Neuroadaptive mechanisms of addiction: studies on the extended amygdala

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Abstract

A conceptual structure for drug addiction focused on allostatic changes in reward function that lead to excessive drug intake provides a heuristic framework with which to identify the neurobiologic neuroadaptive mechanisms involved in the development of drug addiction. The brain reward system implicated in the development of addiction is comprised of key elements of a basal forebrain macrostructure termed the extended amygdala and its connections. Neuropharmacologic studies in animal models of addiction have provided evidence for the dysregulation of specific neurochemical mechanisms not only in specific brain reward circuits (opioid peptides, γ-aminobutyric acid, glutamate and dopamine) but also recruitment of brain stress systems (corticotropin-releasing factor) that provide the negative motivational state that drives addiction, and also are localized in the extended amygdala. The changes in the reward and stress systems are hypothesized to maintain hedonic stability in an allostatic state, as opposed to a homeostatic state, and as such convey the vulnerability for development of dependence and relapse in addiction.

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Keywords: Addiction; Amygdala; Corticotropin-releasing factor; Allostasis; Reward; Ethanol; Cocaine

1. Animal models of addiction

Drug addiction, also known as substance dependence (American Psychiatric Association, 1994), is a chronically relapsing disorder that is characterized by: (1) compulsion to seek and take the drug, (2) loss of control in limiting intake and (3) emergence of a negative emotional state (e.g., dysphoria, anxiety, irritability) when access to the drug is prevented (defined here as dependence; Koob and Le Moal, 1997). Both clinically and preclinically in experimental animals, the occasional but limited use of an abusable drug is distinct from escalated drug use and the emergence of chronic drug dependence. An important goal of current research is to understand the neuropharmacological/neuroadaptive mechanisms within specific neurocircuits that mediate the transition between occasional, controlled drug use and the loss of behavioral control over drug seeking and drug taking that defines chronic addiction (Koob and Le Moal, 1997).

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 is felt at the time of committing the act, and following the act, there may or may not be regret, self-reproach or guilt (American Psychiatric Association, 1994). 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 collapsed cycle of addiction comprised of three stages: preoccupation/anticipation, binge intoxication and withdrawal/negative affect (Fig. 2). 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 and Le Moal, 1997).

Much of the recent progress in understanding the mechanisms of addiction has derived from the study of animal models of addiction on specific drugs such as opiates, stimulants and alcohol. While 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 systems, models of psychological constructs such as positive and negative reinforcement and models of different stages of the addiction cycle (Koob and Le Moal, 1997; Koob et al., 1998a). While much focus in animal studies has been on the synaptic sites and transductive mechanisms in the nervous system on which drugs of abuse act initially to produce their positive reinforcing effects, new animal models of the negative reinforcing effects of dependence have been developed and are beginning to be used to explore how the nervous system adapts to drug use. This review will focus in particular on the neuropharmacological mechanisms that change in the transition from drug taking to drug addiction with a focus on the motivational effects of withdrawal and protracted abstinence (Koob and Le Moal, 1997).

2. Animal models of motivational effects of withdrawal

Initial drug use is thought to arise from the neurochemical actions causing the positive reinforcing effects of a drug. However, the transition from occasional drug use to drug addiction has been hypothesized to require an additional source of reinforcement—the reduction of the aversive (negative) emotional state arising from repeated use (Koob and Le Moal, 2001). Here, drug taking presumably removes the dysphoria, anxiety, irritability and other un-
pleasant feelings produced by drug abstinence. Other somatic physical signs, such as tremor, temperature changes and sweating, which also reflect the state of dependence, are hypothesized to have little if any motivating properties for drug use (Koob, 1996; Koob and Le Moal, 1997, 2001). Indeed, one of the defining features of drug addiction has been characterized as the establishment of such a negative emotional state (Russell, 1976). Consistent with this hy-

