Addiction and the Brain Antireward System

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Key Words

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Abstract

A neurobiological model of the brain emotional systems has been proposed to explain the persistent changes in motivation that are associated with vulnerability to relapse in addiction, and this model may generalize to other psychopathology associated with dysregulated motivational systems. In this framework, addiction is conceptualized as a cycle of decreased function of brain reward systems and recruitment of antireward systems that progressively worsen, resulting in the compulsive use of drugs. Counteradaptive processes, such as opponent process, that are part of the normal homeostatic limitation of reward function fail to return within the normal homeostatic range and are hypothesized to repeatedly drive the allostatic state. Excessive drug taking thus results in not only the short-term amelioration of the reward deficit but also suppression of the antireward system. However, in the long term, there is worsening of the underlying neurochemical dysregulations that ultimately form an allostatic state (decreased dopamine and opioid peptide function, increased corticotropin-releasing factor activity). This allostatic state is hypothesized to be reflected in a chronic deviation of reward set point that is fueled not only by dysregulation of reward circuits per se but also by recruitment of brain and hormonal stress responses. Vulnerability to addiction may involve genetic comorbidity and developmental factors at the molecular, cellular, or neurocircuitry levels that sensitize the brain antireward systems.

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Drug addiction: a chronically relapsing disorder characterized by: compulsion to seek and take the drug, loss of control in limiting intake, and emergence of a negative emotional state (e.g., dysphoria, anxiety, and irritability) when access to the drug is prevented

Neuroadaptation: change in neuronal function of a system with repeated challenge to that system

INTRODUCTION

What is Addiction? The Clinical Syndrome

Drug addiction, also known as substance dependence, is a chronically relapsing disorder characterized by (*a*) compulsion to seek and take the drug, (*b*) loss of control in limiting intake, and (*c*) emergence of a negative emotional state (e.g., dysphoria, anxiety, irritability) when access to the drug is prevented (defined here as dependence) (Koob & Le Moal 2005). The terms addiction and substance dependence (as currently defined by the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition; Am. Psychiatric Assoc. 1994) are used interchangeably throughout this review and refer to a final stage of a usage process that moves from drug use to addiction. Clinically, the occasional but limited use of a drug with the potential for abuse or dependence is distinct from the emergence of a chronic drug-dependent state. An important goal of current neurobiological research is to understand the molecular and neuropharmacological neuroadaptations within specific neurocircuits that mediate the transition from occasional, controlled drug use and the loss of behavioral control over drug seeking and drug taking that defines chronic addiction. The thesis of this review is that a key element of the addiction process is the underactivation of natural motivational systems such that the reward system becomes compromised and that an antireward system becomes recruited to provide the powerful motivation for drug seeking associated with compulsive use (see Antireward sidebar).

A Motivational Perspective of Addiction

Motivation is a state that varies with arousal; it guides behavior in relationship to changes in the environment and shares key common characteristics with our concepts of addiction. The environment can be external (incentives) or internal (central motive states or drives), and such motivation or motivational states are not constant and 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. Solomon argued that there is affective or hedonic habituation (or tolerance) and affective or hedonic withdrawal (abstinence). He defined two processes: the a-process and the b-process. The a-process could consist of either positive or negative hedonic responses. It occurs shortly after presentation of a stimulus, correlates closely with the stimulus intensity, quality, and duration of the reinforcer, and shows tolerance. In contrast, the b-process appears after the a-process has terminated. It 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 behavior (Solomon 1980).

From a drug-taking perspective of brain motivational systems, it was hypothesized that the initial acute effect of a drug was opposed or counteracted by homeostatic changes in brain systems. Certain systems in the brain were hypothesized to suppress or reduce all departures from hedonic neutrality (Solomon & Corbit 1974). This affect control system was conceptualized as a single negative feedback, or opponent, loop that opposes the stimulus-aroused affective state (Poulos & Cappell 1991, Siegel 1975, Solomon & Corbit 1974). 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 an a-process or euphoria, which is followed by a decline in intensity. Then, after the drug wears off, an opposing, aversive negative emotional state emerges, which is the b-process.

More recently, opponent-process theory has been expanded into the domains of the neurocircuitry and neurobiology of drug addiction from a physiological perspective. An allostatic model of the brain motivational systems has been proposed to explain the persistent changes in motivation that are associated with vulnerability to relapse in addiction, and this model may generalize to other psychopathology associated with dysregulated

ANTIREWARD

The concept of an antireward system was developed to explain one component of time-dependent neuroadaptations in response to excessive utilization of the brain reward system. The brain reward system is defined as activation of circuits involved in positive reinforcement with an overlay of positive hedonic valence. The neuroadaptation simply could involve state-shifts on a single axis of the reward system (within-system change; dopamine function decreases). However, there is compelling evidence that brain stress/emotional systems are recruited as a result of excessive activation of the reward system and provide an additional source of negative hedonic valence that are defined here as the antireward system (between-system change; corticotropin-releasing factor function increases). The combination of both a deficit in the reward system (negative hedonic valence) and recruitment of the brain stress systems (negative hedonic valence) provides a powerful motivational state mediated in part by the antireward system (Koob & Le Moal 2005).

Antireward: a concept based on the hypothesis that there are brain systems in place to limit reward that are triggered by excessive activity in the reward system

Opponent process: affective or hedonic habituation (tolerance) and affective or hedonic withdrawal (abstinence)

motivational systems (Koob & Le Moal 2001). In this framework, addiction is conceptualized as a cycle of spiraling dysregulation of brain reward/antireward mechanisms that progressively increases, resulting in the compulsive use of drugs. Counteradaptive processes such as opponent-process that are part of the normal homeostatic limitation of reward function fail to return within the normal homeostatic range and are hypothesized to form an allostatic state. These counteradaptive processes are hypothesized to be mediated by two processes: within-system neuroadaptations and between-system neuroadaptations (Koob & Bloom 1988). A within-system neuroadaptation is a molecular or cellular change within a given reward circuit to accommodate overactivity of hedonic processing associated with addiction, resulting in a decrease in reward function. A between-system neuroadaptation is a circuitry change where a different circuit (brain stress circuit) is activated by excessive engagement of the reward circuit and has opposing actions, again limiting reward function (see Antireward sidebar). The extension of such an allostatic state is further hypothesized to be reflected in a chronic deviation of reward set point that is fueled both by dysregulation of reward circuits per se and by recruitment of brain and hormonal stress responses. The purpose of this review is to explore what neuroadaptational changes occur in the brain emotional systems to account for the allostatic changes in motivation that produce the compulsivity of addiction.

DRUG USE, ABUSE, AND DEPENDENCE: DYNAMICS OF MOTIVATION

Drug Use: Drug Dependence

From a psychiatric-motivational perspective, drug addiction has aspects of both impulse control disorders and compulsive disorders. Impulse control disorders are characterized by an increasing sense of tension or arousal before committing an impulsive act; pleasure, gratification, or relief at the time of committing the act; and there may or may not be regret, self-reproach, or guilt following the act (Am. Psychiatric Assoc. 1994). A classic impulse control disorder is kleptomania, where there is an increase in tension before stealing an object or objects that are not needed and relief after the act but little or no regret or self-reproach. In contrast, compulsive disorders are characterized by anxiety and stress before committing a compulsive repetitive behavior and relief from the stress by performing the compulsive behavior. A classic compulsive disorder is obsessive-compulsive disorder, where obsessions of contamination or harm drive anxiety, and performing repetitive compulsive acts reduces the anxiety. As an individual moves from an impulsive disorder to a compulsive disorder, there is a shift from positive reinforcement driving the motivated behavior to negative reinforcement driving the motivated behavior (Koob 2004). Drug addiction has been conceptualized as a disorder that progresses from impulsivity to impulsivity/compulsivity in a collapsed cycle of addiction composed of three stages: preoccupation/anticipation, binge/intoxication, and withdrawal/negative affect (**Figure 1**). Different theoretical perspectives ranging from experimental psychology, social psychology, and neurobiology can be superimposed on these three stages, which are conceptualized as feeding into each other, becoming more intense, and ultimately leading to the pathological state known as addiction (Koob & Le Moal 1997).

