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Review

Neurobiological mechanisms in the transition from drug use to drug dependence

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Abstract

Drug addiction is a chronic relapsing disorder characterized by compulsive drug intake, loss of control over intake, and impairment in social and occupational function. Animal models have been developed for various stages of the addiction cycle with a focus in our work on the motivational effects of drug dependence. A conceptual framework focused on allostatic changes in reward function that lead to excessive drug intake provides a heuristic framework with which to identify the neurobiologic mechanisms involved in the development of drug addiction. Neuropharmacologic studies in animal models have provided evidence for the dysregulation of specific neurochemical mechanisms in specific brain reward and stress circuits that provide the negative motivational state that drives addiction. The allostatic model integrates molecular, cellular and circuitry neuroadaptations in brain motivational systems produced by chronic drug ingestion with genetic vulnerability, and provides a new opportunity to translate advances in animal studies to the human condition.
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Keywords: Vulnerability; Dysregulation; Drug dependence Allostasis

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1. Addiction

Substance dependence [8] or *addiction*, is a chronically relapsing disorder that is characterized by a compulsion to seek and take a drug (loss of control in limiting intake), and impairment in social and occupational function. Both clinically and in experimental animals, the occasional or limited use of an abusable drug is distinct from repeated drug use and the development of addiction. From a psychiatric perspective, drug addiction has aspects of both impulse control disorders and compulsive disorders (Fig. 1). 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 possibly regret, self-reproach or guilt following the act [8]. 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. 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. Drug addiction has been conceptualized as a disorder that progresses from impulsivity to compulsivity in a cycle of addiction comprised of three stages: preoccupation/anticipation, binge/intoxication, and withdrawal/negative affect (Fig. 2). Different theoretical perspectives ranging

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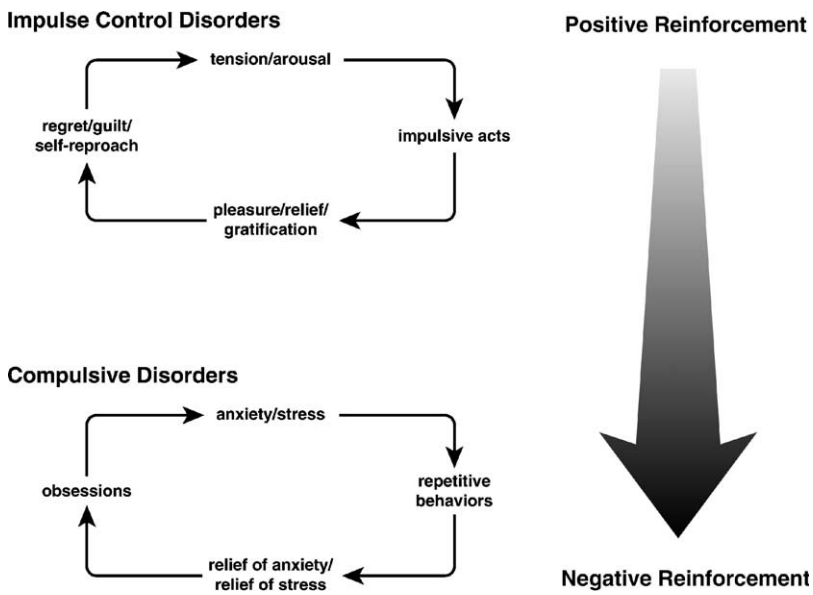

Fig. 1. Diagram showing stages of impulse control disorder and compulsive disorder cycles related to the sources of reinforcement. In impulse control disorders, an increasing tension and arousal occurs before the impulsive act, with pleasure, gratification or relief during the act. Following the act, there may or may not be regret or guilt. In compulsive disorders, there are recurrent and persistent thoughts (obsessions) that cause marked anxiety and stress followed by repetitive behaviors (compulsions) that are aimed at preventing or reducing distress [8]. Positive reinforcement (pleasure/gratification) is associated more closely with impulse control disorders. Negative reinforcement (relief of anxiety or relief of stress) is more closely associated with compulsive disorders (taken with permission from Ref. [22]).

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 [23].

The purpose of current neuroscience research in our laboratory is to understand the cellular and molecular mechanisms that mediate the transition from occasional, controlled drug use to the loss of behavioral control over drug-seeking and drug-taking that defines chronic addiction [23]. Emergence of a negative emotional state (e.g. dysphoria, anxiety, irritability) when access to the drug is prevented (defined here as dependence) [24] has been associated with this transition from drug use to addiction.

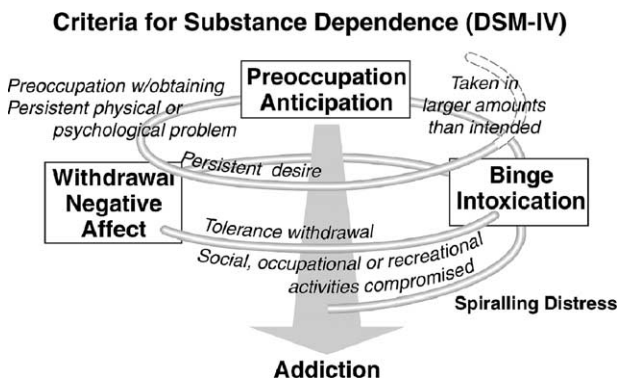

Fig. 2. Diagram describing the spiraling distress/addiction cycle from a psychiatric/addiction perspective. The figure shows the three major components of the addiction cycle with the different criteria for substance dependence for the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, incorporated (taken with permission from Ref. [23]).

