The Neurobiology of Drug Addiction

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Animal models have begun to provide insights into the neurobiological basis of reinforcement in drug addiction. The reinforcing effects of indirect sympathomimetics such as cocaine and amphetamine appear to depend on release of dopamine in the terminal fields of the mesocorticolimbic dopamine system. The acute reinforcing effects of opiates involve not only an activation of dopamine, but also dopamine-independent elements in the terminal regions of the mesocorticolimbic dopamine system. Nicotine's reinforcing effects may involve both dopaminergic and opioid peptidergic systems. Ethanol's reinforcing effects may result from multiple neurotransmitter interactions including γ-aminobutyric acid, glutamate, dopamine, opioid peptides, and serotonin. Subtle changes in neurochemical function and signal transduction and transcription mechanisms in sensitive neuronal elements in the extended amygdala may be mediators of chronic drug action that lead to vulnerability to relapse and may provide exciting insight into the neuroadaptations associated with drug addiction.

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Common to most descriptions of drug addiction or substance dependence is the idea of *a compulsion to take a drug, with a loss of control in limiting intake.*[1,2] The diagnostic criteria that are used to diagnose substance dependence incorporate changes in behavior that when represented in a person's daily repertoire are likely to reflect someone who is drug dependent or drug addicted.[2] These symptoms (three of which must be present) include tolerance; withdrawal; persistent desire or unsuccessful attempts to reduce substance use; use in larger amounts than intended; important social, occupational, or recreational activities reduced because of drug use; a great amount of time spent in obtaining the substance; and continued substance use despite recurrent problems resulting from substance use. Clearly, such criteria define a syndrome where behavioral repertoires are significantly narrowed toward substance use and what most would consider compulsive use. (We are using the word *compulsive* in a generic sense, to mean repetitive, driven behavior, rather than in the context of DSM diagnoses of obsessive-compulsive disorders.) For the purposes of this article, drug addiction will be equated with substance dependence as defined by the American Psychiatric Association.[2] However, it should be kept in mind that the term *dependence* has a different and more specific meaning in the basic pharmacology literature, as will be seen below. Drug abuse,

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in contrast to substance dependence, can be readily defined as a maladaptive pattern of drug use resulting in impairment or distress, and it is important to distinguish between the concepts of drug use, abuse, and addiction.[3] Although no animal model exists that incorporates all the signs and symptoms associated with substance dependence, it is becoming clear that many of the criteria used in DSM-IV can be reproduced in various animal models.[4]

DRUG ADDICTION AND REINFORCEMENT

Because drug addiction centers on compulsive, often excessive use of a substance, the concept of reinforcement or motivation is a crucial part of this syndrome. A reinforcer can be defined operationally as "any event that increases the probability of a response." This definition can also be used as a definition for reward, and the two words are often used interchangeably. However, *reward* often connotes some additional emotional value such as pleasure.[5] This contrasts with the concept of punishment, which would entail the ability of an event or drug to decrease the probability of a response.

Historically, most conceptualizations of drug addiction emphasized the development of *tolerance* and *withdrawal*, but recent discussions on this subject have reduced tolerance and withdrawal to optional criteria. However, some have emphasized selective aspects of tolerance and withdrawal, focusing on motivational measures, not physical signs.[6] The concepts of tolerance and withdrawal are key elements supporting the idea that neuroadaptive processes are initiated to counter the acute effects of a drug. Another neuroadaptive process that has been proposed as a key element in the development of drug addiction is *sensitization*. Sensitization can be defined as the opposite of tolerance: "the increased response to a drug that follows its repeated intermittent presentation."[7] These neuroadaptive processes can then persist long after the drug has cleared from the brain; such neuroadaptations have been explored at all levels of drug addiction research, from the behavioral to the molecular.[8] Motivational hypotheses involving both central nervous system counteradaptive changes[9] and sensitization[7] have particular relevance to drug addiction phenomena.[9]

Many sources of reinforcement contribute to compulsive drug use during the course of drug addiction. The primary pharmacological effect of a drug is thought to produce a direct effect through positive or negative reinforcement (Table 1). Examples of negative reinforcement would include self-medication of an existing aversive state or self-medication of a drug-generated aversive state (such as withdrawal).[9] The secondary pharmacological effects of a drug can also have powerful motivating properties (Table 1). Secondary positive reinforcing effects can be obtained through conditioned positive reinforcement (such as pairing of previously neutral stimuli with acute positive reinforcing effects of drugs). Secondary negative reinforcing effects can be obtained through removal of the conditioned negative reinforcing effects of conditioned abstinence. Using this framework, we can explore the neurobiological bases for the acute positive reinforcing effects of drugs, the negative reinforcing effects imparted by the dependent state, and the conditioned reinforcing effects associated with protracted abstinence and relapse.[10]

TABLE 1. Relationship of addiction components, behavioral constructs, and treatment focus

Addiction Component	Behavioral Construct	Treatment Focus
Pleasure	Positive reinforcement	Motivational
Self-medication	Negative reinforcement	AA and motivational
Habit	Conditioned positive reinforcement	Cognitive/behavioral
Habit	Conditioned negative reinforcement	Cognitive/behavioral

Note: AA = Alcoholics Anonymous.

DRUG ADDICTION AND NEUROTRANSMISSION

All drugs of abuse interact initially with proteins located at the extracellular aspect of specific synapses[11] (summarized in Table 2). For example, opiates activate opioid receptors, and cocaine inhibits reuptake proteins for the monoamine neurotransmitters (dopamine, norepinephrine, and serotonin). Alcohol is thought to act at specific "ethanol-receptive elements," which include the ionotropic γ-aminobutyric acid, type A ($GABA_A$), and *N*-methyl-D-aspartate (NMDA) glutamate receptors as well as voltage-gated ion channels.[12] These initial effects lead, in the short term, to alterations in the functional levels of specific neurotransmitters or to different activation states of specific neurotransmitter receptors in the brain.

However, although the initial effects of drugs of abuse are extracellular, the many effects these drugs elicit are achieved ultimately via the intracellular messenger pathways that transduce these extracellular actions.[11] This mechanism is further discussed below.

TABLE 2. Acute effects of abused drugs on neurotransmitters and receptors

Drug	Action
Opiates	Agonist at opioid receptors
Cocaine	Inhibits monoamine reuptake transporters
Amphetamine	Stimulates monoamine release
Alcohol	Facilitates $GABA_A$ receptor function and inhibits *N*-methyl-D-aspartate (NMDA) glutamate receptor function[a]
Nicotine	Agonist at nicotinic acetylcholine receptors
Cannabinoids	Agonist at cannabinoid receptors[b]
Hallucinogens	Partial agonist at $5\text{-}HT_{2A}$[c] serotonin receptors
Phencyclidine (PCP)	Antagonist at NMDA glutamate receptors

[a]The mechanism by which alcohol produces these effects has not been established, but it does not appear to involve direct alcohol binding to the receptors as is the case for the other drugs listed in this table.
[b]Although a specific receptor for cannabinoids has been identified in the brain, the endogenous ligands for this receptor are under current active investigation.
[c]5-Hydroxytryptamine-2.

POSITIVE REINFORCING EFFECTS OF DRUGS: NEURAL SUBSTRATES

The neural substrates of reward have long been hypothesized to involve the medial forebrain bundle, which contains both ascending and descending pathways that include most of the brain's monoamine systems.[13–15] Much of the early work focused on those structures that supported intracranial self-stimulation: the ventral tegmental area, the basal forebrain, and the medial forebrain bundle that connects these two areas.[13,14,16,17] Recent work on the neurobiology of addiction has provided significant insights into the neurochemical and neuroanatomical components of the medial forebrain bundle, which may provide the key not only to drug reward but also to natural rewards.

The origins and terminal areas of the mesocorticolimbic dopamine system have been the principal focus of research on the neurobiology of drug addiction, and there is now compelling evidence for the importance of this system in drug reward. The major components of this drug reward circuit are the ventral tegmental area (the site of dopaminergic cell bodies), the basal forebrain (the nucleus accumbens, olfactory tubercle, frontal cortex, and amygdala), and the dopaminergic connection between the ventral tegmental area and the basal forebrain. Other components are the opioid peptide, GABA, glutamate, serotonin, and presumably many other neural inputs that interact with the ventral tegmental area and the basal forebrain[18] (Figure 1). The functional significance of this circuitry for different types of drug reward will be discussed in the following sections, and a construct called the extended amygdala will be introduced that provides important insights into the relationship of drug reward to natural reward systems.

