Published in final edited form as:
Physiol Behav. 2012 April 12; 106(1): 58–64. doi:10.1016/j.physbeh.2011.11.004.

Allostasis and Addiction: Role of the Dopamine and Corticotropin-Releasing Factor Systems

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Abstract

Allostasis, originally conceptualized to explain persistent morbidity of arousal and autonomic function, is defined as the process of achieving stability through physiological or behavioral change. Two types of biological processes have been proposed to describe the mechanisms underlying allostasis in drug addiction, a within-system adaptation and a between-system adaptation. In the within-system process, the drug elicits an opposing, neutralizing reaction within the same system in which the drug elicits its primary and unconditioned reinforcing actions, while in the between-system process, different neurobiological systems that the one initially activated by the drug are recruited. In this review, we will focus our interest on alterations in the dopaminergic and corticotropin releasing factor systems as within-system and between-system neuroadaptations respectively, that underlie the opponent process to drugs of abuse. We hypothesize that repeated compromised activity in the dopaminergic system and sustained activation of the CRF-CRF1R system with withdrawal episodes may lead to an allostatic load contributing significantly to the transition to drug addiction.

Keywords

Dopamine; CRF; stress; CeA; extended amygdala; VTA; drugs; dependence; motivation; craving

Allostasis

Allostasis, originally conceptualized to explain persistent morbidity of arousal and autonomic function, is defined as the process of achieving stability through physiological or behavioral change (Sterling and Eyer, 1981, 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. Thus, the very physiological mechanism that allows rapid responses to environmental challenges becomes the engine of pathology if adequate time or resources are not available to shut off the response (Koob and Le Moal, 2001). The concept of allostasis has served as a framework for a large body of research on integrative health psychology, epidemiology, aging, physiology, and neuroscience. Allostasis is based on the hypothesis that there is a

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cumulative physiological risk associated with exposure to physiological or psychosocial stressors during an individual's life. A body of evidence indicates that many psychosocial stressors appear to have small to modest associations with multiple different biological risk factors, reflecting links to most of the known major regulatory systems (e.g., cardiovascular, immune, and central nervous system). For example, disruption of social status impacts cortisol levels, and social support is predictive of cortisol levels (Abbot et al., 2003; Schulkin, 2011). Greater cumulative dysregulation is associated with significantly greater risks for subsequent disease, declines in physical and cognitive functioning, and overall mortality (Seeman et al., 1997, 2001; Karlamangla et al., 2002; Geronimus et al., 2006). Thus, the ability to mobilize resources and use feed-forward mechanisms progressively leads to an allostatic state and ultimately to allostatic load. An allostatic state reflects a new equilibrium, a state of chronic deviation of the regulatory system from its normal (homeostatic) operating level to a pathological (allostatic) operating level (Koob and Le Moal, 1997). Allostatic load can be defined as the "long-term cost of allostasis that accumulates over time and reflects the accumulation of damage that can lead to pathological states" (McEwen, 1998). Cumulative indices of allostatic load have also been positively related to measures of psychosocial stress in young adolescents (Evans et al., 2007) as well as symptoms of posttraumatic stress disorder (PTSD) in the mothers of pediatric cancer survivors (Glover et al., 2006) and adverse perinatal outcomes (Shannon et al., 2007). The concepts of allostasis and allostatic overload provide a conceptual framework to understand the neurobiological mechanisms that underlie vulnerability to disease in general and drug addiction in particular by taking into account the anticipatory neuroadaptations that occur to maintain apparent reward function stability through changes in brain reward mechanisms (Koob and Le Moal, 2001).

Drug Addiction

Drug addiction is a chronically relapsing disorder characterized by compulsion to seek and take the drug, loss of control in limiting drug intake, and emergence of a negative emotional state, reflecting a motivational withdrawal syndrome, when access to the drug is prevented (defined here as dependence; Koob and Le Moal, 1997). 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 and Le Moal, 2008). The elements of impulsivity and compulsivity yield a composite addiction cycle that comprises three stages—preoccupation/anticipation, binge/intoxication, and withdrawal/negative affect—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 behavior to negative reinforcement driving the motivated behavior (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 and Le Moal, 1997).

Motivation, Opponent Process, and Addiction

Motivation is a state that can be defined as a "tendency of the whole animal to produce organized activity" (Hebb, 1972). 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.

