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Invited review

Addiction as a stress surfeit disorder

George F. Koob*, Cara L. Buck, Ami Cohen, Scott Edwards, Paula E. Park, Joel E. Schlosburg, Brooke Schmeichel, Leandro F. Vendruscolo, Carrie L. Wade, Timothy W. Whitfield Jr., Olivier George

Committee on the Neurobiology of Addictive Disorders, The Scripps Research Institute, 10550 North Torrey Pines Road, SP30-2400, La Jolla, CA 92037, USA

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ABSTRACT

Drug addiction has been conceptualized as a chronically relapsing disorder of compulsive drug seeking and taking that progresses through three stages: *binge/intoxication*, *withdrawal/negative affect*, and *preoccupation/anticipation*. Drug addiction impacts multiple motivational mechanisms and can be conceptualized as a disorder that progresses from positive reinforcement (*binge/intoxication* stage) to negative reinforcement (*withdrawal/negative affect* stage). The construct of negative reinforcement is defined as drug taking that alleviates a negative emotional state. Our hypothesis is that the negative emotional state that drives such negative reinforcement is derived from dysregulation of key neurochemical elements involved in the brain stress systems within the frontal cortex, ventral striatum, and extended amygdala. Specific neurochemical elements in these structures include not only recruitment of the classic stress axis mediated by corticotropin-releasing factor (CRF) in the extended amygdala as previously hypothesized but also recruitment of dynorphin–κ opioid aversive systems in the ventral striatum and extended amygdala. Additionally, we hypothesized that these brain stress systems may be engaged in the frontal cortex early in the addiction process. Excessive drug taking engages activation of CRF not only in the extended amygdala, accompanied by anxiety-like states, but also in the medial prefrontal cortex, accompanied by deficits in executive function that may facilitate the transition to compulsive-like responding. Excessive activation of the nucleus accumbens via the release of mesocorticolimbic dopamine or activation of opioid receptors has long been hypothesized to subsequently activate the dynorphin–κ opioid system, which in turn can decrease dopaminergic activity in the mesocorticolimbic dopamine system. Blockade of the κ opioid system can also block anxiety-like and reward deficits associated with withdrawal from drugs of abuse and block the development of compulsive-like responding during extended access to drugs of abuse, suggesting another powerful brain stress/anti-reward system that contributes to compulsive drug seeking. Thus, brain stress response systems are hypothesized to be activated by acute excessive drug intake, to be sensitized during repeated withdrawal, to persist into protracted abstinence, and to contribute to the development and persistence of addiction. The recruitment of anti-reward systems provides a powerful neurochemical basis for the negative emotional states that are responsible for the dark side of addiction.

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1. Conceptual framework for the dark side of addiction

Addiction has been conceptualized as a three-stage cycle—*binge/intoxication*, *withdrawal/negative affect*, and *preoccupation/anticipation*—with two primary sources of reinforcement: positive and negative reinforcement. Positive reinforcement is defined as the process by which presentation of a stimulus increases the probability of a response; negative reinforcement is defined as the process by which removal of an aversive stimulus (or aversive state in the case of addiction) increases the probability of a response. Secondary sources of reinforcement include conditioned positive and conditioned negative reinforcement. Different theoretical perspectives from experimental psychology (positive and negative reinforcement frameworks), social psychology (self-regulation failure framework), and neurobiology (counteradaptive and sensitization framework) can be superimposed on the stages of the

* Corresponding author. Tel.: +1 858 784 7062; fax: +1 858 784 7405.
E-mail address: gkoob@scripps.edu (G.F. Koob).

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addiction cycle (Koob and Le Moal, 1997). These stages are thought to feed into each other, become more intense, and ultimately lead to the pathological state known as *addiction*.

1.1. Motivation, withdrawal, and opponent process

Motivation is a state that involves arousal, emotion, and expectation, all of which direct behavior. William James, describing the far greater variety of impulses in humans, wrote, "some expectation of consequences must in every case like this be aroused; and this expectation, according as it is, that of something desired or of something disliked, must necessarily either reinforce or inhibit the mere impulse" (James, 1918, p. 390). Such motivational states are not constant but rather vary over time. The concept of motivation was inextricably linked with hedonic, affective, or emotional states in addiction in the context of temporal dynamics by Solomon's opponent process theory of motivation. Solomon and Corbit (1974) postulated that hedonic, affective, or emotional states, once initiated, are automatically modulated by the central nervous system through mechanisms that reduce the intensity of hedonic feelings. The *a-process* includes affective or hedonic activation, and the *b-process* includes affective or hedonic withdrawal (abstinence). The *a-process* in drug use consists of positive hedonic responses, occurs shortly after the presentation of a stimulus, correlates closely with the intensity, quality, and duration of the reinforcer, and shows tolerance. In contrast, the *b-process* in drug use appears after the *a-process* has terminated, consists of negative hedonic responses, and is sluggish in onset, slow to build up to an asymptote, slow to decay, and gets larger with repeated exposure. Indeed, one can argue that in fact the *b-process* begins early in response to the *a-process* and opposes the manifestation of the *a-process*, yielding the phenomenon of "apparent tolerance" (Colpaert, 1996). The thesis we have elaborated is that there is a neurocircuitry change of specific neurochemical systems that account for the *b-process*. Thus, such opponent processes are hypothesized to begin early in drug taking, reflecting not only deficits in brain reward system function but also recruitment of function in the brain stress systems. Furthermore, we hypothesize that recruitment of the brain stress systems forms one of the major sources for the development of negative reinforcement in addiction.

The manifestation of a withdrawal syndrome after the removal of chronic drug administration, is thus defined in terms of *motivational* symptoms, such as the emergence of a negative emotional state (e.g., dysphoria, anxiety, and irritability) when access to the drug is prevented (Koob and Le Moal, 2001), which can be exacerbated or even caused by the *physical* signs of withdrawal. Indeed, some have argued that the development of such a negative affective state can define dependence as it relates to addiction (Russell, 1976; Koob et al., 1989; Baker et al., 2004).

Negative emotional states have been characterized in humans during acute and protracted abstinence from all major drugs of abuse (American Psychiatric Association, 1994; Koob, 2012; Khantzian, 1997). Similar results have been observed in animal models with all major drugs of abuse using intracranial self-stimulation as a measure of hedonic tone. Withdrawal from chronic cocaine (Markou and Koob, 1991), amphetamine (Paterson et al., 2000), opioids (Schulteis et al., 1994), cannabinoids (Gardner and Vorel, 1998), nicotine (Epping-Jordan et al., 1998), and ethanol (Schulteis et al., 1995) leads to increases in reward threshold during acute abstinence, and some of these elevations in threshold can last for up to 1 week (Koob, 2009). These observations lend credence to the hypothesis that opponent processes in the hedonic domain have an identifiable neurobiological basis and provide an impetus for defining the mechanisms involved. Understanding the mechanisms that drive this increase in reward thresholds is key to understanding the mechanisms that drive negative reinforcement in addiction.

Such elevations in reward threshold begin rapidly and can be observed within a single session of self-administration (Kenny et al., 2003), bearing a striking resemblance to human subjective reports of acute withdrawal. Dysphoria-like responses also accompany acute opioid and ethanol withdrawal (Liu and Schulteis, 2004; Schulteis and Liu, 2006). Here, naloxone administration following single injections of morphine increased reward thresholds, measured by intracranial self-stimulation (ICSS), and increased thresholds with repeated morphine and naloxone-induced withdrawal experience (Liu and Schulteis, 2004). Similar results were observed during repeated acute withdrawal from ethanol (Schulteis and Liu, 2006).