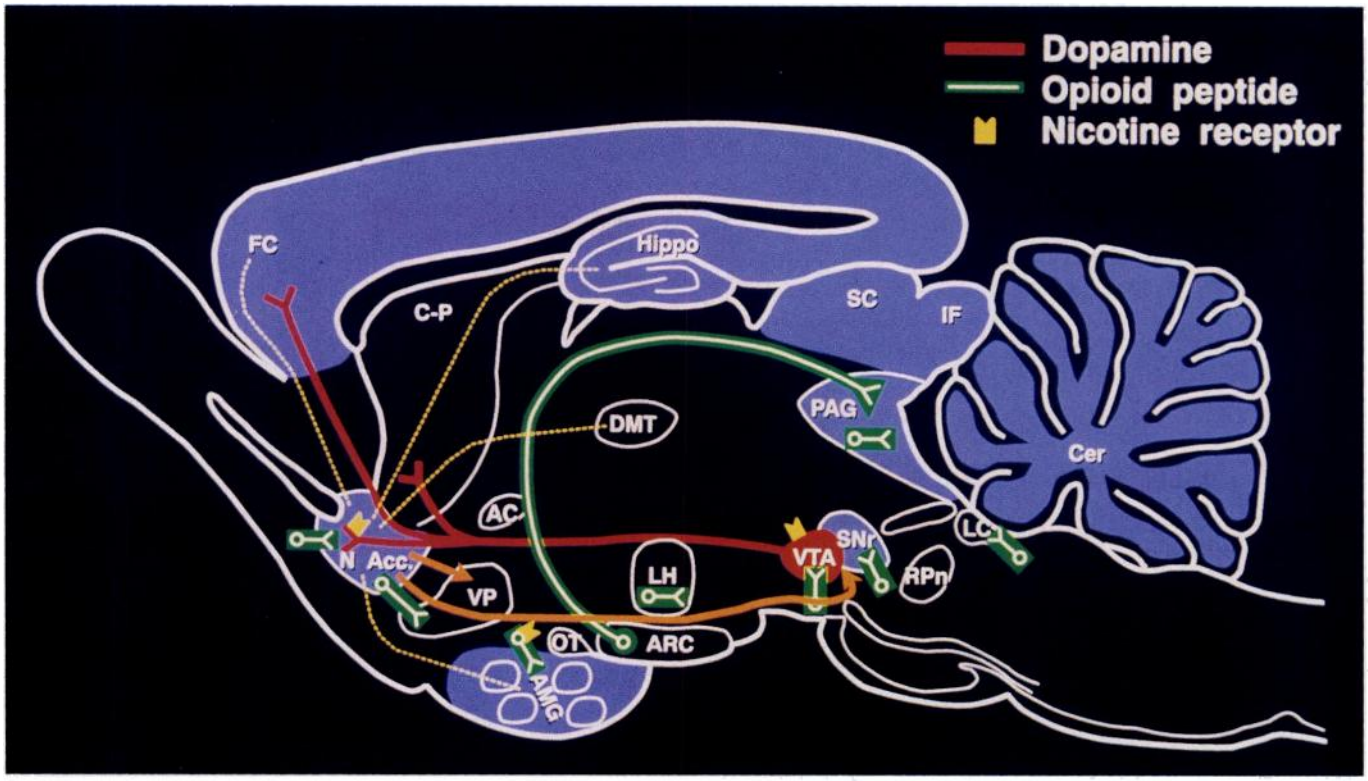
COCAINE AND AMPHETAMINE: THE MESOCORTICOLIMBIC DOPAMINE SYSTEM

Psychomotor stimulants of high abuse potential interact initially with monoamine transporter proteins. These transporter proteins, which have been cloned and characterized,[19–21] are located on monoaminergic nerve terminals and terminate a monoamine signal by transporting the monoamine from the synaptic cleft back into the terminals. Cocaine is a potent inhibitor of all three monoamine transporters, those for dopamine, serotonin, and norepinephrine, and thereby potentiates monoaminergic transmission. Amphetamine and its derivatives also potentiate monoaminergic transmission, but apparently via a distinct mechanism: by increasing monoamine release. It now appears that amphetamine itself serves as a substrate for all three monoamine transporters and is transported into monoaminergic nerve terminals, where it disrupts the storage of the monoamine transmitters. This disruption leads to an increase in extravesicular levels of the monoamines and to the reverse transport of the monoamine into the synaptic cleft via the monoamine transporters.[22] Certain amphetamine derivatives are toxic to monoaminergic nerve terminals via as-yet-unknown effects within the nerve terminal cytoplasm.[23]

Amphetamine and cocaine are psychomotor stimulants and have behavioral effects consistent with that class of drugs, including suppression of hunger and fatigue[24] and induction of euphoria[25] in humans. In animals, these drugs increase motor activity,[26] decrease food intake,[26] have psychomotor stimulant actions on operant behavior,[27] enhance conditioned responding,[27] decrease thresholds for reinforcing brain stimulation,[28,29] produce preferences for environments where the drugs have been previously experienced (place preferences),[30,31] and readily act as reinforcers for drug self-administration.[32]

Both the psychomotor stimulant effects of amphetamine and cocaine[33–35] and their reinforcing actions depend critically on the mesocorticolimbic dopamine system.[36,37] The most direct evidence implicating dopamine generally in the reinforcing actions of cocaine comes from studies of intravenous self-administration. Low doses of dopamine receptor antagonists, when injected systemically, reliably decrease the reinforcing effects of cocaine and amphetamine self-administration in rats.[36,37] Confirmation that dopamine antagonists

FIGURE 1. Sagittal rat brain section illustrating a drug (cocaine, amphetamine, opiate, nicotine, and alcohol) neural reward circuit that includes a limbic-extrapyramidal motor interface. *Yellow dotted lines* indicate limbic afferents to the nucleus accumbens (N Acc.). *Orange* represents efferents from the nucleus accumbens thought to be involved in psychomotor stimulant reward. *Red* indicates projection of the mesocorticolimbic dopamine system thought to be a critical substrate for psychomotor stimulant reward. This system originates in the A10 cell group of the ventral tegmental area (VTA) and projects to the N Acc., olfactory tubercle, ventral striatal domains of the caudate-putamen (C-P), and amygdala (AMG). *Green* indicates opioid peptide-containing neurons, systems that may be involved in opiate, ethanol, and possibly nicotine reward. These opioid peptide systems include the local enkephalin circuits (short segments) and the hypothalamic midbrain beta-endorphin circuit (long segment). *Blue* indicates the approximate distribution of $GABA_A$ receptor complexes, some of which may mediate sedative/hypnotic (ethanol) reward, determined by both tritiated flumazenil binding and expression of the alpha, beta, and gamma subunits of the $GABA_A$ receptor. *Yellow solid structures* indicate nicotinic acetylcholine receptors hypothesized to be located on dopaminergic and opioid peptidergic systems. AC = anterior commissure; ARC = arcuate nucleus; Cer = cerebellum; DMT = dorsomedial thalamus; FC = frontal cortex; Hippo = hippocampus; IF = inferior colliculus; LC = locus coeruleus; LH = lateral hypothalamus; OT = olfactory tract; PAG = periaqueductal gray; RPn = raphe pontis nucleus; SC = superior colliculus; SNr = substantia nigra pars reticulata; VP = ventral pallidum. Modified, with permission, from Koob 1992.[18]



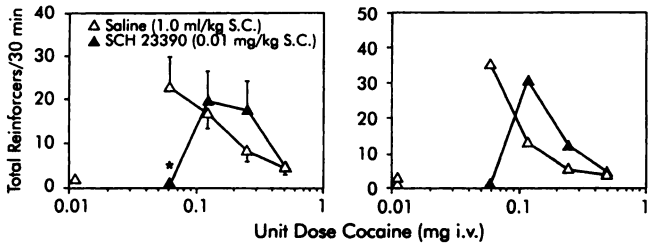
block the reinforcing effects of cocaine comes from dose-effect studies where the antagonists shift the cocaine dose-effect function to the right (Figure 2).[38] In general, experiments investigating the effects of antagonists selective for dopamine receptor subtypes reveal that antagonists for the D_1,[39] D_2,[40,41] and D_3 receptors decrease the reinforcing properties of cocaine.[42]

The reinforcing actions of cocaine were linked specifically to the mesocorticolimbic dopamine system by a series of observations using neurotoxin-induced lesions of this subset of midbrain dopamine projections. Dopamine-selective lesions with 6-hydroxydopamine (6-OHDA) of the nucleus accumbens produced extinction-like responding and significant and long-lasting decreases in self-administration of cocaine and amphetamine over days.[43,44] These decreases in cocaine self-administration following dopamine-selective lesions of the nucleus accumbens have now been observed in a variety of different tests and conditions, including situations where animals show a decrease in the amount of work they would perform for cocaine[32] and situations where other reinforcers such as food were unaffected but cocaine self-administration was abolished.[45]

OPIATES AND OPIOID PEPTIDE SYSTEMS

Opiate drugs such as heroin have long been known to be readily self-administered intravenously by animals,[46]

FIGURE 2. **Shift of the cocaine dose-effect function to the right following pretreatment with dopamine D_1 antagonist SCH-23390. Left: Effects of pretreatment with the D_1 dopamine receptor antagonist SCH-23390 (0.01 mg/kg S.C.) on the cocaine (0.06–0.5 mg) self-administered dose-effect function measured using the within-session dose-effect paradigm (n = 4). Right: The same, but for an individual rat. Reprinted, with permission, from Caine and Koob 1995.[38]**



and if these drugs are provided in limited-access situations, rats and primates[47] will maintain stable levels of opiate intake on a daily basis without obvious signs of physical dependence.[48] In intravenous self-administration studies, systemic and central administration of competitive opiate antagonists decrease opiate reinforcement as measured by an increase in the number of infusions (decrease in the interval between injections) for opiate drugs.[37,48–51] This decrease in reinforcement appears to result from a competitive interaction between the antagonist and agonist at opioid receptors.

The opioid receptor subtype most important for the reinforcing actions of heroin and morphine appears to be the mu receptor. Mu opioid receptor agonists produce dose-dependent decreases in heroin self-administration, and irreversible mu-selective antagonists dose-dependently increase heroin self-administration.[52] Intracerebral injection of quaternary derivatives of opiate antagonists—charged, hydrophilic compounds that do not readily spread from the sites in the brain at which they are injected—dose-dependently block heroin self-administration in nondependent rats.[51,53–55] This antagonism was observed when the antagonists were injected into the ventral tegmental area[53] or the region of the nucleus accumbens.[54] However, rats also will self-administer opioid peptides directly in the region of the nucleus accumbens,[56] and heroin self-administration is not blocked by cocaine-blocking doses of dopamine antagonists,[37] nor by dopamine-selective lesions of the mesocorticolimbic dopamine system.[57] Chronic dopamine receptor blockade does not alter heroin self-administration, a finding that further demonstrates dopamine-independent mechanisms.[58] In addition, whereas opioid peptides injected into either the nucleus accumbens or the ventral tegmental area produce dose-related increases in locomotor activity,[59] the effects of nucleus accumbens injections appear to be independent of dopamine release.[60]

Nevertheless, evidence for a dopamine-dependent action for opiates in the ventral tegmental area is strong. Opiates can produce an increase in dopamine release in the nucleus accumbens similar to that of cocaine and ethanol[61] (but see Hemby et al.[62]). Opioid peptides are self-administered into the ventral tegmental area,[63] and microinjections of opioids into the ventral tegmental area will lower brain stimulation reward thresholds and produce robust place preferences.[64] Altogether, these results suggest that neural elements in the region of the ventral tegmental area and the nucleus accumbens are responsible for the reinforcing properties of opiates, and the findings implicate both dopamine-dependent and dopamine-independent mechanisms of opiate action.[57,65–67]

ALCOHOL: MULTIPLE NEUROCHEMICAL SUBSTRATES

Ethanol, barbiturates, and benzodiazepines all are considered sedative-hypnotics and produce a characteristic euphoria, disinhibition, anxiety reduction, sedation, and hypnosis. These drugs exert anti-anxiety effects that are reflected in a reduction of behavior that would be suppressed by punishment in conflict situations in laboratory animals. This anti-conflict effect correlates well with the capacity of sedative-hypnotics to act as anxiolytics in the clinic,[68] and the anti-conflict effect may be a major component of the reinforcing actions of these drugs.

The sedative and anti-punishment (anxiolytic) effects of sedative-hypnotics are mediated via facilitation of the $GABA_A$ receptor.[69] The actions of sedative-hypnotics on this receptor are complex: the drugs do not bind to the receptor at or near the GABA-binding site. Rather, they bind to other sites on the receptor complex and thereby facilitate, via allosteric effects, activation of the receptor by GABA. The net result is potentiation of GABA-induced Cl^- flux through the receptor ionophore.[70] The $GABA_A$ receptor is a heteromeric complex, and the ability of sedative-hypnotics to facilitate receptor function depends on the actual subunit composition of the receptor, which differs markedly throughout the brain. Although benzodiazepines, barbiturates, and ethanol interact with the $GABA_A$ receptor at distinct sites, the fact that they converge on the functioning of the same protein complex no doubt explains the long-appreciated cross-tolerance and cross-dependence exhibited by these drugs.