This theory postulates that any motivational stimulus activates two opposing motivational processes. The *a-process* consists of either positive or negative hedonic responses, has a fast onset and offset, correlates with the intensity, quality, and duration of the stimulus, and shows tolerance. The *b-process* appears after the *a-process* has terminated, is opposite in direction, sluggish in onset, and slow to build up and decay and gets larger with repeated exposure. The initial acute effect of a drug of abuse (the *a-process* or positive hedonic response) was hypothesized to be opposed or counteracted by the *b-process* as homeostatic changes in brain systems. With repeated exposure to drugs, the *b-process* sensitizes, appears earlier after the unconditioned stimulus, lasts longer, and masks the *a-process*, leading to apparent tolerance (Laulin et al., 1999). Two types of biological processes have been proposed to describe the mechanisms that underlie allostasis in drug addiction: within-system adaptation and between-system adaptation (Koob and Bloom, 1988). In the within-system process, the drug elicits an opposing, neutralizing reaction within the same system in which the drug elicits its primary and unconditioned reinforcing actions, whereas in the between-system process, neurobiological systems that are different from the ones initially activated by the drug are recruited. This review focuses on alterations in the dopaminergic and corticotropin-releasing factor systems as the within-system and between-system neuroadaptations, respectively, that underlie the opponent process of drug abuse.

Role of the Dopaminergic System in the Motivational Response that Underlies the Opponent Process of Drug Abuse

The mesolimbic dopaminergic system is formed by the dopaminergic cell bodies in the ventral tegmental area (VTA) and their projections to the ventral striatum. The VTA also possesses a population of γ-aminobutyric acid (GABA) neurons that provide inhibitory inputs to dopamine cells and influence other structures, such as the pedunculopontine tegmental nucleus and glutamatergic neurons (Dobi et al., 2010). The VTA receives its main excitatory glutamatergic and cholinergic inputs from the ventromedial prefrontal cortex (ventral prelimbic, infralimbic, and dorsal peduncular cortices), ventral subiculum, subthalamic nucleus, parabrachial nucleus, pedunculopontine tegmental nucleus, and laterodorsal tegmental nucleus (Kalivas, 1993). The VTA also receives prominent inputs from the nucleus accumbens shell and ventromedial ventral pallidum (Oades and Halliday, 1987). The dopamine and GABA neurons in the VTA have been shown to be critical for the rewarding properties of psychostimulants. With the possible exception of opioids, all drugs of abuse when self-administered acutely stimulate the dopaminergic system and increase dopamine release in the nucleus accumbens (Volkow et al., 2007). The pattern of firing of dopaminergic neurons in the VTA in response to drugs of abuse has been hypothesized to encode drug reward, attribution of incentive salience, and establishment of response habits (Wise, 1980, 1987, 2002). The attribution of incentive salience refers to a process that transforms sensory information about reward into attractive incentives (Robinson and Berridge, 1993).

Intracranial self-stimulation has a long history as a measure of activity of the brain reward system and acute reinforcing effects of drugs of abuse. 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 and Milner, 1954). All drugs of abuse, when administered acutely, lower brain stimulation reward thresholds (Kornetsky and Esposito, 1979). The acute reinforcing effects of drugs of abuse are mediated by the activation of dopamine, serotonin, opioid peptides, and GABA systems either by actions in the nucleus accumbens and central nucleus of the amygdala (CeA) or by indirect actions in the VTA (Koob and Le Moal, 2001; Nestler, 2005; Koob 2006).

Converging lines of evidence suggest that dopamine is a key neurotransmitter mediating hedonic allostasis in drug addiction. For instance, cocaine self-administration reduces brain reward threshold acutely (minutes after the injection), but is associated with a compensatory increase in brain reward threshold hours and days after the injection that progressively return to baseline (Kenny et al., 2003, Ahmed et al., 2002). However, with repeated prolonged self-administration sessions and increases in cocaine intake this compensatory increase fail to return to baseline between sessions creating a residual hysteresis leading to increased allostatic load that ultimately will lead to the pathological state of addiction.

Drug withdrawal in humans is associated with fatigue, decreased mood, and psychomotor retardation; in animals it is associated with decreased motivation to work for natural rewards (Barr and Phillips, 1999), elevations in reward thresholds (Koob and Le Moal, 2006), 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.

