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Review

Neurobiological mechanisms for opponent motivational processes in addiction

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The conceptualization of drug addiction as a compulsive disorder with excessive drug intake and loss of control over intake requires motivational mechanisms. Opponent process as a motivational theory for the negative reinforcement of drug dependence has long required a neurobiological explanation. Key neurochemical elements involved in reward and stress within basal forebrain structures involving the ventral striatum and extended amygdala are hypothesized to be dysregulated in addiction to convey the opponent motivational processes that drive dependence. Specific neurochemical elements in these structures include not only decreases in reward neurotransmission such as dopamine and opioid peptides in the ventral striatum, but also recruitment of brain stress systems such as corticotropin-releasing factor (CRF), noradrenaline and dynorphin in the extended amygdala. Acute withdrawal from all major drugs of abuse produces increases in reward thresholds, anxiety-like responses and extracellular levels of CRF in the central nucleus of the amygdala. CRF receptor antagonists 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 stress-induced relapse. The combination of loss of reward function and recruitment of brain stress systems provides a powerful neurochemical basis for the long hypothesized opponent motivational processes responsible for the negative reinforcement driving addiction.

Keywords: addiction; opponent process; stress; extended amygdala; corticotropin-releasing factor

1. DEFINITIONS AND CONCEPTUAL FRAMEWORK

Drug addiction, also known as substance dependence, 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 & 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*, 4th edn., American Psychiatric Association 1994). Clinically, 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 (Koob & Le Moal 2008). The elements of impulsivity and compulsivity yield a composite addiction cycle comprising three stages—*preoccupation/anticipation*; *binge/intoxication*; and *withdrawal/negative affect* (figure 1)—in which impulsivity often dominates at the early stages and compulsivity dominates at the terminal stages. As an individual moves from impulsivity to compulsivity, a shift occurs from positive reinforcement driving the motivated behaviour to negative reinforcement driving the motivated behaviour (Koob 2004). These three stages are conceptualized as interacting with each other, becoming more intense and ultimately leading to the pathological state known as addiction (Koob & Le Moal 1997). Different drugs produce different patterns of addiction with an emphasis on different components of the addiction cycle (Koob *et al.* 2008). Common elements include binge/intoxication (dramatic with psychostimulants and ethanol but not present with nicotine), withdrawal/negative affect (dramatic with opioids and alcohol but common to all drugs of abuse) and preoccupation/anticipation (common to all drugs of abuse). The present review will focus on the role of the brain reward and stress systems in one key and common element of addiction: the withdrawal/negative affect stage of the addiction cycle.

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2. OPPONENT PROCESS AND ADDICTION

(a) *Motivation and opponent process*

Motivation is a state that can be defined as a 'tendency of the whole animal to produce organized activity'

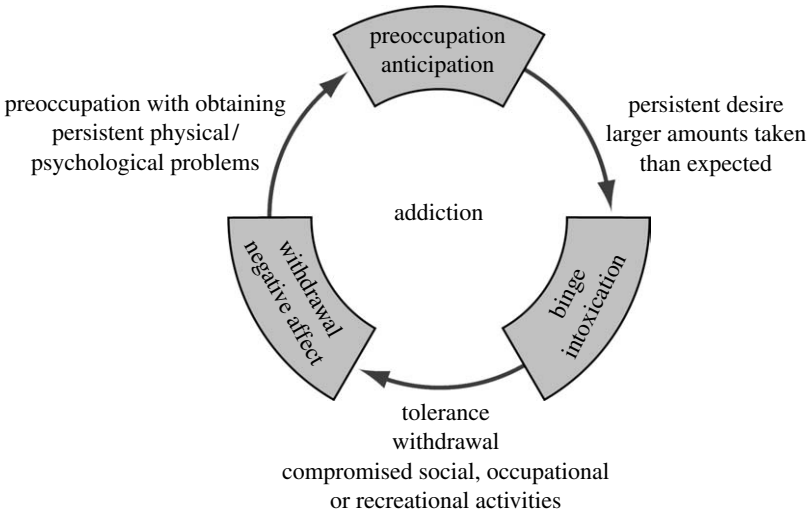

Figure 1. Diagram describing the addiction cycle—preoccupation/anticipation ('craving'), binge/intoxication and withdrawal/negative affect—with the different criteria for substance dependence incorporated from the *Diagnostic and statistical manual of mental disorders*, 4th edn. (Adapted from Koob 2008.)

