Neuropharmacology 56 (2009) 18–31

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Review

Neurobiological substrates for the dark side of compulsivity in addiction

George F. Koob*

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

ARTICLE INFO

Article history:
Received 26 April 2008
Received in revised form 29 July 2008
Accepted 30 July 2008

Keywords:
Addiction
Opponent process
Stress
Extended amygdala
Corticotropin-releasing factor

ABSTRACT

Drug addiction can be defined by a compulsion to seek and take drug, loss of control in limiting intake, and the emergence of a negative emotional state when access to the drug is prevented. Drug addiction impacts multiple motivational mechanisms and can be conceptualized as a disorder that progresses from impulsivity (positive reinforcement) to compulsivity (negative reinforcement). The construct of negative reinforcement is defined as drug taking that alleviates a negative emotional state. The negative emotional state that drives such negative reinforcement is hypothesized to derive from dysregulation of key neurochemical elements involved in reward and stress within the basal forebrain structures involving the ventral striatum and extended amygdala. Specific neurochemical elements in these structures include not only decreases in reward neurotransmission, such as decreases in dopamine and opioid peptide function in the ventral striatum, but also recruitment of brain stress systems, such as corticotropin-releasing factor (CRF), in the extended amygdala. Acute withdrawal from all major drugs of abuse produces increases in reward thresholds, increases in anxiety-like responses, and increases in extracellular levels of CRF in the central nucleus of the amygdala. CRF receptor antagonists also block excessive drug intake produced by dependence. A brain stress response system is 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 compulsivity of addiction. Other components of brain stress systems in the extended amygdala that interact with CRF and may contribute to the negative motivational state of withdrawal include norepinephrine, dynorphin, and neuropeptide Y. The combination of loss of reward function and recruitment of brain stress systems provides a powerful neurochemical basis for a negative emotional state that is responsible for the negative reinforcement driving, at least in part, the compulsivity of addiction.

1. Definitions and conceptual framework for compulsivity in addiction

Drug addiction is a chronically relapsing disorder characterized by (i) compulsion to seek and take the drug, (ii) loss of control in limiting intake, and (iii) emergence of a negative emotional state (e.g., dysphoria, anxiety, irritability) reflecting a motivational withdrawal syndrome when access to the drug is prevented (defined here as dependence) (Koob and Le Moal, 1997). *Addiction* is assumed to be identical to the syndrome of *substance dependence* (as currently defined by the *Diagnostic and Statistical Manual of Mental Disorders*; American Psychiatric Association, 1994). Clinically and in animal models, the occasional but limited use of a drug with the *potential* for abuse or dependence is distinct from escalated drug intake and the emergence of a chronic drug-dependent state.

Drug addiction has been conceptualized as a disorder that involves elements of both impulsivity and compulsivity, where *impulsivity* can be defined behaviorally as "a predisposition toward rapid, unplanned reactions to internal and external stimuli without regard for the negative consequences of these reactions to themselves or others" (Moeller et al., 2001). Impulsivity is measured in two domains: the choice of a smaller, immediate reward over a larger, delayed reward (Rachlin and Green, 1972) or the inability to inhibit behavior by changing the course of action or to stop a response once it is initiated (Logan et al., 1997). Impulsivity is a core deficit in substance abuse disorders (Allen et al., 1998) and in neuropsychiatric disorders such as attention deficit hyperactivity disorder. Operationally, delay-to-gratification tasks (delayed discounting tasks) (impulsive choice) and the stop-signal or go/no-go task (behavioral impulsivity) have been used as measures of impulsivity (Fillmore and Rush, 2002; Green et al., 1994). *Compulsivity* can be defined as elements of behavior that result in perseveration in responding in the face of adverse consequences or perseveration in the face of incorrect responses in choice situations. These elements are analogous to the symptoms of substance

* Tel.: +1 858 784 7062; fax: +1 858 784 7405.
E-mail address: marends@scripps.edu

0028-3908/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuropharm.2008.07.043

dependence as outlined by the American Psychiatric Association: continued substance use despite knowledge of having had a persistent or recurrent physical or psychological problem and a great deal of time spent in activities necessary to obtain the substance (American Psychiatric Association, 2000).

Collapsing the cycles of impulsivity and compulsivity yields a composite addiction cycle comprised of three stages—*preoccupation/anticipation*, *binge/intoxication*, and *withdrawal/negative affect*—where impulsivity often dominates at the early stages and compulsivity dominates at terminal stages. As an individual moves from impulsivity to compulsivity, a shift occurs from positive reinforcement driving the motivated behavior to negative reinforcement driving the motivated behavior (Koob, 2004). Negative reinforcement can be defined as the process by which removal of an aversive stimulus (e.g., negative emotional state of drug withdrawal) increases the probability of a response (e.g., dependence-induced drug intake). These three stages are conceptualized as interacting with each other, becoming more intense, and ultimately leading to the pathological state known as addiction (Koob and Le Moal, 1997) (Table 1). The present review focuses on the role of an animal model of compulsivity that derives from the negative emotional state of the *withdrawal/negative affect* stage of the addiction cycle.

Different drugs produce different patterns of addiction with emphasis on different components of the addiction cycle. Opioids can be considered classic drugs of addiction because subjects meet most of the criteria classically associated with addiction, including dramatic tolerance and withdrawal. A pattern of intravenous or smoked drug-taking evolves, including intense intoxication, the development of tolerance, escalation in intake, and profound dysphoria, physical discomfort, and somatic withdrawal signs during abstinence. Intense preoccupation with obtaining opioids (craving) develops that often precedes the somatic signs of withdrawal and is linked not only to stimuli associated with obtaining the drug but also to stimuli associated with withdrawal and the aversive motivational state. A pattern develops where the drug must be obtained to avoid the severe dysphoria and discomfort of abstinence. Other drugs of abuse follow a similar pattern but may involve more the *binge/intoxication* stage (psychostimulants and alcohol) or less *binge/intoxication* and more *withdrawal/negative affect* and *preoccupation/anticipation* stages (nicotine and cannabinoids).

Alcohol addiction, or alcoholism, can follow a similar trajectory, but the pattern of oral drug taking is often characterized by binges of alcohol intake that can be daily episodes or prolonged days of heavy drinking and is characterized by a severe emotional and somatic withdrawal syndrome. Many alcoholics continue with such a binge/withdrawal pattern for extended periods, but some individuals can evolve into an opioid-like situation in which they must have alcohol available at all times to avoid the negative consequences of abstinence. Tobacco addiction contrasts with the above patterns—the *binge/intoxication* stage forms a minor component of nicotine dependence. The pattern of nicotine intake is one of highly titrated intake of the drug except during periods of sleep. However, during abstinence, users experience negative emotional states, including dysphoria, irritability, and intense craving. Marijuana dependence follows a pattern similar to opioids and tobacco, with a significant intoxication stage, but as chronic use continues, subjects begin to show a pattern of use manifest by chronic intoxication during waking hours and withdrawal characterized by dysphoria, irritability, and sleep disturbances. Psychostimulants, such as cocaine and amphetamines, show a pattern focused on the *binge/intoxication* stage in which binges can be hours or days in duration and often are followed by a withdrawal ("crash") characterized by extreme dysphoria and inactivity.

Table 1
Stages of the addiction cycle

Stage	Source of reinforcement	Animal models
Binge/intoxication	Positive reinforcement	Conditioned place preference Drug self-administration Decreased reward thresholds
Withdrawal/negative affect	Negative reinforcement	Conditioned place aversion Increased self-administration in dependence Increased reward thresholds
Preoccupation/anticipation	Conditioned positive and negative reinforcement	Drug-induced reinstatement Cue-induced reinstatement Stress-induced reinstatement Protracted abstinence

1.1. Motivation, withdrawal, and opponent process

Motivation is a state that can be defined as a "tendency of the whole animal to produce organized activity" (Hebb, 1972), and such motivational states are not constant but rather vary over time. Early work by Wikler stressed the role of changes in drive states associated with dependence. Subjects described withdrawal changes as a "hunger" or primary need and the effects of morphine on such a state as "satiation" or gratification of the primary need (Wikler, 1952). Although Wikler argued that positive reinforcement was retained even in heavily dependent subjects (thrill of the intravenous opioid injection), dependence produced a new source of gratification, that of negative reinforcement (see above).

The concept of motivation was linked inextricably 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 with mechanisms that reduce the intensity of hedonic feelings. The *a-process* includes affective or hedonic habituation (or tolerance), and the *b-process* includes affective or hedonic withdrawal (abstinence). The *a-process* in drug use consists of positive hedonic responses, occurs shortly after 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. The thesis here is that opponent processes begin early in drug-taking, reflect changes in the brain reward and stress systems, and later form one of the major motivations for compulsivity in drug taking.

Thus, dependence or manifestation of a withdrawal syndrome after removal of chronic drug administration is defined in terms of *motivational* aspects of dependence such as emergence of a negative emotional state (e.g., dysphoria, anxiety, irritability) when access to the drug is prevented (Koob and Le Moal, 2001), rather than on the *physical* signs of dependence. Indeed, some have argued that the development of such a negative affective state can define dependence as it relates to addiction:

> The notion of dependence on a drug, object, role, activity or any other stimulus-source requires the crucial feature of negative affect experienced in its absence. The degree of dependence can be equated with the amount of this negative affect, which may range from mild discomfort to extreme distress, or it may be equated with the amount of difficulty or effort required to do without the drug, object, etc. (Russell, 1976).

Rapid acute tolerance and opponent process-like effects in response to the hedonic effects of cocaine have been reported in human studies of smoked coca paste (Van Dyke and Byck, 1982) (Fig. 1A). After a single smoking session, the onset and intensity of the "high" are very rapid via the smoked route of administration, and a rapid tolerance is manifest. The "high" decreases rapidly despite significant blood levels of cocaine. Even more intriguing is that human subjects also actually report a subsequent "dysphoria," again despite high blood levels of cocaine. Intravenous cocaine produced similar patterns of a rapid "rush" followed by an increased "low" in human laboratory studies (Breiter et al., 1997) (Fig. 1B). Electrical brain stimulation reward or intracranial self-stimulation has a long history as a measure of activity of the brain reward system and of the acute reinforcing effects of drugs of abuse. All drugs of abuse, when administered acutely, decrease brain stimulation reward thresholds (Kornetsky and Esposito, 1979) and when administered chronically increase reward thresholds during withdrawal (see above). Brain stimulation reward involves widespread neurocircuitry in the brain, but the most sensitive sites defined by the lowest thresholds involve the trajectory of the medial forebrain bundle that connects the ventral tegmental area with the basal forebrain (Olds and Milner, 1954; Koob et al., 1977). While much emphasis was focused initially on the role of the ascending monoamine systems in the medial forebrain bundle, other non-dopaminergic systems in the medial forebrain bundle clearly have a key role (Hernandez et al., 2006). With intravenous cocaine self-administration in animal models, such elevations in reward threshold begin rapidly and can be observed within a single session of self-administration (Kenny et al., 2003) (Fig. 2), bearing a striking resemblance to human subjective reports. These results demonstrate that the elevation in brain reward thresholds following prolonged access to cocaine failed to return to baseline levels between repeated, prolonged exposure to cocaine self-administration (i.e., residual hysteresis), thus creating a greater and greater elevation in "baseline" ICSS thresholds.