Neuropharmacological studies of the anxiolytic properties of sedative-hypnotics provided some of the first clues to their reinforcing properties and abuse potential.[71] GABAergic antagonists were found to reverse many of the behavioral effects of ethanol, which led to the hypothesis that GABA has a role in the intoxicating effects of ethanol.[72,73] The partial inverse benzodiazepine agonist Ro 15-4513, which has been shown to reverse some of the behavioral effects of ethanol,[70] produces a dose-dependent reduction of oral ethanol (10%) self-administration in rats.[74,75] More recent studies have shown similar effects with potent GABA antagonists microinjected into the brain, with the most effective site to date being the central nucleus of the amygdala.[3]

Ethanol, unlike other sedative-hypnotics, also exerts potent effects on the NMDA glutamate receptor. Ethanol inhibits the functioning of the receptor, again not by blocking the glutamate binding site but via a more complex allosteric effect on the receptor complex, which results in diminished glutamate-induced Na^+ and Ca^{2+} flux through the receptor ionophore.[76] Ethanol antagonism of the NMDA receptor appears to contribute to the intoxicating effects of ethanol,[77,78] and perhaps to the dissociative effects seen in people with high ethanol blood levels.[79] Whether ethanol antagonism of the NMDA receptor also contributes to its reinforcing effects remains to be established. At still higher doses, ethanol can exert more general inhibitory effects on voltage-gated ion channels, particularly Na^+ and Ca^{2+} channels.[76] These actions occur only with extreme concentrations seen clinically and would therefore not appear to be involved in the reinforcing actions of ethanol, although they may contribute to the severe nervous system depression, even coma, that are seen at these blood levels.

Via its initial effects on the $GABA_A$ and NMDA glutamate receptors, ethanol influences several additional neurotransmitter systems in the brain that are believed to mediate its reinforcing properties. Again, considerable focus has been placed on dopamine, which is implicated in the reinforcing actions of low, non–dependence-inducing doses of ethanol. Dopamine receptor antagonists have been shown to reduce lever-pressing for ethanol in nondeprived rats,[80] and extracellular dopamine levels also have been shown to increase in nondependent rats orally self-administering low doses of ethanol.[81] However, virtually complete 6-OHDA denervation of the nucleus accumbens failed to alter voluntary responding for alcohol.[82] Thus, as with opiates, these results suggest that while mesocorticolimbic dopamine transmission may be associated with important aspects of ethanol reinforcement, it may not be critical in this regard, and that other, dopamine-independent neurochemical systems likely contribute to the mediation of ethanol's reinforcing actions. In fact, the view is emerging that multiple neurotransmitters combine to "orchestrate" the reward profile of alcohol.[83]

The brain's serotonin systems also have received attention. Modulation of various aspects of serotonergic transmission, including increases in the synaptic availability of serotonin with precursor loading, blockade of serotonin reuptake, or blockade of certain serotonin receptor subtypes, can decrease ethanol intake.[84] Consistent with a role for serotonergic transmission in ethanol abuse are several double-blind, placebo-controlled clinical studies in which serotonin reuptake inhibitors were reported to produce mild decreases in alcohol consumption in humans.[85] However, these findings remain controversial, and, in general, it is now believed that these compounds are of only limited utility in the treatment of nondepressed alcoholics.

Opioid peptide systems have been implicated in alcohol reinforcement by numerous reports that the opioid receptor antagonists naloxone and naltrexone reduce alcohol self-administration in several animal models.[86] Although opioid antagonists dose-dependently decrease consumption of sweet solutions of water as well as ethanol in operant, free-choice tests,[86] it is possible that antagonism of specific opioid receptor subtypes in specific brain regions might reveal more selective effects.[87] A role for opioid peptides in alcohol reinforcement has been further demonstrated by two double-blind, placebo-controlled clinical trials showing that naltrexone significantly reduces alcohol consumption, frequency of relapse, and craving for alcohol in humans.[88,89] Thus, alcohol interactions with opioid neurotransmission may contribute to certain aspects of alcohol reinforcement that may be of particular importance to the motivation associated with relapse.

NICOTINE: DOPAMINE AND OPIOID PEPTIDES

The initial molecular site of action for nicotine is likely to be a direct agonist action at the nicotinic acetylcholine receptors specifically in the brain mesolimbic dopamine system, although brain nicotinic acetylcholine receptors are widely distributed throughout the brain. Nicotine self-administration is blocked by dopamine antagonists and opioid peptide antagonists.[90,91] Nicotine is thus thought to activate both the mesolimbic dopamine system and opioid peptide systems in the same neural circuitry associated with other drugs of abuse[92] (see Figure 1).

EXTENDED AMYGDALA: A COMMON SUBSTRATE FOR DRUG REWARD

An interesting hypothesis that is gaining support from recent neuroanatomical data and new functional observations is that the neuroanatomical substrates for the reinforcing actions of drugs may involve a common neural circuitry that forms a separate entity within the basal forebrain, termed the *extended amygdala.*[93] The term represents a macrostructure, originally described by Johnston,[94] that is composed of several basal forebrain structures: the bed nucleus of the stria terminalis, the central medial amygdala, the medial part of the nucleus accumbens (e.g., the area labeled the shell),[95] and the area termed the sublenticular substantia innominata. These structures have similarities in morphology, immunohistochemistry, and connectivity.[93] They receive afferent connections from limbic cortices, hippocampus, basolateral amygdala, midbrain, and lateral hypothalamus. Efferent connections from this complex include the posterior medial (sublenticular) ventral pallidum, medial ventral tegmental area, various brainstem projections, and, perhaps most intriguing from a functional point of view, a considerable projection to the lateral hypothalamus.[96]

Recent studies have demonstrated selective effects of D_1 dopamine antagonists in blocking cocaine self-administration when the antagonist is administered directly into the shell of the nucleus accumbens.[97] Moreover, selective activation of dopaminergic transmission occurs in the shell of the nucleus accumbens in response to acute administration of virtually all major drugs of abuse.[98] In addition, the central nucleus of the amygdala has been implicated in the GABAergic and opioidergic influences on the acute reinforcing effects of ethanol,[99,100] as well as on the aversive stimulus effects of drug withdrawal.[101] This concept of the extended amygdala links the extensive recent developments in the neurobiology of drug reward with existing knowledge of the substrates for natural rewards, bridging what have been largely independent research pursuits.

DRUG DEPENDENCE: NEURAL SUBSTRATES

Common to most drugs of abuse is a withdrawal syndrome that is made up of two elements. There are the physical signs of withdrawal, which are characteristic for each drug, such as the well-known tremor and autonomic hyperactivity of alcohol withdrawal and the abdominal discomfort and pain associated with opiate withdrawal. There are also the "psychological" aspects of drug withdrawal, which may be considered more motivational; these signs consist of varying components of a negative emotional state including dysphoria, depression, anxiety, and malaise.[2,10]

The neural substrates for the physical signs of drug withdrawal are not well understood in general and probably involve many different brain sites and neurochemical systems for the various types of drugs of abuse. Such neural substrates are best established for opiates. Much evidence implicates the nucleus locus coeruleus (the brain's predominant noradrenergic nucleus, located in the pons) in the activational properties and stress-like effects of opiate withdrawal.[102–104] In addition, there is evidence that the changes in body temperature associated with opiate withdrawal may be due to interactions in the hypothalamus. Specific neural substrates for different aspects of ethanol withdrawal largely remain to be explored, but some neuropharmacological mechanisms have been identified, including a decrease in GABAergic function and an increase in glutamatergic function[12,105] as well as associated changes in cellular calcium levels.[76,106]

REWARD THRESHOLDS AND DRUG ABSTINENCE

Recent work has focused on the neural substrates and neuropharmacological mechanisms of the motivational effects of drug withdrawal, effects that may contribute to the negative reinforcement associated with drug dependence. For example, cocaine withdrawal in humans in the outpatient setting is characterized by severe depressive symptoms combined with irritability, anxiety, and anhedonia lasting several hours to several days (the "crash") and may be one of the motivating factors in the maintenance of the cocaine dependence cycle.[107] Inpatient studies have shown similar changes in mood and anxiety states, but the changes generally are much less severe.[108] Opiate withdrawal is characterized by severe dysphoria, and ethanol withdrawal produces dysphoria and anxiety. Recent work suggests the same neural systems implicated in the positive reinforcing effects of drugs of abuse may be involved in these aversive motivational effects of drug withdrawal. Using the technique of intracranial self-stimulation to measure reward thresholds throughout the course of drug dependence, recent studies have shown that reward thresholds are increased (reflecting a decrease in reward) following chronic administration of all major drugs of abuse, including opiates, psychostimulants, alcohol, and nicotine. These effects may reflect changes in the activity of the same mesocorticolimbic system

(midbrain-forebrain system) implicated in the positive reinforcing effects of drugs and can last up to 72 hours, depending on the drug and dose administered (Table 3).[109–124]

DRUG DEPENDENCE: NEUROCHEMICAL SUBSTRATES

The neuropharmacological basis for the change in reward function associated with the development of drug dependence has largely followed two neuroadaptive models: sensitization and some form of homeostatic adaptive mechanism.[125] With drugs, sensitization is more likely to occur with intermittent exposure to a drug, in contrast to tolerance, which is more likely to occur with continuous exposure.

In a recent conceptualization of the role of sensitization in drug dependence, a shift in an incentive-salience state described as "wanting" was hypothesized to be progressively increased by repeated exposure to drugs of abuse,[126] and the transition to pathologically strong wanting or craving would define compulsive use. In contrast, a homeostatic adaptive mechanism would exist where the initial acute effect of the drug is opposed or counteracted by homeostatic changes in systems that mediate the primary drug effects.[127–129]

In one formulation, called *opponent process theory*, tolerance and dependence were inextricably linked.[127] Here it was proposed that affective states, pleasant or aversive, were automatically opposed by centrally mediated mechanisms that reduce the intensity of these affective states.