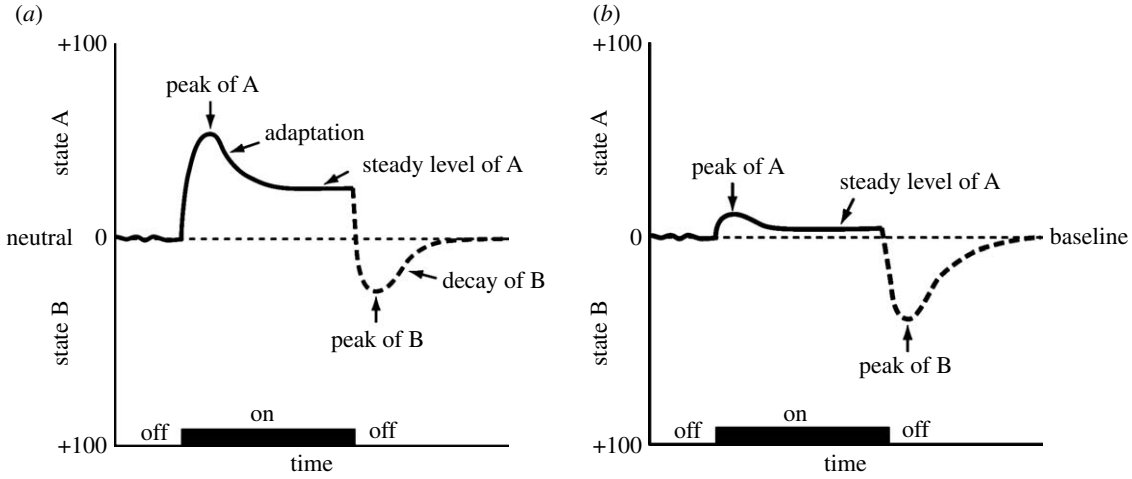

Figure 2. Opponent process theory of affective dynamics relevant to addiction. (*a*) The standard pattern of affective dynamics produced by a relatively novel unconditioned stimulus (first few stimulations). (*b*) The standard pattern of affective dynamics produced by a familiar, frequently repeated unconditioned stimulus (after many stimulations). (Adapted from Solomon 1980.)

(Hebb 1972), and such motivational states are not constant but rather vary over time. 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 & 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 opponent process theory of motivation is defined by two processes. The *a-process* includes affective or hedonic habituation (or tolerance) and the *b-process* includes affective or hedonic withdrawal (abstinence). The a-process consists of either positive or negative hedonic responses, occurs shortly after the presentation of a stimulus, correlates closely with the intensity, quality and duration of the reinforcer and shows tolerance. By contrast, the b-process appears after the a-process has terminated and is sluggish in onset, slow to build up to an asymptote, slow to decay and gets larger with repeated exposure. Thus, the affective dynamics of opponent process theory generate new motives and new opportunities for reinforcing and energizing behaviour (Solomon 1980).

From a drug-taking perspective of brain motivational systems, the initial acute effect of a drug (the a-process or positive hedonic response) was hypothesized to be opposed or counteracted by the b-process as homeostatic changes in brain systems (figure 2). This affect control system was conceptualized as a single negative feedback or opponent loop that opposes the stimulus-aroused affective state and suppresses or reduces all departures from hedonic neutrality (Solomon & Corbit 1974; Siegel 1975; Poulos & Cappell 1991). Affective states, pleasant or aversive, were hypothesized to be automatically opposed by centrally mediated mechanisms that reduce the intensity of these affective states. In this opponent process theory, tolerance and dependence are inextricably linked (Solomon & Corbit 1974). In the context of drug dependence, Solomon argued that the first few self-administrations of an opiate drug produce a pattern of motivational changes similar to that of the a-process or euphoria, followed by a decline in intensity. After the effects of the drug wear off, an opposing, aversive negative emotional state emerges, i.e. the b-process.

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

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 & Le Moal 2001, 2008). In this formulation, addiction is conceptualized as a cycle of increasing dysregulation of brain reward/anti-reward mechanisms, which results in a negative emotional state contributing to the compulsive use of drugs. Counteradaptive processes such as the opponent b-process, which are part of the normal homeostatic limitation of reward function, fail to return to within the normal homeostatic range.

These counteradaptive processes are hypothesized to be mediated by two processes: within- and between-system neuroadaptations (Koob & 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 & Bloom 1988, p. 720). Thus, a within-system neuroadaptation is a molecular or cellular change within a given reward circuit to accommodate the overactivity of hedonic processing associated with addiction resulting in a decrease in reward function.

In a between-system neuroadaptation, 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 & 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 the 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, which, we hypothesize, have a key role in the compulsivity of addiction.