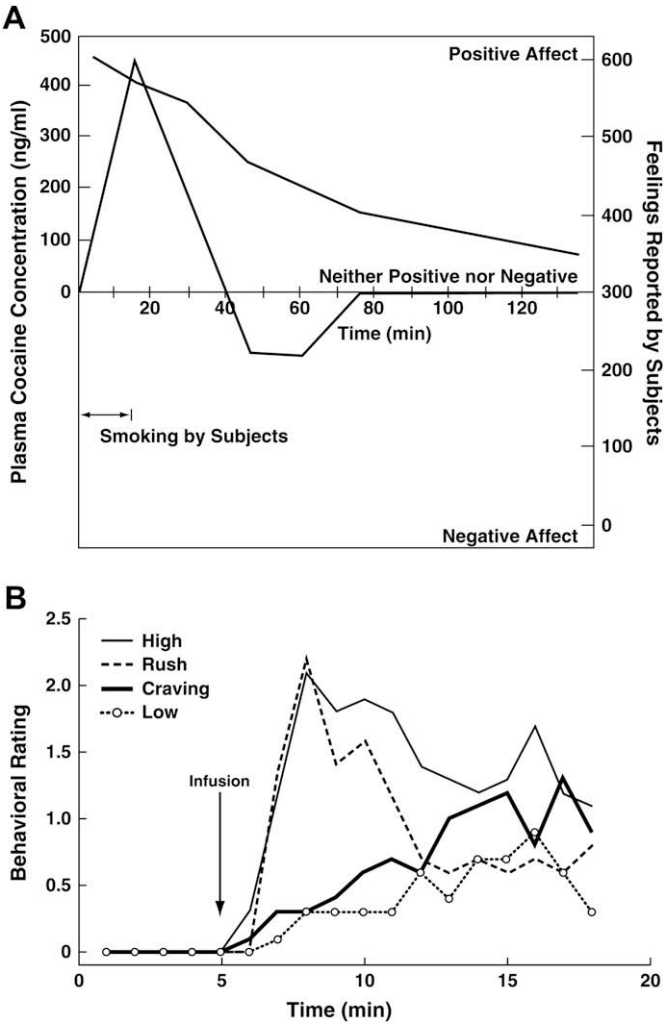

Fig. 1. (A) Dysphoric feelings followed the initial euphoria in experimental subjects who smoked cocaine paste, even though the concentration of cocaine in the plasma of the blood remained relatively high. The dysphoria is characterized by anxiety, depression, fatigue, and a desire for more cocaine. The peak feelings for the subjects were probably reached shortly before the peak plasma concentration, but the first psychological measurements were made later than the plasma assay. Therefore, the temporal sequence of the peaks shown cannot be regarded as definitive. [Taken with permission from Van Dyke and Byck, 1982.] (B) Average behavioral ratings after an infusion of cocaine (0.6 mg/kg over 30 s; $n = 9$). The rush, high, low, and craving ratings were averaged within each category for the subjects who had interpretable cocaine functional magnetic resonance imaging data after motion correction and behavioral ratings time-locked to the scanner. Both peak rush and peak high occurred 3 min post-infusion. Peak low (primary reports of dysphoria and paranoia) occurred 11 min post-infusion. Peak craving occurred 12 min post-infusion. No subject reported effects from the saline infusion on any of the four measures. Ratings obtained for rush, high, low, and craving measures were higher in subjects blinded to the 0.6 mg/kg cocaine dose compared with subjects unblinded to a 0.2 mg/kg cocaine dose. [Taken with permission from Breiter et al., 1997.]

Similar results have been observed showing dysphoria-like responses accompanying 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 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 dysregulation of brain reward function associated with withdrawal from chronic administration of drugs of abuse is a common element of all drugs of abuse. 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 one week. These observations lend credence to the hypothesis that opponent processes can set the stage for one aspect of compulsivity where negative reinforcement mechanisms are engaged.

More recently, opponent process theory has been expanded into the domains of the neurobiology of drug addiction from a neurocircuitry perspective. An allostatic model of the brain motivational systems has been proposed to explain the persistent changes in motivation that are associated with dependence in addiction (Koob and Le Moal, 2001, 2008). In this formulation, addiction is conceptualized as a cycle of increasing dysregulation of brain reward/anti-reward mechanisms that results in a negative emotional state contributing to the compulsive use of drugs. Counteradaptive processes that are part of the normal homeostatic limitation of reward function fail to return within the normal homeostatic range. These counteradaptive processes are hypothesized to be mediated by two mechanisms: within-system neuroadaptations and between-system neuroadaptations (Koob and Bloom, 1988).

In a within-system neuroadaptation, "the primary cellular response element to the drug would itself adapt to neutralize the drug's effects; persistence of the opposing effects after the drug disappears would produce the withdrawal response" (Koob and Bloom, 1988). Thus, a within-system neuroadaptation is a molecular or cellular change within a given reward circuit to

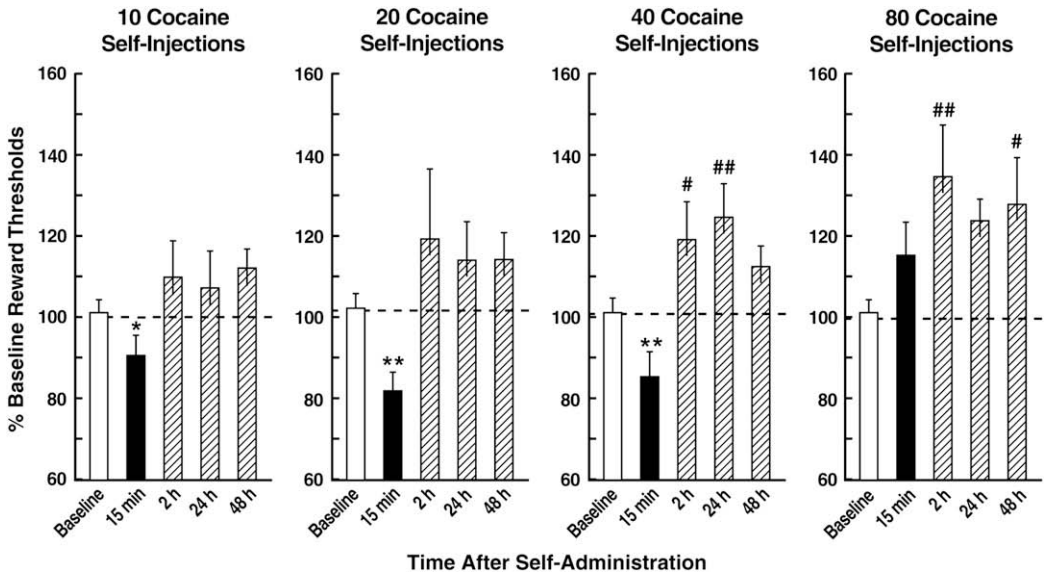

Fig. 2. Rats ($n = 11$) were allowed to self-administer 10, 20, 40, and 80 injections of cocaine (0.25 mg per injection), and intracranial self-stimulation reward thresholds were measured 15 min and 2, 24, and 48 h after the end of each intravenous cocaine self-administration session. The horizontal dotted line in each plot represents 100% of baseline levels. All data are presented as 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; Fisher's LSD test after a statistically significant effect in the repeated-measures analysis of variance. [Taken with permission from Kenny et al., 2003.]

accommodate overactivity of hedonic processing associated with addiction resulting in a decrease in reward function.

The emotional dysregulation associated with the *withdrawal/negative affect* stage also may involve between-system neuroadaptations in which neurochemical systems other than those involved in the positive rewarding effects of drugs of abuse are recruited or dysregulated by chronic activation of the reward system (Koob and Bloom, 1988). Thus, a between-system neuroadaptation is a circuitry change in which another different circuit (anti-reward circuit) is activated by the reward circuit and has opposing actions, again limiting reward function. The purpose of this review is to explore the neuroadaptational changes that occur in the brain emotional systems to account for the neurocircuitry changes that produce opponent processes and are hypothesized to have a key role in the compulsivity of addiction.

1.2. Animal models of compulsivity in addiction measured by negative emotional-like states: place aversion, animal models of anxiety, and reward thresholds

Animal models of the *withdrawal/negative affect* stage include measures of conditioned place aversion (rather than preference) to precipitated withdrawal or spontaneous withdrawal from chronic administration of a drug, increases in reward thresholds using brain stimulation reward (Markou and Koob, 1991; Schulteis et al., 1994, 1995; Epping-Jordan et al., 1998; Gardner and Vorel, 1998; Paterson et al., 2000), and increases in anxiety-like responses (for review, see Shippenberg and Koob, 2002; Sanchis-Segura and Spanagel, 2006).

1.3. Animal models of compulsivity in addiction as defined by increased drug taking: 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 characterizing the development of addiction and has face validity with the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*: "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 acquisition of self-administration, rats typically were 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 intravenous cocaine self-administration in rats may produce different patterns of drug intake, rats were allowed access to intravenously self-administration cocaine for 1 or 6 h per day (Ahmed and Koob, 1998). One hour access (short access or ShA) to intravenous cocaine per session produced low and stable intake as observed previously. In contrast, 6 h access (long access or LgA) to cocaine produced drug intake that gradually escalated over days (Fig. 3). Increased intake was observed in the extended access group during the first hour of the session, with sustained intake over the entire session and an upward shift in the dose-effect function, suggesting an increase in hedonic set point. When animals were allowed access to different doses of cocaine, both the LgA and ShA animals titrated their cocaine intake, but the 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). Escalation also is associated with an increase in break point for cocaine in a progressive-ratio schedule of reinforcement, suggesting an enhanced motivation to seek cocaine or an enhanced efficacy of cocaine reward (Paterson and Markou, 2003; Wee et al., 2008). Such increased self-administration in dependent animals has now been observed with cocaine, methamphetamine, nicotine, heroin, and alcohol (Ahmed et al., 2000; Ahmed and Koob, 1998; Kitamura et al., 2006; O'Dell et al., 2004; George et al., 2007) (Fig. 3). This model is a key element for evaluating the motivational significance of opponent process changes in the brain reward and stress systems