The development of the aversive emotional state that drives the negative reinforcement of addiction is defined here as the "dark side" of addiction. We have argued that drug addiction progresses from a source of positive reinforcement that may early on involve a form of sensitization of incentive salience, as argued by Robinson and Berridge (1993), to sensitization of the brain stress and anti-reward systems that sets up a powerful negative reinforcement process. Anti-reward is a concept developed by Koob and Le Moal (2008), based on the hypothesis that brain systems are in place to limit reward (see footnote in Koob and Le Moal, 1997), with an opponent process concept that forms a general feature of biological systems. Our concept of an anti-reward system is derived from the hypothesis of both within- and between-system neuroadaptations to excessive activation of the reward system at the neurocircuitry level. Within-system neuroadaptations are defined as the process by which the primary cellular response element to the drug (circuit A) itself adapts to neutralize the drug's effects. Persistence of the opposing effects after the drug disappears produces adaptation. A between-system neuroadaptation is a circuitry change, in which circuit B (i.e., the anti-reward circuit) is activated by circuit A (i.e., the reward circuit) (Koob and Bloom, 1988). In the present treatise, we hypothesize that a within-system neuroadaptation can also result from a between-system neuroadaptation, in which circuit B (i.e., the anti-reward circuit) is activated either in parallel or in series to suppress the activity of circuit A (see below).

1.2. Animal models of the transition to an addiction-like state as defined by escalation in drug self-administration with prolonged access

A progressive increase in the frequency and intensity of drug use is one of the major behavioral phenomena that characterize the development of addiction and has face validity with the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) "The substance is often taken in larger amounts and over a longer period than was intended" (American Psychological Association, 1994). A framework with which to model the transition from drug use to drug addiction can be found in recent animal models of prolonged access to intravenous cocaine self-administration. Historically, animal models of cocaine self-administration involved the establishment of stable behavior from day to day to allow the reliable interpretation of data provided by within-subject designs aimed at exploring the neuropharmacological and neurobiological bases of the reinforcing effects of acute cocaine. Up until 1998, after the acquisition of self-administration, rats were typically allowed access to cocaine for 3 h or less per day to establish highly stable levels of intake and patterns of responding between daily sessions. This was a useful paradigm for exploring the neurobiological substrates for the acute reinforcing effects of drugs of abuse.

However, in an effort to explore the possibility that differential access to drugs of abuse may have more face validity for the compulsive-like responding observed in addiction, animals have been allowed extended access to all major drugs of abuse (Fig. 1). Increased intake was observed in the extended access group for intravenous cocaine, methamphetamine, heroin, and nicotine and oral alcohol during extended access and dependence (Ahmed et al., 2000; Ahmed and Koob, 1998; Kitamura et al., 2006; O'Dell et al., 2004; George et al., 2007; Quadros and Miczek, 2009; Vendruscolo et al., 2011). For example, when animals were allowed access for 1 and 6 h to different doses of cocaine, both in an acute test, the long-access (LgA) and short-access (ShA) animals titrated their cocaine intake, but LgA rats consistently self-administered almost twice as much cocaine at any dose tested, further suggesting an upward shift in the set point for cocaine reward in the escalated animals (Ahmed and Koob, 1999; Deroche-Gamonet et al., 2004; Mantsch et al., 2004).

Consistent with the hypothesis that extended access to drugs of abuse produces compulsive-like responding, in which animals will "continue to respond in the face of adverse consequences" (another DSM-IV criteria for Substance Dependence), animals with extended access that show escalation in self-administration also show