Indeed, some have argued that the development of such a negative affective state can define addiction:

> The notion of dependence on a drug, object, role, activity or any other stimulus-source requires the crucial feature of negative affect experienced in its absence. The degree of dependence can be equated with the amount of this negative affect, which may range from mild discomfort to extreme distress, or it may be equated with the amount of difficulty or effort required to do without the drug, object, etc. [41]

2. Dysregulated reward associated with drug withdrawal

Cocaine is a powerfully reinforcing psychostimulant with high addiction potential. In humans, chronic use of cocaine often is associated with a binge-like, uncontrollable pattern of use (in the sense that the binge is not easily stopped) with tolerance and acute withdrawal. This cocaine withdrawal in outpatients is characterized by severe depressive symptoms combined with irritability, anxiety, and anhedonia, lasting several hours to several days (i.e. the 'crash'), and may be one of the major motivating factors in the maintenance of the cocaine-dependence cycle [14,23]. Withdrawal from chronic self-administration of cocaine in rats results in an increase in intracranial self-stimulation (ICSS) reward thresholds that are dose- and time-dependent [29], an effect that is opposite to that of acute cocaine [30], but similar to that of withdrawal from chronic amphetamine

administration [27,37]. Similar results have been observed with acute withdrawal from opiates [44], alcohol [43], nicotine [11] and tetrahydrocannabinol (THC) [13] and are related to the amount of drug that had been administered before withdrawal (Fig. 3) [29].

3. Prolonged access to cocaine as a model of the transition to addiction

Animal procedures of cocaine self-administration provide a framework with which to model the transition from drug use to drug addiction. Animal models of escalation of cocaine intake have been established and are beginning to provide insight into the neurobiological changes that may lead to vulnerability to escalation in drug intake and relapse.

Historically, animal models of cocaine self-administration involved the establishment of stable behavior from day to day to allow the reliable interpretation of data provided by within-subject designs aimed at exploring the neuropharmacological and neurobiological bases of the reinforcing effects of acute cocaine. Typically, after acquisition of self-administration, rats allowed access to cocaine for 3 h or less per day establish highly stable levels of intake and patterns of responding between daily sessions. To explore the possibility that differential access to

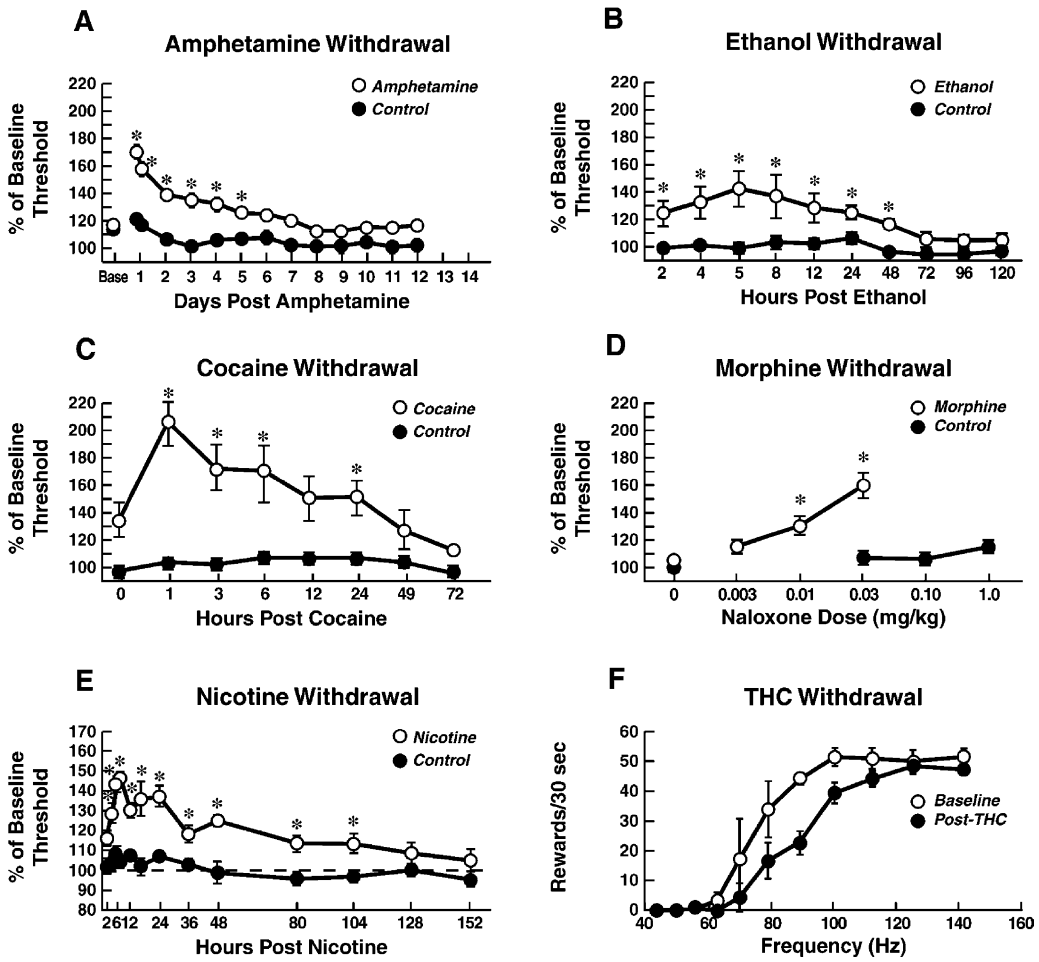

Fig. 3. (A) Mean ICSS thresholds (±SEM) during amphetamine withdrawal (10 mg/kg/day for 6 days). Data are expressed as a percentage of the mean of the last five baseline values prior to drug treatment. Asterisks (*) indicate statistically significant differences from the saline control group ($p < 0.05$) (taken with permission from Ref. [37]). (B) Mean ICSS thresholds (±SEM) during ethanol withdrawal (blood alcohol levels achieved: 197.29 mg%). Elevations in thresholds were time-dependent. Asterisks (*) indicate statistically significant differences from the control group ($p < 0.05$) (taken with permission from Ref. [43]). (C) Mean ICSS thresholds (±SEM) during cocaine withdrawal 24 h following cessation of cocaine self-administration. Asterisks (*) indicate statistically significant differences from the control group ($p < 0.05$) (taken with permission from Ref. [29]). (D) Mean ICSS thresholds (±SEM) during naloxone-precipitated morphine withdrawal. Asterisks (*) indicate statistically significant differences from the control group ($p < 0.05$) (taken with permission from Ref. [44]). (E) Mean ICSS thresholds (±SEM) during spontaneous nicotine withdrawal following surgical removal of osmotic minipumps delivering nicotine hydrogen tartrate (9 mg/kg/day) or saline. Asterisks (*) indicate statistically significant differences from the control group ($p < 0.05$) (data adapted with permission from Ref. [11]). (F) Mean ICSS thresholds (±SEM) during withdrawal from an acute 1.0 mg/kg dose of Δ^9-THC. Withdrawal significantly shifted the reward function to the right (indicating diminished brain reward) (taken with permission from Ref. [13]). Note that because different equipment systems and threshold procedures were used in the collection of the above data, direct comparisons among the magnitude of effects induced by these drugs cannot be made.