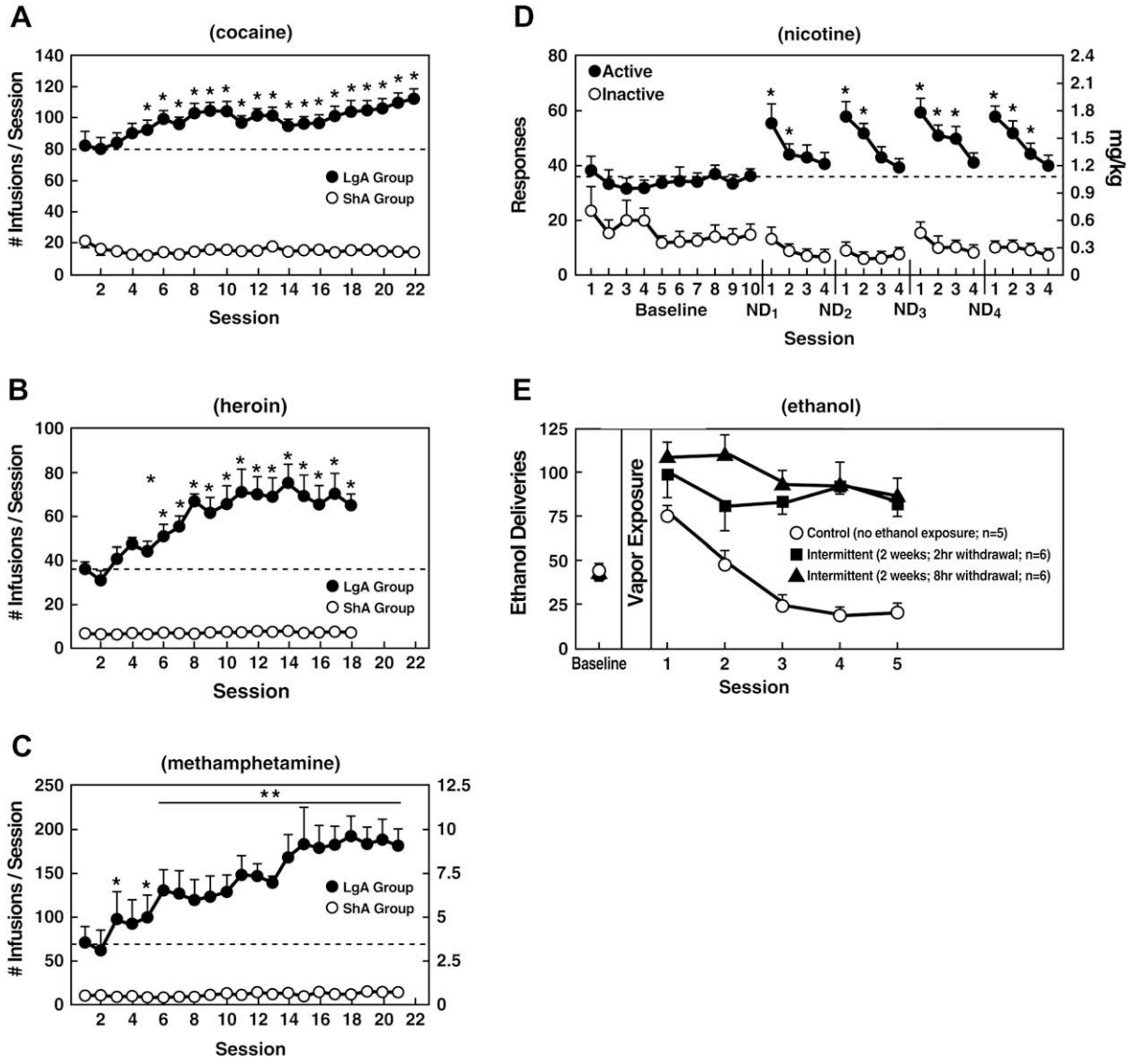

Fig. 3. (A) Effect of drug availability on cocaine intake (mean ± SEM). In 6 h long-access (LgA) rats ($n = 12$) but not in 1 h short-access (ShA) rats ($n = 12$), mean total cocaine intake started to increase significantly from session 5 ($p < 0.05$; sessions 5–22 compared with session 1) and continued to increase thereafter ($p < 0.05$; session 5 compared with sessions 8–10, 12, 13, 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 mg 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 per week. The dotted line indicates the mean (±SEM) number of heroin self-infusions of LgA rats during the first 11 h session. $^{*}p < 0.05$, compared with the first session (paired t-test). [Taken with permission from Ahmed et al., 2000.] (C) Effect of extended access to intravenous methamphetamine self-administration as a function of daily sessions in rats trained to self-administer 0.05 mg/kg/infusion of intravenous methamphetamine during a 6 h session. Short access group (ShA), 1 h session ($n = 6$). Long access group (LgA), 6 h session ($n = 4$). All data were analyzed using two-way analysis of variance (dose × escalation session within ShA or LgA group). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ vs. day 1. [Taken with permission from Kitamura et al., 2006.] (D) Total 23 h active and inactive responses after repeated cycles of 72 h of nicotine deprivation (ND) followed by 4 days of self-administration ($^{*}p < 0.05$ *vs.* baseline). [Taken with permission from George et al., 2007.] (E) Ethanol deliveries (mean ± SEM) in rats trained to respond for 10% ethanol and then either not exposed to ethanol vapor (control, $n = 5$) or exposed to intermittent ethanol vapor (14 h on/10 h off) for 2 weeks and then tested either 2 h ($n = 6$) or 8 h ($n = 6$) after removal from ethanol vapor. $^{*}p < 0.05$, significant increase in operant self-administration of ethanol in rats receiving intermittent vapor exposure compared with control. No difference was observed between rats exposed to intermittent vapor and tested either 2 or 8 h after ethanol withdrawal. [Taken with permission from O'Dell et al., 2004.]

in addiction that lead to compulsivity in addiction. Similar changes in the reinforcing and incentive effects of cocaine as drug intake have been observed following extended access and include increased cocaine-induced reinstatement after extinction and a decreased latency to goal time in a runway model for cocaine reward (Deroche et al., 1999). Altogether, these results suggest that drug taking with extended access changes the motivation to seek the drug. Whether this enhanced drug taking reflects a sensitization of reward or a reward deficit state remains under discussion (Vezina, 2004), but the brain reward and neuropharmacological studies outlined below argue for a reward deficit state driving the increased drug taking during extended access.

The hypothesis that compulsive cocaine use is accompanied by a chronic perturbation in brain reward homeostasis has been tested in an animal model 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 in ShA or control rats across successive self-administration sessions (Ahmed et al., 2002).

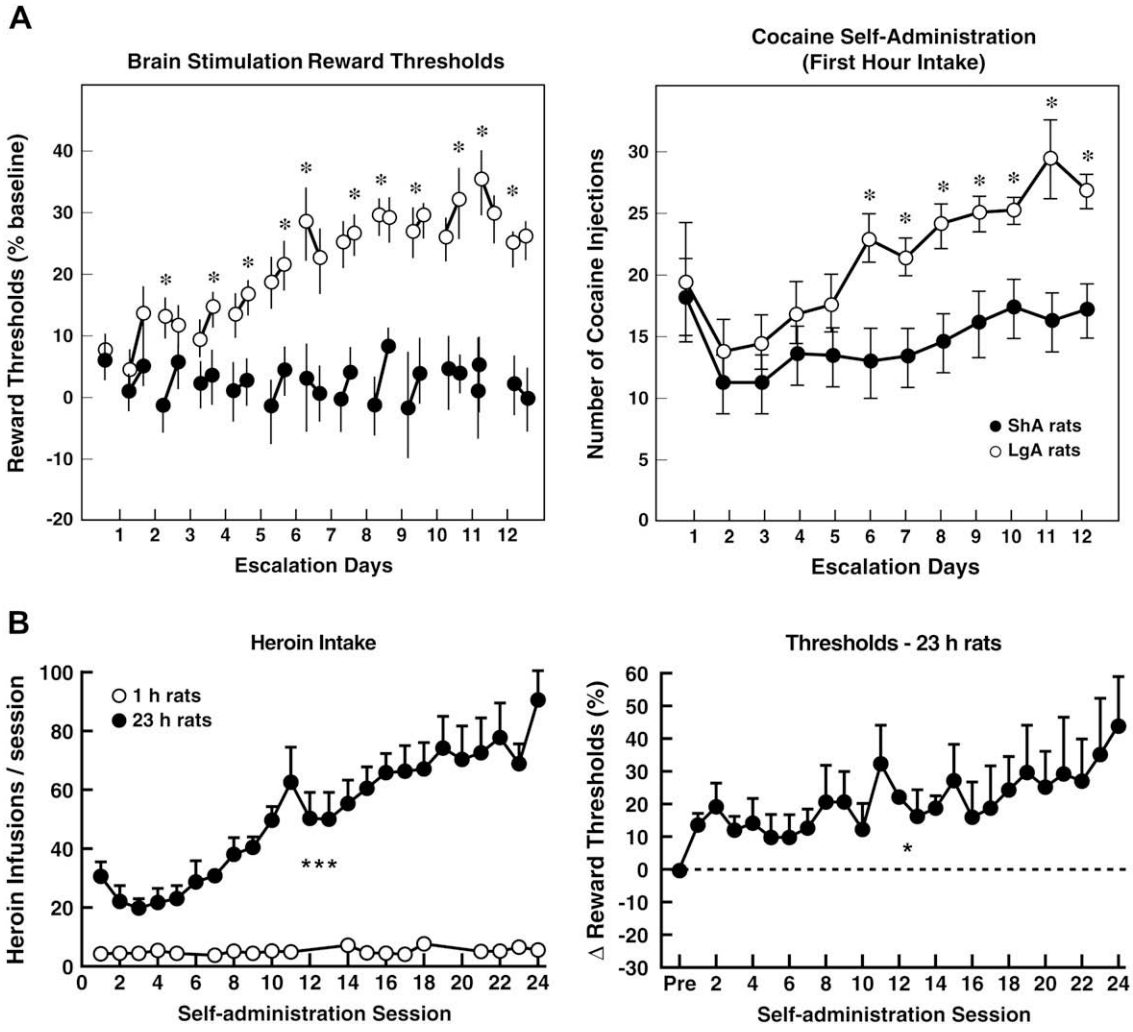

Fig. 4. (A) Relationship between elevation in intracranial self-stimulation reward thresholds and cocaine intake escalation. (Left) Percentage change from baseline ICSS thresholds. (Right) Number of cocaine injections earned during the first hour of each session. Rats first were prepared with bipolar electrodes in either the right or left posterior lateral hypothalamus. One week post-surgery, they were trained to respond for electrical brain stimulation. Reward thresholds measured in μA were assessed according to a modified discrete-trial current-threshold procedure (Markou and Koob, 1993). During the screening phase, the 22 rats tested for self-administration were allowed to self-administer cocaine during only 1 h on a fixed-ratio 1 schedule, after which two balanced groups with the same weight, cocaine intake, and reward thresholds were formed. During the escalation phase, one group had access to cocaine self-administration for only 1 h per day (short-access, ShA) and the other group for 6 h per day (long-access, LgA). The remaining 8 rats were exposed to the same experimental manipulations as the other rats, with the exception that they were not exposed to cocaine (not shown). Reward thresholds were measured in all rats two times per day, 3 h and 17–22 h after each daily self-administration session (ShA and LgA rats) or the control procedure (drug-naive rats; data not shown). Each reward threshold session lasted about 30 min. $^{*}p < 0.05$, compared with drug-naive and/or ShA rats, tests of simple main effects. [Taken with permission from Ahmed et al., 2002.] (B) Unlimited daily access to heroin escalated heroin intake and decreased the excitability of brain reward systems. 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), two-way repeated-measures analysis of variance. Also presented is the percentage change from baseline reward thresholds (±SEM) in 23 h rats. Reward thresholds, assessed immediately after each daily 23 h self-administration session, became progressively more elevated as exposure to self-administered heroin increased across sessions. $^{*}p < 0.05$, main effect of heroin on reward thresholds, two-way repeated-measures analysis of variance. [Taken with permission from Kenny et al., 2006.]

Elevation in baseline reward thresholds temporally preceded and was highly correlated with escalation in cocaine intake (Fig. 4). 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 the dramatic escalation in cocaine consumption that was observed previously. After escalation had occurred, an acute cocaine challenge facilitated brain reward responsiveness to the same degree as before but resulted in higher absolute brain reward thresholds in LgA compared with ShA rats (Ahmed et al., 2002). Similar results have been observed with extended access to heroin (Kenny et al., 2006). Rats allowed 23 h access to heroin also showed a time-dependent increase in reward thresholds that paralleled the increases in heroin intake (Fig. 5) These data provide compelling evidence for brain reward dysfunction in escalated cocaine self-administration, strongly supporting the hedonic allostasis model of drug addiction.

2. Neural substrates for the negative emotional state associated with addiction

2.1. Within-system neuroadaptations that contribute to the negative emotional state component of compulsivity

Within-system neuroadaptations to chronic drug exposure include decreases in function of the same neurotransmitter systems in the same neurocircuits implicated in the acute reinforcing effects of drugs of abuse. One prominent hypothesis is that dopamine systems are compromised in crucial phases of the addiction cycle,