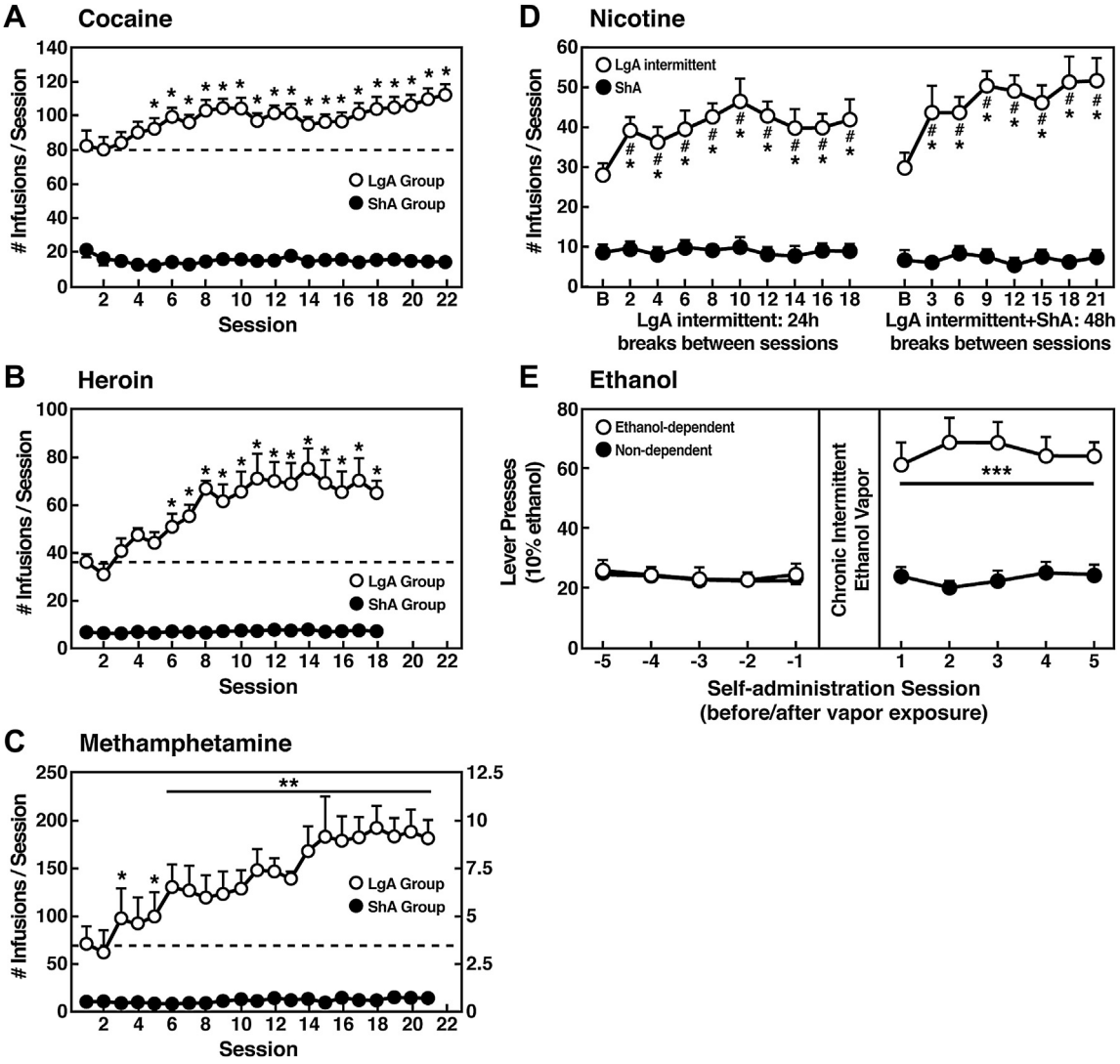

Fig. 1. (A) Effect of drug availability on cocaine intake (mean ± SEM). In long-access (LgA) rats ($n = 12$) but not short-access (ShA) rats ($n = 12$), the mean total cocaine intake started to increase significantly from session 5 ($p < 0.05$; sessions 5 to 22 compared with session 1) and continued to increase thereafter ($p < 0.05$; session 5 compared with sessions 8–10, 12, 13, and 17–22). [Taken with permission from Ahmed and Koob, 1998.] (B) Effect of drug availability on total intravenous heroin self-infusions (mean ± SEM). During the escalation phase, rats had access to heroin (40 μg per infusion) for 1 h (ShA rats, $n = 5$–6) or 11 h per session (LgA rats, $n = 5$–6). Regular 1-h (ShA rats) or 11-h (LgA rats) sessions of heroin self-administration were performed 6 days a week. The dotted line indicates the mean ± SEM number of heroin self-infusions in LgA rats during the first 11-h session. $^{*}p < 0.05$, different from the first session (paired t-test). [Taken with permission from Ahmed et al., 2000.] (C) Effect of extended access to intravenous methamphetamine on self-administration as a function of daily sessions in rats trained to self-administer 0.05 mg/kg/infusion of intravenous methamphetamine during the 6-h session. ShA, 1-h session (each unit dose, $n = 6$). LgA, 6-h session (0.05 mg/kg/infusion, $n = 4$). $^{*}p < 0.05$, $^{**}p < 0.01$, compared with day 1. [Taken with permission from Kitamura et al., 2006.] (D) Nicotine intake (mean ± SEM) in rats that self-administered nicotine under a fixed-ratio (FR) 1 schedule in either 21 h (long access [LgA]) or 1 h (short access [ShA]) sessions. LgA rats increased their nicotine intake on an intermittent schedule with 24–48 h breaks between sessions, whereas LgA rats on a daily schedule did not. The left shows the total number of nicotine infusions per session when the intermittent schedule included 24 h breaks between sessions. The right shows the total number of nicotine infusions per session when the intermittent schedule included 48 h breaks between sessions. $^{\#}p < 0.05$, compared with baseline; $^{*}p < 0.05$, compared with daily self-administration group. $n = 10$ per group. [Taken with permission from Cohen et al., 2012.] (E) Ethanol self-administration in ethanol-dependent and nondependent animals. The induction of ethanol dependence and correlation of limited ethanol self-administration before and excessive drinking after dependence induction following chronic intermittent ethanol vapor exposure is shown. $^{***}p < 0.001$, significant group × test session interaction. With all drugs, escalation is defined as a significant increase in drug intake within-subjects in extended-access groups, with no significant changes within-subjects in limited-access groups. [Taken with permission from Edwards et al., 2011.].

increased responding on a progressive-ratio schedule of reinforcement (Paterson and Markou, 2003; Wee et al., 2008; Walker and Koob, 2007; Fig. 2). Changes in the reinforcing and incentive effects of drug intake that are consistent with the increases in progressive-ratio responding have been observed following extended access and include increased drug-induced reinstatement after extinction, a decreased latency to goal time in a runway model for drug reward, and responding in the face of punishment (Deroche et al., 1999; Jonkman et al., 2012; Ben-Shahar et al., 2008; Vanderschuren and Everitt, 2004; Deroche-Gamonet et al., 2004; Pelloux et al., 2007; Vendruscolo et al., 2012). Altogether, these results suggest that drug taking with extended access changes the motivation to seek the drug. Some have argued that enhanced drug taking reflects a sensitization of reward (Vezina, 2004), but studies of locomotor sensitization suggest that locomotor sensitization occurs independently of escalation (Ben-Shahar et al., 2004; Knackstedt and Kalivas, 2007; Ahmed and Cador, 2006). The increased brain reward thresholds and neuropharmacological studies outlined below argue for a reward deficit state that drives the increased drug taking during extended access.

1.3. *Animals escalate their intake of drugs with extended access, with a parallel increase in reward thresholds*

The hypothesis that compulsive cocaine use is accompanied by a chronic perturbation in brain reward homeostasis has been tested

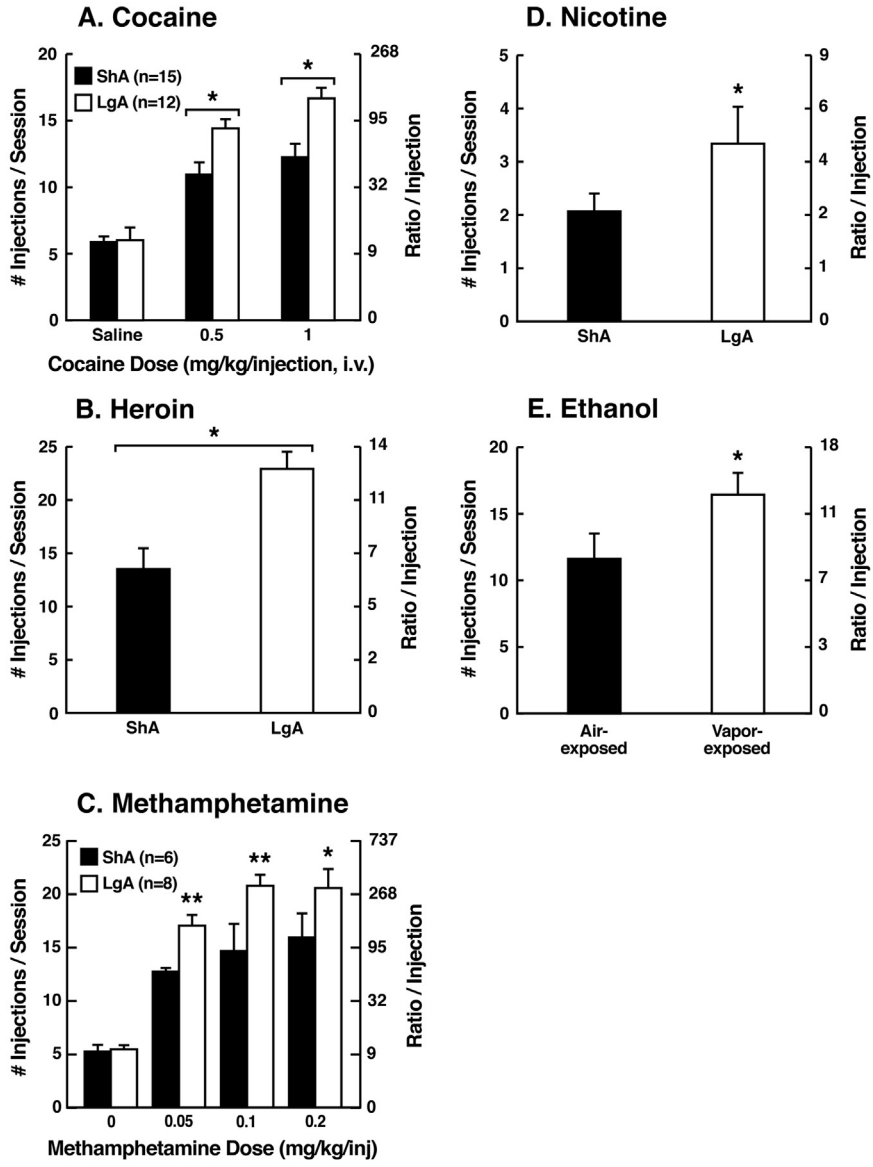

Fig. 2. (A) Dose-response function of cocaine by rats responding under a progressive-ratio schedule. Test sessions under a progressive-ratio schedule ended when rats did not achieve reinforcement within 1 h. The data are expressed as the number of injections per session on the left axis and ratio per injection on the right axis. $^{*}p < 0.05$, compared with ShA rats at each dose of cocaine. [Taken with permission from Wee et al., 2008.] (B) Responding for heroin under a progressive-ratio schedule of reinforcement in ShA and LgA rats. $^{*}p < 0.05$, LgA significantly different from LgA. [Modified with permission from Barbier et al., 2013.] (C) Dose-response for methamphetamine under a progressive-ratio schedule. Test sessions under a progressive-ratio schedule ended when rats did not achieve reinforcement within 1 h. $^{*}p < 0.05$, $^{**}p < 0.01$, LgA significantly different from ShA [Modified from Wee et al., 2007.] (D) Breakpoints on a progressive-ratio schedule in ShA rats that self-administered nicotine for 1 h sessions and long access (LgA) rats that self-administered nicotine in 1 h sessions with 48 h abstinence between sessions. The data are expressed as mean ± SEM. $^{*}p < 0.05$. $n = 9$ rats per group. [Taken with permission from Cohen et al., 2012.] (E) Mean (±SEM) breakpoints for ethanol while in nondependent and ethanol-dependent states 6 h into withdrawal. $^{**}p < 0.01$, main effect of vapor exposure on ethanol self-administration. [Taken with permission from Walker and Koob, 2007.].