Patterns of Drug Dependence

Different drugs produce different patterns of addiction with emphasis on different components of the addiction cycle. Opioids are a classic drug of addiction, in which an evolving pattern of use includes intravenous or smoked drug taking, an intense intoxication with opioids, the development of tolerance, and escalation in intake, as well as profound dysphoria,

physical discomfort, and somatic withdrawal signs during abstinence. Intense preoccupation with obtaining opioids (craving) develops and often precedes the somatic signs of withdrawal. This preoccupation is linked not only to stimuli associated with obtaining the drug but also to stimuli associated with withdrawal and internal and external states of stress. A pattern develops wherein the drug must be obtained to avoid the severe dysphoria and discomfort of abstinence. Alcoholism follows a similar pattern, but the intoxication is less intense and the pattern of drug taking often is characterized by binges of alcohol intake that can be daily episodes or prolonged days of heavy drinking. A binge is now defined as consumption of five standard drinks for males and four standard drinks for females in a two-hour period, or obtaining a blood alcohol level of 0.08 gram percent (Natl. Inst. Alcohol Abuse Alcohol. 2004). Alcoholism is characterized by a severe emotional and somatic withdrawal syndrome and intense craving for the drug that is often driven by negative emotional states but also by positive emotional states. Many alcoholics continue with such a binge/withdrawal pattern for extended periods, but for others the pattern evolves into an opioid-like addiction in which they must have alcohol available at all times to avoid the consequences of abstinence. Nicotine addiction contrasts with the above patterns in that nicotine is associated with even less of a binge/intoxication stage. Cigarette smokers who meet the criteria for substance dependence are likely to smoke throughout the waking hours and to experience negative emotional states with dysphoria, irritability, and intense craving during abstinence. The binge/intoxication stage forms a minor component of nicotine dependence, with the pattern of intake one of highly titrated intake of the drug except during periods of sleep. Psychostimulants such as cocaine and amphetamines show a pattern with a greater emphasis on the binge/intoxication stage. The duration of such binges can be hours or days; binges are often followed by a crash that is characterized by extreme dysphoria and inactivity. Intense craving follows later and is driven by both environmental cues signifying availability of the drug and by internal states often linked to negative emotional states and stress. Marijuana dependence follows a pattern similar to that of opioids and tobacco in that there is a significant intoxication stage, but as chronic use continues, subjects begin to show a pattern of chronic intoxication during waking hours. Withdrawal is characterized by dysphoria, irritability, and sleep disturbances, and although marijuana craving has been less studied to date (Heishman et al. 2001), it is most likely linked both to environmental and internal states similar to those of other drugs of abuse.

Craving: memory of the rewarding aspects of drug use superimposed on a negative emotional state

NEUROBIOLOGICAL SUBSTRATES OF DRUG USE AND DEPENDENCE

Animal Models of Addiction

Much of the recent progress in understanding the neurobiology of addiction has derived from the study of animal models of addiction to specific drugs such as stimulants, opioids, alcohol, nicotine, and Δ^9-tetrahydrocannabinol. Although no animal model of addiction fully emulates the human condition, animal models do permit investigation of specific elements of the process of drug addiction. Such elements can be defined by models of different stages of the addiction cycle, models of psychological constructs such as positive and negative reinforcement, and models of actual symptoms of addiction.

Animal models for the binge/intoxication stage of the addiction cycle can be conceptualized as measuring acute drug reward; reward can be defined as a positive reinforcer with some additional emotional value such as pleasure. Animal models of reward are extensive and well validated. Animals and humans will readily self-administer drugs in the nondependent state. Drugs of abuse have powerful reinforcing properties in that animals will

DSM-IV: *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition

perform many different tasks and procedures to obtain the drugs, even in the nondependent state. Drugs that are self-administered by animals correspond well with those that have high abuse potential in humans, and intravenous drug self-administration is considered an animal model that is predictive of abuse potential (Collins et al. 1984). Using this procedure, the dose, cost of responding, and second-order schedules [working for a stimulus (cue) that then allows the reinforcer to be delivered] all can be manipulated to determine the value of the reward. Oral self-administration of alcohol has also been used as a reward in similar studies in which animals will work to obtain meaningful blood alcohol levels (Samson 1986). Two other animal models have been used extensively to measure indirectly drug reward: conditioned place preference and brain reward thresholds. Animals typically exhibit a conditioned place preference for an environment associated with drugs that are self-administered by humans, and they avoid environments that induce aversive states (conditioned place aversion) (Carboni & Vacca 2003). Lowering of brain-stimulation reward thresholds are also reliable measures of drug reward. Drugs of abuse decrease thresholds for brain stimulation reward, and there is good correspondence between the ability of drugs to decrease brain reward thresholds and their abuse potential (Kornetsky & Bain 1990).

Animal models of the negative reinforcing effects of dependence include the same models used for the rewarding effects of drugs of abuse (described above). However, changes in valence of the reward occur where spontaneous withdrawal from all drugs of abuse increases, instead of lowers, brain reward thresholds (Koob 2004). Animals also show a conditioned place aversion, instead of preference, to precipitated withdrawal from chronic administration of a drug.

More recently, animal models for the transition to addiction have been demonstrated that incorporate animal models of the rewarding effects of drugs as well as the induction of dependence. Rodents will increase the intravenous self-administration of drugs with extended access to the drugs and during withdrawal from the dependent state, as measured both by increased amount of drug administration and working harder to obtain the drug. 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, Kitamura et al. 2006, O'Dell & Koob 2007, Roberts et al. 2000). Equally compelling are studies that show drug taking in the presence of aversive consequences in animals given extended access to the drug. Rats with extended access to cocaine did not suppress drug seeking in the presence of an aversive conditioned stimulus or punishment, which has face validity for the DSM-IV criteria of "continued substance use despite knowledge of having a persistent physical or psychological problem" (Deroche-Gamonet et al. 2004, Vanderschuren & Everitt 2004).

Animal models of craving (preoccupation/anticipation stage) involve the conditioned rewarding effects of drugs of abuse and measures of the conditioned aversive effects of dependence, as well as resistance to extinction and second-order schedules (Shippenberg & Koob 2002). Many of the measures of craving assess the motivational properties of the drugs themselves or of a cue paired with the drugs after extinction. Drug-induced reinstatement involves first extinction and then presentation of a priming injection of a drug. Latency to reinitiate responding, or the amount of responding on the previously extinguished lever, is hypothesized to reflect the motivation for drug-seeking behavior. Similarly, drug-paired or drug-associated stimuli can reinitiate drug-seeking behavior (cue-induced reinstatement). Stress-induced reinstatement occurs when acute stressors can also reinitiate drug-seeking behavior that previously has been extinguished in animals. Protracted abstinence has been linked to the increased brain reward thresholds, and increases in

anxiety-like behavior have been shown to persist after acute withdrawal in animals with a history of dependence. Finally, conditioned opioid withdrawal—where previously neutral stimuli are paired with precipitated opioid withdrawal—has been shown not only to produce place aversions but also to have motivational properties in increasing self-administration of opioids (Kenny et al. 2006).

Neural Basis of Drug Reward—Positive Reinforcing Effects

A key element of drug addiction is neuroadaptation within the brain reward system during the development of addiction, and one must understand the neurobiological bases for acute drug reward to understand how the reward systems change with the development of addiction. A principal focus of research on the neurobiology of the positive reinforcing effects of drugs with dependence potential has been on the activation of the circuitry related to the origins and terminals of the mesocorticolimbic dopamine system. Compelling evidence exists for a critical role of this system in drug reward associated with psychostimulant drugs, and there is evidence that all major drugs of abuse activate this system as measured either by increased extracellular levels of dopamine in the terminal areas [such as medial (shell) point of the nucleus accumbens] or by activation of the firing of neurons in the ventral tegmental area (Di Chiara 2002, Koob 1992). However, although selective neurotoxin-induced lesions of the mesolimbic dopamine system do block cocaine, amphetamine, and nicotine self-administration, rats continue to self-administer heroin and alcohol in the absence of the mesocorticolimbic dopamine system (Pettit et al. 1984, Rassnick et al. 1993b), and place-preference studies show robust place preferences to morphine and nicotine in the presence of major dopamine receptor blockade (Bechara & van der Kooy 1992, Laviolette & van der Kooy 2003). Indeed, an important role for opioid peptides in drug reward, independent of a direct action on dopamine neurons, has been proposed (Koob 1992). Together, these results suggest that multiple parallel pathways mediate drug reward.