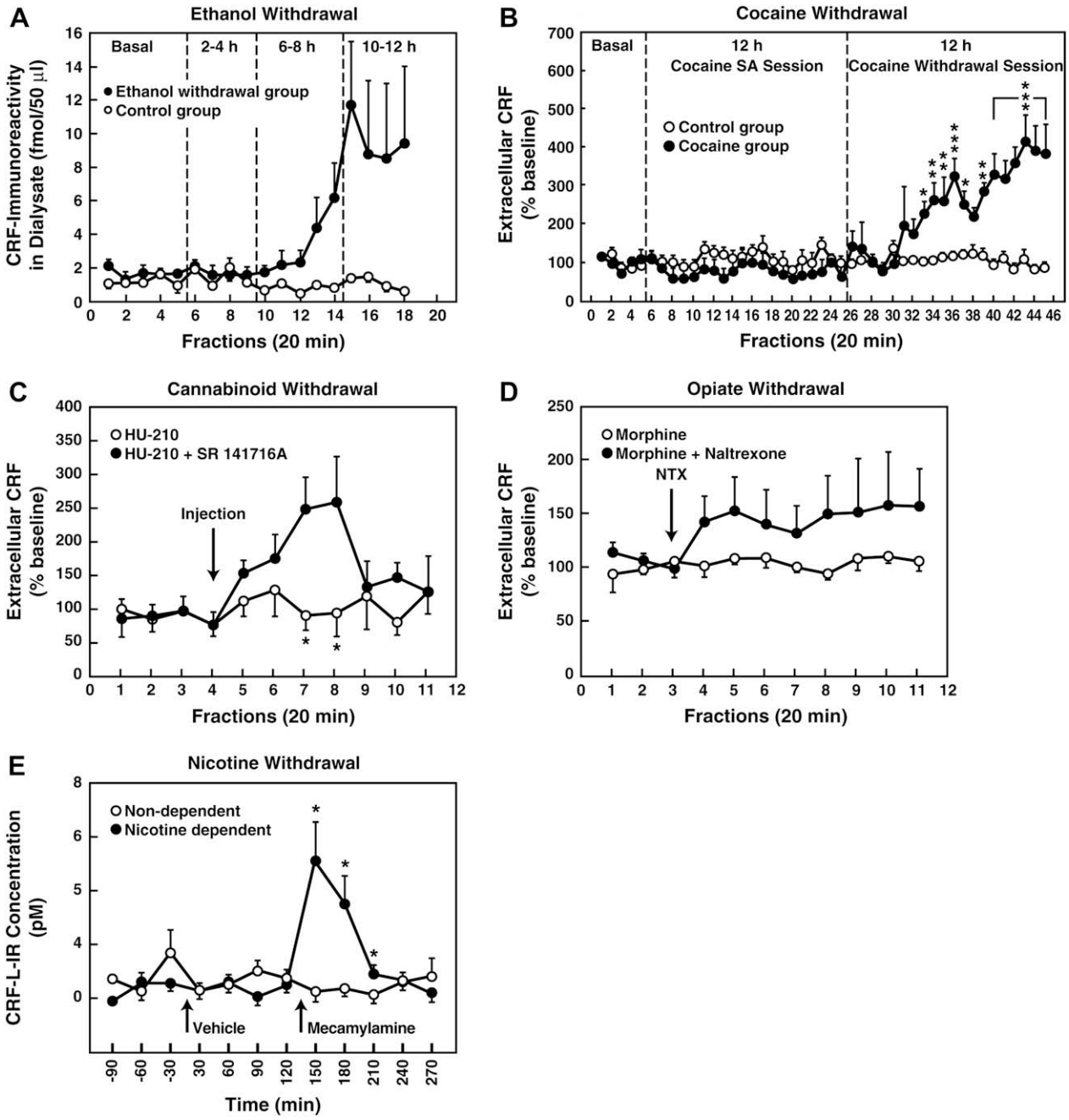

Fig. 5. (A) Effects of ethanol withdrawal on CRF-like immunoreactivity (CRF-L-IR) in the rat amygdala determined by microdialysis. Dialysate was collected over four 2 h periods regularly alternated with non-sampling 2 h periods. The four sampling periods corresponded to the basal collection (before removal of ethanol), and 2–4 h, 6–8 h, and 10–12 h after withdrawal. Fractions were collected every 20 min. Data are expressed as mean ± SEM ($n = 5$ per group). Analysis of variance confirmed significant differences between the two groups over time ($p < 0.05$). [Taken with permission from Merlo-Pich et al., 1995.] (B) Mean (±SEM) dialysate CRF concentrations collected from the central nucleus of the amygdala of rats during baseline, 12 h cocaine self-administration, and a subsequent 12 h withdrawal period (Cocaine group, $n = 5$). CRF levels were measured in rats with the same history of cocaine self-administration training and drug exposure, but not given access to cocaine on the test day (Control group, $n = 6$). Data are expressed as percentages of basal CRF concentrations. Dialysates were collected over 2 h periods alternating with 1 h non-sampling periods as shown by the timeline at the top. During cocaine self-administration, dialysate CRF concentrations in the cocaine group were decreased by about 25% compared with control animals. In contrast, termination of access to cocaine resulted in a significant increase in CRF efflux that began approximately 5 h post-cocaine and reached about 400% of presession baseline levels at the end of the withdrawal session. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, simple main effects after overall mixed-factorial analysis of variance. [Taken with permission from Richter and Weiss, 1999.] (C) Effects of cannabinoid CB_1 antagonist SR 141716A (3 mg/kg) on CRF release from the central nucleus of the amygdala in rats pretreated for 14 days with cannabinoid CB_1 agonist HU-210 (100 mg/kg). Cannabinoid withdrawal induced by SR 141716A was associated with increased CRF release ($^{*}p < 0.005$, $n = 5$–8). Vehicle injections did not alter CRF efflux ($n = 5$–7). Data were standardized by transforming dialysate CRF concentrations into percentages of baseline values based on averages of the first four fractions. [Taken with permission from Rodriguez de Fonseca et al., 1997.] (D) Effects of morphine withdrawal on extracellular CRF in the central nucleus of the amygdala. Withdrawal was precipitated by administration of naltrexone (0.1 mg/kg) in rats prepared with chronic morphine pellet implants. [Taken with permission from Weiss et al., 2001.] (E) Effect of mecamylamine-precipitated (1.5 mg/kg, i.p.) nicotine withdrawal on extracellular levels of CRF-like immunoreactivity in the central nucleus of the amygdala measured by *in vivo* microdialysis in chronic nicotine pump-treated (nicotine-dependent, $n = 7$) and chronic saline pump-treated (non-dependent, $n = 6$) rats. $^{*}p < 0.05$, compared with non-dependent. [Taken with permission from George et al., 2007.]

such as withdrawal and leads to decreased motivation for non-drug-related stimuli and increased sensitivity to the abused drug (Melis et al., 2005). Activation of the mesolimbic dopamine system has long been known to be critical for the acute rewarding properties of psychostimulant drugs and to be associated with the acute reinforcing effects of other drugs of abuse (Koob, 1992; Di Chiara and North, 1992; Nestler, 2005).

However, decreases in activity of the mesolimbic dopamine system and decreases in serotonergic neurotransmission in the nucleus accumbens occur during drug withdrawal in animal studies (Rossetti et al., 1992; Weiss et al., 1992, 1996). Imaging studies in drug-addicted humans have consistently shown long-lasting decreases in the numbers of dopamine D_2 receptors in drug abusers compared with controls (Volkow et al., 2002). In addition, cocaine abusers have reduced dopamine release in response to a pharmacological challenge with a stimulant drug (Volkow et al., 1997; Martinez et al., 2007). Decreases in the number of dopamine D_2 receptors, coupled with the decrease in dopaminergic activity, in cocaine, nicotine, and alcohol abusers results in decreased sensitivity of reward circuits to stimulation by natural reinforcers (Martin-Solch et al., 2001; Volkow and Fowler, 2000). These findings suggest an overall reduction in the sensitivity of the dopamine component of reward circuitry to natural reinforcers and other drugs in drug-addicted individuals.

Psychostimulant withdrawal in humans is associated with fatigue, decreased mood, and psychomotor retardation and in animals is associated with decreased motivation to work for natural rewards (Barr and Phillips, 1999) and decreased locomotor activity (Pulvirenti and Koob, 1993), behavioral effects that may involve decreased dopaminergic function. Animals during amphetamine withdrawal show decreased responding on a progressive-ratio schedule for a sweet solution, and this decreased responding was reversed by the dopamine partial agonist terguride (Orsini et al., 2001), suggesting that low dopamine tone contributes to the motivational deficits associated with psychostimulant withdrawal.

Under this conceptual framework, other within-system neuroadaptations would include increased sensitivity of receptor transduction mechanisms in the nucleus accumbens. Drugs of abuse have acute receptor actions that are linked to intracellular signaling pathways that may undergo adaptations with chronic treatment. Activation of adenylate cyclase, protein kinase A, cyclic adenosine monophosphate response-element binding protein (CREB), and ΔFosB has been observed during opioid withdrawal (Self et al., 1995; Shaw-Lutchman et al., 2002; Nye and Nestler, 1996; Nestler, 2004). The ΔFosB response is hypothesized to represent a neuroadaptive change that extends long into protracted abstinence (Nestler and Malenka, 2004).

2.2. Between-system neuroadaptations that contribute to the negative emotional state component of compulsivity

Brain neurochemical systems involved in arousal-stress modulation also may be engaged within the neurocircuitry of the brain stress systems in an attempt to overcome the chronic presence of the perturbing drug and to restore normal function despite the presence of drug. Both the hypothalamic-pituitary-adrenal axis and the brain stress system mediated by corticotropin-releasing factor (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). Acute withdrawal from all drugs of abuse also produces an aversive or anxiety-like state that can be reversed by CRF antagonists (see below).

The neuroanatomical entity termed the extended amygdala (Heimer and Alheid, 1991) may represent a common anatomical substrate integrating brain arousal-stress systems with hedonic processing systems to produce the between-system opponent process elaborated above. The extended amygdala is composed of the central nucleus of the amygdala, bed nucleus of the stria terminalis, 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). The extended amygdala has long been hypothesized to have a key role not only in fear conditioning (Le Doux, 2000) but also in the emotional component of pain processing (Neugebauer et al., 2004).

2.3. Neuropharmacological studies of the aversive stimulus effects of drug withdrawal

Place aversion has been used to measure the aversive stimulus effects of withdrawal, mostly in the context of opioids (Hand et al., 1988; Stinus et al., 1990). In contrast to conditioned place preference, rats exposed to a particular environment while undergoing precipitated withdrawal to opioids spend less time in the withdrawal-paired environment when subsequently presented with a choice between that environment and an unpaired environment. These aversive stimulus effects can be measured from 24 h to 16 weeks later (Hand et al., 1988; Stinus et al., 1990, 2000). The place aversion does not require maintenance of opioid dependence for its manifestation. Such an association continues to be manifested weeks after animals are "detoxified" (e.g., after the morphine pellets are removed) (see Baldwin and Koob, 1993; Stinus et al., 2000). In addition, a place aversion in opioid-dependent rats can be observed with doses of naloxone below which somatic signs of withdrawal are observed (Schulteis et al., 1994). Although naloxone itself will produce a place aversion in non-dependent rats, the threshold dose required to produce a place aversion decreases significantly in dependent rats (Hand et al., 1988).

A variaton on this approach is to explore the place aversion produced following naloxone injection after a single acute injection of morphine. Acute opioid dependence has been defined as the precipitation of withdrawal-like signs by opioid antagonists following a single dose or short-term administration of an opioid agonist (Martin and Eades, 1964). Rats show a reliable conditioned place aversion precipitated by a low dose of naloxone after a single morphine injection that reflects a motivational component of acute withdrawal (Azar et al., 2003). Acute opioid withdrawal also produces increases in reward thresholds (Liu and Schulteis, 2004), suppression in operant responding (Schulteis et al., 2003) and increased anxiety-like behavior in the elevated plus maze (Zhang and Schulteis, 2008).

Using the conditioned place aversion paradigm, the opioid partial agonist buprenorphine dose-dependently decreased the place aversion produced by precipitated opioid withdrawal in dependent animals. 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). Functional noradrenergic antagonists blocked opioid withdrawal-induced place aversion (Delfs et al., 2000).

Another candidate for the aversive effects of drug withdrawal is dynorphin. Much evidence shows that dynorphin is increased in the nucleus accumbens in response to dopaminergic activation and,

in turn, that overactivity of the dynorphin systems can decrease dopaminergic function. κ opioid agonists are aversive (Land et al., 2008; Pfeiffer et al., 1986), and cocaine, opioid, and ethanol withdrawal is associated with increased dynorphin in the nucleus accumbens and/or amygdala (Spangler et al., 1993; Lindholm et al., 2000; Rattan et al., 1992).

2.4. Neuropharmacological studies of the anxiety-like effects of drug withdrawal

Another common response to acute withdrawal and protracted abstinence from all major drugs of abuse is the manifestation of anxiety-like responses. Animal models have revealed anxiety-like response to all major drugs of abuse during acute withdrawal. The dependent variable is often a passive response to a novel and/or aversive stimulus, such as the open field or elevated plus maze, or an active response to an aversive stimulus, such as defensive burying of an electrified metal probe. Withdrawal from repeated administration of cocaine produces an anxiogenic-like response in the elevated plus maze and defensive burying test, an effect that is reversed by administration of CRF antagonists (Sarnyai et al., 1995; Basso et al., 1999). Precipitated withdrawal in opioid dependence also produces anxiety-like effects (Schulteis et al., 1998; Harris and Aston-Jones, 1993). Ethanol withdrawal produces anxiety-like behavior that is reversed by intracerebroventricular administration of CRF_1/CRF_2 peptidergic antagonists (Baldwin et al., 1991), and small molecule CRF_1 antagonists (Knapp et al., 2004; Overstreet et al., 2004; Funk 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). The effects of CRF antagonists have been localized to the central nucleus of the amygdala (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).