For neuroadaptive mechanisms described by both theoretical positions, several types of adaptation can be envisioned at the molecular, cellular, and system levels. *Within-system* adaptations have been hypothesized wherein neurochemical changes associated with the same neurotransmitters implicated in the acute reinforcing effects of drugs are altered during the development of dependence.[8] Examples of such homeostatic, within-systems adaptive neurochemical events include decreases in dopaminergic and serotonergic transmission in the nucleus accumbens during drug withdrawal as measured by in vivo microdialysis,[121,130] increased sensitivity of opioid receptors in the nucleus accumbens during opiate withdrawal,[131] decreased GABAergic and increased NMDA glutamatergic transmission during ethanol withdrawal,[76,132,133] and differential regional changes in nicotine receptor function.[134,135]

Other neurotransmitter systems may also be recruited in the adaptive responses to drugs of abuse. Such a neuroadaptation, wherein a neurotransmitter system not linked to the acute reinforcing effects of the drug is recruited or altered during chronic drug administration, has been termed a *between-system* adaptation.[8] Particular attention has focused on components of stress responses for between-system adaptations. Corticotropin-releasing factor function appears to be activated during acute withdrawal from alcohol or opiates and thus may mediate aspects of stress associated with abstinence.[136] A role for circulating glucocorticoids in adaptations to the reinforcing effects of a drug of abuse also has been hypothesized.[137]

TABLE 3. Drug effects on thresholds for rewarding brain stimulation

Drug Class	Acute Administration	Withdrawal From Chronic Treatment	Reference
Psychostimulants (cocaine, amphetamines)	↓	↑	109–112, 122
Opiates (morphine, heroin)	↓	↑	113–115
Nicotine	↓	↑	116, 117, 124
Sedative-hypnotics	↓	↑	118, 119

DRUG DEPENDENCE: MOLECULAR AND CELLULAR MECHANISMS

Drug-induced adaptations in neurotransmitter systems would exert their functional effects on the brain ultimately through post-receptor intracellular messenger pathways that mediate neurotransmitter-receptor actions. In a similar way, the development of drug-induced adaptations in neurotransmitter systems occurs via perturbation of these intracellular messenger pathways.

The brain's intracellular messenger pathways are reviewed elsewhere[138] and summarized in Figure 3. Briefly, most neurotransmitter receptors in the brain belong to a family of G protein–coupled receptors, which produce all of their effects on brain function via activation of specific types of G proteins, guanine nucleotide-binding membrane proteins that couple the plasma membrane receptors to intracellular processes. Activated G proteins can then directly regulate the activity of certain ion channels as well as regulate the levels of specific second messengers in the brain, which include adenosine 3',5'-cyclic monophosphate (cAMP), Ca^{2+}, and metabolites of phosphatidylinositol. These second messengers then regulate the activity of enzymes called protein kinases and protein phosphatases, which add and remove, respectively, phosphate groups from other proteins.

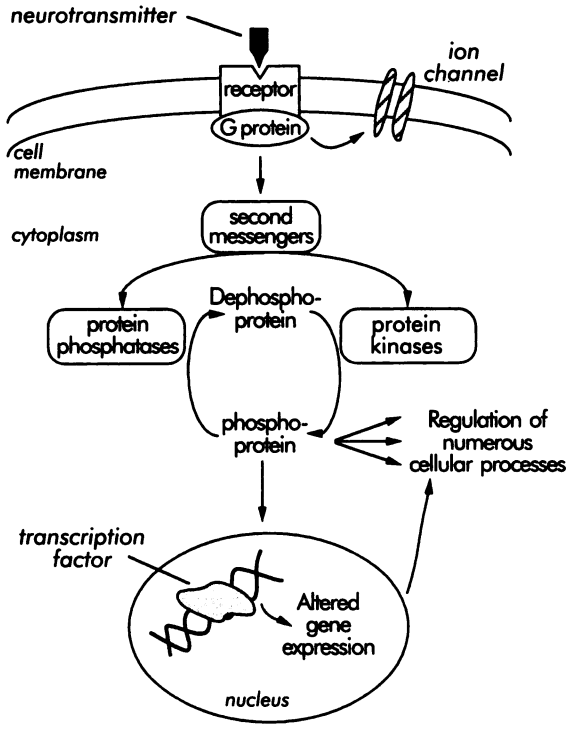
Phosphate groups, because of their charge and size, alter a protein's conformation and therefore its function. Through the phosphorylation of virtually every type of neural protein, neurotransmitter receptor interactions can elicit myriad biological responses in their target neurons. For example, phosphorylation of ion channels alters their probability of opening, and phosphorylation of receptors alters their capability to be activated by ligand as well as to subsequently activate G proteins. Among the proteins regulated by phosphorylation are those that control gene expression and protein synthesis. An example can be seen in transcription factors, proteins that bind to specific DNA sequences in certain genes and thereby increase or decrease the rate at which those genes are transcribed. Phosphorylation of transcription factors is a critical control point in regulating the activity of these proteins.

This transduction of biological action is illustrated well by the acute actions of opiates on the brain (Figure 4).[11] Opiate activation of opioid receptors leads to recruitment of Gi and related G proteins. This, in turn, leads to activation of certain K^+ channels and inhibition of voltage-gated Ca^{2+} channels, although the two actions occur to varying extents in different neuronal cell types. Both are inhibitory actions (more K^+ flows out of the cell and less Ca^{2+} flows into the cell) that mediate some of the relatively rapid inhibitory effects of opiates on the electrical properties of their target neurons. Recruitment of Gi also leads to the inhibition of adenylate cyclase and of the cAMP protein phosphorylation cascade. Similarly, reductions in cellular Ca^{2+} levels alter Ca^{2+}-dependent protein phosphorylation cascades. Altered activity of these protein phosphorylation cascades, which also can vary among different cell types, leads in turn to the regulation of still additional ion channels, which contribute further to the acute effects of the drug. Perhaps more important, these protein phosphorylation mechanisms can lead to changes in many other neural processes within target neurons, including those that trigger the long-term effects of the drugs that lead eventually to tolerance, dependence, withdrawal, sensitization, and, ultimately, addiction.

Repeated exposure to a drug of abuse results in repeated perturbation of intracellular messenger pathways, which eventually elicits long-term adaptations in the pathways that contribute to dependence and tolerance. Insights into the specific molecular and cellular adaptations involved in chronic drug action have been progressing at a rapid rate. Some of the most complete studies involve the locus coeruleus, the major noradrenergic nucleus in the brain, which plays an important role in physical dependence to opiates, as mentioned above.[102,103,139–141] Activation of the locus coeruleus has been shown to mediate many of the signs and symptoms of opiate withdrawal in rodents and nonhuman primates. This knowledge led to the introduction of clonidine, an alpha$_2$-adrenergic agonist, as the first nonopiate treatment of opiate withdrawal.[102,142]

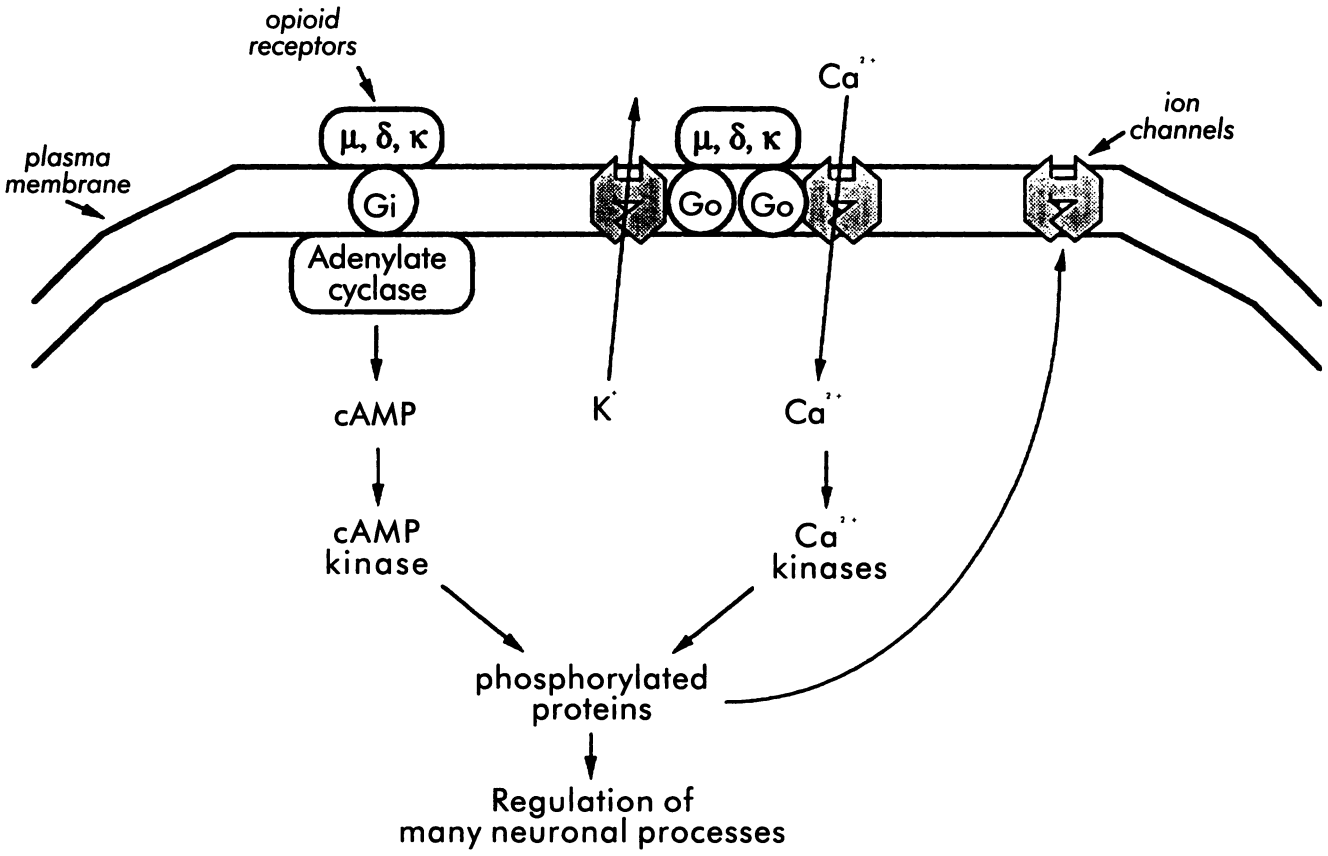
Withdrawal-induced activation of the locus coeruleus has been hypothesized to be due to a combination of intrinsic and extrinsic factors. The intrinsic mechanisms involve regulation of the cAMP pathway in locus coeruleus neurons,[143,144] which has long been considered a molecular site of opiate neuroadaptation.[145–147] Acute administration of opiates inhibits the firing of the neurons via regulation of two ion channels: activation of K^+ channels via direct Gi protein coupling, and inhibition of an Na^+ current indirectly via inhibition of

FIGURE 3. Schematic illustration of the brain's intracellular messenger pathways. Activation of neurotransmitter receptors leads to the activation of specific G proteins, second messengers, and protein phosphorylation systems, which produce multiple effects on neuronal function through the phosphorylation of numerous types of substrate proteins. Among the effects of these intracellular systems on neuronal function is the regulation of gene expression. This can be accomplished through the phosphorylation of transcription factors, which results in alterations in the expression of numerous target genes. G proteins can also exert effects independent of protein phosphorylation—for example, through the direct regulation of ion channels.