in animal models of escalation in drug intake with prolonged access combined with measures of brain stimulation reward thresholds. Animals implanted with intravenous catheters and allowed differential access to intravenous self-administration of cocaine showed increases in cocaine self-administration from day to day in the long-access group (6 h; LgA) but not in the short-access group (1 h; ShA). The differential exposure to cocaine self-administration had dramatic effects on reward thresholds that progressively increased in LgA rats but not ShA rats across successive self-administration sessions (Ahmed et al., 2002). Elevations in baseline reward thresholds temporally preceded and were highly correlated with escalation in cocaine intake (Fig. 3). Post-session elevations in reward thresholds failed to return to baseline levels before the onset of each subsequent self-administration session, thereby deviating more and more from control levels. The progressive elevation in reward thresholds was associated with a dramatic escalation in cocaine consumption that was observed previously (Ahmed et al., 2002). Similar results have been observed with extended access to methamphetamine (Jang et al., 2013) and heroin (Kenny et al., 2006). Rats allowed 6 h access to methamphetamine

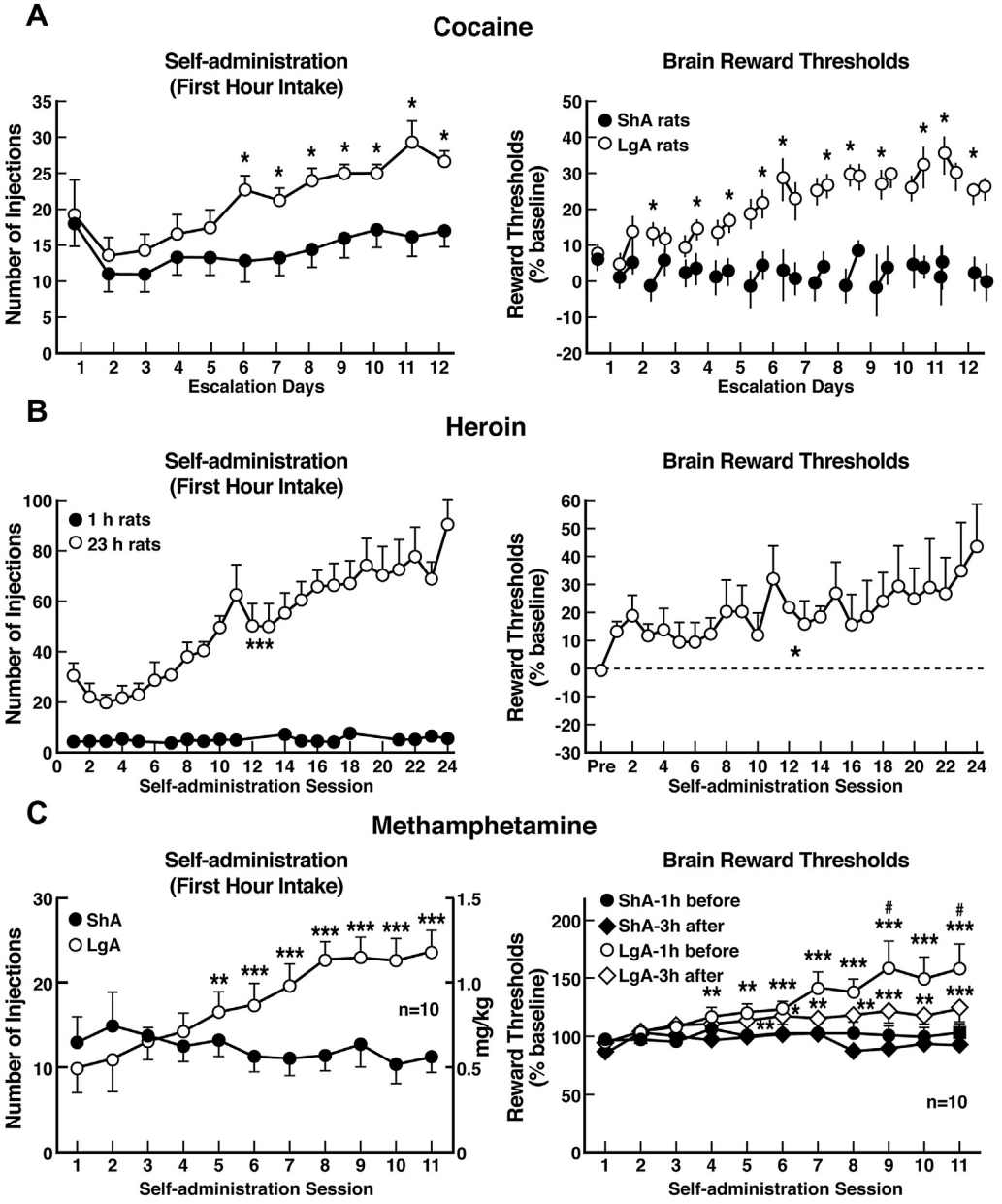

Fig. 3. (A) Relationship between elevation in ICSS reward thresholds and cocaine intake escalation. (Left) Number of injections during first hour of each session. (Right) Percent change from baseline ICSS thresholds. Thresholds were measured 3 h and 17–22 h after each self-administration session. $^{*}p < 0.05$, compared with drug-naive and/or ShA 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 in 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.].

or 23 h access to heroin also showed a time-dependent increase in reward thresholds that paralleled the increases in heroin intake (Fig. 3). Similar results of parallel increases in brain reward thresholds with escalation of nicotine intake have also been observed with extended access to nicotine (Harris et al., 2011).

2. Brain stress system substrates for the dark side of addiction

2.1. Brain stress systems

The brain stress systems can be defined as neurochemical systems that are activated during exposure to acute stressors or in a chronic state of stress and mediate species-typical behavioral responses. These behavioral responses in animals range from freezing to flight and typically have face and predictive validity for similar behavior responses in humans. For example, animals exposed to a stressor will show an enhanced freezing response to a conditioned fear stimulus, an enhanced startle response to a startle stimulus, avoidance of open areas, open arms, or height, and enhanced species-typical responses to an aversive stimulus (e.g., burying a shock probe in the defensive burying test). Key neurotransmitter systems with circumscribed neurocircuitry that mediates behavioral responses to stressors include glucocorticoids, corticotropin-releasing factor (CRF), norepinephrine, and dynorphin, and key neurotransmitter systems that act in opposition to the brain stress systems include neuropeptide Y, nociceptin, and endocannabinoids (for reviews, see Koob, 2008; Sidhpura and Parsons, 2011; Heilig, 2004). For the purposes of this review, two brain stress systems with prominent roles in driving the dark side of addiction will be considered: CRF and dynorphin.