3. Neural substrates for increased drug-taking with extended access

3.1. Within-system neuroadaptations

In a series of studies, dopamine partial agonists have not only been shown to reverse psychostimulant withdrawal but also to block the increase in psychostimulant self-administration associated with extended access. Dopamine partial agonists decrease the reinforcing effects of psychostimulant drugs in non-dependent limited access paradigms (Izzo et al., 2001; Pulvirenti et al., 1998). However, animals with extended access show an increased sensitivity to a dopamine partial agonist (Wee et al., 2007). Long-access rats administered a dopamine D_2 partial agonist showed a shift to the left of the dose–response function similar to results observed with dopamine antagonists (Ahmed and Koob, 2004). These results, combined with the observation that dopamine partial agonists also can reverse psychostimulant withdrawal, suggest that dysregulation of dopamine tone may contribute to the motivational effects of drug withdrawal.

Similar results have been observed in opioid dependence with the opioid partial agonist buprenorphine. Buprenorphine dose-dependently decreased heroin self-administration in opioid-dependent rats (Chen et al., 2006).

3.2. Between-system neuroadaptations

The increase in extracellular CRF in the amygdala during acute withdrawal (Fig. 5) and ability of CRF antagonists to block the anxiogenic-like and aversive-like motivational effects of drug withdrawal would predict 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., in press-a). CRF antagonists also blocked the increased self-administration of ethanol in dependent rats (Funk et al., 2007) (Table 2).

Administration of CRF_1 antagonists systemically reversed the increased self-administration of cocaine associated with extended access, and this reversal was at antagonist doses that were lower than those that decreased short-access self-administration (Specio et al., 2008). Here, rats allowed 6 h access to cocaine showed an increase in cocaine intake over time, whereas 1 h access rats remained stable. Two different CRF_1 antagonists blocked cocaine self-administration in the long-access rats at doses lower than those that blocked cocaine self-administration in short-access rats (Specio et al., 2008).

As noted above, CRF in parts of the extended amygdala is involved in the aversive stimulus effects of opioid withdrawal. The selective CRF_1 antagonist antalarmin blocked the place aversion produced by naloxone in morphine-dependent rats (Stinus et al., 2005). 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). CRF_1 antagonists also selectively blocked the increase in heroin self-administration observed in heroin-dependent rats with extended access (Greenwell et al., in press-a).

Also, as noted above, precipitated withdrawal from chronic nicotine produced anxiogenic-like effects that were blocked by a CRF_1 receptor antagonist (George et al., 2007) and increases in reward thresholds that were reversed by a CRF antagonist (Bruijnzeel et al., 2007). Extracellular CRF has been shown to be increased in the amygdala during withdrawal from chronic nicotine (George et al., 2007) (Fig. 5). From a developmental perspective, increased CRF-like immunoreactivity has been observed in adult rats exposed to nicotine during adolescence and has been linked to an anxiety-like phenotype (Slawecki et al., 2005). 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). These results suggest that CRF in the basal forebrain also may have an important role in the development of the aversive motivational effects that drive the increased drug seeking associated with cocaine, heroin, and nicotine dependence.

A particularly dramatic example of the motivational effects of CRF in dependence can be observed in animal models of ethanol self-administration in dependent animals. During ethanol withdrawal, extrahypothalamic CRF systems become hyperactive, with

Table 2
Role of corticotropin-releasing factor in dependence

Drug	CRF antagonist effects on withdrawal-induced anxiety-like responses	Withdrawal-induced changes in extracellular CRF in CeA	CRF antagonist effects on dependence-induced increases in self-administration
Cocaine	↓	↑	↓
Opioids	↓[a]	↑	↓
Ethanol	↓	↑	↓
Nicotine	↓	↑	↓
Δ^9-Tetrahydrocannabinol	↓	↑	nt

nt, not tested; CeA, central nucleus of the amygdala.
[a] Aversive effects with place conditioning.

an increase in extracellular CRF within the central nucleus of the amygdala and bed nucleus of the stria terminalis of dependent rats (Funk et al., 2006; Merlo-Pich et al., 1995; Olive et al., 2002 (Fig. 5)). The dysregulation of brain CRF systems is hypothesized to underlie not only the enhanced anxiety-like behaviors but also the enhanced ethanol self-administration associated with ethanol withdrawal. Supporting this hypothesis. Exposure to repeated cycles of chronic ethanol vapor produced substantial increases in ethanol intake in rats both during acute withdrawal and during 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., 2002). When administered directly into the central nucleus of the amygdala, a CRF_1/CRF_2 antagonist blocked ethanol self-administration in ethanol-dependent rats (Funk et al., 2006). Systemic injections of small-molecule CRF_1 antagonists also blocked the increased ethanol intake associated with acute withdrawal (Knapp et al., 2004; Overstreet et al., 2004; Funk et al., 2007). These data suggest an important role for CRF, primarily within the central nucleus of the amygdala, in mediating the increased self-administration associated with dependence.

Although less well developed, evidence exists for a role of norepinephrine systems in the extended amygdala in the negative motivational state and increased self-administration associated with dependence. Norepinephrine functional antagonists (β_1 antagonist and α_2 agonist) injected into the lateral bed nucleus of the stria terminalis blocked precipitated opiate withdrawal-induced place aversions (Delfs et al., 2000). The effects of norepinephrine in mediating the motivational effects of opioid withdrawal involve the ventral noradrenergic system. Ventral noradrenergic bundle lesions attenuated opioid withdrawal-induced place aversions (Delfs et al., 2000), but virtually complete lesions of the dorsal noradrenergic bundle from the locus coeruleus with the neurotoxin 6-hydroxydopamine failed to block the place aversion produced by opioid withdrawal (Caille et al., 1999). Functional norepinephrine antagonists block excessive drug intake associated with dependence on ethanol (Walker et al., 2008), cocaine (Wee et al., 2008), and opioids (Greenwell et al., in press-b). A focal point for many of these effects is the extended amygdala but at the level of the bed nucleus of the stria terminalis. Dynorphin, an opioid peptide that binds to κ opioid receptors, has long been known to show activation with chronic administration of psychostimulants and opioids (Nestler, 2004; Koob, 2008), and κ opioid agonists produce aversive effects in animals and humans (Mucha and Herz, 1985; Pfeiffer et al., 1986). A κ opioid antagonist blocks the excessive drinking associated with ethanol withdrawal and dependence (Walker and Koob, 2008). Evidence demonstrates that κ receptor activation can promote CRF release (Song and Takemori, 1992), but recently some have argued that the effects of dynorphin in producing negative emotional states are mediated via activation of CRF systems (Land et al., 2008).

The dynamic nature of the brain stress system response to challenge is illustrated by the pronounced interaction of central nervous system CRF systems and central nervous system norepinephrine systems. Conceptualized as a feed-forward system at multiple levels of the pons and basal forebrain, CRF activates norepinephrine, and norepinephrine in turn activates CRF (Koob, 1999). Much pharmacologic, physiologic, and anatomic evidence supports an important role for a CRF–norepinephrine interaction in the region of the locus coeruleus in response to stressors (Valentino et al., 1991, 1993; Van Bockstaele et al., 1998). However, norepinephrine also stimulates CRF release in the paraventricular nucleus of the hypothalamus (Alonso et al., 1986), the bed nucleus of the stria terminalis, and the central nucleus of the amygdala. Such feed-forward systems were further hypothesized to have powerful functional significance for mobilizing an organism's response to environmental challenge, but such a mechanism may be particularly vulnerable to pathology (Koob, 1999).

Neuropeptide Y (NPY) is a neuropeptide with dramatic anxiolytic-like properties localized to the amygdala and has been hypothesized to have opposite effects to CRF in the negative motivational state of withdrawal from drugs of abuse (Heilig and Koob, 2007). Significant evidence suggests that activation of NPY in the central nucleus of the amygdala can block the motivational aspects of dependence associated with chronic ethanol administration. NPY administered intracerebroventricularly blocked the increased drug intake associated with ethanol dependence (Thorsell et al., 2005a,b). Injection of NPY directly into the central nucleus of the amygdala (Gilpin et al., 2008) and viral vector-enhanced expression of NPY in the central nucleus of the amygdala also blocked the increased drug intake associated with ethanol dependence (Thorsell et al., 2007).

Thus, acute withdrawal from drugs increases CRF in the central nucleus of the amygdala that has motivational significance for the anxiety-like effects of acute withdrawal and the increased drug intake associated with dependence (Fig. 6). Acute withdrawal also may increase the release of norepinephrine in the bed nucleus of the stria terminalis and dynorphin in the nucleus accumbens, and both of which may contribute to the negative emotional state associated with dependence. Decreased activity of NPY in the central nucleus of the amygdala also may contribute to the anxiety-like state associated with ethanol dependence. Activation of brain stress systems (CRF, norepinephrine, dynorphin) combined with inactivation of brain anti-stress systems (NPY) elicits powerful emotional dysregulation in the extended amygdala. Such dysregulation of emotional processing may be a significant contribution to the between-system opponent processes that help maintain dependence and also set the stage for more prolonged state changes in emotionality such as protracted abstinence.

4. Compulsivity in addiction: an allostatic view

Compulsivity in addiction can derive from multiple sources, including enhanced incentive salience, engagement of habit function, and impairment in executive function. However, underlying each of these sources is a negative emotional state that may strongly impact on compulsivity. The development of the negative emotional state that drives the negative reinforcement of addiction has been defined as the "dark side" of addiction (Koob and Le Moal, 2005, 2008) and is hypothesized to be the *b-process* of the hedonic dynamic known as opponent process in which the *a-process* is euphoria. The negative emotional state that comprises the *withdrawal/negative affect* stage consists of key motivational elements, such as chronic irritability, emotional pain, malaise, dysphoria, alexithymia, and loss of motivation for natural rewards, and is characterized in animals by increases in reward thresholds during withdrawal from all major drugs of abuse. Two processes are hypothesized to form the neurobiological basis for the *b-process*: loss of function in the reward systems (within-system neuroadaptation) and recruitment of the brain stress or anti-reward systems (between-system neuroadaptation) (Koob and Bloom, 1988; Koob and Le Moal, 1997). Anti-reward is a construct based on the hypothesis that brain systems are in place to limit reward (Koob and Le Moal, 2008). As dependence and withdrawal develop, brain stress systems such as CRF, norepinephrine, and dynorphin are recruited, producing aversive or stress-like states (Koob, 2003; Nestler, 2001; Aston-Jones et al., 1999). At the same time, within the motivational circuits of the ventral striatum-extended amygdala, reward function decreases. The combination of decreases in reward neurotransmitter function and recruitment of anti-reward systems

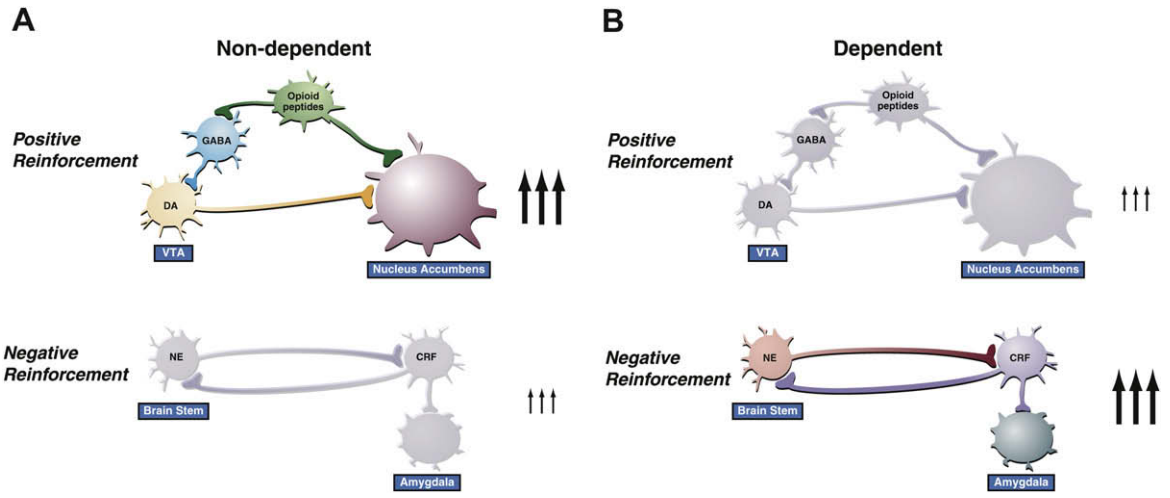

Fig. 6. Neurocircuitry associated with the acute positive reinforcing effects of drugs of abuse and the negative reinforcement of dependence and how it changes in the transition from non-dependent drug taking to dependent drug taking. Key elements of the reward circuit are dopamine (DA) and opioid peptide neurons that intersect at both the ventral tegmental area (VTA) and the nucleus accumbens and are activated during initial use and the early *binge/intoxication* stage. Key elements of the stress circuit are corticotropin-releasing factor (CRF) and noradrenergic (norepinephrine, NE) neurons that converge on γ-aminobutyric acid (GABA) interneurons in the central nucleus of the amygdala that are activated during the development of dependence. [Taken with permission from Koob and Le Moal, 2008.]

provides a powerful source of negative reinforcement that contributes to compulsive drug-seeking behavior and addiction (Fig. 6).