intravenous cocaine self-administration in rats may produce different patterns of drug intake, rats were allowed access to intravenous self-administration of cocaine for 1 or 6 h/day. One-hour access (short access or ShA) to intravenous cocaine per session produced low and stable intake as observed previously. In contrast, with 6-h access (long access or LgA) to cocaine, drug intake gradually escalated over days (Fig. 4) [2]. In the escalation group, there was increased intake during the first hour of the session as well as sustained intake over the entire session and an upward shift in the dose-effect function suggesting an increase in hedonic set point. When animals were allowed access to different doses of cocaine, both the LgA and ShA animals titrated their cocaine intake, but the LgA rats consistently self-administered almost twice as much cocaine at any dose tested, further suggesting an upward shift in the set point for cocaine reward for the escalated animals [3].

To test the hypothesis that escalation in cocaine intake is accompanied by a chronic perturbation in brain reward homeostasis, the effect of differential exposure to cocaine self-administration on brain stimulation reward thresholds was examined as described above (i.e. 1-h ShA and 6-h LgA groups). The animals first were prepared with bipolar electrodes in either the right or left posterior lateral hypothalamus. One week post-surgery, rats were trained to respond for electrical brain stimulation. ICSS thresholds measured in μA were assessed according to a discrete-trial current-threshold procedure [19,30,31]. During the initial experimental phase, rats were allowed to self-administer cocaine during only 1 h on a fixed-ratio 1 schedule after which two balanced groups with the same weight, cocaine intake and ICSS reward thresholds were formed. During the escalation phase, the ShA group had access to cocaine self-administration for only 1 h/day and the LgA group for 6 h/day. Another group of rats was exposed to the same experimental manipulations, except that they were not exposed to cocaine self-administration. ICSS reward thresholds were measured in all rats two times a day, 3 and 17–22 h after each daily self-administration session (ShA and LgA rats) or the control procedure (drug-naive rats). Each ICSS session lasted approximately 30 min. ICSS thresholds progressively elevated for LgA rats, but not for ShA and control rats, across successive self-administration sessions [1]. Elevation in baseline ICSS thresholds temporally preceded and was highly correlated with escalation in cocaine intake. Post-session elevations in ICSS reward thresholds failed to return to baseline levels before the onset of each subsequent self-administration session, thereby deviating more and more from control levels. The progressive elevation in reward thresholds was associated with the dramatic escalation in cocaine consumption that was observed previously. Within 12 days, the first-hour cocaine intake in LgA rats rose to a level almost two times greater than that observed in ShA rats. Total intake in LgA

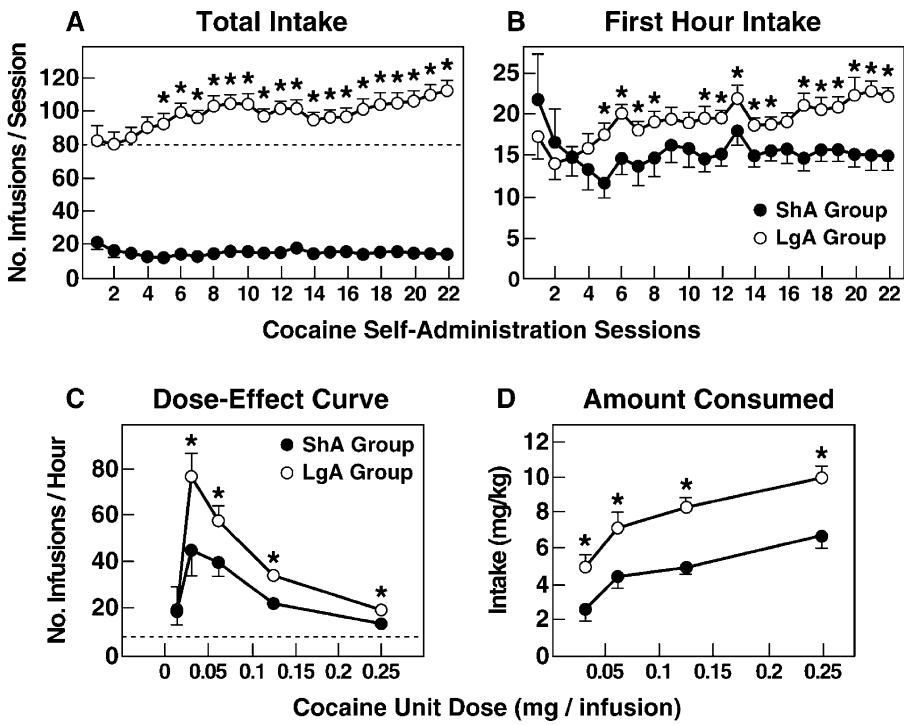

Fig. 4. Effect of drug availability on cocaine intake (mean ± SEM). (A) In long-access (LgA) rats ($n = 12$) but not in short-access (ShA) rats ($n = 12$), mean total cocaine intake started to increase significantly from session 5 (*$p < 0.05$; sessions 5–22 compared to session 1) and continued to increase thereafter (*$p < 0.05$; session 5 compared to sessions 8–10, 12, 13, 17–22). (B) During the first hour, LgA rats self-administered more infusions than ShA rats during session 5–8, 11, 12, 14, 15 and 17–22 ($p < 0.05$). (C) Mean infusions (± SEM) per cocaine dose tested. LgA rats took significantly more infusions than ShA rats at doses of 31.25, 62.5, 125 and 250 μg/infusion ($p < 0.05$). (D) After escalation, LgA rats took more cocaine than ShA rats in the 1-h session regardless of the dose ($p < 0.05$). *$p < 0.05$ (Student's t test after appropriate one-way and two-way analysis of variance) (taken with permission from Ref. [2]).