Specific components of the basal forebrain associated with the amygdala also have been identified with drug reward, particularly alcohol (Koob 2003a). One hypothetical construct, the extended amygdala, includes not only the central nucleus of the amygdala (CeA), but also the bed nucleus of the stria terminalis (BNST) and a transition zone in the medial subregion of the nucleus accumbens (shell of the nucleus accumbens), and these regions share certain cytoarchitectural and circuitry similarities (Heimer & Alheid 1991). As the neural circuits for the reinforcing effects of drugs with dependence potential have evolved, the role of neurotransmitters/neuromodulators also has evolved, and those that have been identified to have a role in the acute reinforcing effects of drugs of abuse in these basal forebrain areas include mesolimbic dopamine, opioid peptide, γ-aminobutyric acid (GABA), glutamate, endocannabinoids, and serotonin (**Table 1**).

Neural Basis of Drug Dependence: Within-System Neuroadaptational Processes

The neural substrates and neuropharmacological mechanisms for the negative motivational effects of drug withdrawal may involve disruption of the same neurochemical systems and neurocircuits implicated in the positive reinforcing effects of drugs of abuse, termed a within-system neuroadaptation (**Table 2**). All drugs of abuse produce elevations in brain reward thresholds during acute withdrawal (Koob & Le Moal 2005), and in animal models of the transition to addiction, increases in brain reward threshold (decreased reward) occur that temporally precede and highly correlate with the increase in drug intake with extended access (Ahmed et al. 2002, Kenny et al. 2006).

Extended amygdala: regions of the basal forebrain that share certain cytoarchitectural and circuitry similarities. The regions are the central nucleus of the amygdala, the bed nucleus of the stria terminalis, and a transition zone in the medial subregion of the nucleus accumbens (shell of the nucleus accumbens)

CeA: central nucleus of the amygdala

BNST: bed nucleus of the stria terminalis

GABA: γ-aminobutyric acid

Table 1 Neurobiological substrates for the acute reinforcing effects of drugs of abuse

Drug of abuse	Neurotransmitter	Site
Cocaine and amphetamines	Dopamine	Nucleus accumbens
	γ-aminobutyric acid	Amygdala
Opiates	Opioid peptides	Nucleus accumbens
	Dopamine	Ventral tegmental area
	Endocannabinoids	
Nicotine	Nicotinic acetylcholine	Nucleus accumbens
	Dopamine	Ventral tegmental area
	γ-aminobutyric acid	Amygdala
	Opioid peptides	
Δ^9-Tetrahydrocannabinol	Endocannabinoids	Nucleus accumbens
	Opioid peptides	Ventral tegmental area
	Dopamine	
Alcohol	Dopamine	Nucleus accumbens
	Opioid peptides	Ventral tegmental area
	γ-aminobutyric acid	Amygdala
	Endocannabinoids	

Table 2 Neurotransmitters implicated in the motivational effects of withdrawal from drugs of abuse

Neurotransmitter	Functional effect
↓ Dopamine	"Dysphoria"
↓ Serotonin	"Dysphoria"
↓ γ-Aminobutyric acid	Anxiety, panic attacks
↓ Neuropeptide Y	Antistress
↑ Dynorphin	"Dysphoria"
↑ Corticotropin-releasing factor	Stress
↑ Norepinephrine	Stress

During such acute withdrawal, there is decreased activity of the mesocorticolimbic dopamine system as well as decreased activity in opioid peptide, GABA, and glutamate in the nucleus accumbens or the amygdala. Repeated administration of psychostimulants produces an initial facilitation of dopamine and glutamate neurotransmission in the nucleus accumbens (Ungless et al. 2001, Vorel et al. 2002). However, chronic administration leads to decreases in dopaminergic and glutamatergic neurotransmission in the nucleus accumbens during acute withdrawal (Kalivas et al. 2003, Weiss et al. 1992), opposite responses of opioid receptor transduction mechanisms in the nucleus accumbens during opioid withdrawal (Shaw-Lutchman et al. 2002), changes in GABA-ergic neurotransmission during alcohol withdrawal (Grobin et al. 1998, Roberto et al. 2004), and differential regional changes in nicotinic acetylcholine receptor function during nicotine withdrawal.

Human imaging studies of addicts during withdrawal or protracted abstinence give results that are consistent with animal studies. There are decreases in dopamine D_2 receptors (hypothesized to reflect hypodopaminergic functioning) and hypoactivity of the orbitofrontal-infralimbic cortex system (Volkow et al. 2003). Decreases in reward neurotransmitter function have been hypothesized to contribute significantly to the negative motivational state associated with acute drug abstinence and may trigger long-term biochemical changes that contribute to the clinical syndrome of protracted abstinence and vulnerability to relapse.

Neural Basis of Drug Dependence: Between-System Neuroadaptational Processes

Different neurochemical systems involved in 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, termed a between-system neuroadaptation. The hypothalamic-pituitary-adrenal (HPA) axis and the brain stress system, both mediated by corticotropin-releasing factor (CRF), are dysregulated by chronic administration of drugs of abuse, with a common response of elevated adrenocorticotropic hormone (ACTH) and corticosterone and extended amygdala CRF during acute withdrawal from all major drugs of abuse (Koob & Le Moal 2005, Kreek & Koob 1998). Acute withdrawal from drugs of abuse also may increase the release of norepinephrine in

HPA: hypothalamic-pituitary-adrenal axis

CRF: corticotropin-releasing factor

ACTH: adrenocorticotropic hormone

the bed nucleus of the stria terminalis and decrease functional levels of neuropeptide Y (NPY) in the extended amygdala (Olive et al. 2002, Roy & Pandey 2002).

For example, with alcohol, CRF may have a key role in mediating the neuroendocrine, autonomic, and behavioral responses to stress and anxiety that drive excessive drinking in dependence (Koob & Heinrichs 1999). Regions of the extended amygdala (including the CeA) contain high amounts CRF terminals, cell bodies, and receptors and comprise part of the "extrahypothalamic" CRF-stress system. (Merchenthaler et al. 1982); numerous studies have demonstrated the involvement of the extended amygdala CRF system in mediating the behavioral responses associated with fear and anxiety (Koob & Heinrichs 1999). During ethanol withdrawal, extrahypothalamic CRF systems become hyperactive, with an increase in extracellular CRF within the CeA and BNST of dependent rats (Funk et al. 2006, Merlo-Pich et al. 1995, Olive et al. 2002, Zorrilla & Koob 2004), and this dysregulation of brain CRF systems is hypothesized to underlie both the enhanced anxiety-like behaviors and the enhanced ethanol self-administration associated with ethanol withdrawal. Supporting this hypothesis, the subtype nonselective CRF-receptor antagonists α-helical CRF_{9-41} and D-Phe CRF_{12-41} (intracerebroventricular administration) reduce both ethanol withdrawal-induced anxiety-like behavior and ethanol self-administration in dependent animals (Baldwin et al. 1991, Valdez et al. 2002). When administered directly into the CeA, CRF receptor antagonists also attenuate anxiety-like behavior (Rassnick et al. 1993a) as well as ethanol self-administration in ethanol-dependent rats (Funk et al. 2006). These data suggest an important role of CRF, primarily within the CeA, in mediating the increased self-administration associated with dependence. Similar results have been observed with the increased intravenous self-administration asociated with extended access to heroin (Greenwell et al. 2007), cocaine (Specio et al. 2007), and nicotine (George et al. 2007).

NPY: neuropeptide Y

These results suggest not only a change in the function of neurotransmitters associated with the acute reinforcing effects of drugs of abuse during the development of dependence, such as decreases in dopamine, opioid peptides, serotonin, and GABA function, but also recruitment of the CRF system **(Figure 2)**. Additional between-system neuroadaptations associated with motivational withdrawal include activation of the dynorphin-κ opioid system, activation of the norepinephrine brain stress system, and dysregulation of the NPY brain antistress system (Koob & Le Moal 2005) (**Table 2**). Additionally, activation of the brain stress systems may contribute not only to the negative motivational state associated with acute abstinence, but also to the vulnerability to stressors observed during protracted abstinence in humans.

The neuroanatomical entity termed the extended amygdala thus may represent a neuroanatomical substrate for the negative effects on reward function produced by stress that help drive compulsive drug administration. As stated above, the extended amygdala is composed of the BNST, the CeA, and a transition zone in the medial subregion of the nucleus accumbens (shell of the nucleus accumbens). 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 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) (**Figure 3**).