2.1.1. Corticotropin-releasing factor

Corticotropin-releasing factor is a 41-amino-acid polypeptide that controls hormonal, sympathetic, and behavioral responses to stressors (Rainnie et al., 2004; Lemos et al., 2012). Central administration of CRF mimics the behavioral response to activation and stress in rodents, and administration of competitive CRF receptor antagonists generally has anti-stress effects (for reviews, see Dunn and Berridge, 1990; Koob et al., 1994, 2001; Sarnyai et al., 2001). Two major CRF receptors have been identified, with CRF_1 receptor activation associated with increased stress responsiveness (Koob and Heinrichs, 1999) and CRF_2 receptor activation associated with decreases in feeding and decreases in stress responsiveness (Spina et al., 1996; Pelleymounter et al., 2000), although there is some controversy in this area (Takahashi et al., 2001). CRF neurons are present in the neocortex, the extended amygdala, the medial septum, the hypothalamus, the thalamus, the cerebellum, and autonomic midbrain and hindbrain nuclei (Swanson et al., 1983). Extensive research has been performed on CRF neurons in the paraventricular nucleus of the hypothalamus (PVN), central nucleus of the amygdala (CeA), and bed nucleus of the stria terminalis (BNST), demonstrating a key role for PVN CRF neurons in controlling the pituitary adrenal response to stress (Turnbull and Rivier, 1997) and a key role for BNST and CeA CRF in mediating the negative affective responses to stress and drug withdrawal (Koob and Kreek, 2007).

The neuroanatomical entity termed the extended amygdala (Heimer and Alheid, 1991) may represent a common anatomical substrate that integrates brain arousal–stress systems with hedonic processing systems to produce the between-system opponent process elaborated above. The extended amygdala is composed of the CeA, BNST, and a transition zone in the medial (shell) subregion of the nucleus accumbens. Each of these regions has cytoarchitectural and circuitry similarities (Heimer and Alheid, 1991). The extended amygdala receives numerous afferents from limbic structures, such as the basolateral amygdala and hippocampus, and sends efferents to the medial part of the ventral pallidum and a large projection to the lateral hypothalamus, thus further defining the specific brain areas that interface classical limbic (emotional) structures with the extrapyramidal motor system (Alheid et al., 1995). CRF in the extended amygdala has long been hypothesized to play a key role not only in fear conditioning (Maier and Watkins, 2005; Sink et al., 2013) but also in the emotional component of pain processing (Neugebauer et al., 2004).

2.1.2. Dynorphin–κ opioid system

Dynorphins are opioid peptides that derive from the prodynorphin precursor and contain the leucine (leu)-enkephalin sequence at the *N*-terminal portion of the molecule and are the presumed endogenous ligands for the κ opioid receptor (Chavkin et al., 1982). Dynorphins are widely distributed in the central nervous system (Watson et al., 1982) and play a role in neuroendocrine regulation, pain regulation, motor activity, cardiovascular function, respiration, temperature regulation, feeding behavior, and stress responsivity (Fallon and Leslie, 1986). Dynorphins bind to all three opioid receptors but show a preference for κ receptors (Chavkin et al., 1982). Dynorphin–κ receptor system activation produces analgesic actions that are similar to other opioids but actions opposite to those of μ opioid receptors in the motivational domain. Dynorphins produce aversive dysphoric-like effects in animals and humans and have been hypothesized to mediate negative emotional states (Shippenberg et al., 2007; Wee and Koob, 2010; Mucha and Herz, 1985; Pfeiffer et al., 1986).

Dopamine receptor activation in the NAc shell stimulates a cascade of events that ultimately lead to cyclic adenosine monophosphate response element binding protein (CREB) phosphorylation and subsequent alterations in gene expression, notably the activation of the expression of prodynorphin mRNA. Subsequent activation of dynorphin systems has been hypothesized to feedback to decrease dopamine release in the mesolimbic dopamine system (Todtenkopf et al., 2004; Pliakas et al., 2001; Nestler, 2004; Mague et al., 2003; Knoll and Carlezon, 2010) and glutamate release in the nucleus accumbens (Hjelmstad and Fields, 2001; Gray et al., 1999). Both of these changes may contribute to the dysphoric syndrome associated with cocaine dependence. *In vivo* microdialysis studies have also provided evidence that κ opioid receptors located in the prefrontal cortex (PFC) and ventral tegmental area also regulate the basal activity of mesocortical dopamine neurons (Margolis et al., 2006; Tejeda, 2009).

In the extended amygdala, enhanced dynorphin action may also activate brain stress responses, such as CRF (Valdez et al., 2007), or CRF in turn may activate dynorphin (Land et al., 2008; McLaughlin et al., 2003). For example, Valdez showed that the reinstatement of cocaine seeking induced by the κ receptor agonist spiradoline in squirrel monkeys was antagonized by the CRF_1 antagonist CP 154,526 (Valdez et al., 2007), and more recent data suggest that dynorphin in the central nucleus of the amygdala may mediate anxiety-like responses to cocaine by blocking cocaine escalation-induced increases in presynaptic GABA release (Kallupi et al., 2013). However, CRF also appears to activate dynorphin, in which nor-BNI pretreatment in mice blocked the stress-induced potentiation of cocaine-induced conditioned place preference (McLaughlin et al., 2003), and injection of CRF produced a place aversion that was also blocked by dynorphin gene deletion or κ receptor antagonism, suggesting that CRF drives dynorphin (Land et al., 2008).

2.2. Between-system neuroadaptations that contribute to the negative emotional state that drives negative reinforcement

Brain neurochemical systems involved in arousal–stress modulation have been hypothesized to be engaged within the neurocircuitry of the brain stress systems in an attempt to overcome the chronic presence of the perturbing drug and restore normal function despite the presence of drug (Koob, 2008). Both the hypothalamic-pituitary-adrenal (HPA) axis and extrahypothalamic brain stress system mediated by CRF are dysregulated by chronic administration of all major drugs with dependence or abuse potential, with a common response of elevated adrenocorticotropic hormone, 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). Indeed, activation of the HPA response may be an early dysregulation associated with excessive drug taking that ultimately "sensitizes" the extrahypothalamic CRF systems (Koob and Kreek, 2007; Vendruscolo et al., 2012).

As noted above, the excessive release of dopamine and opioid peptides produces subsequent activation of dynorphin systems, which has been hypothesized to feedback to decrease dopamine release and also contribute to the dysphoric syndrome associated with cocaine dependence (Nestler, 2004; Beardsley et al., 2005; Jackson et al., 2013; Tejeda et al., 2012). Dynorphins produce aversive dysphoric-like effects in animals and humans and have been hypothesized to mediate negative emotional states (Shippenberg et al., 2007; Wee and Koob, 2010; Mucha and Herz, 1985; Pfeiffer et al., 1986).

A common response to acute withdrawal and protracted abstinence from all major drugs of abuse is the manifestation of anxiety-like responses that are reversed by CRF antagonists. 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). Opioid dependence also produces irritability-like effects that are reversed by CRF antagonists (Navarro-Zaragosa et al., 2010; Iredale et al., 2000). Ethanol withdrawal produces anxiety-like behavior that is reversed by intracerebroventricular administration of CRF_1/CRF_2 peptidergic antagonists (Baldwin et al., 1991), small molecule CRF_1 antagonists (Knapp et al., 2004; Overstreet et al., 2004; Funk et al., 2007), and intracerebral administration of a peptidergic CRF_1/CRF_2 antagonist into the amygdala (Rassnick et al., 1993). The effects of CRF antagonists have been localized to the CeA (Rassnick et al., 1993). Precipitated withdrawal from nicotine produces anxiety-like responses that are also reversed by CRF antagonists (Tucci et al., 2003; George et al., 2007). CRF antagonists injected intracerebroventricularly or systemically also block the potentiated anxiety-like responses to stressors observed during protracted abstinence from chronic ethanol (Breese et al., 2005; Valdez et al., 2003; Huang et al., 2010; Overstreet et al., 2007; Wills et al., 2009).

