamus), *withdrawal/negative affect* (ventral striatum, bed nucleus of the stria terminalis, central nucleus of the amygdala; red structures), *preoccupation/anticipation* (prefrontal cortex, orbitofrontal cortex, hippocampus). Notice significant overlap of the supraspinal processing of pain and addiction in the amygdala. Modified with permission from Blackburn-Munro and Blackburn-Munro (2003) and Koob et al. (2008). ACC, anterior cingulate cortex; AMG, amygdala; BNST, bed nucleus of the stria terminalis; DRG, dorsal root ganglion; DS, dorsal striatum; GP, globus pallidus; Hippo, hippocampus; Hyp, hypothalamus; Insula, insular cortex; OFC, orbitofrontal cortex; PAG, periaqueductal grey; PB, parabrachial nucleus; PPC, posterior parietal cortex; S1, S2, somatosensory cortex; SMA, supplementary motor area; Thal, thalamus; VS, ventral striatum.

the rs242938 SNP of *Crhr1* reported more drinking when exposed to stress.

Genetic associations between CRF signaling and alcohol phenotypes in humans have also been linked to genetic variants of the CRF binding protein gene *CRHBP*. Here, polymorphisms of *CRHBP* would be hypothesized to modulate the amount of CRF that is available to interact with its receptors. Polymorphisms of *CRHBP* have been related to lower electroencephalographic alpha wave power (Enoch et al., 2008), an endophenotype of alcohol use disorder (Enoch et al., 2008; Begleiter and Platz, 1972). *CRHBP* polymorphisms are also more prevalent in individuals with alcohol use disorder with comorbid anxiety disorders (Enoch et al., 1999). Moreover, *CRHBP* polymorphisms have been hypothesized to impact anxiety or drinking in alcohol-dependent individuals (Haass-Koffler et al., 2016) and to be related to the severity of stress-induced alcohol craving (Ray, 2011). Both *CRHR1* and *CRHBP* may coordinate to convey vulnerability. Elevations of *CRHR1* mRNA levels relative to *CRHBP* mRNA levels in mononuclear blood cells were observed in individuals who carried the dual polymorphism, suggesting that CRF_1 receptor activation by CRF predominates over CRF/CRF binding protein interactions in individuals with a high predisposition to the development of alcohol use disorder (Ribbe et al., 2011). In a panel of schizophrenia patients, individual *CRHBP* and *CRHR1* SNPs together have been shown to predict alcohol use disorder comorbidity (Ribbe et al., 2011).

4. *Preoccupation/anticipation* stage: executive function, protracted abstinence, and stress-induced reinstatement

4.1. Hypothesis

The prefrontal cortex in humans engages general function and control at least partially via inhibitory control over the basal ganglia to mediate impulsivity and the extended amygdala to mediate compulsivity. The hypothesis here is that activation of the HPA axis and extrahypothalamic CRF system negatively impacts the prefrontal cortex to impair this top-down connectivity and help feed growing allostatic changes in the extended amygdala brain stress systems and residual vulnerability to stress-induced relapse.

4.2. Prefrontal cortex, CRF, and top-down control

Drug addiction in humans is associated with the dysregulation of frontal cortex function in humans in two domains: cognitive impairments (including poor working memory, inattention, and impairments in delay discounting; Volkow et al., 2011; Jentsch and Taylor, 1999) and cue-induced craving (which activates the dorsolateral prefrontal cortex, anterior cingulate gyrus, and medial orbitofrontal cortex; Jasinska et al., 2014; Niendam et al., 2012). Such activation of the reward/salience systems during acute craving episodes is further potentiated in humans because of a decrease in the inhibitory function of the prefrontal cortex (ventromedial prefrontal cortex, orbitofrontal cortex, and cingulate cortex; Bechara et al., 1999; Johnstone et al., 2007; Goldstein and Volkow, 2011). The interaction between the "STOP" signal that is processed by the ventromedial prefrontal cortex and "GO" signal that is processed by the dorsolateral prefrontal cortex may be another source of allostatic load in protracted abstinence that is associated with the *preoccupation/anticipation* stage (Johnstone et al., 2007; Koob and Volkow, 2016; Fig. 11).