(b) *Animal models of addiction relevant to opponent process*

Animal models of addiction on specific drugs such as stimulants, opioids, alcohol, nicotine and Δ^9-tetrahydrocannabinol can be defined by the models relevant to different stages of the addiction cycle. Animal models of reward and reinforcement (binge/intoxication stage) are extensive and well validated, and include intravenous drug self-administration, conditioned place preference and brain stimulation reward (Shippenberg & Koob 2002; table 1). Animal models of the withdrawal/negative affect stage include measures of conditioned place aversion (rather than preference) to precipitated or spontaneous withdrawal from chronic administration of a drug, increases in reward thresholds using brain stimulation reward and dependence-induced increased drug-taking and drug-seeking behaviours (table 1). Such increased self-administration in dependent animals has now been observed with cocaine, methamphetamine, nicotine, heroin and alcohol (Ahmed & Koob 1998; Ahmed *et al.* 2000; O'Dell *et al.* 2004; Kitamura *et al.* 2006; George *et al.* 2007; figure 3). This model will be a key element for evaluating the motivational significance of opponent process changes in the brain reward and stress systems in addiction outlined below. Animal models of the preoccupation/anticipation ('craving') stage involve reinstatement of drug seeking following extinction elicited by the drugs themselves, by cues linked to the drug and by exposure to stressors (Weiss *et al.* 2001; Shaham *et al.* 2003) and measures of protracted abstinence (table 1). In stress-induced reinstatement, acute stressors can reinitiate drug-seeking behaviour in animals that have been extinguished. In rats with a history of drug dependence, protracted abstinence can be defined as a period after acute withdrawal has disappeared, usually two- to eight-weeks post-drug.

3. WITHIN-SYSTEM NEUROADAPTATIONS IN ADDICTION

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 & Esposito 1979). 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 connecting the ventral tegmental area (VTA) with the basal forebrain (Olds & Milner 1954). 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).