Another measure of negative emotional states during drug withdrawal in animals is conditioned place aversion, in which animals avoid an environment previously paired with an aversive state. Such place aversions, when used to measure the aversive stimulus effects of withdrawal, have been observed largely in the context of opioids (Hand et al., 1988; Stinus et al., 1990). Systemic administration of a CRF_1 receptor antagonist and direct intracerebral administration of a peptide CRF_1/CRF_2 antagonist also decreased opioid withdrawal-induced place aversions (Stinus et al., 2005; Heinrichs et al., 1995; Contarino and Papaleo, 2005). These effects have been hypothesized to be mediated by actions in the extended amygdala. The selective CRF_1 antagonist antalarmin blocked the place aversion produced by naloxone in morphine-dependent rats (Stinus et al., 2005), and a CRF peptide antagonist injected into the CeA also reversed the place aversion produced by methylnaloxonium injected into the CeA (Heinrichs et al., 1995). CRF_1 knockout mice failed to show conditioned place aversion to opioid withdrawal and failed to show an opioid-induced increase in dynorphin mRNA in the nucleus accumbens (Contarino and Papaleo, 2005).

A compelling test of the hypothesis that CRF-induced increases in anxiety-like responses during drug withdrawal has motivational significance in contributing to negative emotional states is the observation that CRF antagonists can reverse the elevation in reward thresholds produced by drug withdrawal. Nicotine and alcohol withdrawal-induced elevations in reward thresholds were reversed by a CRF antagonist (Bruijnzeel et al., 2007, 2010). These effects have been localized to both the CeA and nucleus accumbens shell (Marcinkiewcz et al., 2009).

Enhanced dynorphin action is hypothesized to mediate the depression-like, aversive responses to stress and dysphoric-like responses during withdrawal from drugs of abuse (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; Beardsley et al., 2005; Jackson et al., 2013: Tejeda et al., 2012). For example, pretreatment with a κ-opioid receptor antagonist blocked stress-induced analgesia and stress-induced immobility (McLaughlin et al., 2003), decreased anxiety-like behavior in the elevated plus maze and open field, decreased conditioned fear in fear-potentiated startle (Knoll et al., 2007), significantly reduced the footshock-induced reinstatement of responding previously reinforced by cocaine in rats (Beardsley et al., 2005), attenuated stress-induced reinstatement of nicotine-induced conditioned place preference in rats (Jackson et al., 2013), and blocked depressive-like behavior induced by cocaine and nicotine withdrawal (Chartoff et al., 2012; Tejeda et al., 2012).

3. Brain stress substrates that mediate drug taking with extended access

3.1. Corticotropin-releasing factor, compulsive-like drug seeking, and the extended amygdala

The ability of CRF antagonists to block the anxiogenic-like and aversive-like motivational effects of drug withdrawal predicted motivational effects of CRF antagonists in animal models of extended access to drugs. 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., 2009; Fig. 4). For example, systemic administration of a CRF_1 antagonist blocked the increased self-administration of nicotine associated with withdrawal in extended-access (23 h) animals (George et al., 2007).

CRF antagonists also blocked the increased self-administration of ethanol in dependent rats (Funk et al., 2007; Fig. 4). For example, exposure to repeated cycles of chronic ethanol vapor produced substantial increases in ethanol intake in rats during both acute withdrawal and protracted abstinence (2 weeks post-acute withdrawal; O'Dell et al., 2004; Rimondini et al., 2002). Intracerebroventricular administration of a CRF_1/CRF_2 antagonist blocked the dependence-induced increase in ethanol self-administration during both acute withdrawal and protracted abstinence (Valdez et al., 2004). Systemic injections of small-molecule CRF_1 antagonists also blocked the increased ethanol intake associated with acute withdrawal (Funk et al., 2007) and protracted abstinence (Gehlert

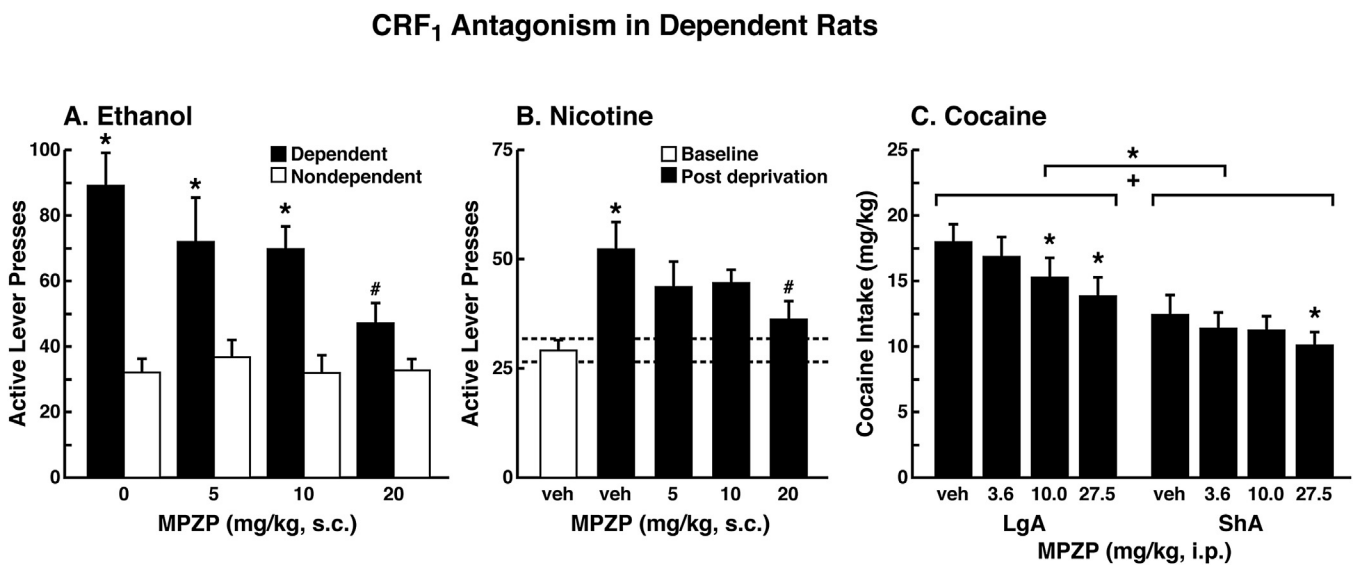

Fig. 4. (A) The effect of the CRF_1 receptor antagonist MPZP on operant self-administration of alcohol in dependent and nondependent rats. Testing was conducted when dependent animals were in acute withdrawal (6–8 h after removal from vapors). Dependent rats self-administered significantly more than nondependent animals, and MPZP dose-dependently reduced alcohol self-administration only in dependent animals. The data are expressed as mean + SEM lever presses for alcohol. [Taken with permission from Richardson et al., 2008.] (B) Abstinence-induced escalation of nicotine intake is blocked by a CRF_1 receptor antagonist. Effect of MPZP (s.c., −1 h) on nicotine self-administration during the active period in rats given extended access to nicotine. $^{*}p < 0.05$, compared with baseline; $^{\#}p < 0.05$, compared with after-abstinence vehicle treatment; $n = 8$. The data are expressed as mean + SEM lever presses for nicotine. [Taken with permission from George et al., 2007.] (C) MPZP reduces cocaine intake in ShA and LgA rats. The data are expressed as mean + SEM cocaine intake (mg/kg). $^{*}p < 0.05$, $^{**}p < 0.01$, compared with vehicle. [Taken with permission from Specio et al., 2008.].

et al., 2007). When administered directly into the CeA, a CRF_1/CRF_2 antagonist blocked ethanol self-administration in ethanol-dependent rats (Funk et al., 2006, 2007). Altogether, these results suggest that CRF in the basal forebrain may also play an important role in the development of the aversive motivational effects that drive the increased drug seeking associated with cocaine, heroin, nicotine, and alcohol dependence.