adenylate cyclase and of cAMP-dependent protein kinase[148] (Figure 5). In contrast, chronic exposure to opiates increases the amount of adenylate cyclase and cAMP-dependent protein kinase expressed in the neurons. This up-regulated cAMP pathway has been shown to contribute to the increase in the intrinsic electrical excitability of locus coeruleus neurons that underlies the cellular forms of tolerance and dependence exhibited by these neurons.[144,147] The up-regulated cAMP pathway would contribute to tolerance by opposing inhibition of the neurons by the continued presence of opiates and thereby help return firing rates toward control levels. It would also contribute to dependence: upon removal of opiate, the up-regulated cAMP pathway, now unopposed, would drive the firing of the neurons far above control levels. A major unanswered question is the precise mechanism (for instance, at the level of transcription, translation, or protein modification) by which chronic opiate exposure leads to the up-regulation of the cAMP pathway.[143] Recent work has

FIGURE 4. **Schematic illustration of opiate-regulated signal transduction pathways. Opiates produce their effects in target neurons via interactions with three major classes of receptors, termed mu, delta, and kappa opioid receptors. There are two major signal transduction pathways through which each of these receptors has been shown to influence target neuron functioning. First, opiates, via coupling to a pertussis toxin–sensitive G protein (presumably Gi), inhibit adenylate cyclase and thereby reduce cellular cAMP levels, the activity of cAMP-dependent protein kinase, and the phosphorylation state of numerous substrate proteins for the protein kinase. Such substrate proteins include ion channels and many other types of neuronal proteins known to be regulated by cAMP-dependent phosphorylation. Through this action, therefore, opiates induce many and diverse types of effects in target neurons. Second, opiates, via coupling to Gi and/or Go, increase the conductance of certain types of K^+ channels and decrease the conductance of voltage-dependent Ca^{2+} channels. In most cases, the opiate-regulated K^+ channel appears to be identical to the inward rectifying channel regulated by several other types of neurotransmitter receptors (such as D_2 dopaminergic, alpha$_2$ adrenergic, and 5-HT_{1A} serotonergic receptors) also via coupling with a pertussis toxin–sensitive G protein. Regulation of the K^+ and Ca^{2+} channels inhibits the electrical properties of the target neurons. Such regulation also leads to decreases in intracellular Ca^{2+} levels and, consequently, to decreases in the activity of Ca^{2+}-dependent protein kinases (both Ca^{2+}/calmodulin-dependent protein kinases and protein kinase C) and the phosphorylation state of numerous types of substrate proteins for these protein kinases. As with regulation of the cAMP system, opiate-induced changes in Ca^{2+}-dependent protein phosphorylation lead to many changes in neuronal function.**



implicated the transcription factor CREB (cAMP response element binding protein) as one mediator of these adaptations.[146,149,150]

Increased activation of the major glutamatergic input to the locus coeruleus that arises from a brainstem area called the paragigantocellularis appears to be one of the major extrinsic mechanisms of withdrawal-induced activation of the locus coeruleus.[151,152] The driving force for this increase in glutamatergic tone remains to be elucidated. Chronic opiate exposure could lead to intrinsic changes in the glutamatergic neurons of the paragigantocellularis themselves or in neurons that drive those neurons in some neural circuit.[143]

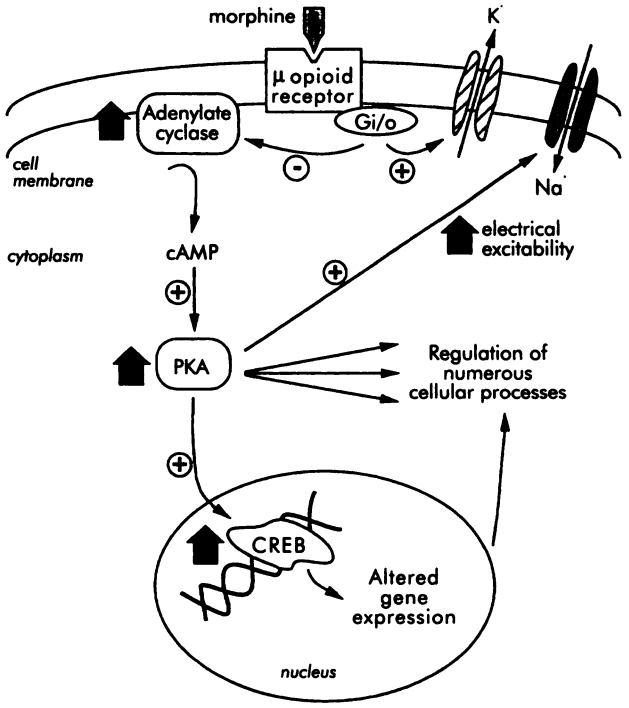
Much less is known about the molecular and cellular mechanisms of motivational dependence, although there is some evidence to suggest that similar mechanisms may be involved. Several drugs of abuse up-regulate the cAMP pathway in the nucleus accumbens after chronic administration.[144,153,154] This up-regulation could mediate some of the documented electrophysiological changes in the nucleus accumbens associated with chronic drug exposure, such as enhanced responsiveness of D_1 dopamine receptors after chronic cocaine treatment.[138] Moreover, studies involving direct administration of activators or inhibitors of the cAMP pathway into the nucleus accumbens are consistent with the interpretation that up-regulation of the cAMP pathway in this brain region may contribute to an aversive state during drug withdrawal.[153] A major task now will be to explore these mechanisms directly in animal models of dependence that reflect both the positive and the negative reinforcing effects of dependence.

The persistence of changes in drug reinforcement mechanisms that characterize drug addiction suggests that the underlying molecular mechanisms are long-lasting, and indeed considerable attention has been given to drug regulation of gene expression. Current research focuses on two types of transcription factors, CREB and novel Fos-like proteins (termed chronic FRAs, or Fos-related antigens), as possible mediators of chronic drug action.[155–157] However, it has not yet been possible to relate regulation of a specific transcription factor to specific features of drug reinforcement.

DRUG TOLERANCE: NEURAL SUBSTRATES

Tolerance to the reinforcing actions of drugs of abuse may also be an important mechanism for drug addiction. However, the measurement in animal models with such phenomena as intravenous self-administration has been limited.[158] One would hypothesize that the neural substrates for drug tolerance would overlap significantly with those associated with acute withdrawal, since tolerance and withdrawal appear to be components of the same neuroadaptive process. However, tolerance also depends on learning processes, and this has been most explored in the context of opiate drugs

FIGURE 5. **Scheme illustrating opiate actions in the locus coeruleus. Opiates acutely inhibit locus coeruleus neurons by increasing the conductance of a K^+ channel (light cross-hatch) via coupling with subtypes of Gi and/or Go and by decreasing an Na^+-dependent inward current (dark cross-hatch) via coupling with Gi/o and the consequent inhibition of adenylate cyclase. Reduced levels of cAMP decrease protein kinase activity (PKA) and the phosphorylation of the responsible channel or pump. Inhibition of the cAMP pathway also decreases phosphorylation of numerous other proteins and thereby affects many additional processes in the neuron. For example, it reduces the phosphorylation state of cAMP response element binding protein (CREB), which may initiate some of the longer-term changes in locus coeruleus function. Upward bold arrows summarize effects of chronic morphine in the locus coeruleus. Chronic morphine increases levels of adenylate cyclase, protein kinase activity, and several phosphoproteins, including CREB. These changes contribute to the altered phenotype of the drug-addicted state. For example, the intrinsic excitability of locus coeruleus neurons is increased via enhanced activity of the cAMP pathway and Na^+-dependent inward current, which contributes to the tolerance, dependence, and withdrawal exhibited by these neurons. This altered phenotypic state may be maintained in part by up-regulation of CREB expression. Reprinted, with permission, from Nestler 1996.[146]**



and sedative-hypnotics such as alcohol.[159] Mechanisms for these associative processes may involve several neurotransmitters independently of their role in acute withdrawal. Norepinephrine and serotonin have long been shown to be involved in the development of tolerance to ethanol and barbiturates.[12] More recently, co-administration of glutamate receptor antagonists and opiates has been shown to block the development of tolerance to opiates.[160] This is again consistent with an associative component of tolerance.

Mechanisms at the molecular level for tolerance also probably overlap with those of dependence.[144] For example, up-regulation of the cAMP pathway could be a mechanism of tolerance, as mentioned earlier: the changes would be expected to oppose the acute actions of opiates of inhibiting adenylate cyclase. In addition, tolerance appears to involve the functional uncoupling of opioid receptors from their G proteins. The mechanisms underlying this uncoupling remain unknown, but they could involve drug-induced changes in the phosphorylation state of the receptors or G proteins that reduce their affinity for each other. Such phosphorylation of the receptor could occur via cAMP- or Ca^{2+}-dependent protein kinases known to be regulated by opiate exposure, or by other types of protein kinases (termed G protein receptor kinases or GRKs) that phosphorylate and desensitize receptors only when they are in their ligand-bound conformation.[146] Another possible mechanism of tolerance is drug-induced changes in the ion channels that mediate the acute effects of the drugs. For example, alterations in the phosphorylation state, amount, or even type of channel could conceivably contribute to drug tolerance.[143,161]

RELAPSE: NEURAL SUBSTRATES

Limited animal models exist for the study of relapse,[162] and this has significantly hampered the study of neurobiological mechanisms associated with this process. Neuropharmacological probes have been employed to reinstate self-administration in animals trained and then extinguished on intravenous drug self-administration; these probes have shown that drugs that activate the mesolimbic dopamine system rapidly reinstate intravenous self-administration.[163,164]

There are a limited number of observations using other models. Acamprosate, a drug being marketed in Europe to prevent relapse in alcoholics, has potential glutamate modulatory action.[165] It blocks the increase in drinking observed in rodents after a forced abstinence, again in nondependent rats,[166] and has efficacy in preventing relapse in detoxified human alcoholics.[167] Similarly, opioid antagonists were shown to prevent the increase in drinking of ethanol in animals after stress,[168] and subsequently naltrexone was shown to have efficacy in preventing relapse in detoxified human alcoholics.[88,89] Finally, a recent study reports that agonists selective for D_1 dopamine receptors, but not for D_2-like receptors, can block reinstatement of lever-pressing inferred to represent cocaine-seeking behavior.[169]

One thing that is clear from current studies of relapse is the need for better animal models. As improved animal models are developed, it will become possible to obtain a more complete understanding of the neurobiological mechanisms underlying this critical feature of drug addiction at the molecular, cellular, and system levels.

NEUROBIOLOGICAL SUBSTRATES AND CLINICAL IMPLICATIONS

To summarize, drug addiction centers on alteration of the neurobiological substrates of reinforcement. Much is known about the substrates for the acute positive reinforcing effects of drugs of abuse. The mesolimbic dopamine system and its connections form a focal point for our understanding of both dopamine-dependent and dopamine-independent effects. Indirect sympathomimetics such as cocaine and amphetamine are critically dependent on increased dopaminergic activity in the terminal areas of the mesolimbic dopamine system. Nicotine, opiates, and ethanol all activate the mesolimbic dopamine system but also recruit the actions of other neurotransmitters such as opioid peptides, serotonin, GABA, and glutamate. The neural substrates associated with the motivational aspects of dependence—tolerance, acute drug withdrawal, protracted abstinence, and vulnerability—remain largely to be determined but may involve molecular, cellular, and system-level adaptations to the same neurochemical elements implicated in the acute reinforcing actions of drugs of abuse. A subsystem of the basal forebrain termed the extended amygdala may play a particularly important role in the motivational aspects of drug reinforcement, both positive and negative.