An overall conceptual theme argued here is that drug addiction represents a break with homeostatic brain regulatory mechanisms that regulate the emotional state of the animal. The dysregulation of emotion begins with the binge and subsequent acute withdrawal, but leaves a residual neuroadaptive trace that allows rapid "re-addiction" even months and years after detoxification and abstinence. Thus, the emotional dysregulation of drug addiction represents more than simply a homeostatic dysregulation of hedonic function; it also represents a dynamic break with homeostasis of this system that has been termed allostasis.

Allostasis, originally conceptualized to explain persistent morbidity of arousal and autonomic function, is defined as "stability through change." Allostasis is far more complex than homeostasis and has several unique characteristics (Sterling and Eyer, 1988). 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* can be defined as a state of chronic deviation of the regulatory system from its normal (homeostatic) operating level. *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).

Allostatic mechanisms have been hypothesized to be involved in maintaining a functioning brain reward system that has relevance for the pathology of addiction (Koob and Le Moal, 2001). Two components are hypothesized to adjust to challenges to the brain produced by drugs of abuse: overactivation of brain reward transmitters and circuits and recruitment of the brain anti-reward or brain stress systems. Thus, the very physiological mechanism that allows rapid responses to environmental challenge becomes the source of pathology if adequate time or resources are not available to shut off the response (e.g., the interaction between CRF and norepinephrine in the brainstem and basal forebrain that could lead to pathological anxiety) (Koob, 1999).

Repeated challenges, such as with drugs of abuse, lead to attempts of the brain via molecular, cellular, and neurocircuitry changes to maintain stability but at a cost. For the drug addiction framework elaborated here, the residual deviation from normal brain reward threshold regulation is termed an *allostatic state*. This state represents a combination of chronic elevation of reward set point fueled by decreased function of reward circuits and recruitment of anti-reward systems, both of which leading to the compulsivity of drug-seeking and drug-taking. 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 the dysregulation of brain emotional systems impacts on the cognitive domain linked to impairments in executive function, and how individuals differ at the molecular-genetic level of analysis to convey loading on these circuits remain challenges for future research.

Acknowledgments

The author would like to thank Michael Arends and Mellany Santos for their outstanding assistance with the preparation of this manuscript. Research was supported by National Institutes of Health grants AA06420 and AA08459 from the National Institute on Alcohol Abuse and Alcoholism, DA10072, DA04043, and DA04398 from the National Institute on Drug Abuse, and DK26741 from the National Institute of Diabetes and Digestive and Kidney Diseases. Research also was supported by the Pearson Center for Alcoholism and Addiction Research. This is publication number 19480 from The Scripps Research Institute.

References

Ahmed, S.H., Koob, G.F., 1998. Transition from moderate to excessive drug intake: change in hedonic set point. Science 282, 298–300.
Ahmed, S.H., Koob, G.F., 1999. Long-lasting increase in the set point for cocaine self-administration after escalation in rats. Psychopharmacology 146, 303–312.
Ahmed, S.H., Koob, G.F., 2004. Changes in response to a dopamine antagonist in rats with escalating cocaine intake. Psychopharmacology 172, 450–454.
Ahmed, S.H., Walker, J.R., Koob, G.F., 2000. Persistent increase in the motivation to take heroin in rats with a history of drug escalation. Neuropsychopharmacology 22, 413–421.
Ahmed, S.H., Kenny, P.J., Koob, G.F., Markou, A., 2002. Neurobiological evidence for hedonic allostasis associated with escalating cocaine use. Nature Neuroscience 5, 625–626.
Alheid, G.F., De Olmos, J.S., Beltramino, C.A., 1995. Amygdala and extended amygdala. In: Paxinos, G. (Ed.), The Rat Nervous System. Academic Press, San Diego, CA, pp. 495–578.
Allen, T.J., Moeller, F.G., Rhoades, H.M., Cherek, D.R., 1998. Impulsivity and history of drug dependence. Drug and Alcohol Dependence 50, 137–145.

Alonso, G., Szafarczyk, A., Balmefrezol, M., Assenmacher, I., 1986. Immunocytochemical evidence for stimulatory control by the ventral noradrenergic bundle of parvocellular neurons of the paraventricular nucleus secreting corticotropin-releasing hormone and vasopressin in rats. Brain Research 397, 297–307.

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, fourth ed. American Psychiatric Press, Washington, DC. text revision.

Aston-Jones, G., Delfs, J.M., Druhan, J., Zhu, Y., 1999. The bed nucleus of the stria terminalis: a target site for noradrenergic actions in opiate withdrawal. In: McGinty, J.F. (Ed.), Advancing from the Ventral Striatum to the Extended Amygdala: Implications for Neuropsychiatry and Drug Abuse. Annals of the New York Academy of Sciences, vol. 877. New York Academy of Sciences, New York, pp. 486–498.

Azar, M.R., Jones, B.C., Schulteis, G., 2003. Conditioned place aversion is a highly sensitive index of acute opioid dependence and withdrawal. Psychopharmacology 170, 42–50.

Baldwin, H.A., Koob, G.F., 1993. Rapid induction of conditioned opiate withdrawal in the rat. Neuropsychopharmacology 8, 15–21.

Baldwin, H.A., Rassnick, S., Rivier, J., Koob, G.F., Britton, K.T., 1991. CRF antagonist reverses the "anxiogenic" response to ethanol withdrawal in the rat. Psychopharmacology 103, 227–232.

Barr, A.M., Phillips, A.G., 1999. Withdrawal following repeated exposure to d-amphetamine decreases responding for a sucrose solution as measured by a progressive ratio schedule of reinforcement. Psychopharmacology 141, 99–106.

Basso, A.M., Spina, M., Rivier, J., Vale, W., Koob, G.F., 1999. Corticotropin-releasing factor antagonist attenuates the "anxiogenic-like" effect in the defensive burying paradigm but not in the elevated plus-maze following chronic cocaine in rats. Psychopharmacology 145, 21–30.

Breese, G.R., Overstreet, D.H., Knapp, D.J., Navarro, M., 2005. Prior multiple ethanol withdrawals enhance stress-induced anxiety-like behavior: inhibition by CRF_1- and benzodiazepine-receptor antagonists and a $5\text{-}HT_{1a}$-receptor agonist. Neuropsychopharmacology 30, 1662–1669.

Breiter, H.C., Gollub, R.L., Weisskoff, R.M., Kennedy, D.N., Makris, N., Berke, J.D., Goodman, J.M., Kantor, H.L., Gastfriend, D.R., Riorden, J.P., Mathew, R.T., Rosen, B.R., Hyman, S.E., 1997. Acute effects of cocaine on human brain activity and emotion. Neuron 19, 591–611.

Bruijnzeel, A.W., Marcinkiewcz, C., Isaac, S., Booth, M.M., Dennis, D.M., Gold, M.S., 2007. The effects of buprenorphine on fentanyl withdrawal in rats. Psychopharmacology 191, 931–941.

Caille, S., Espejo, E.F., Reneric, J.P., Cador, M., Koob, G.F., Stinus, L., 1999. Total neurochemical lesion of noradrenergic neurons of the locus coeruleus does not alter either naloxone-precipitated or spontaneous opiate withdrawal nor does it influence ability of clonidine to reverse opiate withdrawal. Journal of Pharmacology and Experimental Therapeutics 290, 881–892.

Chen, S.A., O'Dell, L., Hoefer, M., Greenwell, T.N., Zorrilla, E.P., Koob, G.F., 2006. Unlimited access to heroin self-administration: independent motivational markers of opiate dependence. Neuropsychopharmacology 31, 2692–2707 (corrigedum: 31, 2802).

Contarino, A., Papaleo, F., 2005. The corticotropin-releasing factor receptor-1 pathway mediates the negative affective states of opiate withdrawal. Proceedings of the National Academy of Sciences USA 102, 18649–18654.

Delfs, J.M., Zhu, Y., Druhan, J.P., Aston-Jones, G., 2000. Noradrenaline in the ventral forebrain is critical for opiate withdrawal-induced aversion. Nature 403, 430–434.

Deroche, V., Le Moal, M., Piazza, P.V., 1999. Cocaine self-administration increases the incentive motivational properties of the drug in rats. European Journal of Neuroscience 11, 2731–2736.

Deroche-Gamonet, V., Belin, D., Piazza, P.V., 2004. Evidence for addiction-like behavior in the rat. Science 305, 1014–1017.

Di Chiara, G., North, R.A., 1992. Neurobiology of opiate abuse. Trends in Pharmacological Sciences 13, 185–193.

Epping-Jordan, M.P., Watkins, S.S., Koob, G.F., Markou, A., 1998. Dramatic decreases in brain reward function during nicotine withdrawal. Nature 393, 76–79.

Fillmore, M.T., Rush, C.R., 2002. Impaired inhibitory control of behavior in chronic cocaine users. Drug and Alcohol Dependence 66, 265–273.

Funk, C.K., O'Dell, L.E., Crawford, E.F., Koob, G.F., 2006. Corticotropin-releasing factor within the central nucleus of the amygdala mediates enhanced ethanol self-administration in withdrawn, ethanol-dependent rats. Journal of Neuroscience 26, 11324–11332.

Funk, C.K., Zorrilla, E.P., Lee, M.J., Rice, K.C., Koob, G.F., 2007. Corticotropin-releasing factor 1 antagonists selectively reduce ethanol self-administration in ethanol-dependent rats. Biological Psychiatry 61, 78–86.

Gardner, E.L., Vorel, S.R., 1998. Cannabinoid transmission and reward-related events. Neurobiology of Disease 5, 502–533.

George, O., Ghozland, S., Azar, M.R., Cottone, P., Zorrilla, E.P., Parsons, L.H., O'Dell, L.E., Richardson, H.N., Koob, G.F., 2007. CRF-CRF_1 system activation mediates withdrawal-induced increases in nicotine self-administration in nicotine-dependent rats. Proceedings of the National Academy of Sciences USA 104, 17198–17203.

Gilpin, N.W., Richardson, H.N., Lumeng, L., Koob, G.F., 2008. Dependence-induced alcohol drinking by alcohol-preferring (P) rats and outbred Wistar rats. Alcoholism: Clinical and Experimental Research 32, 1688–1696.

Green, L., Fristoe, N., Myerson, J., 1994. Temporal discounting and preference reversals in choice between delayed outcomes. Psychonomic Bulletin and Review 1, 383–389.

Greenwell, T.N., Funk, C.K., Cottone, P., Richardson, H.N., Chen, S.A., Rice, K., Lee, M.J., Zorrilla, E.P., Koob, G.F., in press-a. Corticotropin-releasing factor-1 receptor antagonists decrease heroin self-administration in long-, but not short-access rats. Addiction Biology (in press).