3.2. *Dynorphin, compulsive-like drug seeking, and the extended amygdala*

Recent evidence suggests that the dynorphin–κ opioid system also mediates the compulsive-like drug responding (methamphetamine, heroin, and alcohol) with extended access and dependence. Evidence from our laboratory has shown that κ opioid receptor antagonism with a small-molecule κ antagonist selectively blocked responding on a progressive-ratio schedule for cocaine in rats with extended access (Wee et al., 2009). Even more compelling is that excessive drug self-administration can also be blocked by κ antagonists (Walker et al., 2010; Wee et al., 2009; Whitfield et al., 2011; Schlosburg et al., 2011) and may be mediated by the shell of the nucleus accumbens (Nealey et al., 2011). However, the neurobiological circuits involved in mediating the effects of activation of the dynorphin–κ opioid system on the escalation of drug intake with extended access, the specific sites of action for κ receptor antagonists to mediate dramatic effects of a κ antagonist on the escalation of drug self-administration with extended access, and the signaling cascades that mediate the activation of the dynorphin–κ opioid system on the escalation of drug self-administration remain unknown.

3.3. *Corticotropin-releasing factor, stress, and the frontal cortex*

Converging lines of evidence suggest that impairment of medial PFC (mPFC) cognitive function and overactivation of the CeA may be linked to the development of compulsive-like responding for drugs of abuse during extended access (George et al., 2008; Briand et al., 2008a,b). Extended access to cocaine self-administration induced an escalated pattern of cocaine intake associated with an impairment of working memory and decrease in the density of dorsomedial PFC (dmPFC) neurons that lasts for months after cocaine cessation (George et al., 2008). Whereas long access (LgA) and short access (ShA) rats exhibited a high percentage of correct responses in the delayed-non-matching-to-sample task under low cognitive demand (delay < 10 s), increasing the working memory load (i.e., close to the capacity limit of working memory) by increasing the delay from 10 s to 70 and 130 s revealed a robust working memory deficit in LgA rats. Furthermore, the magnitude of escalation of cocaine intake was negatively correlated with working memory performance in ShA and LgA rats with the 70 s and 130 s delays but not with the 10 s delay or with baseline performance during training, demonstrating that the relationship between escalation of cocaine intake and behavioral performance in this task was restricted to working memory performance under high cognitive demand. The density of neurons and oligodendrocytes in the dmPFC was positively correlated with working memory performance. A lower density of neurons or oligodendrocytes in the dmPFC was associated with more severe working memory impairment. Working memory was also correlated with the density of oligodendrocytes in the orbitofrontal cortex (OFC), suggesting that OFC alterations after escalated drug intake may play a role in working memory deficits. However, no correlation was found between working memory performance and neuronal density in the OFC, suggesting that OFC neurons may be less vulnerable to the deleterious effects of chronic cocaine exposure than dmPFC neurons. Thus, PFC dysfunction may exacerbate the loss of control associated with compulsive drug use and facilitate the progression to drug addiction.

Similar results have been observed in an animal model of binge alcohol consumption, even before the development of dependence. Using an animal model of escalation of alcohol intake with chronic intermittent access to alcohol, in which rats are given continuous

(24 h per day, 7 days per week) or intermittent (3 days per week) access to alcohol (20% vol/vol) using a two-bottle choice paradigm, FBJ murine osteosarcoma viral oncogene homolog (Fos) expression in the mPFC, CeA, hippocampus, and nucleus accumbens were measured and correlated with working memory and anxiety-like behavior (George et al., 2012). Abstinence from alcohol in rats with a history of escalation of alcohol intake specifically recruited γ-aminobutyric acid (GABA) and CRF neurons in the mPFC and produced working memory impairments associated with excessive alcohol drinking during acute (24–72 h) but not protracted (16–68 day) abstinence. The abstinence from alcohol was associated with a functional disconnection of the mPFC and CeA but not mPFC and nucleus accumbens. These results show that recruitment of a subset of GABA and CRF neurons in the mPFC during withdrawal and disconnection of the PFC CeA pathway may be critical for impaired executive control over motivated behavior, suggesting that dysregulation of mPFC interneurons may be an early index of neuroadaptation in alcohol dependence.

4. Brain stress systems in addiction: an allostatic view

For the *binge/intoxication stage* of the addiction cycle, studies of the acute reinforcing effects of drugs of abuse *per se* have identified key neurobiological substrates. Evidence is strong for a role for dopamine in the acute reinforcing actions of psychostimulants, opioid peptide receptors in the acute reinforcing effects of opioids, and GABA and opioid peptides in the acute reinforcing actions of alcohol. Important anatomical circuits include the mesocorticolimbic dopamine system that originates in the ventral tegmental area and projects to the nucleus accumbens. However, acute drug use, even binge drug use, is not addiction. The *withdrawal/negative affect* stage can be defined as the presence of motivational signs of withdrawal in humans, including chronic irritability, physical pain, emotional pain (i.e., hyperkatifeia; Shurman et al., 2010), malaise, dysphoria, alexithymia, and loss of motivation for natural rewards. It is characterized in animals by increases in reward thresholds during withdrawal from all major drugs of abuse. More compelling, in animal models of the transition to addiction, similar changes in brain reward thresholds occur that temporally precede and are highly correlated with escalation in drug intake (Ahmed et al., 2002; Kenny et al., 2006; Jang et al., 2013). Such acute withdrawal is associated with decreased activity of the mesocorticolimbic dopamine system, reflected by electrophysiological recordings and *in vivo* microdialysis. Human imaging studies of individuals with addiction during withdrawal or protracted abstinence have generated results that are consistent with animal studies. There are 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). These are hypothesized to be within-system neuroadaptations that may reflect presynaptic release or postsynaptic receptor plasticity.

More importantly for the present thesis, as dependence and withdrawal develop, brain anti-reward systems, such as CRF and dynorphin, are recruited in the extended amygdala. We hypothesize that this brain stress neurotransmitter that is known to be activated during the development of excessive drug taking comprises a between-system opponent process, and this activation is manifest when the drug is removed, producing anxiety, hyperkatifeia, and irritability symptoms associated with acute and protracted abstinence. Indeed there is evidence of CRF immunoreactivity in the ventral tegmental area, and a CRF_1 receptor antagonist injected directly into the ventral tegmental area blocked social stress-induced escalation of cocaine self-administration (Boyson et al., 2011). Altogether, these observations suggest between-system/within-system neuroadaptations that were originally hypothesized for dynorphin by Carlezon and Nestler (Carlezon et al., 1998), in which activation of CREB by excessive dopamine and opioid peptide receptor activation in the nucleus accumbens triggers the induction of dynorphin to feedback to suppress dopamine release. Thus, we hypothesize that anti-reward circuits are recruited as between-system neuroadaptations (Koob and Bloom, 1988) during the development of addiction and produce aversive or stress-like states (Nestler, 2001; Koob, 2003; Aston-Jones et al., 1999) via at least two mechanisms: direct activation of stress-like, fear-like states in the extended amygdala (CRF) and indirect activation of a depression-like state by suppressing dopamine (dynorphin; Fig. 5).