However, perhaps even more compelling support of the integration of the extended amygdala and emotional states comes from the extensive data from the classical studies of Le Doux, which show a convergence of the

expression of the conditioned fear response in the CeA (Phelps & Le Doux 2005) and data showing that the central nucleus of the amygdala is a key component of neurocircuitry involved in emotional pain processing (Price 2002) (**Figure 3**). Studies on the neurocircuitry of fear conditioning show that auditory stimuli from the auditory cortex and pain from the somatosensory cortex converge on the lateral amygdala, which then projects to the CeA to elicit the various autonomic and behavioral responses to conditioned fear (Phelps & Le Doux 2005). The spino (trigemino)-ponto-amygdaloid pathway that projects from the dorsal horn to the mesencephalic parabrachial area to the CeA has been hypothesized to be involved in emotional pain processing (Bester et al. 1995). Together, these neurochemical studies (from addiction neurobiology) and neuroanatomical studies (from behavioral neuroscience) point to a rich substrate for the integration of emotional stimuli related to the "dark side of addiction," defined as the development of the aversive emotional state that drives the negative reinforcement of addiction.

The dark side of addiction (Koob & Le Moal 2005) is hypothesized to involve a long-term, persistent plasticity in the activity of neural circuits mediating motivational systems that derives from recruitment of antireward systems that drive aversive states. 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. Antireward is a concept developed based on the hypothesis that there are brain systems in place to limit reward (Koob & Le Moal 1997). As dependence and withdrawal develop, brain antireward systems such as CRF, norepinephrine, and dynorphin are recruited (**Figures 2** and **3**), producing aversive or stress-like states (Aston-Jones et al. 1999, Koob 2003a, Nestler 2001). At the same time, within the motivational circuits of the ventral striatum-extended amygdala, there are decreases in reward function. The combination of decreases in reward neurotransmitter function and recruitment of antireward systems provides a powerful source of negative reinforcement that contributes to compulsive drug-seeking behavior and addiction.

Neural Bases of Protracted Abstinence and Relapse

The dark side may also contribute to the critical problem in drug addiction of chronic relapse, wherein addicts return to compulsive drug taking long after acute withdrawal. Neurotransmitter/neuromodulator systems implicated in stress-induced relapse include CRF, glucocorticoids, and norepinephrine in stress-induced relapse, suggesting reactivation of antireward systems during relapse (Piazza & Le Moal 1996, See et al. 2003, Shaham et al. 2000). Thus, the dysregulations that comprise the dark side of drug addiction persist during protracted abstinence to set the tone for vulnerability to craving by activation of the drug-, cue-, and stress-induced reinstatement neurocircuits now driven by a reorganized and hypofunctioning prefrontal system (Le Moal 1995).

The preoccupation/anticipation 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. Although often linked to the construct of craving, craving per se has been difficult to measure in human clinical studies (Tiffany et al. 2000) and often does not correlate with relapse. Craving can be defined as memory of the rewarding effects of a drug superimposed upon a negative emotional state. Nevertheless, the stage of the addiction cycle in which the individual reinstates drug-seeking behavior after abstinence remains a challenging focus for identifying neurobiological mechanisms and developing medications for treatment.

Table 3 Craving

***Craving*:** a hypothetical construct that can be defined as the memory of the rewarding effects of a drug, superimposed upon a negative motivational state (Markou et al. 1998).
***Craving Type 1*:** craving induced by drugs or stimuli, such as environmental cues, that have been paired with drug self-administration.
***Animal models of Craving Type 1*:** drug or cue-induced reinstatement where administration of a drug previously self-administered or a cue previously paired with access to drug reinstates responding for a lever that has been extinguished.
***Craving Type 2*:** a state change characterized by anxiety and dysphoria or a residual negative emotional state that combines with Craving Type 1 situations to produce relapse to drug seeking.
***Animal models of Craving Type 2*:** stress-induced reinstatement of drug seeking after extinction, or increased drug taking in animals after a prolonged deprivation.

Animal models of craving can be divided into two domains: drug seeking induced by stimuli paired with drug taking, and drug seeking induced by an acute stressor or a state of stress (**Table 3**). Craving Type 1 animal models involve the use of drug-primed reinstatement and cue-induced reinstatement in animals that have acquired drug self-administration and then had been subjected to extinction of responding for the drug. Craving Type 2 animal models involve stress-induced reinstatement in animals that have acquired drug self-administration and then have been subjected to extinction of responding for the drug (Shippenberg & Koob 2002) (see sidebar Memory of Addiction: An Allostatic View).

Most evidence from animal studies suggests that drug-induced reinstatement is by the medial prefrontal cortex/nucleus accumbens/glutamatergic circuit modulated by dopamine in the frontal cortex (McFarland & Kalivas 2001). In contrast, neuropharmacological and neurobiological studies using animal models for cue-induced reinstatement involve a glutamatergic projection from the basolateral amygdala to the nucleus accumbens as a critical substrate with a possible feed-forward mechanism through the prefrontal cortex system involved in drug-induced reinstatement and dopamine modulation in the basolateral amygdala (Everitt & Wolf 2002, Weiss et al. 2001). In contrast, stress-induced reinstatement of drug-related responding in animal models appears to depend on the activation of both CRF and norepinephrine in elements of the extended amygdala (CeA and BNST) (Shaham et al. 2003, Shalev et al. 2002). Protracted abstinence, largely described in alcohol-dependence models, appears to involve overactive glutamatergic and CRF systems (De Witte et al. 2005, Valdez et al. 2002).

MEMORY OF ADDICTION: AN ALLOSTATIC VIEW

Craving has been defined as the memory of the pleasant rewarding effects of drugs of abuse superimposed on a negative emotional state (Koob 2000). In the context of the present treatise, the memory linked to drug cues (Craving Type 1) and mediated by the reward system becomes even more powerful when superimposed on a residual negative emotional state hypothesized to exist in protracted abstinence. The Craving Type 2 state also can be potentiated by associations formed from the linking of previously neutral stimuli with the motivational effects of drug withdrawal (Kenny et al. 2006). Interestingly, these Craving Type 2 associations appear to be processed via the same structures as those linked to Craving Type 1 associations (i.e., basolateral amygdala) (Schulteis et al. 2002). Thus, memory mechanisms may contribute to the allostatic state by associative mechanisms linked to both the reward and antireward systems.

VULNERABILITY TO ADDICTION

Individual Differences—Drug Seeking

Large individual differences and diverse sources of vulnerability account for the

passage from controlled social or occasional use to dependence and the propensity to enter the addiction cycle. The number of individuals meeting the criteria for drug addiction for a given drug as a function of ever having used the drug varies significantly between drugs, ranging from approximately 9% for marijuana to 31% for tobacco (Anthony et al. 1994). These differences may relate to the rate of access of the drug to the brain, which may be as basic as drug pharmacology and pharmacokinetics or as complicated as the social environmental access. In contrast, individual variables such as genetic background and environmental history, and their addition, correlation, or interaction, may also play key roles and may interconnect with availability (Rutter et al. 2006) (**Figure 4**).

Other factors that can contribute to individual vulnerability for drug use initiation or relapse are (*a*) comorbidity with psychopathological conditions, (*b*) temperamental and personality traits and genetic factors, developmental factors, and socioeconomic status, and (*c*) stress and life events. Each of these factors presumably interacts with the neurobiological processes involved in the sensitivity to drugs and in self-regulation and executive capacities. Initiation of use and abuse is more associated with vulnerability factors, whereas the movement to addiction is more associated with neurobiological factors (Glantz & Pickens 1992).

Individual Differences—Sensitivity to Antireward Neuroadaptations

Preadolescent and adolescent exposure to alcohol, tobacco, or drugs of abuse significantly increases the propensity for dependence in adulthood. Adolescents first intoxicated with alcohol at age 16 or younger are two to three times more likely to develop dependence (Hingson et al. 2003). Similar results have been reported for tobacco, where there is a relation between the age of initiation and the intensity of smoking later in life. It has been argued that regular smoking during adolescence raises the risk for adult smoking by a factor of 16 compared to nonsmoking during young ages (Chassin et al. 1990). Thus, early onset of drug use is a predictor of subsequent drug problems, and it is a linear relationship with age from 13–21 (Grant & Dawson 1998).

In humans, rates of drug and alcohol abuse and dependence are higher in males than in females (SAMHSA 2004). The relatively lower rate in females has long reflected the fact that women experience more social and educational constraints, which may serve as protective factors; however, evidence from recent surveys indicates that identical percentages of girls and boys had used alcohol, tobacco, and illicit drugs for the period of observation. Indeed, recent clinical evidence suggests that in comparison with males, females meet criteria for drug dependence more quickly and the course to addiction is faster. In addition, females differ in their vulnerability to relapse to drug use during abstinence periods and are more likely to relapse owing to stress and depression (see review in Lynch 2006).