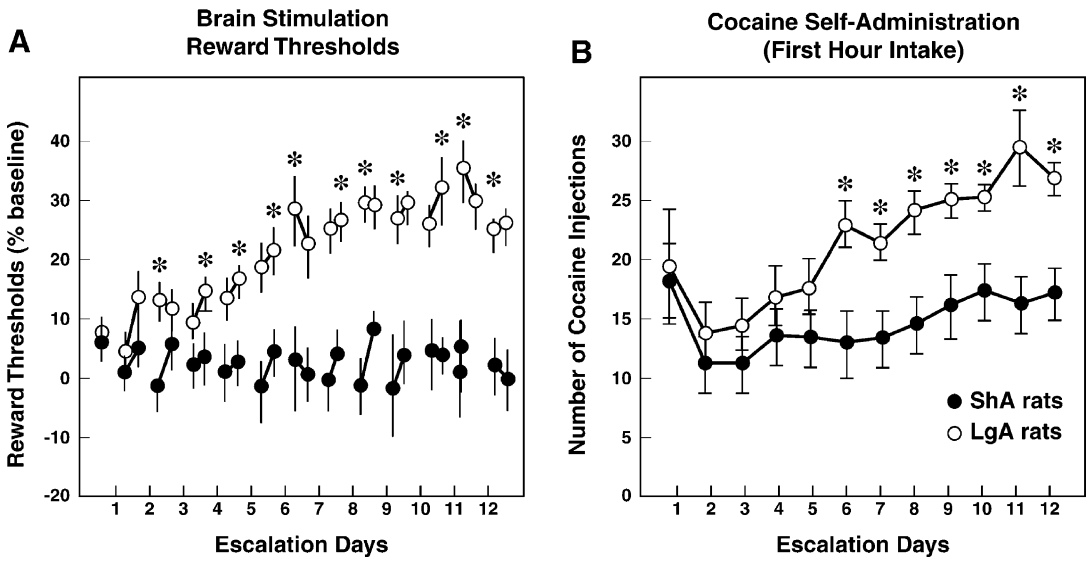

Fig. 5. Relationship between elevation in ICSS reward thresholds and cocaine intake escalation. (A) Percent change from baseline ICSS thresholds. (B) Number of cocaine injections earned during the first hour of each session. Asterisks (*) indicate statistically significant differences compared to drug-naive and/or ShA rats ($p < 0.05$) (taken with permission from Ref. [1]).

rats also increased almost continually over the same time period from 75.5 (± 13.9) to 125 (± 4.3) cocaine injections (Fig. 5). The gradual elevation in ICSS reward thresholds associated with drug intake escalation did not result from a general inability to respond, as demonstrated by the lack of differences between groups in response latencies for ICSS [1]. Finally, the rate of elevation in reward thresholds measured 1 h before the daily access to cocaine (i.e. slope of elevation) was highly correlated with the escalation in total cocaine intake ($r = 0.78$, $p < 0.01$). Finally, after escalation had occurred, an acute cocaine challenge facilitated brain reward responsiveness to the same degree as before but resulted in higher absolute brain reward levels in LgA compared to ShA rats. These results demonstrate that the elevation in brain reward thresholds following prolonged access to cocaine failed to return to baseline levels between repeated, prolonged exposure to cocaine self-administration (i.e. residual hysteresis), thus creating a greater and greater elevation in 'baseline' ICSS thresholds. These data provide compelling evidence for brain reward dysfunction in escalated cocaine self-administration that cannot be attributed readily to tolerance. Thus, these data provide strong support for a hedonic allostasis model of drug addiction.

The elevations in reward threshold begin rapidly and can be observed within a single session of self-administration. Self-administration of only 10 or 20 cocaine injections (0.25 mg/injection; equivalent to 4.94 ± 0.23 and 9.88 ± 0.46 mg/kg) lowered reward thresholds 15 min later, but had no effect at 2, 24 or 48 h after administration. Forty cocaine injections (19.64 ± 0.94 mg/kg) lowered reward thresholds 15 min later, but significantly elevated thresholds 2 and 24 h later, indicating withdrawal-like reward deficits. Finally, self-administration of 80 cocaine injections (39.53 ± 1.84 mg/kg) tended to elevate thresholds when measured 15 min later, and led to significant threshold elevations 2 and 48 h after administration. These data demonstrate that cocaine self-administration increased or decreased brain reward function depending on the amount of cocaine self-administered and time after self-administration. These data add support to the hypothesis that both the positive and negative effects of self-administered cocaine on brain reward function contribute to cocaine's addictive properties (Fig. 6) [20].

4. Prolonged access to heroin as a model of the transition to addiction

The transition from stable to escalated levels of cocaine self-administration has been shown to depend upon duration of drug availability. The generality of this phenomenon was assessed by studying the effects of duration of availability on heroin self-administration. Two groups of rats were trained on a 1-h continuous access schedule of self-administration, after which access to heroin (40 μg/injection) was increased to 11 h in one group (LgA group), or kept to 1 h in the other group (ShA group). After 18 sessions on this regimen, both ShA and LgA rats were tested for extinction and stress-induced reinstatement of heroin-seeking behavior. In LgA rats, both total and first hour intake gradually escalated over time. After escalation, LgA rats were slower to extinguish heroin-seeking behavior and responded more to the reinstating effect of stress after extinction. These findings demonstrated that (1) the escalation process in drug consumption is common to both opiate and stimulant self-administration, and (2) escalation in heroin consumption is associated with a persistent increase in the motivation for taking heroin [5].