The clinical implications of this work are numerous. Understanding the biological basis of a disease provides important insight for therapeutic intervention. Disturbances in specific signal transduction pathways in the brain that underlie addiction provide a conceptual anchor for psychotherapeutic as well as pharmacotherapeutic intervention. There are already new treatments for opiate and ethanol dependence that are based on a neurobiological understanding of these dis-

orders, and considerable activity is now centered on developing treatments for cocaine dependence as well. Basic research in the neurobiology of addiction also provides the key elements for identifying the biological basis of vulnerability to drug abuse and relapse that will guide the development of sound prevention interventions in vulnerable individuals.

References

1. World Health Organization: International Statistical Classification of Diseases and Related Health Problems, 10th revision. Geneva, World Health Organization, 1990
2. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th edition. Washington, DC, American Psychiatric Association, 1994
3. Institute of Medicine: Pathways of Addiction. Washington, DC, National Academy Press, 1996
4. Markou A, Weiss F, Gold LH, et al: Animal models of drug craving. Psychopharmacology (Berl) 1993; 112:163–182
5. White FJ, Wolf ME: Psychomotor stimulants, in The Biological Bases of Drug Tolerance and Dependence, edited by Pratt JA. London, Academic Press, 1991, pp 153–197
6. Koob GF: Dopamine, addiction and reward. Seminars in the Neurosciences 1992; 4:139–148
7. Stewart J, Badiani A: Tolerance and sensitization to the behavioral effects of drugs. Behav Pharmacol 1993; 4:289–312
8. Koob GF, Bloom FE: Cellular and molecular mechanisms of drug dependence. Science 1988; 242:715–723
9. Wikler A: Dynamics of drug dependence: implications of a conditioning theory for research and treatment. Arch Gen Psychiatry 1973; 28:611–616
10. Koob GF, Markou A, Weiss F, et al: Opponent process and drug dependence: neurobiological mechanisms. Seminars in the Neurosciences 1993; 5:351–358
11. Nestler EJ, Fitzgerald LW, Self DW: Substance abuse: neurobiology, in The American Psychiatric Press Review of Psychiatry, vol 14, edited by Oldham JM, Riba MB. Washington, DC, American Psychiatric Press, 1995, pp 51–81
12. Tabakoff B, Hoffman PL: Alcohol: neurobiology, in Substance Abuse: A Comprehensive Textbook, edited by Lowinson JH, Ruiz P, Millman RB. Baltimore, Williams and Wilkins, 1992, pp 152–185
13. Olds J, Milner P: Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. Journal of Comparative and Physiological Psychology 1954; 47:419–427
14. Stein L: Chemistry of reward and punishment, in Psychopharmacology: A Review of Progress (1957–1967) (US Public Health Service publ no 1836), edited by Efron DH. Washington, DC, US Government Printing Office, 1968, pp 105–123
15. Nauta WJH, Haymaker W: Hypothalamic nuclei and fiber connections, in The Hypothalamus, edited by Haymaker W, Anderson E, Nauta WJH. Springfield, IL, Charles C Thomas, 1969, pp 136–209
16. Liebman JL, Cooper SJ: The Neuropharmacological Basis of Reward. Oxford, Clarendon, 1989
17. Valenstein ES, Campbell JF: Medial forebrain bundle-lateral hypothalamic area and reinforcing brain stimulation. Am J Physiol 1966; 210:270–274
18. Koob GF: Drugs of abuse: anatomy, pharmacology, and function of reward pathways. Trends Pharmacol Sci 1992; 13:177–184
19. Kilty JE, Lorang D, Amara SG: Cloning and expression of a cocaine-sensitive rat dopamine transporter. Science 1991; 254:578–579
20. Blakely RD, Berson HE, Fremeau RT, et al: Cloning and expression of a functional serotonin transporter from rat brain. Nature 1991; 354:66–70
21. Giros B, El Mestikawy S, Bertrand L, et al: Cloning and functional characterization of a cocaine-sensitive dopamine transporter. FEBS Lett 1991; 295:149–154
22. Rudnick G, Clark J: From synapse to vesicle: the reuptake and storage of biogenic amine neurotransmitters. Biochim Biophys Acta 1993; 1144:249–263
23. O'Callaghan JP, Miller DB: Neurotoxicity profiles of substituted amphetamines in the C57BL/6J mouse. J Pharmacol Exp Ther 1994; 270:741–751
24. Angrist B, Sudilovsky A: Central nervous system stimulants: historical aspects and clinical effects, in Handbook of Psychopharmacology, vol 11, edited by Iversen LL, Iversen SD, Snyder SH. New York, Plenum, 1976, pp 99–165
25. Fischman MW, Schuster CR, Hatano Y: A comparison of the subjective and cardiovascular effects of cocaine and lidocaine in humans. Pharmacol Biochem Behav 1983; 18:123–127
26. Groppetti A, Zambotti F, Biazzi A, et al: Amphetamine and cocaine on amine turnover, in Frontiers in Catecholamine Research, edited by Usdin E, Snyder SH. New York, Pergamon, 1973, pp 917–925
27. Spealman RD, Goldberg SR, Kelleher RT, et al: Some effects of cocaine and two cocaine analogs on schedule-controlled behavior of squirrel monkeys. J Pharmacol Exp Ther 1977; 202:500–509
28. Kornetsky C, Esposito RU: Reward and detection thresholds for brain stimulation: dissociative effects of cocaine. Brain Res 1981; 209:496–500
29. Kornetsky C, Esposito RU: Euphorigenic drugs: effects on the reward pathways of the brain. Federation Proceedings 1979; 38:2473–2476
30. Mucha RF, van der Kooy D, O'Shaughnessy M, et al: Drug reinforcement studied by the use of place conditioning in rat. Brain Res 1982; 243:91–105
31. Carr GD, Fibiger HC, Phillips AG: Conditioned place preference as a measure of drug reward, in The Neuropharmacological Basis of Reward, edited by Liebman JM, Cooper SJ. New York, Oxford University Press, 1989, pp 264–319
32. Koob GF, Vaccarino FJ, Amalric M, et al: Positive reinforcement properties of drugs: search for neural substrates, in Brain Reward Systems and Abuse, edited by Engel J, Oreland L. New York, Raven, 1987, pp 35–50
33. Kelly PH, Seviour PW, Iversen SD: Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. Brain Res 1975; 94:507–522
34. Kelly PH, Iversen SD: Selective 6OHDA-induced destruction of mesolimbic dopamine neurons: Abolition of psychostimulant-induced locomotor activity in rats. Eur J Pharmacol 1976; 40:45–55
35. Pijnenburg AJJ, Honig WMM, Van Rossum JM: Inhibition of *d*-amphetamine-induced locomotor activity by injection of haloperidol into the nucleus accumbens of the rat. Psychopharmacologia 1975; 41:87–95
36. Yokel RA, Wise RA: Increased lever pressing for amphetamine after pimozide in rats: implications for a dopamine theory of reward. Science 1975; 187:547–549
37. Ettenberg A, Pettit HO, Bloom FE, et al: Heroin and cocaine intravenous self-administration in rats: mediation by separate neural systems. Psychopharmacology (Berl) 1982; 78:204–209
38. Caine SB, Koob GF: Pretreatment with the dopamine agonist 7-OH-DPAT shifts the cocaine self-administration dose-effect function to the left under different schedules in the rat. Behav Pharmacol 1995; 6:333–347
39. Koob GF, Le HT, Creese I: The D_1 dopamine receptor antagonist SCH 23390 increases cocaine self-administration in the rat. Neurosci Lett 1987; 79:315–320