Greenwell, T.N., Walker, B.M., Cottone, P., Zorrilla, E.P., Koob, G.F., in press-b. The α_1 adrenergic receptor antagonist prazosin reduces heroin self-administration in rats with extended access to heroin administration. Pharmacology Biochemistry and Behavior (in press).

Hand, T.H., Koob, G.F., Stinus, L., Le Moal, M., 1988. Aversive properties of opiate receptor blockade: evidence for exclusively central mediation in naive and morphine-dependent rats. Brain Research 474, 364–368.

Harris, G.C., Aston-Jones, G., 1993. β-Adrenergic antagonists attenuate withdrawal anxiety in cocaine- and morphine-dependent rats. Psychopharmacology 113, 131–136.

Hebb, D.O., 1972. Textbook of Psychology, third ed. W.B. Saunders, Philadelphia, PA.

Heilig, M., Koob, G.F., 2007. A key role for corticotropin-releasing factor in alcohol dependence. Trends in Neurosciences 30, 399–406.

Heimer, L., Alheid, G., 1991. Piecing together the puzzle of basal forebrain anatomy. In: Napier, T.C., Kalivas, P.W., Hanin, I. (Eds.), The Basal Forebrain: Anatomy to Function. Advances in Experimental Medicine and Biology, vol. 295. Plenum Press, New York, pp. 1–42.

Heinrichs, S.C., Menzaghi, F., Schulteis, G., Koob, G.F., Stinus, L., 1995. Suppression of corticotropin-releasing factor in the amygdala attenuates aversive consequences of morphine withdrawal. Behavioural Pharmacology 6, 74–80.

Hernandez, G., Hamdani, S., Rajabi, H., Conover, K., Stewart, J., Arvanitogiannis, A., Shizgal, P., 2006. Prolonged rewarding stimulation of the rat medial forebrain bundle: neurochemical and behavioral consequences. Behavioral Neuroscience 120, 888–904.

Izzo, E., Orsini, C., Koob, G.F., Pulvirenti, L., 2001. A dopamine partial agonist and antagonist block amphetamine self-administration in a progressive ratio schedule. Pharmacology Biochemistry and Behavior 68, 701–708.

Kenny, P.J., Polis, I., Koob, G.F., Markou, A., 2003. Low dose cocaine self-administration transiently increases but high dose cocaine persistently decreases brain reward function in rats. European Journal of Neuroscience 17, 191–195.

Kenny, P.J., Chen, S.A., Kitamura, O., Markou, A., Koob, G.F., 2006. Conditioned withdrawal drives heroin consumption and decreases reward sensitivity. Journal of Neuroscience 26, 5894–5900.

Kitamura, O., Wee, S., Specio, S.E., Koob, G.F., Pulvirenti, L., 2006. Escalation of methamphetamine self-administration in rats: a dose-effect function. Psychopharmacology 186, 48–53.

Knapp, D.J., Overstreet, D.H., Moy, S.S., Breese, G.R., 2004. SB242084, flumazenil, and CRA1000 block ethanol withdrawal-induced anxiety in rats. Alcohol 32, 101–111.

Koob, G.F., 1992. Drugs of abuse: anatomy, pharmacology, and function of reward pathways. Trends in Pharmacological Sciences 13, 177–184.

Koob, G.F., 1999. Corticotropin-releasing factor, norepinephrine and stress. Biological Psychiatry 46, 1167–1180.

Koob, G.F., 2003. Neuroadaptive mechanisms of addiction: studies on the extended amygdala. European Neuropsychopharmacology 13, 442–452.

Koob, G.F., 2004. Allostatic view of motivation: implications for psychopathology. In: Bevins, R.A., Bardo, M.T. (Eds.), Motivational Factors in the Etiology of Drug Abuse. Nebraska Symposium on Motivation, vol. 50. University of Nebraska Press, Lincoln, NE, pp. 1–18.

Koob, G.F., 2008. A role for brain stress systems in addiction. Neuron 59, 11–34.

Koob, G.F., Bloom, F.E., 1988. Cellular and molecular mechanisms of drug dependence. Science 242, 715–723.

Koob, G.F., Le Moal, M., 1997. Drug abuse: hedonic homeostatic dysregulation. Science 278, 52–58.

Koob, G.F., Le Moal, M., 2001. Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology 24, 97–129.

Koob, G.F., Le Moal, M., 2005. Plasticity of reward neurocircuitry and the "dark side" of drug addiction. Nature Neuroscience 8, 1442–1444.

Koob, G.F., Le Moal, M., 2008. Addiction and the brain antireward system. Annual Review of Psychology 59, 29–53.

Koob, G.F., Winger, G.D., Meyerhoff, J.L., Annau, Z., 1977. Effects of d-amphetamine on concurrent self-stimulation of forebrain and brain stem loci. Brain Research 137, 109–126.

Koob, G.F., Heinrichs, S.C., Menzaghi, F., Pich, E.M., Britton, K.T., 1994. Corticotropin releasing factor, stress and behavior. Seminars in the Neurosciences 6, 221–229.

Kornetsky, C., Esposito, R.U., 1979. Euphorigenic drugs: effects on the reward pathways of the brain. Federation Proceedings 38, 2473–2476.

Land, B.B., Bruchas, M.R., Lemos, J.C., Xu, M., Melief, E.J., Chavkin, C., 2008. The dysphoric component of stress is encoded by activation of the dynorphin kappa-opioid system. Journal of Neuroscience 28, 407–414.

Le Doux, J.E., 2000. Emotion circuits in the brain. Annual Review of Neuroscience 23, 155–184.

Lindholm, S., Ploj, K., Franck, J., Nylander, I., 2000. Repeated ethanol administration induces short- and long-term changes in enkephalin and dynorphin tissue concentrations in rat brain. Alcohol 22, 165–171.

Liu, J., Schulteis, G., 2004. Brain reward deficits accompany naloxone-precipitated withdrawal from acute opioid dependence. Pharmacology Biochemistry and Behavior 79, 101–108.

Logan, G.D., Schachar, R.J., Tannock, R., 1997. Impulsivity and inhibitory control. Psychological Science 8, 60–64.

Mantsch, J.R., Yuferov, V., Mathieu-Kia, A.M., Ho, A., Kreek, M.J., 2004. Effects of extended access to high versus low cocaine doses on self-administration, cocaine-induced reinstatement and brain mRNA levels in rats. Psychopharmacology 175, 26–36.