Fig. 3. (A) Mean ICSS thresholds (± S.E.M.) 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 control group (p < 0.05). (Taken with permission from Paterson et al., 2000.) (B) Mean ICSS thresholds (± S.E.M.) 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 Schulteis et al., 1995.) (C) Mean ICSS thresholds (± S.E.M.) 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 Markou and Koob, 1991.) (D) Mean ICSS thresholds (± S.E.M.) during naloxone-precipitated morphine withdrawal. Asterisks (*) indicate statistically significant differences from the control group (p < 0.05). (Taken with permission from Schulteis et al., 1994.) (E) Mean ICSS thresholds (± S.E.M.) 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 Epping-Jordan et al., 1998b.) (F) Mean ICSS thresholds (± S.E.M.) during withdrawal from an acute 1.0 mg/kg dose of Δ⁶-9-tetrahydrocannabinol (THC). Withdrawal significantly shifted the reward function to the right (indicating diminished brain reward). (Taken with permission from Gardner and Vorel, 1998.) Note that because different equipment systems and threshold procedures were used in the collection of the above data, direct comparisons among these drugs cannot be made.
Hypothesis, all major drugs of abuse have been found to produce a negative emotional state in dependent humans during acute abstinence. The combination of the positive reinforcing effects of the drugs with reduction of the negative emotional states of drug abstinence provides a powerful motivational force for the compulsive drug taking that characterizes addiction.

One likely mechanism for this negative emotional state may be a reduction in brain reward function. In studies employing intracranial self-stimulation (ICSS) behavior, to
directly study brain reward circuits, animals that have been made chronically dependent show increased reward thresholds reflecting decreased reward during withdrawal (for reviews, see Koob and Le Moal, 1997; Koob et al., 1993; Koob, 1996; Fig. 3). These decreases in reward have been observed following the withdrawal from psychomotor stimulants, opiates, ethanol, tetrahydrocannabinol (THC) and nicotine, and are dose-related to the amount of drug that had been administered before withdrawal (Schulteis et al., 1994; Epping-Jordan et al., 1998b; Gardner and Vorel, 1998).

### 3. Extended amygdala: neuroanatomical construct for integrating changes in reward associated with drug dependence

A neuroanatomical entity termed the extended amygdala (Heimer and Alheid, 1991) may represent a common anatomical substrate for acute drug reward and the negative effects of compulsive drug administration on reward function. The extended amygdala is comprised of the bed nucleus of the stria terminalis (BNST), the central nucleus of the amygdala and a transition zone in the medial subregion of the nucleus accumbens (shell of the nucleus accumbens; Heimer and Alheid, 1991). Each of these regions share certain cytoarchitectural and circuitry similarities (Heimer and Alheid, 1991). The extended amygdala receives numerous afferents from limbic structures such as the basolateral amygdala and hippocampus and sends efferents not only to the medial part of the ventral pallidum but also a large projection to the lateral hypothalamus, thus further defining the specific brain areas that interface classical limbic (emotional) structures with the extrapyramidal motor system.

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**Fig. 6.** (A) Effects of SCH23390 (0, 0.5, 1.0, 2.0 µg/0.33 µl/side = 0, 1.0, 2.0, 4.0 total dose) microinjected into the accumbens shell (AccSh), central amygdala (CeA) or dorsal striatum (CPu) on cocaine self-administration (0.25 mg i.v.; FR5 TO20 s) in separate groups of rats (values are group means and standard errors, n = 6/brain region) in the first 20 min of the session. Asterisks indicate significantly different from vehicle injection (*p < 0.05; **p < 0.01) by Neuman–Keuls a posteriori test following significant main effect of dose by ANOVA. (Taken with permission from Caine et al., 1995.) (B) Effects of SCH23390 (0, 0.4, 0.8, 1.6, 3.2 µg/0.33 µl/side = 0, 0.8, 1.6, 3.2, 6.4 µg total bilateral dose) microinjected into the dorsal lateral bed nucleus of the stria terminalis on cocaine self-administration (0.25 mg/injection i.v.; FR5 TO20 s) within the first 20 min of the session. Values are group means and standard errors (n = 7). Asterisks (*) indicate statistically significant differences from vehicle (saline) injection (p < 0.05) by post hoc comparisons using Bonferroni correction following the observation of a significant main effect of drug using a within-subjects analysis of variance. (Taken with permission from Epping-Jordan et al., 1998a.)

**Fig. 7.** The effect of SR 95531 injections into the central nucleus of the amygdala and the bed nucleus of the stria terminalis on responding for ethanol (EtOH) and water. Data are expressed as the mean ± S.E.M. numbers of responses for ethanol and water during 30 min sessions for each injection site. Asterisks indicate significant differences from the corresponding saline control values (*p < 0.05, **p < 0.01 for ethanol responses; *p < 0.05 for water responses; adjusted means test). (Taken with permission from Hyytia and Koob, 1995.)
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 (Alheid et al., 1995) 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. These structures have close interconnections with the lateral rather than the medial hypothalamus and interconnections with the ventral tegmental area. Prominent afferents to the central division include the posterior basolateral amygdala, subparafascicular thalamus and insular and medial frontal cortices (Fig. 4).