40. Woolverton WL, Virus RM: The effects of a D_1 and a D_2 dopamine antagonist on behavior maintained by cocaine or food. Pharmacol Biochem Behav 1989; 32:691–697
41. Bergman J, Kamien JB, Spealman RD: Antagonism of cocaine self-administration by selective dopamine D_1 and D_2 antagonists. Behav Pharmacol 1990; 1:355–363
42. Caine SB, Koob GF: Modulation of cocaine self-administration in the rat through D-3 dopamine receptors. Science 1993; 260:1814–1816
43. Roberts DCS, Koob GF, Klonoff P, et al: Extinction and recovery of cocaine self-administration following 6-hydroxydopamine lesions of the nucleus accumbens. Pharmacol Biochem Behav 1980; 12:781–787
44. Lyness WH, Friedle NM, Moore KE: Destruction of dopaminergic nerve terminals in nucleus accumbens: effect of *d*-amphetamine self-administration. Pharmacol Biochem Behav 1979; 11:553–556
45. Caine SB, Koob GF: Effects of mesolimbic dopamine depletion on responding maintained by cocaine and food. J Exp Anal Behav 1994; 61:213–221
46. Schuster CR, Thompson T: Self administration of and behavioral dependence on drugs. Annu Rev Pharmacol 1969; 9:483–502
47. Deneau G, Yanagita T, Seevers MH: Self-administration of psychoactive substances by the monkey: a measure of psychological-dependence. Psychopharmacologia 1969; 16:30–48
48. Koob GF, Pettit HO, Ettenberg A, et al: Effects of opiate antagonists and their quaternary derivatives on heroin self-administration in the rat. J Pharmacol Exp Ther 1984; 229:481–486
49. Goldberg SR, Woods JH, Schuster CR: Nalorphine-induced changes in morphine self-administration in rhesus monkeys. J Pharmacol Exp Ther 1971; 176:464–471
50. Weeks JR, Collins RJ: Changes in morphine self-administration in rats induced by prostaglandin E_1 and naloxone. Prostaglandins 1976; 12:11–19
51. Vaccarino FJ, Pettit HO, Bloom FE, et al: Effects of intracerebroventricular administration of methyl naloxonium chloride on heroin self-administration in the rat. Pharmacol Biochem Behav 1985; 23:495–498
52. Negus SS, Henriksen SJ, Mattox SR, et al: Effects of antagonists selective for mu, delta and kappa opioid receptors on the reinforcing effects of heroin in rats. J Pharmacol Exp Ther 1993; 265:1245–1252
53. Britt MD, Wise RA: Ventral tegmental site of opiate reward: antagonism by a hydrophilic opiate receptor blocker. Brain Res 1983; 258:105–108
54. Vaccarino FJ, Bloom FE, Koob GF: Blockade of nucleus accumbens opiate receptors attenuates intravenous heroin reward in the rat. Psychopharmacology (Berl) 1985; 86:37–42
55. Schroeder RL, Weinger MB, Vakassian L, et al: Methylnaloxonium diffuses out of the rat brain more slowly than naloxone after direct intracerebral injection. Neurosci Lett 1991; 121:173–177
56. Goeders NE, Lane JD, Smith JE: Self-administration of methionine enkephalin into the nucleus accumbens. Pharmacol Biochem Behav 1984; 20:451–455
57. Pettit HO, Ettenberg A, Bloom FE, et al: Destruction of dopamine in the nucleus accumbens selectively attenuates cocaine but not heroin self-administration in rats. Psychopharmacology (Berl) 1984; 84:167–173
58. Stinus L, Cador M, Le Moal M: Interaction between endogenous opioids and dopamine within the nucleus accumbens. Ann NY Acad Sci 1992; 654:254–273
59. West TE: The effects of nucleus accumbens injections of receptor-selective opiate agonists on brain stimulation reward. Doctoral dissertation, Concordia University, Montreal, Quebec, Canada, 1991
60. Pert A, Sivit C: Neuroanatomical focus for morphine and enkephalin-induced hypermotility. Nature 1977; 265:645–647
61. Di Chiara G, Imperato A: Opposite effects of mu and kappa opiate agonists on dopamine release in the nucleus accumbens and in the dorsal caudate of freely moving rats. J Pharmacol Exp Ther 1988; 244:1067–1080
62. Hemby SE, Martin TJ, Co C, et al: The effects of intravenous heroin administration on extracellular nucleus accumbens dopamine concentrations as determined by in vivo microdialysis. J Pharmacol Exp Ther 1995; 273:591–598
63. Bozarth MA, Wise RA: Intracranial self-administration of morphine into the ventral tegmental area in rats. Life Sci 1981; 28:551–555
64. Di Chiara G, North RA: Neurobiology of opiate abuse. Trends Pharmacol Sci 1992; 13:185–193
65. Stinus L, Nadaud D, Deminiere JM, et al: Chronic flupentixol treatment potentiates the reinforcing properties of systemic heroin administration. Biol Psychiatry 1989; 26:363–371
66. Spyraki C, Fibiger HC, Phillips AG: Attenuation of heroin reward in rats by disruption of the mesolimbic dopamine system. Psychopharmacology (Berl) 1983; 79:278–283
67. Shippenberg TS, Herz A, Spanagel R, et al: Conditioning of opioid reinforcement: neuroanatomical and neurochemical substrates. Ann NY Acad Sci 1992; 654:347–356
68. Sepinwall J, Cook L: Behavioral pharmacology of anti-anxiety drugs, in Handbook of Psychopharmacology, vol 13, edited by Iversen LL, Iversen SD, Snyder SH. London, Plenum, 1978, pp 345–393
69. Richards G, Schoch P, Haefely W: Benzodiazepine receptors: new vistas. Seminars in the Neurosciences 1991; 3:191–203
70. Suzdak PD, Glowa JR, Crawley JN, et al: A selective imidazobenzodiazepine antagonist of ethanol in the rat. Science 1986; 234:1243–1247
71. Koob GF, Britton KT: Neurobiological substrates for the anti-anxiety effects of ethanol, in The Pharmacology of Alcohol and Alcohol Dependence, edited by Begleiter H, Kissin B. New York, Oxford University Press, 1996, pp 477–506
72. Frye GD, Breese GR: GABAergic modulation of ethanol-induced motor impairment. J Pharmacol Exp Ther 1982; 223:750–756
73. Liljequist S, Engel J: Effects of GABAergic agonists and antagonists on various ethanol-induced behavioral changes. Psychopharmacology (Berl) 1982; 78:71–75
74. Samson HH, Tolliver GA, Pfeffer AO, et al: Oral ethanol reinforcement in the rat: effect of the partial inverse benzodiazepine agonist Ro 15-4513. Pharmacol Biochem Behav 1987; 27:517–519
75. Rassnick S, D'Amico E, Riley E, et al: GABA antagonist and benzodiazepine partial inverse agonist reduce motivated responding for ethanol. Alcohol Clin Exp Res 1993; 17:124–130
76. Fitzgerald LW, Nestler EJ: Molecular and cellular adaptations in signal transduction pathways following ethanol exposure. Clin Neurosci 1995; 3:165–173
77. Hoffman PL, Rabe C, Moses F, et al: *N*-methyl-D-aspartate receptors and ethanol: inhibition of calcium flux and cyclic GMP production. J Neurochem 1989; 52:1937–1940
78. Lovinger DM, White G, Weight FF: Ethanol inhibits NMDA-activated ion current in hippocampal neurons. Science 1989; 243:1721–1724
79. Tsai G, Gastfriend DR, Coyle JT: The glutamatergic basis of human alcoholism. Am J Psychiatry 1995; 152:332–340
80. Pfeffer AO, Samson HH: Haloperidol and apomorphine effects on ethanol reinforcement in free feeding rats. Pharmacol Biochem Behav 1988; 29:343–350
81. Weiss F, Lorang MT, Bloom FE, et al: Ethanol self-administration stimulates dopamine release in the rat nucleus accumbens: genetic and motivational determinants. J Pharmacol Exp Ther 1993; 267:250–258
82. Rassnick S, Stinus L, Koob GF: The effects of 6-hydroxydopamine lesions of the nucleus accumbens and the mesolimbic dopamine system on oral self-administration of ethanol in the rat. Brain Res 1993; 623:16–24
83. Engel JA, Enerback C, Fahlke C, et al: Serotonergic and dopaminergic involvement in ethanol intake, in Novel Pharmacological Interventions for Alcoholism, edited by Naranjo CA, Sellers EM. New York, Springer, 1992, pp 68–82

84. Sellars EM, Higgins GA, Sobell MB: 5-HT and alcohol abuse trends. Pharmacol Sci 1992; 13:69–75
85. Naranjo C, Kadlec K, Sanhueza P, et al: Fluoxetine differentially alters alcohol intake and other consummatory behaviors in problem drinkers. Clin Pharmacol Ther 1990; 47:490–498
86. Hubbell CL, Marglin SH, Spitalnic SJ, et al: Opioidergic, serotonergic, and dopaminergic manipulations and rats' intake of a sweetened alcoholic beverage. Alcohol 1991; 8:355–367
87. Hyytia P: Involvement of μ-opioid receptors in alcohol drinking by alcohol-preferring AA rats. Pharmacol Biochem Behav 1993; 45:697–701
88. O'Malley SS, Jaffe AJ, Chang G, et al: Naltrexone and coping skills therapy for alcohol dependence: a controlled study. Arch Gen Psychiatry 1992; 49:881–887
89. Volpicelli JR, Alterman AI, Hayashida M, et al: Naltrexone in the treatment of alcohol dependence. Arch Gen Psychiatry 1992; 49:876–880
90. Malin DH, Lake JR, Carter VA, et al: Naloxone precipitates nicotine abstinence syndrome in the rat. Psychopharmacology (Berl) 1993; 112:339–342
91. Malin DH, Lake JR, Carter VA, et al: The nicotine antagonist mecamylamine precipitates nicotine abstinence syndrome in the rat. Psychopharmacology (Berl) 1994; 115:180–184
92. Corrigall WA, Franklin KBJ, Coen KM, et al: The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. Psychopharmacology (Berl) 1992; 107:285–289
93. Alheid GF, Heimer L: New perspectives in basal forebrain organization of special relevance for neuropsychiatric disorders: the striatopallidal, amygdaloid, and corticopetal components of substantia innominata. Neuroscience 1988; 27:1–39
94. Johnston JB: Further contributions to the study of the evolution of the forebrain. J Comp Neurol 1923; 35:337–481
95. Heimer L, Alheid G: Piecing together the puzzle of basal forebrain anatomy, in The Basal Forebrain: Anatomy to Function, edited by Napier TC, Kalivas PW, Hanin I. New York, Plenum, 1991, pp 1–42
96. Heimer L, Zahm DS, Churchill L, et al: Specificity in the projection patterns of accumbal core and shell in the rat. Neuroscience 1991; 41:89–125
97. Caine SB, Heinrichs SC, Coffin VL, et al: Effects of the dopamine D-1 antagonist SCH 23390 microinjected into the accumbens, amygdala or striatum on cocaine self-administration in the rat. Brain Res 1995; 692:47–56
98. Pontieri FE, Tanda G, Di Chiara G: Intravenous cocaine, morphine, and amphetamine preferentially increase extracellular dopamine in the "shell" as compared with the "core" of the rat nucleus accumbens. Proc Natl Acad Sci USA 1995; 92:12304–12308
99. Hyytia P, Koob GF: $GABA_A$ receptor antagonism in the extended amygdala decreases ethanol self-administration in rats. Eur J Pharmacol 1995; 283:151–159
100. Heyser CJ, Roberts AJ, Schulteis G, et al: Central administration of an opiate antagonist decreases oral ethanol self-administration in rats (abstract). Society for Neuroscience Abstracts 1995; 21:1698
101. Pich EM, Lorang M, Yeganeh M, et al: Increase of extracellular corticotropin-releasing factor-like immunoreactivity levels in the amygdala of awake rats during restraint stress and ethanol withdrawal as measured by microdialysis. J Neurosci 1995; 15:5439–5447
102. Aghajanian GK: Tolerance of locus coeruleus neurons to morphine and suppression of withdrawal response by clonidine. Nature 1978; 276:186–188
103. Taylor JR, Elsworth JD, Garcia EJ, et al: Clonidine infusions into the locus coeruleus attenuate behavioral and neurochemical changes associated with naloxone-precipitated withdrawal. Psychopharmacology (Berl) 1988; 96:121–134
104. Maldonado R, Stinus L, Gold LH, et al: Role of different brain structures in the expression of the physical morphine withdrawal syndrome. J Pharmacol Exp Ther 1992; 261:669–677
105. Grant KA, Valverius P, Hudspith M, et al: Ethanol withdrawal seizures and the NMDA receptor complex. Eur J Pharmacol 1990; 176:289–296
106. Littleton J, Little H, Laverty R: Role of neuronal calcium channels in ethanol dependence: from cell cultures to the intact animal. Ann NY Acad Sci 1992; 654:324–334
107. Gawin FH, Kleber HD: Abstinence symptomatology and psychiatric diagnosis in cocaine abusers: clinical observations. Arch Gen Psychiatry 1986; 43:107–113
108. Weddington WW, Brown BS, Haertzen CA, et al: Changes in mood, craving, and sleep during short-term abstinence reported by male cocaine addicts: a controlled, residential study. Arch Gen Psychiatry 1990; 47:861–868
109. Esposito RU, Motola AHD, Kornetsky C: Cocaine: acute effects on reinforcement thresholds for self-stimulation behavior to the medial forebrain bundle. Pharmacol Biochem Behav 1978; 8:437–439
110. Kokkinidis L, Zacharko RM, Predy PA: Post-amphetamine depression of self-stimulation responding from the substantia nigra: reversal by tricyclic antidepressants. Pharmacol Biochem Behav 1980; 13:379–383
111. Kokkinidis L, Zacharko RM, Anisman H: Amphetamine withdrawal: a behavioral evaluation. Life Sci 1986; 38:1617–1623
112. Frank RA, Martz S, Pommering T: The effect of chronic cocaine on self-stimulation train-duration thresholds. Pharmacol Biochem Behav 1988; 29:755–758
113. Schaefer GJ, Michael RP: Changes in response rates and reinforcement thresholds for intracranial self-stimulation during morphine withdrawal. Pharmacol Biochem Behav 1986; 25:1263–1269
114. Schulteis G, Markou A, Cole M, et al: Decreased brain reward produced by ethanol withdrawal. Proc Natl Acad Sci USA 1995; 92:5880–5884
115. Hubner CB, Kornetsky C: Heroin, 6-acetylmorphine, and morphine effects on threshold for rewarding and aversive brain stimulation. J Pharmacol Exp Ther 1992; 260:562–567
116. Huston-Lyons D, Kornetsky C: Effects of nicotine on the threshold for rewarding brain stimulation in rats. Pharmacol Biochem Behav 1992; 41:755–759
117. Bauco P, Wise RA: Potentiation of lateral hypothalamic and midline mesencephalic brain stimulation reinforcement by nicotine: examination of repeated treatment. J Pharmacol Exp Ther 1994; 271:294–301
118. Kornetsky C, Moolten M, Bain G: Ethanol and rewarding brain stimulation, in Neuropharmacology of Ethanol, edited by Meyer RE, Koob GF, Lewis MJ, et al. Boston, Birkhauser, 1991, pp 179–199
119. Schulteis G, Markou A, Cole M, et al: Decreased brain reward produced by ethanol withdrawal. Proc Natl Acad Sci USA 1995; 92:5880–5884
120. Leith NJ, Barrett RJ: Amphetamine and the reward system: evidence for tolerance and post-drug depression. Psychopharmacologia 1976; 46:19–25
121. Parsons LH, Koob GF, Weiss F: Serotonin dysfunction in the nucleus accumbens of rats during withdrawal after unlimited access to intravenous cocaine. J Pharmacol Exp Ther 1995; 274:1182–1191
122. Markou A, Koob GF: Post-cocaine anhedonia: an animal model of cocaine withdrawal. Neuropsychopharmacology 1991; 4:17–26
123. Markou A, Koob GF: Construct validity of a self-stimulation threshold paradigm: effects of reward and performance manipulations. Physiol Behav 1992; 51:111–119
124. Legault M, Wise RA: Effects of withdrawal from nicotine on intracranial self-stimulation (abstract). Society for Neuroscience Abstracts 1994; 20:1032
125. Koob GF: Drug addiction: the yin and yang of hedonic homeostasis. Neuron 1996; 16:893–896
126. Robinson TE, Berridge KC: The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Rev 1993; 18:247–291