Clear evidence also shows that adverse early experiences contribute to adolescent and adult psychopathology. Early experiences, prenatal or postnatal stress, and deleterious life events have pervasive and profound effects on adaptive abilities, and these changes reflect permanently altered gene expression—epigenetic changes—and their downstream effects on the HPA axis (Meaney & Szyf 2005). In rats, prenatally stressed offspring will present as adults with increased vulnerability to drug abuse, and the increased sensitivity correlates with a dysregulated HPA axis (Deminière et al. 1992). Preadolescence and adolescence are particularly sensitive periods that are affected by social and familial environments as well as social status, but individual responses to experiences during these periods also reflect a genetic contribution (Gunnar & Quevedo 2006) and the development of coping strategies (Skinner & Zimmer-Gembeck 2006). The ways in which this early exposure changes the brain to make it more sensitive to reward and stress dysregulation is largely unknown at this time.

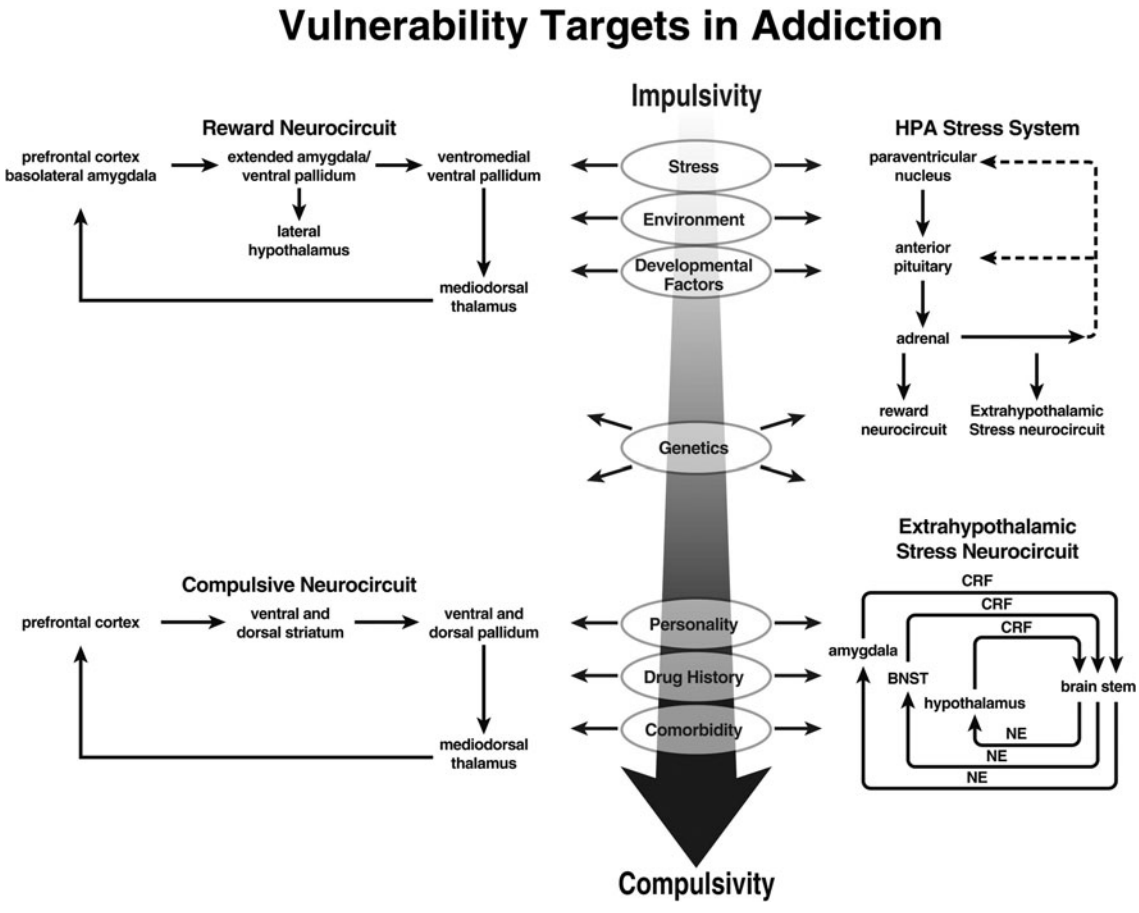


Figure 4

Brain circuits hypothesized to be recruited at different stages of the addiction cycle as addiction moves from positive reinforcement to negative reinforcement. The top left diagram illustrates an increase in the inactivity of a brain reward system circuit with a focus on the extended amygdala and an increase in the drug- and cue-induced reinstatement circuit with a focus on the prefrontal cortex and basolateral amygdala, which both drive positive reinforcement and impulsivity. The bottom left diagram illustrates a decrease in the brain reward circuit and an increase in the behavioral output or compulsivity circuit, both involved in driving negative reinforcement and compulsivity. The top right diagram refers to the hypothalamic-pituitary-adrenal axis, which (*a*) feeds back to regulate itself, (*b*) activates the brain reward neurocircuit, and (*c*) facilitates the extrahypothalamic stress neurocircuit. The bottom right diagram refers to the brain stress circuits in feed-forward loops. Superimposed on the transition from impulsivity to compulsivity are sources of vulnerability. Stress, development, and the environment are hypothesized to have an early influence in the process. Comorbidity, personality, and drug history are hypothesized to have a later influence. Genetics interacts at all levels with these factors both directly and through epigenetic mechanisms. BNST, bed nucleus of the stria terminalis; CRF, corticotropin-releasing factor; HPA, hypothalamic-pituitary-adrenal axis; NE, norepinephrine. Figure adapted from Koob & LeMoal (2004, 2006).

Psychopathological comorbidities are prominent factors in vulnerability for addiction and overlap significantly with the dark side perspective (**Figure 4**). A psychodynamic self-medication hypothesis deeply rooted in clinical research focuses on underlying developmental difficulties, emotional disturbances, structural factors, building of the

self, and personality organization (Khantzian 1985, 1990). Two critical elements, disordered emotions and disordered self-care, and two contributory elements, disordered self-esteem and disordered relationships, are hypothesized to be the basis for drug self-medication. Individuals are hypothesized to take drugs as a means to cope with painful and threatening emotions, in an attempt to medicate dysregulated affective states, unbearable painful affect, or an inability to express personal feelings and/or use appropriate language to express feelings. The choice of drug is hypothesized to be appropriate to the emotional state being self-medicated (Khantzian 1997). An extension of the Khantzian hypothesis is that excessive drug taking can cause the dysregulated emotional state that leads to each class of drugs being self-administered as an antidote to dysphoric states and act temporarily as a replacement for a defect in the psychological structure of these individuals caused by the drug (Koob 2003b).

From the perspective of comorbid psychiatric disorders, some of the strongest associations are found with mood disorders, antisocial personality disorders, and conduct disorders (Glantz & Hartel 1999). Approximately 35% of the subjects with dependence met lifetime criteria for mood disorders, 45% for anxiety, and 50% for conduct or antisocial disorders (Merikangas et al. 1998). Recent data (Grant et al. 2004a–c) show similar results (21%–29% for mood disorders, 22%–25% for anxiety, and 32%–70% for personality disorders).

A key neurobiological element involved in all of the above-identified vulnerabilities to drug use initiation and dependence is stress axis dysregulation. Drugs of abuse acutely activate the HPA response to stress, and as dependence develops, ultimately engage brain stress systems. These basic observations have led to the hypothesis that the brain and brain pituitary stress systems have a role in the initial vulnerability to drugs, the development of dependence, and the vulnerability to stress-induced relapse (Kreek & Koob 1998; Piazza & Le Moal 1996, 1998) (**Figure 4**). The enhanced propensity to self-administer drugs that is produced by stressors is linked to increased activation of the mesolimbic dopamine system mediated by stress hormone release. Glucocorticoids via glucocorticoid receptors facilitate dopamine-dependent behaviors by modulating dopamine transmission in the ventral striatum and the shell part of nucleus accumbens and thus may drive the extrahypothalamic CRF system (see above).

Genetic and Epigenetic Mechanisms

Genetic contributions to drug addiction face methodologically complex problems and interpretive issues as observed with other psychopathologies. Twin studies and analogous family studies with other sorts of biological relatives, coupled with epidemiological analyses, have provided evidence of genetic influences on addictions (Merikangas et al. 1998). However, there is no single gene for addiction. Genetic contributions to addiction result from complex genetic differences, ranging from alleles that control drug metabolism to hypothesized genetic control over drug sensitivity and environmental influences (Crabbe 2002, Rutter et al. 2006, Uhl & Grow 2004). Estimates from twin and adoption studies give ranges of 40% to 60% heritability. To date, molecular gene-finding methods and association and linkage studies are still inherently limited by relatively weak effects of specific genes and methodological problems.