Rats exhibit high levels of CRF-expressing neurons in the cortex. Abstinence from alcohol in rats with a history of escalation of alcohol intake specifically recruited GABAergic ($GAD_{67}+$) and CRFergic neurons in the medial prefrontal cortex (George et al., 2012). These animals also exhibited working memory impairments that were associated with excessive alcohol drinking during acute (24–72 h) but not protracted (16–68 days) abstinence. Moreover, abstinence from alcohol was associated with a functional disconnection between the medial prefrontal cortex and central nucleus of the amygdala but not between the medial prefrontal cortex and nucleus accumbens, suggesting the recruitment of a subset of GABAergic and CRFergic neurons in the medial prefrontal cortex during withdrawal. Disconnection of the prefrontal cortex from the central nucleus of the amygdala pathway may be critical for impairments in executive control over motivated behavior, suggesting that the dysregulation of medial prefrontal cortex interneurons may be an early index of neuroadaptation in alcohol dependence (George et al., 2012).

Vulnerability to relapse is common in individuals with a history of addiction. A key challenge is to understand the mechanisms of relapse.

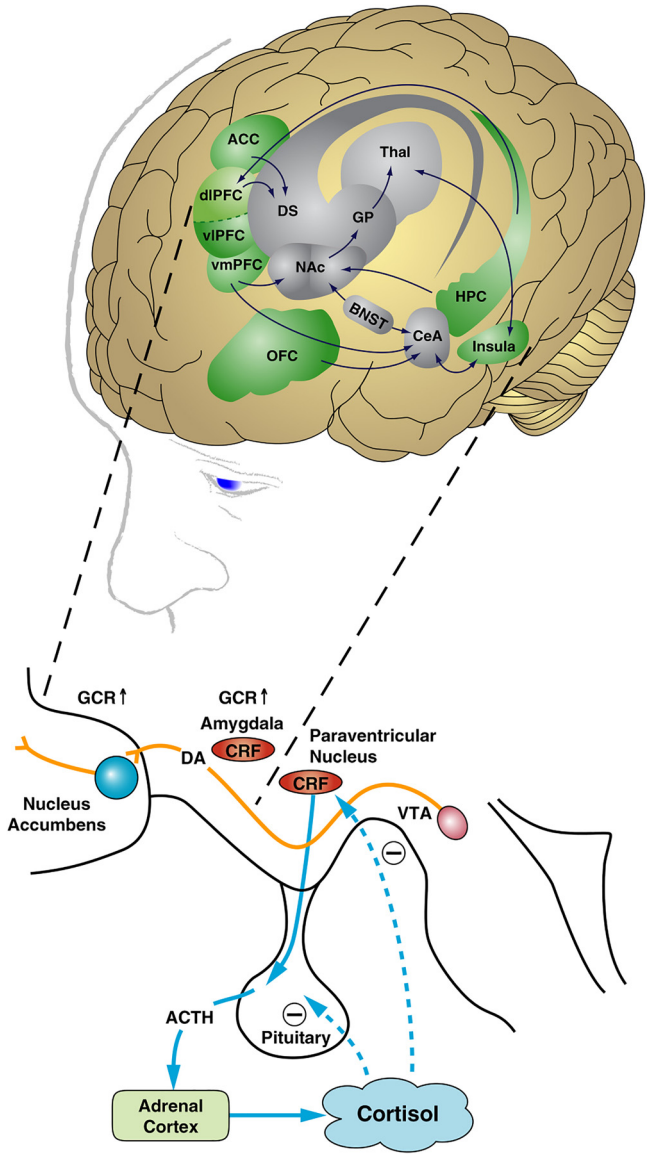

Fig. 11. Conceptual framework of the way in which dysregulation of the hypothalamic-pituitary-adrenal axis and extrahypothalamic CRF systems can influence the *preoccupation/anticipation* stage of the addiction cycle to drive allostasis in addiction. Here, CRF in the prefrontal cortex in parallel with the activation of glucocorticoid receptors by chronic dysregulation of glucocorticoid function (bottom) can drive an increase in craving and a decrease in inhibitory control that are associated with protracted abstinence. ACC, anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex; OFC, orbitofrontal cortex; DS, dorsal striatum; NAc, nucleus accumbens; GP, globus pallidus; Thal, thalamus; BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; HPC, hippocampus; DA, dopamine; CRF, corticotropin-releasing factor; VTA; ventral tegmental area; ACTH, adrenocorticotropic hormone.

As noted above, higher levels of corticosterone may increase the salience of objects or cues that are associated with psychostimulant administration and the sensation-seeking aspects of drug reward (Piazza et al., 1993). Glucocorticoids feedback and drive extrahypothalamic CRF in the extended amygdala in the *withdrawal/negative affect* stage, but these allostatic changes also impact the *preoccupation/anticipation* stage. Discernment of the ways in which glucocorticoids interact with cortical CRF neurons and the resulting functional consequences remains a challenge for future studies.