The medial division of the extended amygdala includes the medial BNST, medial nucleus of the amygdala and the medial sublenticular extended amygdala. These structures have been defined largely as the medial division by their network of intrinsic associative connections and extensive relations to the medial hypothalamus (Alheid et al., 1995). Prominent afferents to the medial division include the anterior olfactory nucleus, agranular insular cortex, accessory olfactory nucleus and infralimbic cortex, ventral subiculum and basomedial amygdala. Notable efferents from the medial division include the ventral striatum, the ventromedial hypothalamus and the mesencephalic central gray. The lateral BNST, which forms a key element of the central division of the extended amygdala, has high amounts of dopamine and norepinephrine terminals, CRF terminals, CRF cell bodies, neuropeptide Y (NPY) terminals and galanin cell bodies, and receives afferents from the prefrontal cortex, insular cortex and amygdalopiriform area. The medial BNST, in contrast, contains high amounts of vasopressin, is sexually dimorphic and receives afferents from structures such as the infralimbic cortex, entorhinal cortex and subiculum (Dong et al., 2001; McDonald et al., 1999; Kozicz, 2001; Gray and Magnuson, 1992; Phelix and Paull, 1990; Allen et al., 1984).

4. Role of elements of the extended amygdala in the positive reinforcing effects of drugs of abuse

The structures comprising the extended amygdala may further define the neural substrates for the acute reinforcing actions of drugs of abuse (Koob, 1992, 1996; Koob et al., 1998b). Acute administration of all the major drugs of abuse produces increases in extracellular levels of dopamine in the...
shell of the nucleus accumbens (Pontieri et al., 1995). The ventromedial shell of the nucleus also expresses high levels of dopamine D3 receptor mRNA (Diaz et al., 1995), and the shell of the nucleus accumbens, the BNST and the central nucleus of the amygdala are particularly sensitive to the cocaine antagonist activity of a dopamine D1 antagonist (Caine et al., 1995; Epping-Jordan et al., 1998a; Figs. 5 and 6). The central nucleus of the amygdala also has a role in ethanol reinforcement. Microinjection of γ-aminobutyric acid (GABA) antagonists or opioid peptide antagonists into the central nucleus can attenuate lever pressing for oral ethanol (Hyytia and Koob, 1995; Heyser et al., 1999; Figs. 7 and 8).

5. Role of elements of the extended amygdala in the negative reinforcing effects of dependence

Perhaps more intriguing is recent evidence that the extended amygdala may be an important substrate for the changes in the reward system associated with dependence. In animals dependent on ethanol, microinjections of previously ineffective doses of a GABA agonist into the central nucleus of the amygdala decreased ethanol self-administration (Roberts et al., 1996), suggesting that the GABAergic system has been altered to become more responsive to agonists during the course of dependence (Fig. 9). Thus, the same neurochemical components in the extended amygdala...
dala involved in acute drug actions may become compromised during the development of dependence.

6. Recruitment of neurotransmitters associated with the aversive stress-like effects of drug abstinence

Additional neurochemical systems also may be engaged within the neurocircuitry of the extended amygdala (Koob and Bloom, 1988) in an attempt to overcome the chronic presence of the perturbing drug and to restore normal function despite the presence of drug. Increases in extracellular levels of CRF in the central nucleus of the amygdala have been observed during withdrawal from ethanol, opiates, cocaine and THC (Koob et al., 1994; Fig. 10). More compelling is the recruitment of a motivational role for CRF activity in animals while dependent. Ethanol is a powerful modulator of “stress” systems—both acute and chronic ethanol activate the hypothalamic–pituitary–adrenal axis, and this appears to be the result of release of CRF in the hypothalamus to in turn activate the classic neuroendocrine stress response (Rivier et al., 1984; Rasmussen et al., 2000). Recent evidence suggests that chronic ethanol also may interact with an extensive extrahypothalamic, extraneuroendocrine CRF system implicated in behavioral responses to stress (for a review, see Koob et al., 1994). The anxiogenic-like effect of ethanol withdrawal can be reversed by intracerebral administration of a CRF antagonist into the central nucleus of the amygdala (Rassnick et al., 1993). Increases in extracellular

Fig. 11. Effects of the nonselective CRF antagonist d-Phe-CRF12–41 on responding for ethanol and water 2 h following chronic ethanol vapor exposure. Control rats were exposed to air vapor. Rats were microinjected i.c.v. with 0–10 μg of d-Phe-CRF12–41 (n=10–12 per group) using a within-subjects Latin square design 2 h after removal from the vapor chambers. The number of lever presses for ethanol and water ± S.E.M. was measured 10 min after injection. Following the initial test session, rats were re-exposed to ethanol vapor or air, and the procedures were repeated until the Latin square design was complete (*p<0.05, Tukey’s test, compared to controls). (Taken with permission from Valdez et al., 2002.)