127. Solomon RL, Corbit JD: An opponent-process theory of motivation, I: temporal dynamics of affect. Psychol Rev 1974; 81:119–145
128. Siegel S: Evidence from rats that morphine tolerance is a learned response. Journal of Comparative and Physiological Psychology 1975; 89:498–506
129. Poulos CX, Cappell H: Homeostatic theory of drug tolerance: a general model of physiological adaptation. Psychol Rev 1991; 98:390–408
130. Weiss F, Markou A, Lorang MT, et al: Basal extracellular dopamine levels in the nucleus accumbens are decreased during cocaine withdrawal after unlimited-access self-administration. Brain Res 1992; 593:314–318
131. Stinus L, Le Moal M, Koob GF: Nucleus accumbens and amygdala as possible substrates for the aversive stimulus effects of opiate withdrawal. Neuroscience 1990; 37:767–773
132. Roberts AJ, Cole M, Koob GF: Intra-amygdala muscimol decreases operant ethanol self-administration in dependent rats. Alcohol Clin Exp Res 1996; 20:1289–1298
133. Weiss F, Parsons LH, Schulteis G, et al: Ethanol self-administration restores withdrawal-associated deficiencies in accumbal dopamine and 5-hydroxytryptamine release in dependent rats. J Neurosci 1996; 16:3474–3485
134. Collins AC, Bhat RV, Pauly JR, et al: Modulation of nicotine receptors by chronic exposure to nicotinic agonists and antagonists, in The Biology of Nicotine Dependence, edited by Bock G, Marsh J. New York, Wiley, 1990, pp 87–105
135. Dani JA, Heinemann S: Molecular and cellular aspects of nicotine abuse. Neuron 1996; 16:905–908
136. Koob GF, Heinrichs SC, Menzaghi F, et al: Corticotropin-releasing factor, stress and behavior. Seminars in the Neurosciences 1994; 7:221–229
137. Piazza PV, Le Moal M: Pathophysiological basis of vulnerability to drug abuse: role of an interaction between stress, glucocorticoids, and dopaminergic neurons. Annu Rev Pharmacol Toxicol 1996; 36:359–378
138. Henry DJ, White FJ: Repeated cocaine administration causes persistent enhancement of D_1 dopamine receptor sensitivity within the rat nucleus accumbens. J Pharmacol Exp Ther 1991; 258:882–890
139. Maldonado R, Koob GF: Destruction of the locus coeruleus decreases physical signs of opiate withdrawal. Brain Res 1993; 605:128–138
140. Rasmussen K, Beitner-Johnson DB, Krystal JH, et al: Opiate withdrawal and rat locus coeruleus: behavioral, electrophysiological, and biochemical correlates. J Neurosci 1990; 10:2308–2317
141. Koob GF, Maldonado R, Stinus L: Neural substrates of opiate withdrawal. Trends Neurosci 1992; 15:186–191
142. Gold MS, Redmond DE, Kleber HD: Clonidine blocks acute opiate-withdrawal symptoms. Lancet 1978; 2:599–602
143. Nestler EJ: Molecular mechanisms of drug addiction. J Neurosci 1992; 12:2439–2450
144. Nestler EJ, Hope BT, Widnell KL: Drug addiction: a model for the molecular basis of neural plasticity. Neuron 1993; 11:995–1006
145. Collier HOJ: Cellular site of opiate dependence. Nature 1980; 283:625–629
146. Nestler EJ: Under siege: The brain on opiates. Neuron 1996; 16:897–900
147. Sharma SK, Klee WA, Nirenberg M: Dual regulation of adenylate cyclase accounts for narcotic dependence and tolerance. Proc Natl Acad Sci USA 1975; 72:3092–3096
148. Alreja M, Aghajanian GK: Opiates suppress a resting sodium-dependent inward current and activate an outward potassium current in locus coeruleus neurons. J Neurosci 1993; 13:3525–3532
149. Widnell KL, Russell D, Nestler EJ: Regulation of expression of cAMP response element-binding protein in the locus coeruleus in vivo and in a locus coeruleus-like cell line in vitro. Proc Natl Acad Sci USA 1994; 91:10947–10951
150. Maldonado R, Blendy JA, Tzavara E, et al: Reduction of morphine abstinence in mice with a mutation in the gene encoding CREB. Science 1996; 273:657–659
151. Rasmussen K, Aghajanian GK: Withdrawal-induced activation of locus coeruleus neurons in opiate-dependent rats: attenuation by lesion of the nucleus paragigantocellularis. Brain Res 1989; 505:346–350
152. Akaoka H, Aston-Jones G: Opiate withdrawal–induced hyperactivity of locus coeruleus neurons is substantially mediated by augmented excitatory acid input. J Neurosci 1991; 11:3830–3839
153. Self DW, Nestler EJ: Molecular mechanisms of drug reinforcement and addiction. Annu Rev Neurosci 1995; 18:463–495
154. Nestler EJ: Molecular neurobiology of drug addiction. Neuropsychopharmacology 1994; 11:77–87
155. Hope BT, Nye HE, Kelz MB, et al: Induction of a long-lasting AP-1 complex composed of altered Fos-like proteins in brain by chronic cocaine and other chronic treatments. Neuron 1994; 13:1235–1244
156. Hyman SE: Addiction to cocaine and amphetamine. Neuron 1996; 16:901–904
157. Widnell K, Self DW, Lane SB, et al: Regulation of CREB expression: in vivo evidence for a functional role in morphine action in the nucleus accumbens. J Pharmacol Exp Ther 1996; 276:306–315
158. Li DH, Depoortere RY, Emmett-Oglesby MW: Tolerance to the reinforcing effects of cocaine in a progressive ratio paradigm. Psychopharmacology (Berl) 1994; 116:326–332
159. Young AM, Goudie AJ: Adaptive processes regulating tolerance to the behavioral effects of drugs, in Psychopharmacology: The Fourth Generation of Progress, edited by Bloom FE, Kupfer DJ. New York, Raven, 1995, pp 733–742
160. Trujillo KA, Akil H: Inhibition of morphine tolerance and dependence by the NMDA receptor antagonist MK-801. Science 1991; 251:85–87
161. Kovoor A, Henry DJ, Chavkin C: Agonist-induced desensitization of the mu opioid receptor-coupled potassium channel (GIRK1). J Biol Chem 1995; 270:589–595
162. Koob GF: Animal models of drug addiction, in Psychopharmacology: The Fourth Generation of Progress, edited by Bloom FE, Kupfer DJ. New York, Raven, 1995, pp 759–772
163. deWit H, Stewart J: Reinstatement of cocaine-reinforced responding in the rat. Psychopharmacology (Berl) 1981; 75:134–143
164. Stewart J, deWit H: Reinstatement of drug-taking behavior as a method of assessing incentive motivational properties of drugs, in Methods of Assessing the Reinforcing Properties of Abused Drugs, edited by Bozarth MA. New York, Springer-Verlag, 1987, pp 211–227
165. O'Brien CP, Eckardt MJ, Linnoila VMI: Pharmacotherapy of alcoholism, in Psychopharmacology: The Fourth Generation of Progress, edited by Bloom FE, Kupfer DJ. New York, Raven, 1995, pp 1745–1755
166. Heyser CJ, Schulteis G, Durbin P, et al: Chronic acamprosate decreases deprivation-induced ethanol self-administration in rats. Neuropsychopharmacology (in press)
167. Sass H, Soyka M, Mann K, et al: Relapse prevention by acamprosate: results from a placebo-controlled study on alcohol dependence. Arch Gen Psychiatry 1996; 53:673–680
168. Volpicelli JR, Davis MA, Olgin JE: Naltrexone blocks the post-shock increase of ethanol consumption. Life Sci 1986; 38:841–847
169. Self DW, Barnhart WJ, Lehman DA, et al: Opposite modulation of cocaine-seeking behavior by D_1- and D_2-like dopamine receptor agonists. Science 1996; 271:1586–1589