In contrast, studies using genetic animal models have provided some insights into potential genetic targets from inbred strains, selected lines, quantitative trait loci mapping, and knockout methodology. Rats exposed to a mildly stressful situation display differential levels of reactivity, a measure of novelty seeking and disinhibition. High responders subsequently display higher responses to drugs of abuse than do low responders with a higher reactivity of the stress axis and a higher utilization of dopamine in the ventral striatum

(Piazza & Le Moal 1996, 1998). High-alcohol-preferring rats have been selectively bred to show high voluntary consumption of alcohol, increased anxiety-like responses, and numerous neuropharmacological phenotypes, such as decreased dopaminergic activity and decreased NPY activity. In an alcohol-preferring and alcohol-nonpreferring cross, a quantitative trait locus was identified on chromosome 4, a region to which the gene for NPY has been mapped. In the inbred preferring and nonpreferring quantitative trait loci analyses, loci on chromosomes 3, 4, and 8 have been identified that correspond to loci near the genes for the dopamine D_2 and serotonin $5HT_{1B}$ receptors (Carr et al. 1998).

Advances in molecular biology have led to the ability to systematically inactivate the genes that control the expression of proteins that make up receptors or neurotransmitter/neuromodulators in the central nervous system using the gene knockout and transgenic knock-in approaches. Although such an approach does not guarantee that these genes are the ones that convey vulnerability in the human population, they provide viable candidates for exploring the genetic basis of endophenotypes associated with addiction.

For opioids, the μ-opioid receptor has been identified as a key site for the acute reinforcing effects of opioids. Opiate (morphine) reinforcement as measured by conditioned place preference or self-administration is absent in μ-knockout mice, and there is no development of somatic signs of dependence to morphine in these mice. Knockout of the μ-opioid receptor also decreases nicotine reward, cannabinoid reward, and alcohol drinking in mice, which suggests a more global role of the μ-opioid receptor in drug reinforcement (Gaveriaux-Ruff & Kieffer 2002).

For ethanol, knockout studies have implicated numerous neurotransmitter systems in ethanol preference, again a measure of initial acute reinforcing effects of ethanol but not necessarily a measure of vulnerability to addiction. Known reward neurotransmitters (e.g., opioid, dopamine, GABA, and serotonin) and novel modulators (e.g., protein kinases and G-protein-activated inwardly rectifying K^+ channels) have been suggested by knockout studies to modulate ethanol preference (see Crabbe et al. 2006 for a review).

In studies involving psychostimulants, dopamine D_1 receptor knockout mice show no response to D_1 receptor agonists or antagonists and show a blunted response to the locomotor-activating effects of cocaine and amphetamine. D_1 knockout mice also are impaired in their acquisition of intravenous cocaine self-administration in comparison with wild-type mice. D_2 knockout mice have severe motor deficits and blunted responses to psychostimulants and opiates, but the effects on psychostimulant reward are less consistent. Dopamine-transporter knockout mice are dramatically hyperactive but also show a blunted response to psychostimulants. Thus, knockout studies suggest key roles for D_1 receptors and the dopamine transporter in the actions of psychomotor stimulants (Caine et al. 2002).

Finally, new vistas in vulnerability focus on the genetic-environment interface. These mechanisms, termed epigenetic, can maintain an acquired differentiated characteristic to strengthen synaptic connections and trace associations to long-term behavioral changes. A dramatic feature of addiction is the striking longevity of the behavioral abnormalities, which indicates that addiction processes produce long-term and probably permanent changes in specific circuitry in the brain. Such permanent changes in gene expression patterns may be obtained through permanent changes in chromatin remodeling without changes in DNA sequences. The concept of chromatin remodeling (an important determinant of gene expression) has provided one example of how stable changes in gene expression may be produced in neurons and glia to provoke long-lasting changes in physiology and behavior (Colvis et al. 2005, Levenson & Sweatt 2005). Thus, stress, trauma, prenatal stress, and early-life rearing experiences may alter addiction pathology later in life, via

Allostasis: stability through change

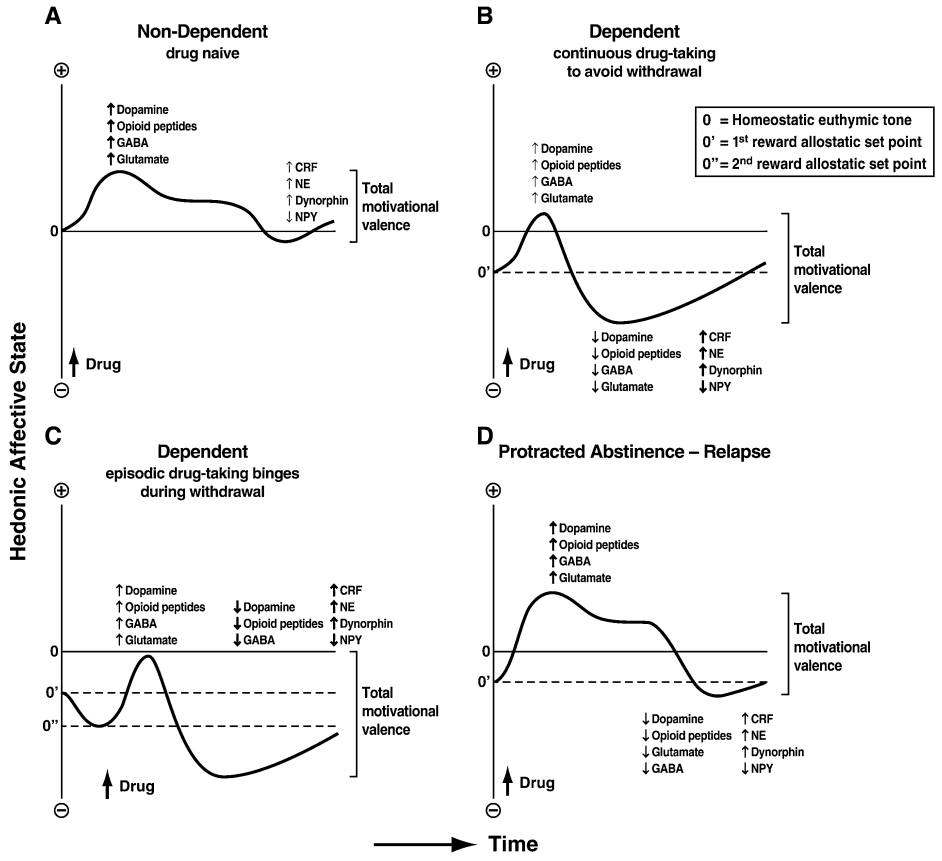
gene expression changes (Lemaire et al. 2006, Meaney 2001, Vallée et al. 1999, Weaver et al. 2004). Chronic use of drugs, presumably via regulation of intracellular signaling cascades, leads to the regulation of specific transcription factors, and regulation of these factors causes changes in histone acetylation and even DNA modification at particular target genes (Colvis et al. 2005). Such a schema expands the realm of factors that control individual susceptibility to addiction.

ALLOSTATIC VIEW OF ADDICTION

Homeostasis to Allostasis of the Reward System

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. 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, as with other chronic physiological disorders such as high blood pressure, worsens over time, is subject to significant environmental influences, and leaves a residual neuroadaptive trace that allows rapid "readdiction" even months and years after detoxification and abstinence. These characteristics of drug addiction have led us to reconsider drug addiction as not simply a homeostatic dysregulation of hedonic function and executive function, but rather as a dynamic break with homeostasis of these systems, termed allostasis.

Allostasis as a physiological concept was developed originally by neurobiologist Peter



Sterling and epidemiologist James Eyer to explain the basis for the increase in patterns of human morbidity and mortality associated with the baby boom generation (individuals born after World War II), and has been argued to provide a more parsimonious explanation of the neuroadaptive changes that occur in the brain reward and stress systems to drive the pathological condition of addiction (Koob & Le Moal 2001).

Allostasis is defined as stability through change. Allostasis is far more complex than homeostasis and has several unique characteristics that differ from homeostasis (Sterling & Eyer 1988). Allostasis involves a feed-forward mechanism rather than the negative feedback mechanisms of homeostasis. A feed-forward mechanism has many advantages because when increased need produces a signal in homeostasis, negative feedback can correct the need, but the time required may be long and the resources may not be available. In allostasis, however, there is continuous reevaluation of need and continuous readjustment of all parameters toward new set points. Thus, there is a fine matching of resources to needs.