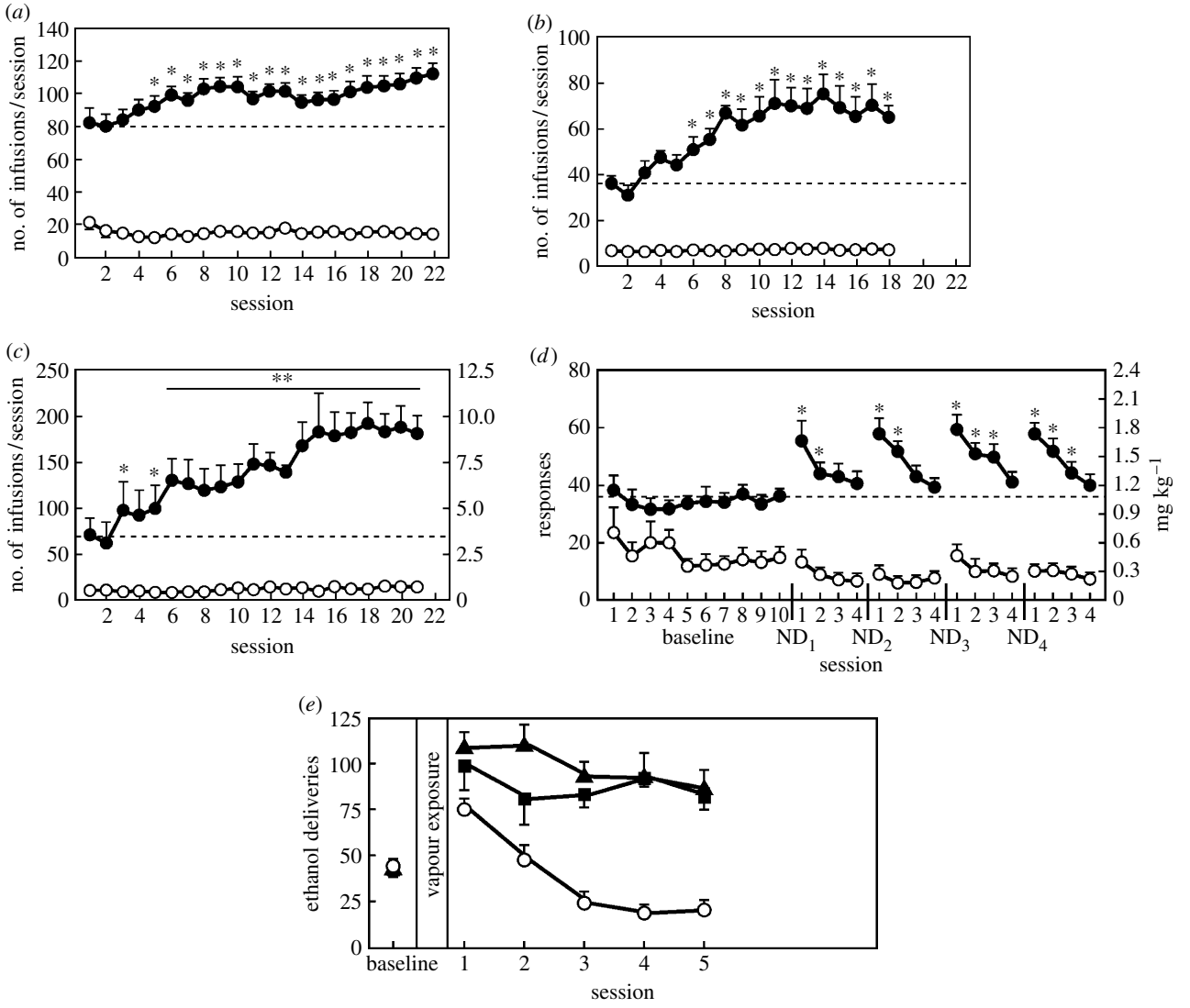

Figure 3. Increases in drug intake associated with extended access and dependence. (*a*) Effect of drug availability on cocaine intake (mean ± s.e.m.). In long-access (LgA) rats ($n=12$; filled circles) but not in short-access (ShA) rats ($n=12$; open circles), mean total cocaine intake started to increase 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 and 17–22). (Adapted from Ahmed & Koob 1998.) (*b*) Effect of drug availability on total intravenous heroin self-infusions (mean ± s.e.m.). During the escalation phase, rats had access to heroin (40 mg per infusion) for 1 hour (ShA rats, $n=5$–6; open circles) or 11 hours per session (LgA rats, $n=5$–6; filled circles). Regular 1-hour (ShA rats) or 11-hour (LgA rats) sessions of heroin self-administration were performed 6 days per week. The dotted line indicates the mean (± s.e.m.) number of heroin self-infusions of LgA rats during the first 11-hour session. $^{*}p<0.05$ compared with first session (paired *t*-test). (Adapted 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^{-1} per infusion of intravenous methamphetamine during a 6-hour session. Short-access (open circles) group, 1-hour session ($n=6$). Long-access (filled circles) group, 6-hour session ($n=4$). All data were analysed using two-way ANOVA (dose × escalation session within ShA or LgA group). $^{*}p<0.05$ and $^{**}p<0.01$ versus day 1. (Adapted from Kitamura *et al.* 2006.) (*d*) Total 23-hour active (filled circles) and inactive (open circles) responses after repeated cycles of 72 hours of nicotine deprivation (ND) followed by 4 days of self-administration ($^{*}p<0.05$ versus baseline). (Adapted from George *et al.* 2007.) (*e*) Ethanol deliveries (mean ± s.e.m.) in rats trained to respond for 10% ethanol and then either not exposed to ethanol vapour (control, $n=5$; circles) or exposed to intermittent ethanol vapour (14 hours on/10 hours off) for two weeks and then tested either 2 hours ($n=6$; squares) or 8 hours ($n=6$; triangles) after removal from ethanol vapour. No difference was observed between rats exposed to intermittent vapour and tested either 2 or 8 hours after ethanol withdrawal. (Adapted from O'Dell *et al.* 2004.)

Measures of brain reward function during acute abstinence from all major drugs with dependence potential have revealed increases in brain reward thresholds measured by direct brain stimulation reward (Markou & Koob 1991; Schulteis *et al.* 1994, 1995; Epping-Jordan *et al.* 1998; Gardner & Vorel 1998; Paterson *et al.* 2000). These increases in reward thresholds may reflect decreases in the activity of reward neurotransmitter systems in the midbrain and forebrain implicated in the positive reinforcing effects of drugs.

The acute reinforcing effects of drugs of abuse are mediated by the activation of dopamine (DA), serotonin, opioid peptides and γ-aminobutyric acid (GABA) systems either by direct actions in the basal forebrain (notably the nucleus accumbens and central

nucleus of the amygdala) or by indirect actions in the VTA (Koob & Le Moal 2001; Nestler 2005; Koob 2006). Much evidence exists to support the hypothesis that the mesolimbic DA system is dramatically activated by psychostimulant drugs during limited-access self-administration and to some extent by all drugs of abuse. Serotonin systems, particularly those involving serotonin 5-HT_{1B} receptor activation in the nucleus accumbens, also have been implicated in the acute reinforcing effects of psychostimulant drugs. Opioid peptides in the ventral striatum have been hypothesized to mediate the acute reinforcing effects of ethanol self-administration, largely based on the effects of opioid antagonists. μ-Opioid receptors in both the nucleus accumbens and the VTA mediate the reinforcing effects of opioid drugs. GABAergic systems are activated pre- and post-synaptically in the amygdala by ethanol at intoxicating doses, and GABA antagonists block ethanol self-administration (for reviews, see Nestler 2005; Koob 2006).