Measures of brain reward function using intracranial self-stimulation have revealed elevations in brain reward thresholds during acute abstinence from all major drugs with dependence potential (Markou and Koob, 1991; Schulteis et al., 1994, 1995; Epping-Jordan et al., 1998; Gardner and Vorel, 1998; Paterson et al., 2000).

Decreases in activity of the mesolimbic dopamine system and decreases in serotonergic neurotransmission in the nucleus accumbens occur during drug withdrawal in animal studies (Weiss et al., 1992, 1996). Decreases in the number of dopamine D2 receptors in human subjects with cocaine dependence and primate cocaine self-administration (Nader et al., 2006), coupled with a decrease in dopaminergic activity in rodent studies, have led to the hypothesis of overall decreased sensitivity of reward circuits to stimulation by natural reinforcers and other drugs in drug-addicted individuals (Martin-Soelch et al., 2001; Volkow and Fowler, 2000). Indeed, cocaine abusers and alcoholics exhibit reduced dopamine release in response to a pharmacological challenge with a stimulant drug (Volkow et al., 1997; Martinez et al. 2007), and increased sensitivity of drug taking in response to dopamine receptor antagonist administration (leftward shift in the dose-response curve) has been observed in rats with extended access compared with rats with limited access to cocaine and methamphetamine (Ahmed et al., 2004; Wee et al., 2007), suggesting the reduced number or function of dopamine receptors in drug-dependent subjects. These findings demonstrate that decreases in the function of the dopaminergic system are implicated in both the acute reinforcing effect of drugs of abuse and the motivational response to drug withdrawal. Moreover, initial activation of the VTA by opiates is required to trigger the subsequent decreased opiate receptor function in the VTA that mediates the withdrawal-induced increases in anxiety-like behavior (Radke et al., 2011), suggesting that the emergence of anxiety during withdrawal from acute opiate exposure begins with activation of VTA mesolimbic dopamine circuitry, providing an early response mechanism for the opponent process view of withdrawal. Further evidence of the dopaminergic system in the development of hedonic allostasis has been obtained in rats with a history of escalation of alcohol drinking (Barak et al., 2011). Withdrawal from chronic alcohol is associated with decreased dopaminergic neurons activity in the VTA and decreased DA release in the nucleus accumbens (Diana et al., 1993; Bailey et al., 2001; Shen 2003; Shen et al., 2007; Darden and Hunt, 1977; Rossetti et al., 1992; Diana et al., 1993; Weiss et al., 1996; Smith et al., 2008). The decreased DA levels in the nucleus accumbens during acute withdrawal from alcohol is associated with increased craving for alcohol, and the emergence of a negative

emotional state Ahmed and Koob, 1998; Koob and Le Moal, 2001; Koob, 2003). Moreover, normalizing withdrawal-induced decreases in dopamine levels in the nucleus accumbens with intra-VTA infusion of glial cell-derived neurotrophic factor reduces alcohol intake (Barak et al., 2011), suggesting that decreased dopamine levels in the nucleus accumbens play a key role in allostatic mechanisms and in the reduction of hedonic set point during withdrawal.

The decrease in dopaminergic function associated with drug withdrawal suggests that complete blockade of the dopaminergic system may exacerbate the motivational response to drug withdrawal, but studies in rats and mice show that conditioned place aversion to nicotine withdrawal is blocked by the dopamine receptor antagonist α-flupenthixol and in dopamine D_2 receptor knockout mice (Grieder et al., 2010). This result demonstrates that although the decrease in dopaminergic function contributes to the emergence of withdrawal symptoms and is key for the reduction in hedonic set point, dopaminergic function is still required to mediate the motivational response associated with the opponent process of chronic nicotine exposure and suggests that a change in the specific pattern of dopaminergic signaling and not simply decreased signaling may mediate the craving for drugs and motivational response to drug withdrawal.