A critical problem in drug addiction is chronic relapse, in which addicted individuals return to compulsive drug taking long after acute withdrawal. This corresponds to the *preoccupation/anticipation* stage of the addiction cycle outlined above. Koob and Le Moal also hypothesized that the dysregulations that comprise the "dark side" of drug addiction persist during protracted abstinence to set the tone for vulnerability to "craving" by activating drug-, cue-, and stress-induced reinstatement neurocircuits that are now driven by a reorganized and possibly hypofunctioning prefrontal system. Here, a hypofunctioning cortical system would be argued to play a permissive role, in which subcortical structures that drive addiction are not inhibited. Thus, the hypothesized allostatic, dysregulated reward and sensitized stress state produces the motivational symptoms of acute withdrawal and protracted abstinence and provides the basis by which drug priming, drug cues, and acute stressors acquire even more power to elicit drug-seeking behavior (Vendruscolo et al., 2012). The combination of decreases in reward system function and recruitment of anti-reward systems provides a powerful source of negative reinforcement that contributes to

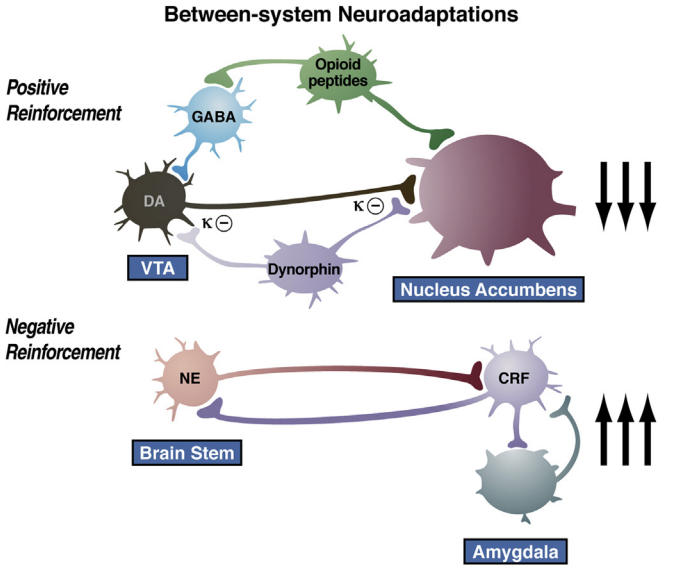

Fig. 5. Neurocircuitry framework for the between-systems neuroadaptations hypothesized to mediate the transition to dependence in addiction. (Top) The hypothesis outlined here is that excessive activation of elements of the brain reward system (dopamine and opioid peptides via μ opioid receptors) in turn activates dynorphin in the ventral striatum, which in turn suppresses dopamine release to contribute to the negative emotional (dysphoric-like) effects of drug withdrawal. (Bottom) The hypothesis outlined here is that activation of elements of the brain stress systems in the extended amygdala during withdrawal (CRF, norepinephrine, and dynorphin) sensitize via feed-forward mechanisms and also contribute to the negative emotional (anxiety-like) effects of drug withdrawal.

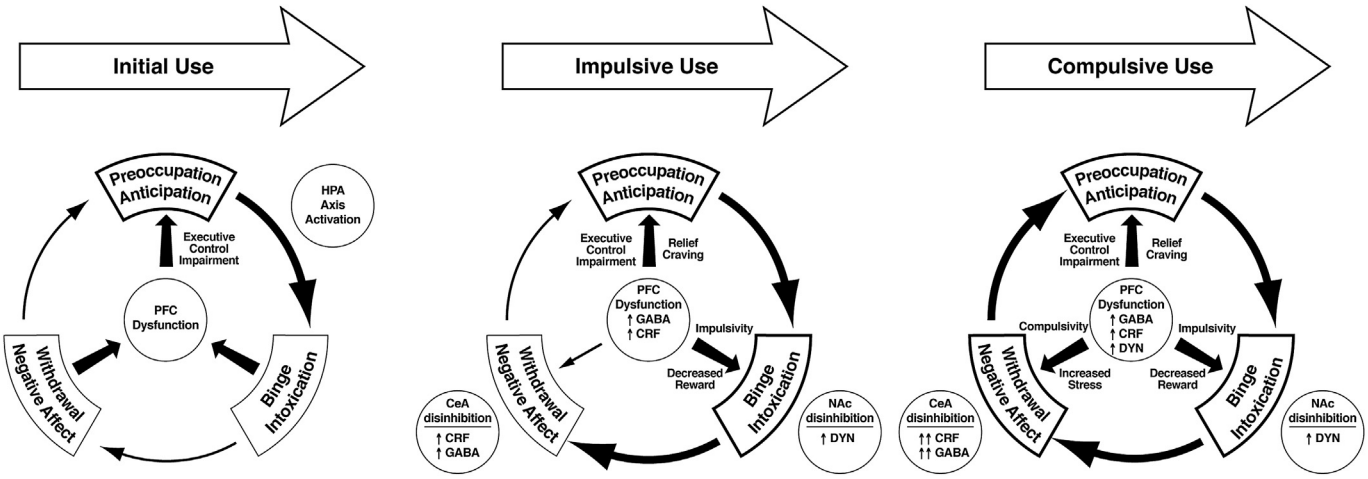

Fig. 6. The progression of compulsive drug use over time mediates recruitment of brain stress systems. The schematic illustrates the shift in underlying motivational mechanisms. As the addictive process progresses over time, the initial positively reinforcing, pleasurable drug effects are augmented by negatively reinforcing relief from a negative emotional state. The data summarized in the present treatise suggest that the neuroadaptations that encompass the recruitment of extrahypothalamic CRF and dynorphin brain stress systems are key to this shift. Initial use is characterized by activation of the hypothalamic–pituitary–adrenal axis to drive the *binge/intoxication* stage. Impulsive use is characterized by prefrontal cortex dysfunction with activation of corticotropin-releasing factor (CRF), γ-aminobutyric acid (GABA), and possibly dynorphin in the prefrontal cortex and subsequent disinhibition of the nucleus accumbens and extended amygdala that in turn drive increases in dynorphin in the nucleus accumbens and CRF in the extended amygdala. Compulsive use involves a pronounced activation of CRF in the extended amygdala, dynorphin-induced decreases in dopamine in the nucleus accumbens, and a pronounced loss of executive control in the prefrontal cortex, all leading to the spiraling distress and loss of control associated with full-blown dependence mediated by negative reinforcement.

compulsive drug-seeking behavior and addiction. A compelling argument can be made that the neuroplasticity that charges the CRF stress system may indeed begin much earlier that previously thought via stress actions in the PFC.

The overall conceptual theme argued here is that drug addiction represents an excessive and prolonged engagement of homeostatic brain regulatory mechanisms that regulate the response of the body to stressors. The dysregulation of the stress axis begins with the binge and subsequent acute withdrawal, triggering a cascade of changes from activation of the HPA axis to activation of CRF in the prefrontal cortex, to activation of CRF in the extended amygdala to activation of dynorphin in the ventral striatum (Fig. 6). This cascade of overactivation of the stress axis represents more than simply a transient homeostatic dysregulation; it also represents a dynamic homeostatic dysregulation that has been termed *allostasis*.

Allostasis, originally conceptualized to explain persistent morbidity of arousal and autonomic function, can be defined as "stability through change." Allostasis involves a feed-forward mechanism rather than the negative feedback mechanisms of homeostasis, with continuous re-evaluation of need and continuous readjustment of all parameters toward new set points. An *allostatic state* has been defined as a state of chronic deviation of the regulatory system from its normal (homeostatic) operating level (Koob and Le Moal, 2001). *Allostatic load* was defined as the "long-term cost of allostasis that accumulates over time and reflects the accumulation of damage that can lead to pathological states" (McEwen, 2000).

Repeated challenges, such as with drugs of abuse, lead to attempts of the brain stress systems at the molecular, cellular, and neurocircuitry level to maintain stability but at a cost. For the drug addiction framework elaborated here, the residual activation of the brain stress systems to produce the consequent negative emotional state is termed an *allostatic state*. This state represents a combination of recruitment of anti-reward systems and consequent chronic decreased function of reward circuits, both of which lead to the compulsive drug seeking and loss of control over intake. How these systems are modulated by other known brain emotional systems localized to the basal forebrain, where the ventral striatum and extended amygdala project to convey emotional valence, how frontal cortex dysregulations in the cognitive domain linked to impairments in executive function contribute to the dysregulation of the extended amygdala, and how individuals differ at the molecular-genetic level of analysis to convey loading on these circuits remain challenges for future research.

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