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

Substantial evidence for increased sensitivity of receptor transduction mechanisms in the nucleus accumbens, including activation of adenylate cyclase, protein kinase A, cyclic adenosine monophosphate response-element binding protein (CREB) and ΔFosB, has been observed during administration of drugs of abuse (Self *et al.* 1995; Nye & Nestler 1996; Shaw-Lutchman *et al.* 2002; Nestler 2004; see Nestler 2008), and the ΔFosB response is hypothesized to represent a neuroadaptive change that extends long into protracted abstinence (Nestler & Malenka 2004).

Alcohol dependence has long been associated with changes in GABAergic neurotransmission. Chronic ethanol decreases $GABA_A$ receptor function (Morrow *et al.* 1988) and increases in GABA release in interneurons in the central nucleus of the amygdala (Roberto *et al.* 2004). The observation that very low doses of the $GABA_A$ agonist muscimol, when injected into the central nucleus of the amygdala, block the increased ethanol intake associated with acute withdrawal suggests that the changes in GABAergic function in the central nucleus of the amygdala may have some motivational significance in ethanol dependence (Roberts *et al.* 1996).

Thus, decreases in reward neurotransmission have been hypothesized to reflect a within-system neuroadaptation and contribute significantly to the negative motivational state associated with acute drug abstinence. Decreased reward system function also may persist in the form of long-term biochemical changes that contribute to the clinical syndrome of protracted abstinence and vulnerability to relapse. For example, while the activation of CREB and c-*fos* triggered by the activation of DA systems is relatively short lived, more long-term changes in other transcription factors such as ΔFosB may persist for weeks (Nestler *et al.* 2001).

4. BETWEEN-SYSTEM NEUROADAPTATIONS IN ADDICTION

The neuroanatomical entity termed the extended amygdala (Heimer & 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, the 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 & 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).

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 the 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; Koob *et al.* 1994; Merlo-Pich *et al.* 1995; Delfs *et al.* 2000; Rasmussen *et al.* 2000; Olive *et al.* 2002). Acute withdrawal from all drugs of abuse produces an anxiety-like state that can be reversed by CRF antagonists, and CRF antagonists also block the increased intake of drug associated with dependence (table 2).

A particularly dramatic example of the motivational effects of CRF in dependence can be observed in animal models of ethanol self-administration in

Table 2. Role of CRF in dependence (nt, not tested; CeA, central nucleus of the amygdala).

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

[a]Aversive effects with place conditioning.