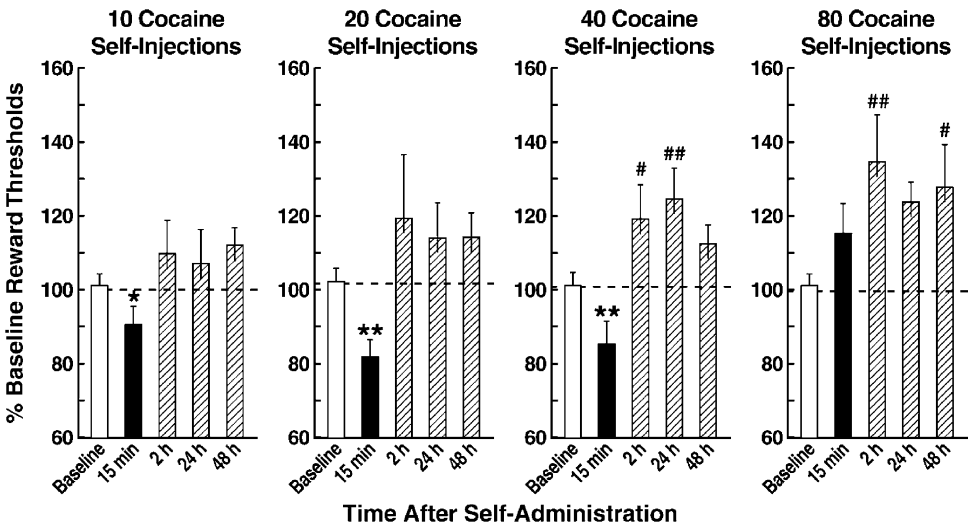

Fig. 6. Effects of various numbers of cocaine self-administration injections on brain reward thresholds. Rats were allowed to self-administer 10, 20, 40 and 80 injections of cocaine (0.25 mg/injection), and ICSS thresholds were measured 15 min and 2, 24 and 48 h after the end of each intravenous cocaine self-administration session ($n = 11$). The horizontal dotted line in each plot represents 100% of baseline levels. All data are presented as mean ± SEM percentage of baseline ICSS thresholds. $*p < 0.05$, $**p < 0.01$ compared to baseline; paired t-test. $\#p < 0.05$, $\#\#p < 0.01$ compared to baseline; Fisher's LSD test after a statistically significant effect in the repeated-measures analysis of variance (taken with permission from Ref. [20]).

A subsequent study characterized heroin intake using 23-h sessions of heroin self-administration. Male Wistar rats were trained to nose-poke for food and water administration in 23-h sessions for 5 days prior to and following recovery from surgical implantation of jugular catheters. A lever was introduced, and rats were allowed to self-administer heroin (0.06 mg/kg/0.1 ml infusion/s; fixed-ratio 1; 20-s time out) for 5–6 weeks. Total heroin intake increased markedly by week 3, peaked by week 5, and thereafter remained at a stable level. Then, to verify dependence, somatic signs of heroin withdrawal were examined by precipitated withdrawal using a naloxone injection (1 mg/kg, subcutaneously) immediately after the active phase (6 pm–6 am) of the 23-h session. Naloxone produced a robust precipitation of withdrawal signs. Immediately following this withdrawal test, rats were allowed to continue self-administering heroin in 23-h sessions. The animals continued to show an escalated pattern of heroin intake. Then, the influence of the partial opiate agonist buprenorphine on this behavior was examined using an injection of buprenorphine (0, 0.01, 0.04, and 0.2 mg/kg, subcutaneously) 15 min prior to the active phase. Pretreatment with buprenorphine produced a dose-dependent reduction in heroin intake, with the largest reduction by the 0.2 mg/kg dose. These results suggest that rats will self-administer heroin to the point of producing dependence, and that heroin self-administration in dependent animals may be attenuated in this model by a partial opiate agonist. Changes in patterns of teroin, food and water intake in this model can provide an independent measure of the onset of dependence that will prove useful for analysis of the effects of neuro pharmacological treatments on the development and maintenance of dependence (Chen et al., unpublished results).

5. Neuropharmacological and molecular mechanisms involved in escalated cocaine intake with extended access

Cocaine increases the availability of monoamines at the synaptic level in the brain, and much is known about the neuropharmacological bases of the reinforcing effects of acute administration of cocaine. Early work suggested a primary role for the mesolimbic dopamine system that projects to the basal forebrain [21]. More recent evidence suggests that both dopaminergic and serotonergic terminals within a basal forebrain macrostructure termed the extended amygdala (central nucleus of the amygdala, bed nucleus of the stria terminalis [BNST], and a transition area in the region of the shell of the nucleus accumbens) play an important role in the rewarding effects of acute cocaine [25]. Significant evidence also shows that these systems can be dysregulated by prolonged self-administration of cocaine yielding an opponent-process-like change in the neurochemistry of the extended amygdala. Continuous self-administration of cocaine for 12 h produces decreases in extracellular levels of dopamine and serotonin in the nucleus accumbens as measured by in vivo microdialysis [36]. Further, there are dramatic increases in extracellular levels of the brain stress neurotransmitter corticotropin-releasing factor (CRF) in the central nucleus of the amygdala during acute withdrawal [40]. Both of these changes are hypothesized to contribute to the neurochemical representation of the 'opponent loop' conceptualized by Solomon [45].

Neuropharmacological studies of the basis for escalated cocaine intake currently are under intense investigation. One hypothesis is that pre-synaptic release of dopamine may by 'sensitized' in escalated animals. To investigate

possible alterations in cocaine-induced elevations of nucleus accumbens dopamine during cocaine self-administration by escalated (LgA) and non-escalated (ShA) rats, a microdialysis study was conducted in rats given access to 1 h (ShA) and 6 h (LgA) of cocaine per day. After 25 cocaine sessions, the self-administration behavior in the LgA group had escalated in a manner such that these animals consumed significantly more cocaine during the first hour of self-administration than did animals in the ShA group. Each animal was prepared with a microdialysis probe into the nucleus accumbens. Animals previously given 6-h access to cocaine per day consumed significantly more cocaine during the microdialysis test session than did animals previously given only 1-h access per day. Nucleus accumbens dopamine levels in the LgA group were maintained consistently at a significantly higher and stable level during cocaine self-administration than were dopamine levels in the ShA group. Analysis of the cocaine content of these samples revealed a nearly identical ratio between the percent increase in dialysate dopamine levels to dialysate cocaine levels, indicating that the dopaminergic response to cocaine was similar between the two treatment groups (Fig. 7). Together these data indicate that there is no enhanced functioning of the pre-synaptic dopamine system relative to the amount of cocaine present in the nucleus accumbens in escalated animals [4].