Yet, it is precisely this ability to mobilize resources quickly and use feed-forward mechanisms that leads to an allostatic state and an ultimate cost to the individual that is known as allostatic load (McEwen 1998). An allostatic state can be defined as a state of chronic deviation of the regulatory system from its normal (homeostatic) operating level. An allostatic load can be defined as the "long-term cost of allostasis that accumulates over time and reflects the accumulation of damage that can

Figure 5

Conceptualization of the hedonic responses associated with drug intake at various stages of drug addiction correlated with changes in neurotransmitter systems within the extended amygdala circuitry hypothesized to mediate drug reward [arbitrarily defined as dopamine, opioid peptides, γ-aminobutyric acid (GABA), and glutamate] and antireward [arbitrarily defined as corticotropin-releasing factor (CRF), norepinephrine (NE), neuropeptide Y (NPY), and dynorphin]. (*A*) The hedonic response to an acute drug administration in a drug-naive individual with activity in neurotransmitter systems involved in reward predominating with a minor antireward opponent process-like response. (*B*) The hedonic response to an acute drug administration in a drug-Dependent (big "D"; see What is Addiction? section) individual while taking drug regularly. Initial activity in neurotransmitter systems involved in reward is followed by a decrease in function of neurotransmitter systems involved in reward and a major antireward opponent process-like response. *0′* (zero prime) refers to the change in hedonic set point produced by chronic dysregulation of reward neurotransmitters and chronic recruitment of antireward neurotransmitters. This change in hedonic set point is the allostatic state of reward dysregulation conceptualized in Koob & Le Moal (2001). (*C*) The hedonic response to an acute drug administration in a drug-Dependent individual during withdrawal. A major antireward opponent process-like response at the beginning of the time course is followed by modest activity in neurotransmitter systems involved in reward triggered by a drug administration during withdrawal. *0′* (zero prime) refers to the change in hedonic set point associated with the development of Dependence while still taking drug. *0″* (zero double prime) refers to the hedonic set point during peak withdrawal after cessation of drug taking. (*D*) The hedonic response to an acute drug administration in a formerly drug-Dependent individual during protracted abstinence. Note that a previously drug-Dependent individual was hypothesized to remain at a residual *0′* state, termed protracted abstinence. Robust activity in neurotransmitter systems involved in reward triggered by a drug administration is followed by an exaggerated antireward opponent process-like response (i.e., dysregulation of reward neurotransmitters and recruitment of antireward neurotransmitters) that drives the subject back to below *0′*. "Total motivational valence" refers to the combined motivation for compulsive drug use driven by both positive reinforcement (the most positive state above the *0* euthymic set point) and negative reinforcement (movement from the most negative state to *0* set point). The magnitude of a response is designated by the thickness of the arrows. The large upward arrow at the bottom of each panel refers to drug administration. The total time scale is estimated to be approximately eight hours. Figure modified with permission from Koob & Le Moal (2006).

lead to pathological states." Allostatic load is the consequence of repeated deviations from homeostasis that take on the form of changed set points that require increasing amounts of energy to defend, and ultimately reach, the level of pathology (McEwen 2000).

Temporal Dynamics of Allostasis

The failure of allostatic change to habituate or not to shut off is inherent in a feed-forward system that is in place for rapid, anticipated challenge to homeostasis. However, the same physiological mechanism that allows rapid response to environmental challenge becomes the engine of pathology if adequate time or resources are not available to shut off the response. Thus, for example, chronically elevated blood pressure is "appropriate" in an allostasis model to meet environmental demand of chronic arousal but is "certainly not healthy" (Sterling & Eyer 1988). Another example of such a feed-forward system is illustrated in the interaction between CRF and norepinephrine in the brainstem and basal forebrain that could lead to pathological anxiety (Koob 1999). Allostatic mechanisms also have been hypothesized to be involved in maintaining a functioning brain reward system that has relevance for the pathology of addiction (Koob & 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 antireward or brain stress systems (**Figure 5**). Repeated challenges, as in the case of 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 described as an allostatic state. This state represents a combination of chronic elevation of reward set point fueled by decreased function of reward circuits, recruitment of antireward systems, loss of executive control, and facilitation of stimulus-response associations, all of which lead to the compulsivity of drug seeking and drug taking (see below).

Addiction as a Model of Psychopathology of Motivational Processes: "Nondrug Addictions"

Allostatic-like changes in reward function also may apply to any number of pathological states that are challenged by external and internal events, including depression and drug addiction. Other impulse control disorders, some listed by the DSM-IV, have characteristics similar to drug addiction in several domains. Such disorders include those with documented diagnostic criteria such as kleptomania, trichotillomania, pyromania, and compulsive gambling. Other disorders such as compulsive shopping, compulsive sexual behavior, compulsive eating, compulsive exercise, and compulsive computer use have fallen outside the realm of accepted diagnostic disorders. However, many of these disorders take on characteristics of impulsivity and compulsivity and have common face validity with the phenotype of addiction. For example, many of these disorders are associated with self-regulation failures from a social psychology perspective (Baumeister et al. 1994), and many have characteristic impulsivity problems associated with impulse control disorders and can move to compulsivity as the disorder progresses. A case can be made that there is strong face validity with the addiction cycle of preoccupation/anticipation (craving), binge/intoxication, and withdrawal/negative affect stages for compulsive gambling, compulsive shopping, compulsive eating, compulsive sexual behavior, and compulsive exercise.

Neurobiological studies are under way with these "nondrug addictions" and suggest some similarities with the neurobiological profiles associated with drug addiction. For example, there is a decrease in dopamine D_2 receptor activity in compulsive eating (Wang et al. 2002) and gambling (Comings et al. 1996, Zack & Poulos 2007) and some evidence

of frontal cortex deficits in compulsive gambling (Tanabe et al. 2007). Stressors also have been shown to affect relapse in these disorders (Ledgerwood & Petry 2006). Refinement of the human neuropsychological and neurobiological measures will further elucidate whether the same neurobiological circuits related to emotional function dysregulated in drug addiction are dysregulated in nondrug addiction.

SUMMARY POINTS

1. A key element of addiction is the development of a negative emotional state during drug abstinence.
2. The neurobiological basis of the negative emotional state derives from two sources: decreased reward circuitry function and increased antireward circuitry function.
3. The antireward circuitry function recruited during the addiction process can be localized to connections of the extended amygdala in the basal forebrain.
4. Neurochemical elements in the antireward system of the extended amygdala have as a focal point the extrahypothalamic corticotropin-releasing factor system.
5. Other neurotransmitter systems implicated in the antireward response include norepinephrine, dynorphin, neuropeptide Y, and nociceptin.
6. Vulnerability to addiction involves multiple targets in both the reward and antireward system, but a common element is sensitization of brain stress systems.
7. Dysregulation of the brain reward system and recruitment of the brain antireward system are hypothesized to produce an allostatic emotional change that can lead to pathology.
8. Nondrug addictions may be hypothesized to activate similar allostatic mechanisms.

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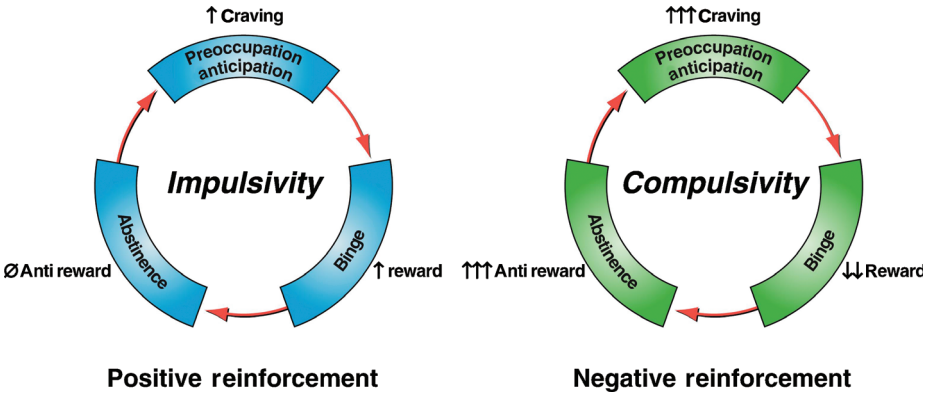

Figure 1

Diagram describing the addiction cycle that is conceptualized as having three major components: preoccupation/anticipation ("craving"), binge/intoxication, and withdrawal/negative affect. Note that as the individual moves from the impulsivity stage to the compulsivity stage, there is a shift from positive reinforcement associated with the binge/intoxication component to negative reinforcement associated with the withdrawal/negative affect component. Craving is hypothesized to increase in the compulsivity stage because of an increase in the need state for the drug that is driven not only by loss of the positive reinforcing effects of the drugs (tolerance), but also by generation of an antireward state that supports negative reinforcement.