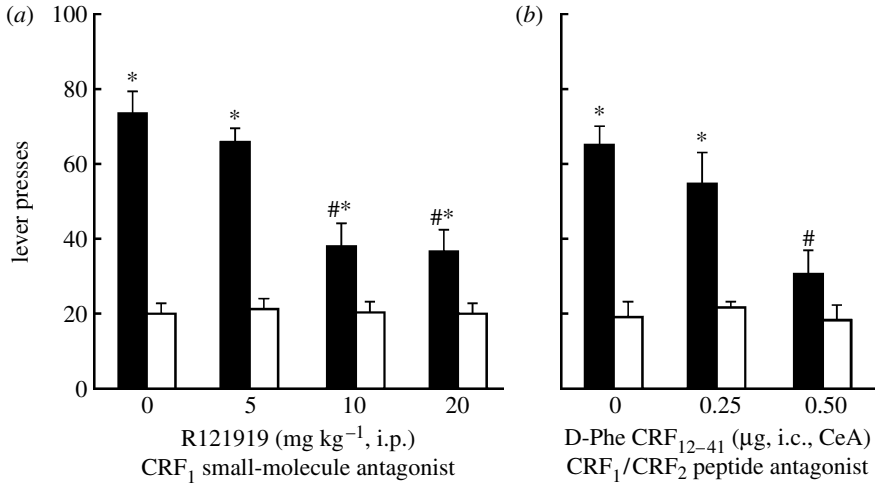

Figure 4. (*a*) Effects of CRF_1 receptor small-molecule antagonist R121919 on ethanol self-administration in dependent (filled bars) and non-dependent (opened bars) rats. Ethanol dependence was induced by intermittent exposure to ethanol vapours for four weeks. Animals were subsequently tested for ethanol and water self-administration following 2 hours of acute withdrawal. Withdrawn, ethanol-dependent animals displayed a significant increase in ethanol lever pressing compared with non-dependent animals. R121919 significantly decreased ethanol self-administration in withdrawn, dependent but not non-dependent animals. Neither ethanol vapour exposure nor R121919 altered water responding. $^{*}p<0.001$ compared with same drug dose in non-dependent animals. $^{\#}p<0.0001$ compared with vehicle treatment in dependent animals. (Adapted from Funk *et al.* 2007.) (*b*) Effects of CRF_1/CRF_2 peptide antagonist D-Phe $CRF_{12–41}$ administered directly into the central nucleus of the amygdala on ethanol and water self-administration in ethanol-dependent (filled bars) and non-dependent (open bars) rats. Ethanol dependence was induced by intermittent exposure to ethanol vapours for four weeks. Animals were subsequently tested for ethanol and water self-administration after 2 hours of acute withdrawal. Withdrawn, ethanol-dependent animals displayed a significant increase in ethanol lever pressing compared with non-dependent animals. D-Phe $CRF_{12–41}$ significantly decreased ethanol self-administration in withdrawn, dependent but not non-dependent animals when administered directly into the central nucleus of the amygdala. Neither ethanol vapour exposure nor D-Phe $CRF_{12–41}$ altered water responding. $^{*}p<0.0001$ compared with same drug dose in non-dependent animals. $^{\#}p<0.0001$ compared with vehicle treatment in dependent animals. Error bars indicate s.e.m. (Adapted from Funk *et al.* 2006.)

dependent animals. During ethanol withdrawal, extra-hypothalamic CRF systems become hyperactive, with an increase in extracellular CRF within the central nucleus of the amygdala and bed nucleus of the stria terminalis of dependent rats (Merlo-Pich *et al.* 1995; Olive *et al.* 2002; Funk *et al.* 2006; table 2). The dysregulation of brain CRF systems is hypothesized to underlie both the enhanced anxiety-like behaviours and the enhanced ethanol self-administration associated with ethanol withdrawal. Supporting this hypothesis, the subtype non-selective CRF receptor antagonists α-helical $CRF_{9–41}$ and D-Phe $CRF_{12–41}$ (intracerebroventricular administration) reduce both ethanol withdrawal-induced anxiety-like behaviour and ethanol self-administration in dependent animals (Baldwin *et al.* 1991; Rimondini *et al.* 2002; O'Dell *et al.* 2004; Valdez *et al.* 2004). When administered directly into the central nucleus of the amygdala, CRF receptor antagonists also attenuate anxiety-like behaviour (Rassnick *et al.* 1993) and ethanol self-administration in ethanol-dependent rats (Funk *et al.* 2006, 2007; figure 4). 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.

Systemic injections of small-molecule CRF_1 antagonists also block both the anxiety-like responses and the increased ethanol intake associated with acute withdrawal (Knapp *et al.* 2004; Overstreet *et al.* 2004; Funk *et al.* 2007). Similar interactions with CRF have been observed with the dependence associated with extended access to intravenous self-administration of cocaine (Specio *et al.* 2008), nicotine (George *et al.* 2007) and heroin (T. N. Greenwell, C. K. Funk, P. Cotton, H. N. Richardson, S. A. Chen, K. Rice, M. J. Lee, E. P. Zorrilla & G. F. Koob 2006, unpublished results).

Although less well developed, functional noradrenaline (NA) antagonists that block the anxiogenic-like and aversive effects of opiate withdrawal also block excessive drug intake associated with ethanol dependence (Walker *et al.* 2008), cocaine (Wee *et al.* 2008) and opioids (T. N. Greenwell , C. K. Funk, P. Cotton, H. N. Richardson, S. A. Chen, K. Rice, M. J. Lee, E. P. Zorrilla & G. F. Koob 2006, unpublished results). A focal point for many of these effects also is the extended amygdala but at the level of the bed nucleus of the stria terminalis.

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–NA systems. Conceptualized as a feed-forward system at multiple levels (e.g. in the pons and basal forebrain), CRF activates NA and NA in turn activates CRF (Koob 1999). 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).

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 (Pfeiffer *et al.* 1986; Land *et al.* 2008), and withdrawal from cocaine, opioids and ethanol is associated with increased dynorphin in the nucleus accumbens and/or amygdala (Rattan *et al.* 1992; Spangler *et al.* 1993; Lindholm *et al.* 2000). A κ-antagonist blocks the excessive drinking associated with ethanol withdrawal and dependence (Walker & Koob 2008). Evidence demonstrates that κ-receptor activation can produce CRF release (Song & Takemori 1992), but recently some have argued that the effects of dynorphin in producing negative emotional states are mediated via the activation of CRF systems (Land *et al.* 2008).