Role of the Corticotropin-Releasing Factor System in the Motivational Response that Underlies the Opponent Process of Drug Abuse

Within the domain of changes in reward function, the primary deficit is hypothesized to be a neuroadaptational shift in how rewards are processed. More specifically, a loss of positive reinforcement and a recruitment of negative reinforcement are hypothesized to occur within a specific basal forebrain area termed the extended amygdala. The extended amygdala has been identified by neuroanatomical studies (Alheid and Heimer, 1988; Koob et al., 1998) as a separate entity within the basal forebrain and has been hypothesized to be a common neural circuit for the reinforcing actions of drugs (Alheid and Heimer, 1988). The extended amygdala is composed of three major structures: CeA and medial amygdala (MeA), bed nucleus of the stria terminalis (BNST), and a transition zone in the posterior and medial portions of the nucleus accumbens (Alheid et al, 1995). Further examination of this anatomical system reveals two major divisions: central division and medial division. The central division of the extended amygdala includes the CeA, central sublenticular extended amygdala, lateral BNST, and a transition area in the medial and caudal portions of the nucleus accumbens. These structures are within the central division and are largely defined by their network of intrinsic connections and extensive connections to the lateral hypothalamus (Alheid et al., 1995). The medial division of the extended amygdala includes the medial BNST, MeA, and medial sublenticular extended amygdala. These structures, in turn, have been defined as the medial division by their network of intrinsic associative connections and extensive relations to the medial hypothalamus (Alheid et al., 1995). The lateral BNST, which forms a key element of the central division of the extended amygdala, has high amounts of dopamine and norepinephrine terminals, CRF terminals, and CRF cell bodies and receives afferents from the prefrontal cortex, insular cortex, and amygdalopiriform area. The medial BNST, in contrast, contains high amounts of vasopressin, is sexually dimorphic, and receives afferents from structures such as infralimbic cortex, entorhinal cortex, and subiculum (Dong et al., 2001; McDonald et al., 1999; Kozicz, 2001; Gray and Magnuson, 1992; Phelix and Paull, 1990; Allen et al., 1984). Evidence suggests that the central division may be involved in receiving cortical information and regulating the hypothalamic-pituitary-adrenal axis (Gray et al., 1993), whereas the medial division may be more involved in sympathetic and physiological responses and receive olfactory information (Pompei et al., 1991; Lesur et al., 1989; Nijsen et al., 2001).

A role for the extended amygdala in the aversive effects of drug withdrawal includes changes in opioidergic, GABAergic, and CRF neurotransmission during acute withdrawal. The CRF system in the CeA is activated during acute cocaine, alcohol, opioid, Δ^9-tetrahydrocannabinol, and nicotine withdrawal as measured by *in vivo* microdialysis and neuropharmacological probes (Richter and Weiss, 1999; Heinrichs et al., 1995; Merlo-Pich et al., 1995; George et al., 2007). Similar effects have been observed with alcohol in the lateral BNST (Olive et al., 2002). Rats undergoing cocaine withdrawal also show increases in anxiety-like responses that are reversed by administration of a competitive CRF antagonist (Sarynai et al., 1995; Basso et al., 1999). Similar results have been observed with nicotine (George et al., 2007), alcohol (Rassnick et al., 1993, Koob et al., 1994), and opiates (Schulteis et al., 1994, Heinrichs et al., 1995; Basso et al., 1999). Moreover, CRF_1 but not CRF_2 receptor activation mediates nicotine withdrawal-induced deficits in brain reward function (Bruijnzeel et al., 2009), an effect localized to the CeA and nucleus accumbens shell, but not BNST (Marcinkiewcz et al., 2009). The ability of CRF antagonists to block the anxiogenic-like and aversive-like motivational effects of drug withdrawal would predict the motivational effects of CRF antagonists in animal models of extended access to drugs. Indeed, CRF_1 antagonists blocked the increased self-administration of cocaine (Goeders and Guerin, 2000), nicotine (George et al., 2007), heroin (Greenwell et al., 2009) in animals showing compulsive drug seeking after extended access to these drugs. Similar effects have been observed in animal models of compulsive alcohol seeking associated with dependence (Koob, Neuron 2007). Taken together, the increase in CRF levels during drug withdrawal coinciding with the emergence of a negative emotional state that opposes the acute positive hedonic effect of drugs of abuse suggest that activation of the CRF-CRF1R system may represent one of the opponent process mechanisms leading to an allostatic state. Moreover, repeated episodes of withdrawal potentiate the effect of abstinence on the CRF-CRF1R system and may lead to a more intense negative emotional state (George et al., 2007; Zorrilla et al., 2001; Holter et al., 1998; Brown et al., 1998; Breese et al., 2005, 2011). This hyperactivation of the CRF-CRF1R system after repeated withdrawal either by a sensitization mechanism or a failure to return to baseline level after renewed access to the drug may represent the allostatic load responsible for the transition to drug dependence.