In a separate study, after escalation was established, both ShA and LgA rats were tested with different subcutaneous doses of cis-flupenthixol, a dopamine D_1/D_2 receptor antagonist (Ahmed and Koob, unpublished results). In both groups, increasing doses of cis-flupenthixol first produced an increase in the rate of cocaine self-administration and then a dramatic suppression of behavior. This biphasic dose-effect function which replicates previous findings [12] was dramatically shifted to the left in LgA rats compared to ShA rats, thereby decreasing the threshold dose at which behavior was suppressed. These data point to a change in dopamine receptor function after escalation. Further studies are needed to determine the nature of the receptor change (D_1 or D_2/D_3 or $D_1/D_2/D_3$ synergism) and the brain site of the receptor change (possibly within the extended amygdala).

To explore the possibility that multiple neurochemical systems may be involved in the differential expression of self-administration in ShA versus LgA rats, Affymetrix DNA arrays were used for transcriptional profiling in escalating cocaine self-administering rats versus non-escalating and drug-naive animals. A small number of transcripts changed specifically with escalation, while many more changed in both escalating and non-escalating rats. Most of the changes were observed in the lateral hypothalamus, an output of the nucleus accumbens. Fewer changes were seen in the prefrontal cortex, nucleus accumbens and amygdala. Many of the transcripts altered in escalation in the lateral hypothalamus encode for proteins involved in developmental processes such as neurite extension and synaptogenesis, while others are involved in neuronal excitability and glutamatergic transmission. Examples were *N*-syndecan, expressed on growing axons; neuroligin 3, a synaptic adhesion molecule; Na^+, K^+-ATPase isoforms implicated nerve regeneration; and MAP1a. Expression of NR2D also was induced in the lateral hypothalamus of escalating rats. This developmental *N*-methyl-D-aspartate subunit has slow kinetics that could facilitate synaptic strengthening in development. Additionally, transgenic mice expressing NR2D in the adult have reduced hippocampal plasticity and amygdala kindling. A reduction in cellular excitability in the lateral hypothalamus of escalating rats also is suggested by increased expression of selected potassium channels. Transcripts for the chemokine fractalkine and platelet-derived growth factor (both of which are trophic,

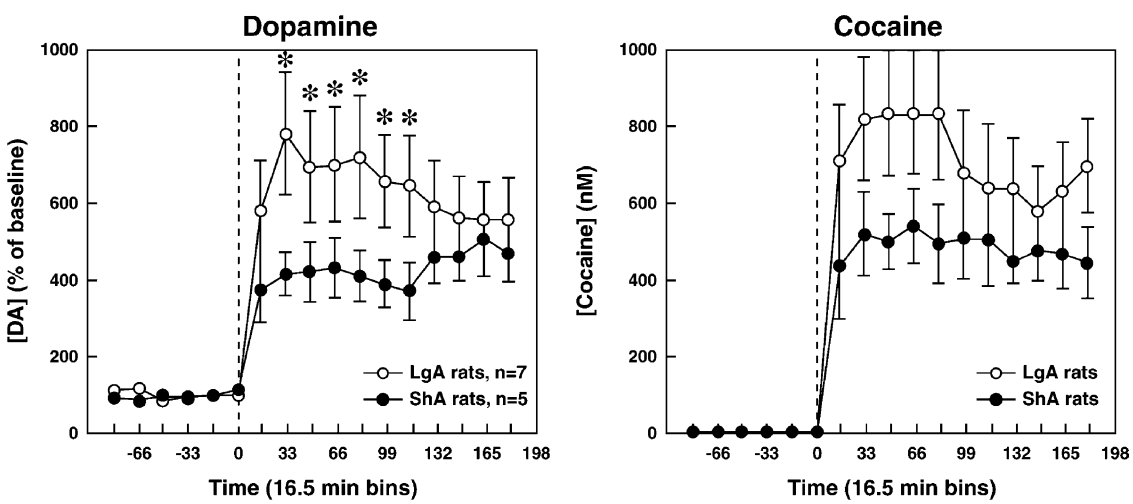

Fig. 7. Effects of escalated levels of cocaine self-administration on nucleus accumbens dopamine (A) and cocaine (B) levels in ShA rats ($n = 5$) and LgA rats ($n = 7$) after escalation (mean ± SEM). Forty-eight hours after the last session of self-administration, both ShA and LgA rats were allowed to self-administer intravenous cocaine (0.25 mg/injection) during a 3 h session. The vertical dotted line indicates the onset of self-administration. Asterisks (*) indicate statistically significant differences from ShA rats ($p < 0.05$) (taken with permission from Ref. [4]).

neuroprotective and reduce glutamate neurotransmission) were increased in the lateral hypothalamus. Together these results point to a crucial role for the lateral hypothalamus in the loss of control over cocaine intake and suggest a process of synaptic rearrangement accompanied by reduced neuronal excitability and firing rate (Ahmed et al., unpublished results).

Recent studies have provided support for the role of CRF in the motivational effects associated with cocaine and opiate dependence. Using the defensive burying test, an 'anxiogenic-like' effect following chronic cocaine treatment was demonstrated. This 'anxiety-like' response was attenuated by intracerebroventricular pretreatment with the CRF antagonist D-Phe-CRF_{12-41}, with the highest dose of the CRF antagonist reversing the observed anxiogenic-like response [9]. These data suggest that brain CRF may be involved in the development of anxiety-like responses related to cocaine withdrawal and could be important for the development of cocaine dependence. In a separate study, in order to evaluate the role of brain CRF in negative motivational states associated with opiate dependence, the effects of suppression of amygdala CRF systems on the characteristic aversive state of precipitated withdrawal in morphine-dependent rats was examined. In a place conditioning paradigm, administration of the CRF antagonist α-helical-CRF_{9-41} bilaterally into the central nucleus of amygdala reversed the withdrawal-induced conditioned place aversion produced by injection of the opiate antagonist methylnaloxonium into the same site [18]. These results indicate that suppression of intra-amygdala CRF systems weakens the aversive stimulus properties of conditioned opiate withdrawal, and suggest a general role for CRF in coordinating behavioral responses to negative motivational effects of drug withdrawal.