Significant evidence also suggests that the activation of neuropeptide Y (NPY) in the central nucleus of the amygdala can block the motivational aspects of dependence associated with chronic ethanol administration. NPY administered intracerebroventricularly blocks the anxiogenic-like effects of withdrawal from ethanol (N. G. Gilpin 2008, personal communication) and blocks the increased drug intake associated with ethanol dependence (Thorsell *et al.* 2005*a*,*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 block 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 (figure 5). Acute withdrawal also may increase the release of NA in the bed nucleus of the stria terminalis and dynorphin in the nucleus accumbens, both of which possibly contributing to the negative emotional state associated with dependence (figure 5). Decreased activity of NPY in the central nucleus of the amygdala also may contribute to the anxiety-like state associated with ethanol dependence. The activation of brain stress systems (CRF, NA, dynorphin) combined with the inactivation of brain anti-stress systems (NPY) in the extended amygdala may elicit the powerful emotional dysregulation associated with addiction. 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.

The neuroadaptations outlined above also may contribute to the critical problem in drug addiction, that of chronic relapse, where individuals with addiction return to compulsive drug taking long after acute withdrawal. The preoccupation/anticipation (craving) stage of the addiction cycle has long been hypothesized to be a key element of relapse in humans and defines addiction as a chronic relapsing disorder. Craving can be defined as the memory of the rewarding effects of a drug superimposed upon a negative emotional state.

From a within-system framework, changes in the dopaminergic system that persist well past acute withdrawal are hypothesized to contribute to craving and include psychomotor sensitization and increases in incentive salience (Robinson & Berridge 1993), decreases in DA D_2 receptors (Volkow *et al.* 2002) and persistent changes in signal transduction factors that may contribute to both chronic dysphoria (CREB activation) and sensitization of craving (ΔFosB; Nestler 2005). Evidence that subordinate primates socially isolated during development showed increased vulnerability to intravenously self-administer cocaine and had significantly reduced DA D_2 receptors provides compelling evidence that dopaminergic tone can regulate hedonic set point outside of acute withdrawal from drugs of abuse (Morgan *et al.* 2002).

From the perspective of between-system neuroadaptations, the brain stress systems outlined above are hypothesized to contribute directly to the preoccupation/anticipation (craving) stage via protracted abstinence. Protracted abstinence can be defined as the persistence of a negative emotional state long past acute withdrawal. This state in humans is characterized by low-level dysphoria, sleep disturbances and increased sensitivity to stress and pain. In animals, protracted abstinence is characterized by increased sensitivity to a stressor and increased drug seeking long after acute withdrawal, both of which having been observed in alcohol studies (Valdez & Koob 2004). Using CRF as an example in protracted abstinence, CRF is hypothesized to contribute to a residual negative emotional state that provides a basis for drug seeking (Valdez *et al.* 2002; Valdez & Koob 2004).

5. OPPONENT PROCESS, REWARD SET POINT AND ALLOSTASIS

The development of the aversive emotional state that drives the negative reinforcement of addiction has been defined as the 'dark side' of addiction (Koob & Le Moal 2005, 2008) and is hypothesized to be the b-process of the hedonic dynamic known as opponent process when