Interaction Between the Dopamine and Corticotropin-Releasing Factor Systems

The mesolimbic dopaminergic and extended amygdala CRF systems have long been studied independently and often viewed as mutually exclusive in the drug addiction field. However, recent work has demonstrated that these two systems can powerfully interact with each other, suggesting that dysregulation of this interaction may be lead to the development of drug dependence and relapse. Very few studies have investigated the role of dopamine in CRF release in the extended amygdala, despite the fact that the VTA sends heavy dopamine projections to the extended amygdala (Fallon and Moore, 1978) and PVN (Liposits and Paull, 1989) and directly innervates CRF-containing neurons in the CeA (Eliava et al., 2003) and BNST (Meloni et al., 2006). Early studies with 6-hydroxydopamine lesions of the mesolimbic dopamine system showed a decreased number and staining intensity of CRF neurons in the CeA associated with an increase in CRF mRNA levels (Smialowska et al., 1999). In contrast, stimulation of D_1 or D_2 receptors stimulates CRF mRNA expression in PVN neurons but not in the CeA (Eaton et al., 1996; Smialowska et al., 2001), suggesting that dopamine does not directly control CRF release in the extended amygdala. However, recent electrophysiological studies suggest a key role for dopamine in CRF neurotransmission. Dopamine enhances glutamatergic transmission in the BNST through activation of $D_{1/2}$ receptors and CRF_1 receptors, suggesting that dopamine stimulates the local release of CRF in the extended amygdala (Kash et al., 2008). Cocaine potentiates the

dopamine receptor- and CRF_1 receptor-dependent short-term potentiation of *N*-methyl-D-aspartate (NMDA) receptor function in the BNST (Kash et al., 2008). On the other hand, cocaine withdrawal, a condition known to be associated with decreased dopamine levels is associated with an enhancement of CRF1 receptor-dependent long-term potentiation in the CeA (Fu et al., 2007; Pollandt et al., 2006-75-76), and with an impairment of D1 receptor-dependent long-term potentiation of the intrinsic excitability in the BNST, a deficit that can be mimicked by chronic treatment with CRF (Francesconi et al., 2010). Similarly blockade of D_1 receptors prevented the CRF-enhanced startle response, a behavioral assay believed to reflect stress or anxiety-like states (Meloni et al., 2006).

In addition, CRF neurons in the BNST, CeA, and PVN project to the VTA (Rodaros et al., 2007; Swanson et al., 1983), and the VTA expresses CRF_1 and CRF_2 receptors (Sauvage and Steckler, 2001; Ungless et al., 2003). Neuroanatomical studies show that CRF is colocalized in glutamatergic and GABAergic afferents and synapses with dopaminergic as well as non-dopaminergic neurons in the VTA (Tagliaferro and Morales, 2008). Moreover, a subpopulation of GABAergic and dopaminergic neurons in the VTA also express CRF binding protein (CRF-BP), a protein that participates in the regulation of CRF signaling at the synapse (Wang and Morales, 2008). Consistent with these anatomical data, CRF has been found to increase dopamine neuron firing (Kalivas, 1987, Wanat et al., 2008), dopamine release (Bagozi et al., 2006; Muramatsu et al., 2006; Lavicky et al., 1993) and footshock stress induces a long-lasting release in CRF in the VTA (Wang et al., 2005), while CRF1 receptor knock down in the VTA reduce dopamine release in the prefrontal cortex (Refojo et al., 2011). The effect of CRF on the activation of the dopaminergic system may be explained by different mechanisms. CRF has been shown to decrease somatodendritic dopamine release in the VTA through inhibition of voltage-operated Ca2+ gated channels (Kim et al., 2009), a mechanism that may increase dopamine release in the limbic system by decreasing autoreceptor activation. Also, CRF activates CRF_1 receptors presynaptically on glutamatergic terminals to stimulate glutamate release in the VTA and activate dopaminergic cells, but only in cocaine-experienced animals (Ungless et al., 2003). CRF receptor antagonists in the VTA have been shown to block glutamate and dopamine release in the VTA and footshock stress-induced reinstatement of cocaine seeking (Wang et al., 2005). More recent studies suggest a direct postsynaptic action on dopaminergic neurons (Hahn et al., 2009), and although CRF can control glutamate release in the VTA through activation of CRF_2 receptors in naive animals, it appears that recruitment of CRF_1 receptors only occurs in cocaine-experienced subjects (Hahn et al., 2009). These results suggest that exposure to drugs of abuse may sensitize the dopaminergic system to the effect of CRF to facilitate relapse in drug-dependent subjects. However, unanswered questions are whether withdrawal-induced increases in rats that self-administer drugs to the point of dependence also lead to activation of glutamatergic afferents to the VTA and subsequent dopamine release as observed after footshock stress, and whether the glutamatergic afferents contributes to the decreased basal level of dopamine in the nucleus accumbens observed during drug withdrawal through activation of VTA GABAergic neurons (Tagliaferro and Morales, 2008).