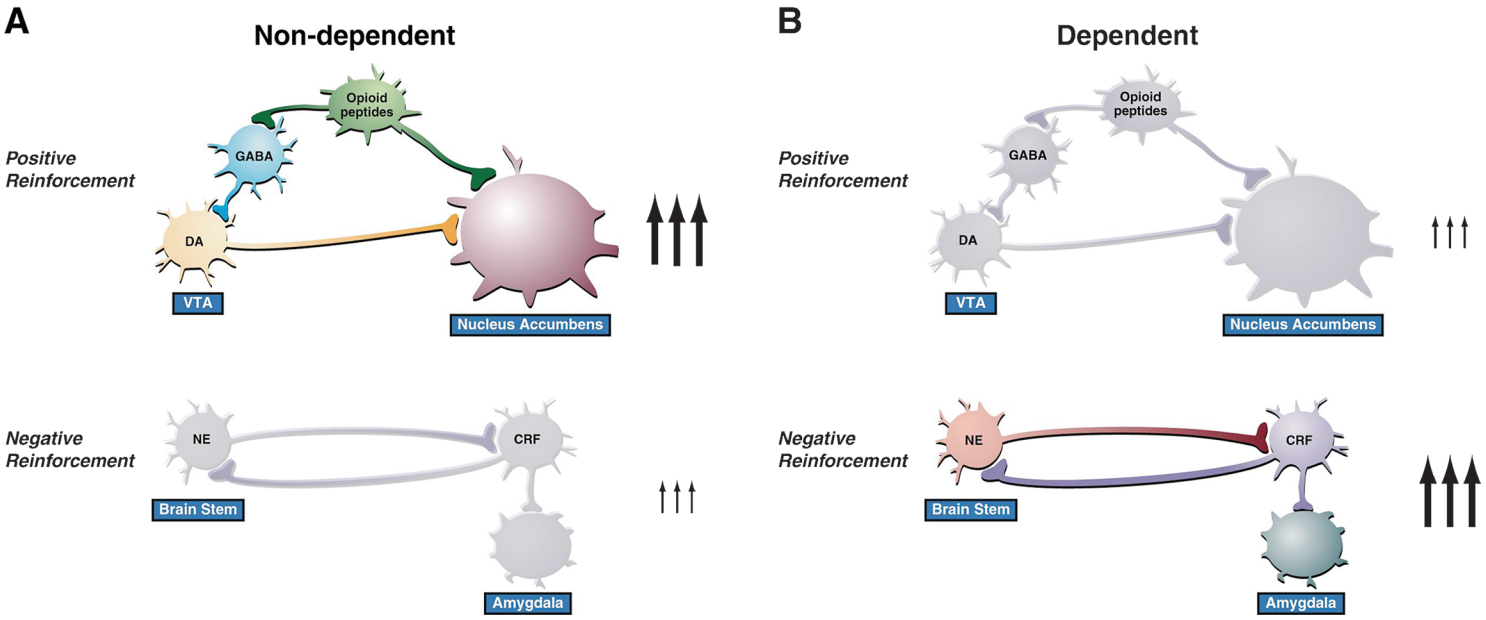

Figure 2

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 and opioid peptide neurons that intersect at both the ventral tegmental area 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, gamma-aminobutyric acid; NE, norepinephrine; VTA, ventral tegmental area. Figure modified with permission from Nestler (2005).

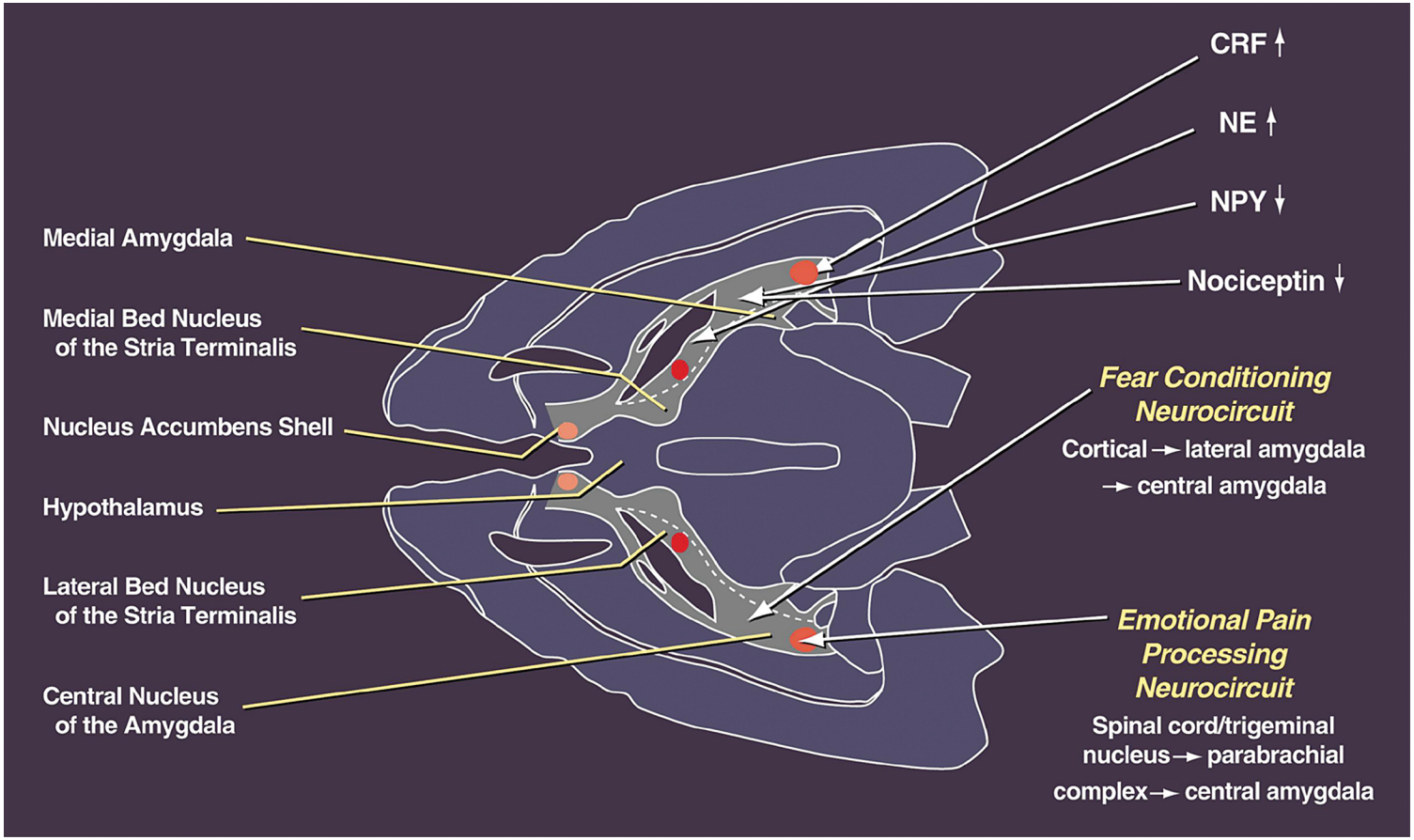

Figure 3

Construct of the extended amygdala illustrated in a horizontal plane of a rodent brain. Key elements include the central nucleus of the amygdala, the bed nucleus of the stria terminalis, and a transition zone in the medial (shell) part of the nucleus accumbens. The extended amygdala receives significant projections from the prefrontal cortex and insular cortex and sends efferent projections to the lateral hypothalamus and ventral tegmental area. Neuropharmacological components that contribute to the constructs of the "dark side" include activation of CRF in the central nucleus of the amygdala, activation of norepinephrine in the bed nucleus of the stria terminalis, and decreases in function of neuropeptide Y and nociceptin in the central nucleus of the amygdala. The central nucleus of the amygdala is also a key structure integrating neurocircuitry of the expression fear and conditioned fear as well as emotional pain responses. CRF, corticotropin-releasing factor; NE, norepinephrine; NPY, neuropeptide Y. Brain schematic modified with permission from Heimer & Alheid (1991).

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