Fig. 12. (A) Mean (±S.E.M.) difference between pre- and post-conditioning scores before and after pairing of a particular environment with intra-amygdala administration of methylnaloxonium and/or the CRF partial agonist α-helical CRF9–41 in nondependent (n=15) and morphine-dependent rats (methylnaloxonium alone, n=12; methylnaloxonium + α-helical CRF9–41, n=17; α-helical CRF9–41 alone, n=12; *p<0.05, **p<0.005, pre- vs. post-conditioning scores within group; †p<0.05). (Taken with permission from Heinrichs et al., 1995). (B) Effects of infusing noradrenergic drugs into the bed nucleus of the stria terminalis on conditioned place aversion and somatic signs of opiate withdrawal. Effects of the β-noradrenergic receptor antagonist cocktail betaxolol/ICI 118,551 on place aversion and somatic signs. All data are expressed as mean ± S.E.M. (n=6–8 animals per dose; *p<0.05, analysis of variance followed by Fisher’s PLSD for multiple comparisons). ACSF, artificial cerebrospinal fluid; R-Prop, R-propranolol; S-Prop, S-propranolol. (Taken with permission from Delfs et al., 2000.)
levels of CRF are observed in the amygdala and BNST during ethanol withdrawal (Merlo-Pich et al., 1995; Olive et al., 2002). Even more compelling is the observation that a competitive CRF antagonist that has no effect on ethanol self-administration in nondependent rats effectively eliminates excessive drinking in dependent rats (Valdez et al., 2002; Fig. 11).

Motivational effects of opiate withdrawal also can be modified by blocking CRF receptors and norepinephrine receptors in the extended amygdala. Opiate-dependent rats show a robust place aversion when injected with low doses of opioid antagonists, doses below which produce physical signs of opiate withdrawal (Schulteis et al., 1994). This opiate withdrawal-induced place aversion can be blocked by local administration of a CRF antagonist into the central nucleus of the amygdala (Heinrichs et al., 1995) or local administration of a β-noradrenergic receptor antagonist into the BNST (Delfs et al., 2000; Fig. 12). Activation of c-fos selectively in the extended amygdala in the basal forebrain parallels the development of opiate withdrawal-induced place aversion (Gracy et al., 2001). Together, these results suggest a motivational effect of CRF and the noradrenergic brain stress systems in opiate dependence.

7. Allostatic view of neurotransmitter neuroadaptation associated with development of addiction

Allostasis from the addiction perspective has been defined as the process of maintaining apparent reward function stability through changes in brain reward mechanisms (Koob and Le Moal, 2001; Fig. 13). The allostatic state represents a chronic deviation of reward set point that often is not overtly observed while the individual is actively taking drug. The allostatic state is fueled not only by dysregulation of reward circuits per se, but also by the activation of brain and hormonal stress responses. From the perspective of a given drug, it is unknown whether the hypothesized reward dysfunction is specific to that drug, common to all addictions, or a combination of both perspectives. However, from the data generated to date, and the established anatomical connections, the manifestation of this allostatic state as compulsive ethanol taking and loss of control over ethanol taking is hypothesized to be critically based on dysregulation of specific neurotransmitter function in the central division of the extended amygdala. It is further hypothesized that the pathology of this neurocircuitry is the basis for the emotional dysfunction long associated with drug addiction and alcoholism in humans, and some of this

Fig. 13. Diagram illustrating an extension of Solomon and Corbit’s (1974) 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 nondependent 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. Allostatic points refer to the progressive change in set point for reward (decreased reward) associated with repeated drug administration. CRF, corticotropin-releasing factor; GABA, γ-aminobutyric acid; NPY, neuropeptide Y. 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 Koob and Le Moal, 2001.)
Acknowledgements

This is publication number 15828-NP from The Scripps Research Institute. Research was supported by National Institutes of Health grants AA06420 and AA08459 from the National Institute on Alcohol Abuse and Alcoholism, DA04043 and DA04398 from the National Institute on Drug Abuse and DK26741 from the National Institute of Diabetes and Digestive and Kidney Diseases. The author gratefully acknowledges the editorial and research assistance of Mr. Michael A. Arends.

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