6. Neuroanatomical substrates for escalated drug intake

The term 'extended amygdala' has been formulated to represent a neuroanatomical macrostructure in the basal forebrain that shares similarities in morphology, neurochemistry and connectivity. It is composed of several basal forebrain structures: the BNST, the central and medial amygdala, and a transition zone in the posterior medial part of the nucleus accumbens (e.g. shell) [17]. This system receives afferents from limbic and olfactory cortices and projects heavily to the hypothalamus and midbrain. As such, the extended amygdala links the basal forebrain to the classical reward systems of the lateral hypothalamus via the medial forebrain bundle reward system. A guiding hypothesis is that many of the neuropharmacological effects of drugs, including their reinforcing effects, may be mediated by this circuitry. Neuroadaptive changes in this extended amygdala circuit also may lead to the aversive effects and dysregulated reward system hypothesized to be the motivation for transition to drug addiction [25].

Further examination of this anatomical system reveals two major divisions: the *central division* and the *medial division*. These two divisions have important differences in structure and afferent and efferent connections [6] that may be of heuristic value for the present review. The central division of the extended amygdala includes the central nucleus of the amygdala, the central sublenticular extended amygdala, the lateral BNST, and a transition area in the medial and caudal portions of the nucleus accumbens and medial portions of the olfactory tubercle. The lateral BNST, which forms a key element of the central division of the extended amygdala, has high amounts of dopamine, norepinephrine, NPY and CRF terminals, and CRF and galanin cell bodies, and receives afferents from the prefrontal cortex, insular cortex and amygdalopiriform area. Notable efferents from the central division include the lateral hypothalamus, ventral tegmental area, tegmental pedunculopontine nucleus, and various brain stem nuclei. The medial division of the extended amygdala includes the medial BNST, medial nucleus of the amygdala, and the medial sublenticular extended amygdala [6]. The medial BNST contains high amounts of vasopressin, is sexually dimorphic, and receives afferents from structures such as the infralimbic cortex, entorhinal cortex, and subiculum [7,10,15,26,32,38]. Notable efferents from the medial division include the ventral striatum, the ventromedial hypothalamus, and mesencephalic central gray (Fig. 8).

Evidence suggests that the lateral BNST may be involved in receiving cortical information and regulating the hypothalamic pituitary adrenal axis [16], whereas the medial BNST may be more involved in sympathetic and physiological responses and receiving olfactory information [28,35,39]. To date, most manipulations resulting in modification of the reinforcing effects of drugs of abuse have been in the central nucleus of the amygdala and the lateral nucleus of the BNST [25].

7. An allostatic physiological framework for the transition from drug use to drug addiction

Using the arousal/stress continuum as their physiological framework, Sterling and Eyer [47] argued that homeostasis was not adequate to explain the physiological basis for changes in patterns of human morbidity and mortality associated with modern life. *Allostasis*, simply defined as the process of achieving stability through change, originally was formulated as a hypothesis to explain such mind-body interactions [47].

The concept of allostasis has several unique characteristics that give it more explanatory power than homeostasis in characterizing the physiological responses required in an ever changing environment. These characteristics include a continuous re-evaluation of the organism's needs and

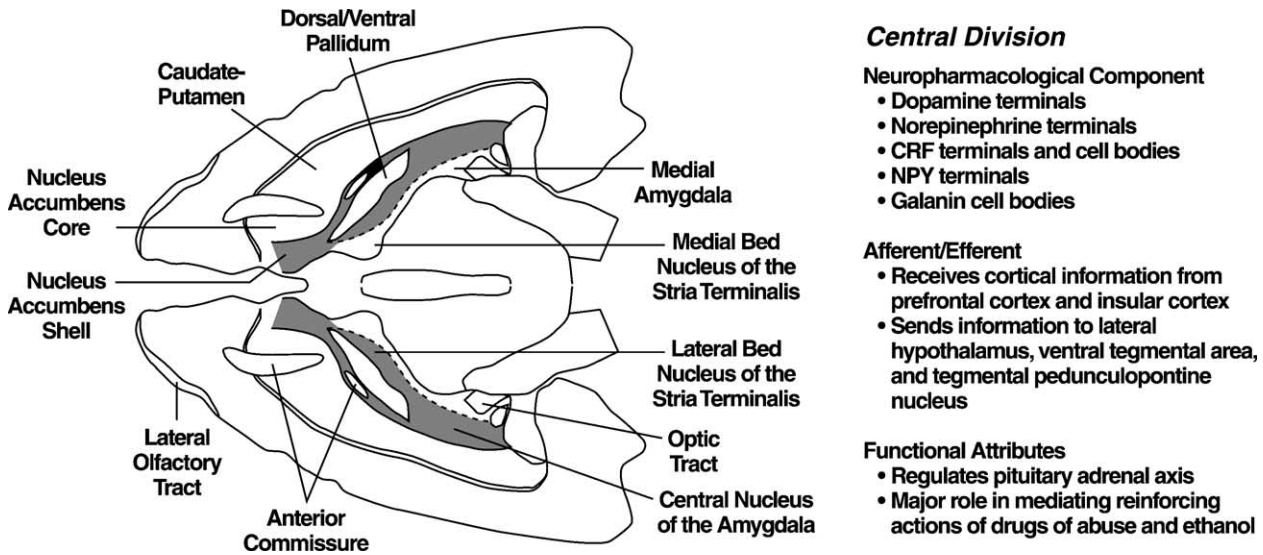

Fig. 8. Diagram illustrating the *central division* of the extended amygdala, its neuropharmacological components, afferent and efferent connections, and functional attributes. Based on anatomical integration of Refs. [6,17] (taken with permission from Ref. [22]).

continuous readjustments to new set points depending on demand. Homeostatic systems, in contrast, cannot anticipate need or make adjustments in advance, but in fact react only to deviations from the normal range by forcing a parameter to a specific set point (e.g. the average or 'normal' set point) [47]. The remarkable capacity to adjust and fine tune physiological responses in an allostatic system, however, has a 'dark side' when arousal (demand) becomes excessive.