Another mechanism of interaction between the CRF and dopaminergic systems is through the dynorphin/κ opioid system. Indeed, CRF stimulates dynorphin release (Nikolarakis et al., 1986; Song and Takemori, 1992; for review, see Bruchas et al., 2010), which can in turn decrease dopamine release in the PFC and striatum through activation of κ receptors on dopaminergic terminals (for review, see Bruijnzeel, 2009).

Taken together, these results demonstrate that the dopamine and CRF systems can interact with each other in the VTA and the extended amygdala at every stage of the addiction process. Activation of the dopaminergic system by drugs of abuse may transiently sensitize

the CRF system during the initial exposure to the drug, while drug withdrawal will lead to a sustained activation of the CRF system in the extended amygdala. This increase in the CRF-CRF1R system during withdrawal will not only represent the emergence of the *b-process* but may contribute to the habituation of the *a-process* through a decrease dopamine release in the limbic system by the recruitment of the dynorphin system. Finally, acute stress after abstinence in dependent subjects may exacerbate CRF release in the VTA and provoke relapse through activation of dopamine neurons (see Figure 1).

Conclusions

Acute withdrawal from drugs of abuse produces opponent process-like changes in reward neurotransmitters in specific elements of reward circuitry associated with the mesolimbic dopaminergic system and recruitment of the extended amygdala and CRF stress systems that motivationally oppose the acute hedonic effects of drugs of abuse. Such changes in the dopamine and CRF these brain systems associated with the development of motivational aspects of withdrawal are hypothesized to be a major source of neuroadaptive changes that drive and maintain addiction. Decreased dopaminergic function in the nucleus accumbens and extended amygdala may participate in the habituation of the *a-process*, i.e., or the acute reinforcing efficacy of natural rewards and drugs of abuse, whereas recruitment of the CRF-CRF_1 systems and possibly dynorphin/κ opioid system in the CeA, BNST, and VTA during withdrawal may participate in the emergence of the *b-process*, i.e, or negative emotional state that drives the motivation to seek drugs. Although some tantalizing evidence suggests that the dopaminergic and CRF systems may closely interact with each other, research in this domain is scarce. Unknown is whether the initial activation of the dopaminergic system in the VTA (*a-process*) is required for the increase in CRF release in the extended amygdala and VTA (*b-process*) in drug-dependent and withdrawn subjects that leads to compulsive drug seeking and increased craving for the drug. As such, repeated withdrawal episodes and sustained activation of the CRF-CRF1R system may lead to an allostatic load contributing significantly to the transition to drug addiction.

Acknowledgments

This is publication number 21324 from The Scripps Research Institute. This work was supported by National Institutes of Health grant DA04398, DA10072, DA04343, and DA023597 from the National Institute on Drug Abuse, AA08459, and AA06420 from the National Institute on Alcohol Abuse and Alcoholism, and the Pearson Center for Alcoholism and Addiction Research. The authors would like to thank Michael Arends for his help with manuscript preparation.