Markou, A., Koob, G.F., 1991. Post-cocaine anhedonia: an animal model of cocaine withdrawal. Neuropsychopharmacology 4, 17–26.
Markou, A., Koob, G.F., 1993. Intracranial self-stimulation thresholds as a measure of reward. In: Sahgal, A. (Ed.), Behavioural Neuroscience: A Practical Approach, vol. 2. IRL Press, Oxford, pp. 93–115.
Martin, W.R., Eades, C.G., 1964. A comparison between acute and chronic physical dependence in the chronic spinal dog. Journal of Pharmacology and Experimental Therapeutics 146, 385–394.
Martinez, D., Narendran, R., Foltin, R.W., Slifstein, M., Hwang, D.R., Broft, A., Huang, Y., Cooper, T.B., Fischman, M.W., Kleber, H.D., Laruelle, M., 2007. Amphetamine-induced dopamine release: markedly blunted in cocaine dependence and predictive of the choice to self-administer cocaine. American Journal of Psychiatry 164, 622–629.
Martin-Solch, C., Magyar, S., Kunig, G., Missimer, J., Schultz, W., Leenders, K.L., 2001. Changes in brain activation associated with reward processing in smokers and nonsmokers: a positron emission tomography study. Experimental Brain Research 139, 278–286.
McEwen, B.S., 2000. Allostasis and allostatic load: implications for neuropsychopharmacology. Neuropsychopharmacology 22, 108–124.
Melis, M., Spiga, S., Diana, M., 2005. The dopamine hypothesis of drug addiction: hypodopaminergic state. International Review of Neurobiology 63, 101–154.
Merlo-Pich, E., Lorang, M., Yeganeh, M., Rodriguez de Fonseca, F., Raber, J., Koob, G.F., Weiss, F., 1995. Increase of extracellular corticotropin-releasing factor-like immunoreactivity levels in the amygdala of awake rats during restraint stress and ethanol withdrawal as measured by microdialysis. Journal of Neuroscience 15, 5439–5447.
Moeller, F.G., Barratt, E.S., Dougherty, D.M., Schmitz, J.M., Swann, A.C., 2001. Psychiatric aspects of impulsivity. American Journal of Psychiatry 158, 1783–1793.
Mucha, R.F., Herz, A., 1985. Motivational properties of kappa and mu opioid receptor agonists studied with place and taste preference conditioning. Psychopharmacology 86, 274–280.
Nestler, E.J., 2001. Molecular basis of long-term plasticity underlying addiction. Nature Reviews Neuroscience 2, 119–128.
Nestler, E.J., 2004. Historical review: molecular and cellular mechanisms of opiate and cocaine addiction. Trends in Pharmacological Sciences 25, 210–218.
Nestler, E.J., 2005. Is there a common molecular pathway for addiction? Nature Neuroscience 8, 1445–1449.
Nestler, E.J., Malenka, R.C., 2004. The addicted brain. Scientific American 290, 78–85.
Neugebauer, V., Li, W., Bird, G.C., Han, J.S., 2004. The amygdala and persistent pain. Neuroscientist 10, 221–234.
Nye, H.E., Nestler, E.J., 1996. Induction of chronic Fos-related antigens in rat brain by chronic morphine administration. Molecular Pharmacology 49, 636–645.
O'Dell, L.E., Roberts, A.J., Smith, R.T., Koob, G.F., 2004. Enhanced alcohol self-administration after intermittent versus continuous alcohol vapor exposure. Alcoholism: Clinical and Experimental Research 28, 1676–1682.
Olds, J., Milner, P., 1954. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. Journal of Comparative and Physiological Psychology 47, 419–427.
Olive, M.F., Koenig, H.N., Nannini, M.A., Hodge, C.W., 2002. Elevated extracellular CRF levels in the bed nucleus of the stria terminalis during ethanol withdrawal and reduction by subsequent ethanol intake. Pharmacology Biochemistry and Behavior 72, 213–220.
Orsini, C., Koob, G.F., Pulvirenti, L., 2001. Dopamine partial agonist reverses amphetamine withdrawal in rats. Neuropsychopharmacology 25, 789–792.
Overstreet, D.H., Knapp, D.J., Breese, G.R., 2004. Modulation of multiple ethanol withdrawal-induced anxiety-like behavior by CRF and CRF_1 receptors. Pharmacology Biochemistry and Behavior 77, 405–413.
Paterson, N.E., Markou, A., 2003. Increased motivation for self-administered cocaine after escalated cocaine intake. Neuroreport 14, 2229–2232.
Paterson, N.E., Myers, C., Markou, A., 2000. Effects of repeated withdrawal from continuous amphetamine administration on brain reward function in rats. Psychopharmacology 152, 440–446.
Pfeiffer, A., Brantl, V., Herz, A., Emrich, H.M., 1986. Psychotomimesis mediated by κ opiate receptors. Science 233, 774–776.
Pulvirenti, L., Koob, G.F., 1993. Lisuride reduces psychomotor retardation during withdrawal from chronic intravenous amphetamine self-administration in rats. Neuropsychopharmacology 8, 213–218.
Pulvirenti, L., Balducci, C., Piercy, M., Koob, G.F., 1998. Characterization of the effects of the partial dopamine agonist terguride on cocaine self-administration in the rat. Journal of Pharmacology and Experimental Therapeutics 286, 1231–1238.
Rachlin, H., Green, L., 1972. Commitment, choice and self-control. Journal of the Experimental Analysis of Behavior 17, 15–22.
Rasmussen, D.D., Boldt, B.M., Bryant, C.A., Mitton, D.R., Larsen, S.A., Wilkinson, C.W., 2000. Chronic daily ethanol and withdrawal: 1. Long-term changes in the hypothalamo-pituitary-adrenal axis. Alcoholism: Clinical and Experimental Research 24, 1836–1849.
Rassnick, S., Heinrichs, S.C., Britton, K.T., Koob, G.F., 1993. Microinjection of a corticotropin-releasing factor antagonist into the central nucleus of the amygdala reverses anxiogenic-like effects of ethanol withdrawal. Brain Research 605, 25–32.
Rattan, A.K., Koo, K.L., Tejwani, G.A., Bhargava, H.N., 1992. The effect of morphine tolerance dependence and abstinence on immunoreactive dynorphin (1–13) levels in discrete brain regions, spinal cord, pituitary gland and peripheral tissues of the rat. Brain Research 584, 207–212.
Richter, R.M., Weiss, F., 1999. In vivo CRF release in rat amygdala is increased during cocaine withdrawal in self-administering rats. Synapse 32, 254–261.
Rimondini, R., Arlinde, C., Sommer, W., Heilig, M., 2002. Long-lasting increase in voluntary ethanol consumption and transcriptional regulation in the rat brain after intermittent exposure to alcohol. FASEB Journal 16, 27–35.
Rivier, C., Bruhn, T., Vale, W., 1984. Effect of ethanol on the hypothalamic-pituitary-adrenal axis in the rat: role of corticotropin-releasing factor (CRF). Journal of Pharmacology and Experimental Therapeutics 229, 127–131.
Rodriguez de Fonseca, F., Carrera, M.R.A., Navarro, M., Koob, G.F., Weiss, F., 1997. Activation of corticotropin-releasing factor in the limbic system during cannabinoid withdrawal. Science 276, 2050–2054.
Rossetti, Z.L., Hmaidan, Y., Gessa, G.L., 1992. Marked inhibition of mesolimbic dopamine release: a common feature of ethanol, morphine, cocaine and amphetamine abstinence in rats. European Journal of Pharmacology 221, 227–234.
Russell, M.A.H., 1976. What is dependence? In: Edwards, G. (Ed.), Drugs and Drug Dependence. Lexington Books, Lexington, MA, pp. 182–187.
Sanchis-Segura, C., Spanagel, R., 2006. Behavioural assessment of drug reinforcement and addictive features in rodents: an overview. Addiction Biology 11, 2–38.
Sarnyai, Z., Biro, E., Gardi, J., Vecsernyes, M., Julesz, J., Telegdy, G., 1995. Brain corticotropin-releasing factor mediates "anxiety-like" behavior induced by cocaine withdrawal in rats. Brain Research 675, 89–97.
Schulteis, G., Markou, A., Gold, L.H., Stinus, L., Koob, G.F., 1994. Relative sensitivity to naloxone of multiple indices of opiate withdrawal: a quantitative dose–response analysis. Journal of Pharmacology and Experimental Therapeutics 271, 1391–1398.
Schulteis, G., Markou, A., Cole, M., Koob, G., 1995. Decreased brain reward produced by ethanol withdrawal. Proceedings of the National Academy of Sciences USA 92, 5880–5884.
Schulteis, G., Yackey, M., Risbrough, V., Koob, G.F., 1998. Anxiogenic-like effects of spontaneous and naloxone-precipitated opiate withdrawal in the elevated plus-maze. Pharmacology Biochemistry and Behavior 60, 727–731.
Schulteis, G., Morse, A.C., Liu, J., 2003. Repeated experience with naloxone facilitates acute morphine withdrawal: potential role for conditioning processes in acute opioid dependence. Pharmacology Biochemistry and Behavior 76, 493–503.
Self, D.W., McClenahan, A.W., Beitner-Johnson, D., Terwilliger, R.Z., Nestler, E.J., 1995. Biochemical adaptations in the mesolimbic dopamine system in response to heroin self-administration. Synapse 21, 312–318.
Shaw-Lutchman, T.Z., Barrot, M., Wallace, T., Gilden, L., Zachariou, V., Impey, S., Duman, R.S., Storm, D., Nestler, E.J., 2002. Regional and cellular mapping of cAMP response element-mediated transcription during naltrexone-precipitated morphine withdrawal. Journal of Neuroscience 22, 3663–3672.
Shippenberg, T.S., Koob, G.F., 2002. Recent advances in animal models of drug addiction and alcoholism. In: Davis, K.L., Charney, D., Coyle, J.T., Nemeroff, C. (Eds.), Neuropsychopharmacology: the Fifth Generation of Progress, 2002. Lippincott Williams and Wilkins, Philadelphia, PA, pp. 1381–1397.
Slawecki, C.J., Thorsell, A.K., Khoury, A.E., Mathe, A.A., Ehlers, C.L., 2005. Increased CRF-like and NPY-like immunoreactivity in adult rats exposed to nicotine during adolescence: relation to anxiety-like and depressive-like behavior. Neuropeptides 39, 369–377.
Solomon, R.L., Corbit, J.D., 1974. An opponent-process theory of motivation: 1. Temporal dynamics of affect. Psychological Review 81, 119–145.
Song, Z.H., Takemori, A.E., 1992. Stimulation by corticotropin-releasing factor of the release of immunoreactive dynorphin A from mouse spinal cords in vitro. European Journal of Pharmacology 222, 27–32.
Spangler, R., Unterwald, E.M., Kreek, M.J., 1993. "Binge" cocaine administration induces a sustained increase of prodynorphin mRNA in rat caudate-putamen. Molecular Brain Research 19, 323–327.
Specio, S.E., Wee, S., O'Dell, L.E., Boutrel, B., Zorrilla, E.P., Koob, G.F., 2008. CRF_1 receptor antagonists attenuate escalated cocaine self-administration in rats. Psychopharmacology 196, 473–482.
Sterling, P., Eyer, J., 1988. Allostasis: a new paradigm to explain arousal pathology. In: Fisher, S., Reason, J. (Eds.), Handbook of Life Stress, Cognition and Health. John Wiley, Chichester, pp. 629–649.
Stinus, L., Le Moal, M., Koob, G.F., 1990. Nucleus accumbens and amygdala are possible substrates for the aversive stimulus effects of opiate withdrawal. Neuroscience 37, 767–773.
Stinus, L., Caille, S., Koob, G.F., 2000. Opiate withdrawal-induced place aversion lasts for up to 16 weeks. Psychopharmacology 149, 115–120.
Stinus, L., Cador, M., Zorrilla, E.P., Koob, G.F., 2005. Buprenorphine and a CRF1 antagonist block the acquisition of opiate withdrawal-induced conditioned place aversion in rats. Neuropsychopharmacology 30, 90–98.
Thorsell, A., Slawecki, C.J., Ehlers, C.L., 2005a. Effects of neuropeptide Y and corticotropin-releasing factor on ethanol intake in Wistar rats: interaction with chronic ethanol exposure. Behavioural Brain Research 161, 133–140.
Thorsell, A., Slawecki, C.J., Ehlers, C.L., 2005b. Effects of neuropeptide Y on appetitive and consummatory behaviors associated with alcohol drinking in wistar rats with a history of ethanol exposure. Alcoholism: Clinical and Experimental Research 29, 584–590.
Thorsell, A., Rapunte-Canonigo, V., O'Dell, L., Chen, S.A., King, A., Lekic, D., Koob, G.F., Sanna, P.P., 2007. Viral vector-induced amygdala NPY overexpression reverses increased alcohol intake caused by repeated deprivations in Wistar rats. Brain 130, 1330–1337.
Tucci, S., Cheeta, S., Seth, P., File, S.E., 2003. Corticotropin releasing factor antagonist, α-helical CRF_{9-41}, reverses nicotine-induced conditioned, but not unconditioned, anxiety. Psychopharmacology 167, 251–256.

Valdez, G.R., Zorrilla, E.P., Roberts, A.J., Koob, G.F., 2003. Antagonism of corticotropin-releasing factor attenuates the enhanced responsiveness to stress observed during protracted ethanol abstinence. Alcohol 29, 55–60.

Valdez, G.R., Roberts, A.J., Chan, K., Davis, H., Brennan, M., Zorrilla, E.P., Koob, G.F., 2002. Increased ethanol self-administration and anxiety-like behavior during acute withdrawal and protracted abstinence: regulation by corticotropin-releasing factor. Alcoholism: Clinical and Experimental Research 26, 1494–1501.

Valentino, R.J., Page, M.E., Curtis, A.L., 1991. Activation of noradrenergic locus coeruleus neurons by hemodynamic stress is due to local release of corticotropin-releasing factor. Brain Research 555, 25–34.

Valentino, R.J., Foote, S.L., Page, M.E., 1993. The locus coeruleus as a site for integrating corticotropin-releasing factor and noradrenergic mediation of stress responses. In: Tache, Y., Rivier, C. (Eds.), Corticotropin-Releasing Factor and Cytokines: Role in the Stress Response. Annals of the New York Academy of Sciences, vol. 697. New York Academy of Sciences, New York, pp. 173–188.

Van Bockstaele, E.J., Colago, E.E., Valentino, R.J., 1998. Amygdaloid corticotropin-releasing factor targets locus coeruleus dendrites: substrate for the co-ordination of emotional and cognitive limbs of the stress response. Journal of Neuroendocrinology 10, 743–757.

Van Dyke, C., Byck, R., 1982. Cocaine. Scientific American 246, 128–141.

Vezina, P., 2004. Sensitization of midbrain dopamine neuron reactivity and the self-administration of psychomotor stimulant drugs. Neuroscience and Biobehavioral Reviews 27, 827–839.

Volkow, N.D., Fowler, J.S., 2000. Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. Cerebral Cortex 10, 318–325.

Volkow, N.D., Wang, G.J., Fowler, J.S., Logan, J., Gatley, S.J., Hitzemann, R., Chen, A.D., Dewey, S.L., Pappas, N., 1997. Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subjects. Nature 386, 830–833.

Volkow, N.D., Fowler, J.S., Wang, G.J., 2002. Role of dopamine in drug reinforcement and addiction in humans: results from imaging studies. Behavioural Pharmacology 13, 355–366.

Walker, B.M., Koob, G.F., 2008. Pharmacological evidence for a motivational role of κ-opioid systems in ethanol dependence. Neuropsychopharmacology 33, 643–652.

Walker, B.M., Rasmussen, D.D., Raskind, M.A., Koob, G.F., 2008. α_1-Noradrenergic receptor antagonism blocks dependence-induced increases in responding for ethanol. Alcohol 42, 91–97.

Wee, S., Wang, Z., Woolverton, W.L., Pulvirenti, L., Koob, G.F., 2007. Effect of aripiprazole, a partial D_2 receptor agonist, on increased rate of methamphetamine self-administration in rats with prolonged access. Neuropsychopharmacology 32, 2238–2247.

Wee, S., Mandyam, C.D., Lekic, D.M., Koob, G.F., 2008. α_1-Noradrenergic system role in increased motivation for cocaine intake in rats with prolonged access. European Neuropsychopharmacology 18, 303–311.

Weiss, F., Markou, A., Lorang, M.T., Koob, G.F., 1992. Basal extracellular dopamine levels in the nucleus accumbens are decreased during cocaine withdrawal after unlimited-access self-administration. Brain Research 593, 314–318.

Weiss, F., Parsons, L.H., Schulteis, G., Hyytia, P., Lorang, M.T., Bloom, F.E., Koob, G.F., 1996. Ethanol self-administration restores withdrawal-associated deficiencies in accumbal dopamine and 5-hydroxytryptamine release in dependent rats. Journal of Neuroscience 16, 3474–3485.

Weiss, F., Ciccocioppo, R., Parsons, L.H., Katner, S., Liu, X., Zorrilla, E.P., Valdez, G.R., Ben-Shahar, O., Angeletti, S., Richter, R.R., 2001. Compulsive drug-seeking behavior and relapse: neuroadaptation, stress, and conditioning factors. In: Quinones-Jenab, V. (Ed.), The Biological Basis of Cocaine Addiction. Annals of the New York Academy of Sciences, vol. 937. New York Academy of Sciences, New York, pp. 1–26.

Wikler, A., 1952. A psychodynamic study of a patient during experimental self-regulated re-addiction to morphine. Psychiatric Quarterly 26, 270–293.

Zhang, Z., Schulteis, G., 2008. Withdrawal from acute morphine dependence is accompanied by increased anxiety-like behavior in the elevated plus maze. Pharmacology Biochemistry and Behavior 89, 392–403.