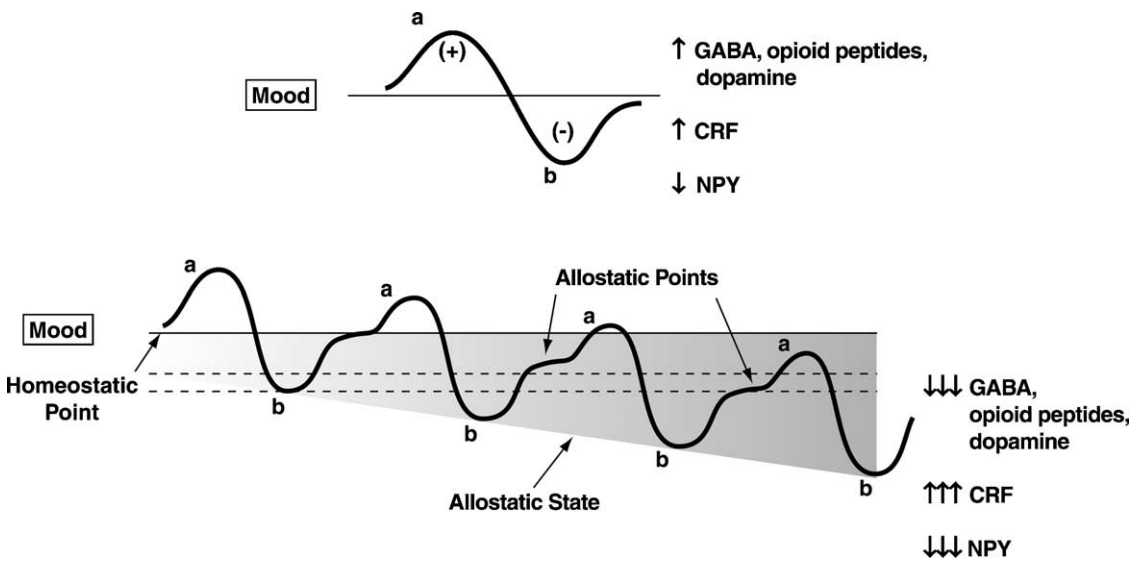

Fig. 9. Diagram illustrating an extension of Solomon and Corbit's [46] opponent-process model of motivation to outline the conceptual framework of the allostatic hypothesis. Both panels represent the affective response to the presentation of a drug. (Top) This diagram represents the initial experience of a drug with no prior drug history. The *a-process* represents a positive hedonic or positive mood state, and the *b-process* represents the negative hedonic or negative mood state. The affective stimulus (state) has been argued to be a sum of both an a-process and a b-process. An individual experiencing a positive hedonic mood state from a drug of abuse with sufficient time between re-administering the drug is hypothesized to retain the a-process. In other words, an appropriate counteradaptive opponent-process (b-process) that balances the activational process (a-process) does not lead to an allostatic state. (Bottom) The changes in the affective stimulus (state) in an individual with repeated frequent drug use that may represent a transition to an allostatic state in the brain reward systems and, by extrapolation, a transition to addiction. Note that the apparent b-process never returns to the original homeostatic level before drug-taking is reinitiated, thus creating a greater and greater allostatic state in the brain reward system. In other words, the counteradaptive opponent-process (b-process) does not balance the activational process (a-process) but in fact shows a residual hysteresis. While these changes are exaggerated and condensed over time in the present conceptualization, the hypothesis here is that even during post-detoxification, a period of 'protracted abstinence', the reward system is still bearing allostatic changes. In the non-dependent state, reward experiences are normal, and the brain stress systems are not greatly engaged. During the transition to the state known as addiction, the brain reward system is in a major underactivated state while the brain stress system is highly activated. DA, dopamine; CRF, corticotropin-releasing factor; GABA, γ-aminobutyric acid; NPY, neuropeptide. The following definitions apply: *allostasis*, the process of achieving stability through change; *allostatic state*, a state of chronic deviation of the regulatory system from its normal (homeostatic) operating level; *allostatic load*, the cost to the brain and body of the deviation, accumulating over time, and reflecting in many cases pathological states and accumulation of damage (modified with permission from Ref. [24]).

Allostasis as a concept was extended to the domains of stress and the hypothalamic pituitary axis by Bruce McEwen [33,34], and anxiety disorders and central CRF by Schulkin et al. [42]. The concept of *allostatic load* was introduced, which is the price the body pays to adapt to adverse psychosocial or physical situations [34]. *Allostatic state* was introduced to explain the concept of how movement of physiological parameters out of the homeostatic range could lead to a chronic condition of heightened vulnerability to pathology such as alcoholism [24]. An allostatic state can be defined as a state of chronic deviation of the regulatory systems from their normal state of operation with establishment of a new set point.

Changes in the brain systems associated with the development of motivational aspects of drug withdrawal are hypothesized to be a major source of potential allostatic changes that drive the transition from drug use to drug addiction. Withdrawal from drugs produces changes in reward neurotransmitters opposite to those experienced during positive reinforcement in specific elements of reward circuitry associated with the extended amygdala, as well as recruitment and disruption of brain stress systems that oppose the hedonic effects of drugs of abuse. In this context, allostasis from the drug addiction perspective is the process of maintaining apparent reward function stability through changes in reward and stress system neurocircuitry. Decreases in the function of dopamine, serotonin and opioid peptides are hypothesized to contribute to a shift in reward set point as well as recruitment of the brain stress systems such as CRF (Fig. 9) [24]. All of these changes are hypothesized to be focused on a dysregulation of function within the neurocircuitry of the basal forebrain macrostructure of the extended amygdala.

The challenge for future studies is to characterize the specific elements within the extended amygdala critical for the allostatic changes that dysregulate the neurocircuitry and how molecular events within these elements can in effect 'load' the system toward dysregulation. Particularly intriguing will be future studies of the interaction of the extended amygdala with the motivational regulatory systems of the lateral hypothalamus.

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