4.3. Protracted abstinence

Environmental cues and contexts play a key role in relapse. The argument herein is that a critical component of relapse involves what we argue is residual hyperkatifeia. Two-thirds of relapse to alcohol use disorder can be attributed to stress (Marlatt and Gordon, 1980). A factor analysis of Marlatt's relapse taxonomy found that negative emotion, including elements of anger, frustration, sadness, anxiety, and guilt, is a key factor in relapse (Zywiak et al., 1996), and negative affect was the leading precipitant of relapse in a large-scale replication of Marlatt's taxonomy (Lowman et al., 1996). Another term for the state of stress and vulnerability to relapse, post-acute withdrawal, is protracted abstinence, which has been defined in humans as a Hamilton Depression rating ≥ 8 with the following three items that are consistently reported by subjects: depressed mood, anxiety, and guilt (Mason et al., 1994).

During protracted abstinence, there may be residual glucocorticoid system activation that contributes to the *preoccupation/anticipation* stage. Preclinical data suggest that during protracted abstinence in rats, after acute withdrawal (usually ≥ 2 weeks), glucocorticoid receptors are upregulated. Using an animal model of compulsive-like alcohol seeking in rats, dependent animals exhibited glucocorticoid receptor mRNA downregulation in several stress/reward-related brain areas during acute withdrawal and glucocorticoid receptor upregulation during protracted alcohol abstinence (Vendruscolo et al., 2012). More specifically, glucocorticoid receptor levels increased in the nucleus accumbens core, central nucleus of the amygdala, and ventral bed nucleus of the stria terminalis during protracted alcohol abstinence, suggesting receptor adaptation when alcohol exposure ceased (Fig. 11). As noted above, a functional role for glucocorticoid receptors in alcohol dependence was demonstrated by showing that chronic glucocorticoid receptor blockade during the course of alcohol vapor exposure prevented the escalation of alcohol intake and blocked the increase in progressive-ratio responding. However, chronic glucocorticoid receptor antagonism also blocked escalated and compulsive alcohol drinking during protracted abstinence in rats with a history of alcohol dependence (Vendruscolo et al., 2012). Similar effects were observed with acute mifepristone administration during protracted abstinence in rats (Vendruscolo et al., 2015), and mifepristone also blocked craving for alcohol in a human laboratory study of non-treatment-seeking alcohol-dependent individuals and decreased their drinking (Vendruscolo et al., 2015). As noted above, escalated alcohol intake during protracted abstinence may also involve glucocorticoid receptors and re-engagement of the motivational impact of incentive salience that is observed in the *binge/intoxication* stage (Piazza et al., 1989). Thus, opposite changes in glucocorticoid receptor levels during acute alcohol withdrawal and protracted abstinence may play a role in the sensitivity to stress/reward and escalated alcohol intake during the three stages of alcohol use disorder.

4.4. Stress-induced relapse

A surrogate for human stress-induced relapse in animal studies is stress-induced reinstatement (Shaham et al., 2000). One key brain region that mediates stress-induced reinstatement in animal models appears to be the bed nucleus of the stria terminalis in the extended amygdala, and a key neurotransmitter is central CRF (Shaham et al., 2000). The bed nucleus of the stria terminalis is linked to CRF-related effects on anxiety-like behavioral responses (Davis et al., 1997). CRF receptor antagonism in the bed nucleus of the stria terminalis interferes with footshock-induced relapse, but this does not occur when the CRF antagonist is infused in the amygdala. Conversely, when CRF is infused directly in the bed nucleus of the stria terminalis, cocaine self-administration increases, but this does not occur when CRF is directly infused in the amygdala (Erb and Stewart, 1999). Thus, the bed nucleus of the stria terminalis also appears to be linked to some of the withdrawal