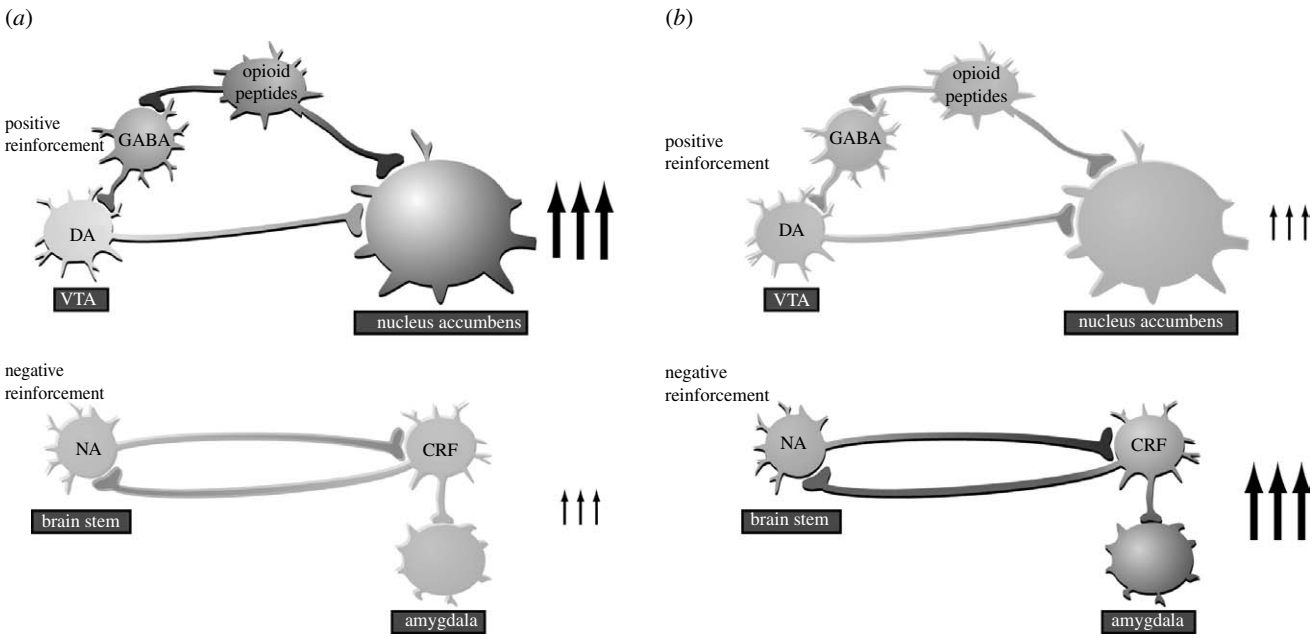

Figure 5. Neurocircuitry associated with the acute positive reinforcing effects of drugs of abuse and the negative reinforcement of dependence and how it changes in the transition from (*a*) non-dependent drug taking to (*b*) dependent drug taking. Key elements of the reward circuit are DA and opioid peptide neurons that intersect at both the VTA and the nucleus accumbens and are activated during initial use and the early binge/intoxication stage. Key elements of the stress circuit are CRF and noradrenergic neurons that converge on GABA interneurons in the central nucleus of the amygdala that are activated during the development of dependence. CRF, corticotropin-releasing factor; DA, dopamine; GABA, γ-aminobutyric acid; NA, noradrenaline; VTA, ventral tegmental area. (Adapted from Koob & Le Moal 2008.)

the a-process is euphoria. The negative emotional state that comprises the withdrawal/negative affect stage defined above consists of key motivational elements, such as chronic irritability, emotional pain, malaise, dysphoria, alexithymia and loss of motivation for natural rewards, 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 & Bloom 1988; Koob & Le Moal 1997). Anti-reward is a construct based on the hypothesis that brain systems are in place to limit reward (Koob & Le Moal 2008). As dependence and withdrawal develop, brain stress systems such as CRF, NA and dynorphin are recruited (figure 5), producing aversive or stress-like states (Aston-Jones *et al.* 1999; Nestler 2001; Koob 2003). 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 provides a powerful source of negative reinforcement that contributes to compulsive drug-seeking behaviour and addiction (figure 5).

The overall conceptual theme argued here is that drug addiction represents a break with homeostatic brain regulatory mechanisms that regulate the emotional state of the animal. However, the view that drug addiction represents a simple break with homeostasis is not sufficient to explain a number of key elements of addiction. Drug addiction, similar to other chronic physiological disorders such as high blood pressure that worsens over time, is subject to significant environmental influences and leaves a residual neuroadaptive trace that allows rapid 're-addiction' even months and years after detoxification and abstinence. These characteristics of drug addiction imply more than simply a homeostatic dysregulation of hedonic function and executive function, but rather a dynamic break with homeostasis of these systems, which have been termed allostasis.

Allostasis, originally conceptualized to explain persistent morbidity of arousal and autonomic function, is defined as 'stability through change' and a continuous readjustment of all parameters towards a new set point (Sterling & Eyer 1988). As such, an *allostatic state* can be defined as a state of chronic deviation of the regulatory system from its normal (homeostatic) operating level. Thus, the very physiological mechanism that allows rapid responses to environmental challenge becomes the engine of pathology if adequate time or resources are not available to shut off the response.

Two components are hypothesized to adjust to challenges to the brain produced by drugs of abuse to engage an allostatic-like state: (i) overactivation of brain reward transmitters and circuits and (ii) recruitment of the brain anti-reward or brain stress systems (figure 5). Repeated challenges, such as the case with drugs of abuse, lead to attempts of the brain via molecular, cellular and neurocircuitry changes to maintain stability but at a cost. For the drug addiction framework elaborated here, the residual deviation from normal brain reward threshold regulation is termed the allostatic state. This state represents a combination of chronic elevation of reward set point fueled from the opponent process, motivational perspective 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 extended amygdala (e.g. vasopressin, orexin, nociceptin), where the extended amygdala projects to convey emotional valence, and how individuals differ at the molecular–genetic level of analysis to convey loading on these circuits remain challenges for future research.

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