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Highlights

- The opponent process theory postulates that drugs trigger two opposing motivational process.
- The *a-process* has fast onset and offset and the *b-process* is opposite, slower to start and last longer.
- Decreased dopaminergic function in the NAC and CeA mediate the habituation of the *a-process*.
- Activation of the CRF systems in the CeA and VTA mediates the increase in *b-process* in dependent subjects.
- Interaction between the dopamine and CRF systems may represent the opponent-process mechanisms of drug withdrawal.

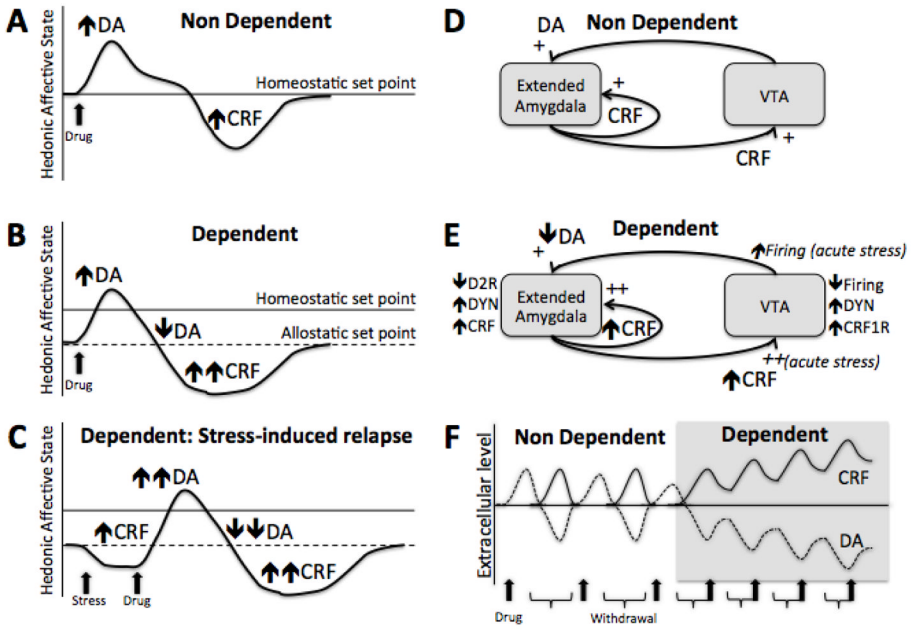

Figure 1. Hypothetical interactions between the dopamine and CRF systems as a mechanism underlying the allostatic load in the transition to drug addiction

A) The hedonic response to an acute drug administration in a drug-naive individual with activity in the dopaminergic system involved in reward predominating with a minor anti-reward opponent process-like response of the CRF system. B) The hedonic response to an acute drug administration in a drug-dependent individual while taking drug regularly. Initial activity in the dopaminergic system involved in reward is followed by a decrease in function of the dopaminergic system involved in reward, and a major anti-reward opponent process-like response of the CRF system. Note the change in hedonic set point, reflecting an allostatic state produced by chronic dysregulation of the dopamine and CRF systems. C) The hedonic response to an acute stressor followed by a drug administration in a drug-dependent individual during withdrawal. Acute stress produces a recruitment of the CRF system and a further decrease in hedonic response, below the allostatic set point. This major dysphoria triggers drug intake accompanied by an intense activity of the dopaminergic system and is followed by a compensatory decrease in the dopaminergic system and increase in the CRF system to reestablish the allostatic set point. Note that depending on the intensity and frequency of withdrawal episodes and stress-induced relapse, an allostatic load can develop so that the allostatic set point is further shifted away from the homeostatic set point (see C and F). D) Interaction between the dopaminergic system originating from the VTA and the CRF system from the extended amygdala in a drug naïve subject. E) Interaction between the dopaminergic and CRF system in a drug dependent subjects. Note that neuroadaptations in the dopamine, dynorphin and CRF systems represent changes during withdrawal, except for italicized neuroadaptations representing changes during acute stress (see also C). F) Dysregulation of the dopamine and CRF system during chronic access to the drug. When the drug is consumed occasionally (non dependent), changes in the dopamine and CRF systems are maintained within the homeostatic range and have time to return to baseline level. As the frequency of use increases, the initial increase in the dopamine system is blunted and is followed by a greater increase in the CRF system. The failure to self-regulate these systems and the impossibility to return to baseline lead to an allostatic load that will contribute significantly to the transition to drug dependence.