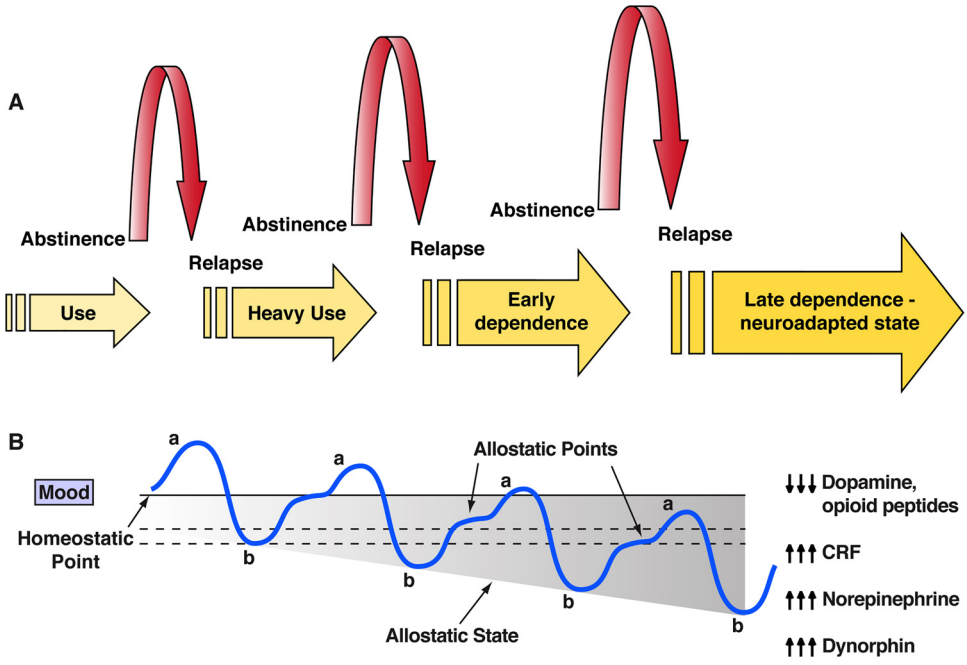

Fig. 12. Allostatic change in emotional state associated with the transition to addiction. (A) Schematic of the progression of dependence over time, illustrating the shift in underlying motivational mechanisms. From initial, positive reinforcing, pleasurable effects of the drug, the addictive process progresses over time to a point at which it is maintained by negative reinforcing relief from a negative emotional state. Neuroadaptations that encompass the recruitment of extrahypothalamic CRF systems are key to this shift. Taken with permission from Heilig and Koob (2007). (B) The *a-process* represents a positive hedonic or positive mood state, and the *b-process* represents the negative hedonic or negative mood state. The affective stimulus (state) has been argued to be the sum of both the *a-process* and *b-process*. An individual who experiences a positive hedonic mood state from a drug of abuse with sufficient time between re-administering the drug is hypothesized to retain the *a-process*. An appropriate counteradaptive opponent process (*b-process*) that balances the activational process (*a-process*) does not lead to an allostatic state. Changes in the affective stimulus (state) in an individual with repeated frequent drug use may represent a transition to an allostatic state in the brain reward systems and, by extrapolation, a transition to addiction. Notice that the apparent *b-process* never returns to the original homeostatic level before drug taking begins again, thus creating a progressively greater allostatic state in the brain reward system. The counteradaptive opponent-process (*b-process*) does not balance the activational process (*a-process*) but in fact shows residual hysteresis. Although these changes that are illustrated in the figure are exaggerated and condensed over time, the hypothesis is that even during post-detoxification (a period of protracted abstinence), the reward system still bears allostatic changes. The following definitions apply: *allostasis*, the process of achieving stability through change; *allostatic state*, a state of chronic deviation of the regulatory system from its normal (homeostatic) operating level; *allostatic load*, the cost to the brain and body of the deviation, accumulating over time, and reflecting in many cases pathological states and the accumulation of damage. Modified with permission from Koob and Le Moal (2001).

symptoms that are experienced when individuals with a history of drug abuse who are stressed begin to crave the drug again.

5. Allostasis in addiction as a model of psychopathology of motivational processes

Allostatic-like changes in stress function may also apply to other pathological states that are challenged by external and internal events. The argument is that such allostatic changes dramatically impact the hedonic reward systems to drive compulsive drug seeking via the construct of negative reinforcement (Fig. 12). Severe compulsive disorders, such as obsessive-compulsive disorder, are known to be associated with compulsive-like behavior to reduce discomfort, often resulting in high anxiety in the context of obsessions about fear of harm or contamination (Hollander, 1993). Other psychiatric disorders within the obsessive-compulsive spectrum take on characteristics of compulsivity and have common face validity with the phenotype of addiction in the sense that negative emotional states can develop that appear to drive compulsive behavior. These such disorders as kleptomania ("Disruptive, Impulse-Control, and Conduct Disorders"), gambling disorder ("Substance-Related and Addictive Disorders"), and trichotillomania ("Obsessive-Compulsive and Related Disorders"; American Psychiatric Association, 2013). Similarly, elements of compulsivity can be found in compulsive shopping, compulsive sexual behavior, compulsive eating, compulsive exercise, and compulsive computer use (Hollander and Benzaquen, 1997). Refinement of the human neuropsychological and neurobiological measures using a neuroclinical approach (Kwako and Koob, 2017) will help elucidate whether the same neurobiological circuits that are related to emotional function that are dysregulated in drug addiction overlap with those that are dysregulated in other stress-related psychopathologies.

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