REVIEW ARTICLE

MECHANISMS OF DISEASE

Drug Addiction

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DRUG ADDICTION IS A CHRONIC, RELAPSING DISORDER IN WHICH compulsive drug-seeking and drug-taking behavior persists despite serious negative consequences. Addictive substances induce pleasant states (euphoria in the initiation phase) or relieve distress. Continued use induces adaptive changes in the central nervous system that lead to tolerance, physical dependence, sensitization, craving, and relapse (Table 1). The addictive drugs discussed here are opioids, cannabinoids, ethanol, cocaine, amphetamines, and nicotine.

The World Health Organization[1] and the American Psychiatric Association[2] use the term "substance dependence" rather than "drug addiction." "Drug addiction," however, emphasizes the behavioral connotation of the term and is less likely to be confused with physical dependence.[3] We use both terms interchangeably in this review. The American Psychiatric Association's definition of substance dependence[2] requires a patient to meet at least three of the seven criteria listed in Table 1. Tolerance and physical dependence reflect physiological adaptation to the effects of a drug, whereas the remaining criteria define uncontrollable drug consumption. However, tolerance and physical dependence are neither necessary nor sufficient for a diagnosis of substance dependence. Substance abuse[2] or harmful use,[1] a less severe disorder, may result in dependence.

Theories of addiction have mainly been developed from neurobiologic evidence and data from studies of learning behavior and memory mechanisms. They overlap in some aspects and are not mutually exclusive. None of them alone can explain all aspects of addiction. It is not our purpose to present a detailed assessment of these theories, especially because of the complexity of the problem. Generally, addictive drugs can act as positive reinforcers (producing euphoria) or as negative reinforcers (alleviating symptoms of withdrawal or dysphoria). Environmental stimuli (cues) associated with drug use itself can also induce a conditioned response (withdrawal or craving) in the absence of the drug.[4,5]

Koob and Le Moal[6,7] have proposed that the organism tries to counteract the effects of a given drug through a vicious circle in which the hedonic set point (the point at which pleasure is achieved) continually changes in response to the administration of the substance. They argue that drug addiction results from dysregulation of the reward mechanism and subsequent allostasis, the ability to achieve stability through change. Robinson and Berridge[8,9] emphasize the dissociation between the incentive value of the drug ("wanting") and its pleasurable or hedonic effects ("liking"), so that the brain system involved in the reward mechanism becomes hypersensitized to both the direct effects of the drug and associated stimuli that are not directly attributable to the drug. This hypersensitization causes pathologic wanting, or craving, independently of the presence of withdrawal symptoms and leads to compulsive drug-seeking and drug-taking behavior. Although liking progressively decreases, drugs become pathologically wanted (craving). Complementary to this incentive–sensitization theory,[8,9] compulsive drug-seeking and drug-taking behavior is facilitated by difficulties in decision making and the ability to judge the consequences of one's own actions. These cognitive difficulties have been linked to deficits in the activation of areas in the prefrontal cortex.[10,11] An overlap in

Table 1. Definitions of Terms Used in Drug Addiction.

Craving (formerly called **psychological dependence**) is an intense desire to re-experience the effects of a psychoactive substance. Craving is the cause of relapse after long periods of abstinence.

Physical or physiological dependence is an outdated term that refers to physical tolerance and the withdrawal syndrome.

Priming refers to a new exposure to a formerly abused substance. This exposure can precipitate rapid resumption of abuse at previous levels or at higher levels.

Relapse is a resumption of drug-seeking or drug-taking behavior after a period of abstinence. Priming, environmental cues (people, places, or things associated with past drug use), and stress can trigger intense craving and cause a relapse.

Reward is a stimulus that the brain interprets as intrinsically positive or as something to be attained.

Sensitization is the increase in the expected effect of a drug after repeated administration (e.g., increased locomotor activation after the administration of psychostimulants). Sensitization also refers to persistent hypersensitivity to the effect of a drug in a person with a history of exposure to that drug (or to stress). Sensitization is one of the neurobiologic mechanisms involved in craving and relapse.

Substance abuse is characterized by recurrent and clinically significant adverse consequences related to the repeated use of substances, such as failing to fulfill major role obligations, use of drugs in situations in which it is physically hazardous, occurrence of substance-related legal problems, and continued drug use despite the presence of persistent or recurrent social or interpersonal problems.

Substance dependence is a cluster of cognitive, behavioral, and physiological symptoms indicating that a person is continuing to use a substance despite having clinically significant substance-related problems. For substance dependence to be diagnosed, at least three of the following must be present: symptoms of tolerance; symptoms of withdrawal; the use of a substance in larger amounts or for longer periods than intended; persistent desire or unsuccessful attempts to reduce or control use; the spending of considerable time in efforts to obtain the substance; a reduction in important social, occupational, or recreational activities because of drug use; and continued use of a substance despite attendant health, social, or economic problems.

Withdrawal syndrome is a constellation of signs and symptoms that follows the abrupt discontinuation or reduction in the use of a substance or after blockage of the actions of a substance with antagonists (e.g., naloxone in heroin addiction). The syndrome can also be produced by cues associated with substance use (**conditioned withdrawal**). Symptoms tend to be the opposite of those produced after short-term exposure to a drug. Withdrawal is one of the causes of compulsive drug-taking behavior and short-term relapse.

memory mechanisms and the mechanisms of drug addiction has also been proposed.[12]

FACTORS INFLUENCING DRUG ABUSE AND DEPENDENCE

PHARMACOLOGIC AND PHYSICOCHEMICAL PROPERTIES OF DRUGS

Pharmacologic and physicochemical properties of drugs are important factors in how drugs are consumed. Liposolubility increases the passage of a drug through the blood–brain barrier, water solubility facilitates the injection of a drug, volatility favors the inhalation of drugs in vapor form, and heat resistance favors smoking of the drug.[13] Characteristics such as rapid onset and intensity of effect increase the potential for abuse[14,15]; therefore, substances that rapidly reach high levels in the brain are usually preferred (e.g., flunitrazepam is preferred over triazolam, and smoking "crack" cocaine is preferred to intranasal administration).[16,17] A short half-life (e.g., that of heroin) produces more abrupt and intense syndromes of withdrawal than does a long half-life (e.g., that of methadone).[13]

PERSONALITY AND PSYCHIATRIC DISORDERS

Personality traits and mental disorders are major conditioning factors in drug addiction. Risk-taking or novelty-seeking traits favor the use of addictive drugs.[18] Polydrug use is frequent among those with drug addiction, and many fulfill the criteria for dependence on or abuse of (or both) more than one substance.[19] Psychiatric disorders, particularly schizophrenia, bipolar disorder, depression, and attention-deficit–hyperactivity disorder, are associated with an increased risk of abuse. A dual diagnosis (substance abuse and mental disorder) has unfavorable implications for management and outcome.[20]

GENETIC FACTORS

Genetic factors that influence the metabolism and the effects of drugs contribute to the risk of addiction.[21] Men whose parents were alcoholics have an increased likelihood of alcoholism even when they were adopted at birth and raised by parents who were not alcoholic, and they also have a reduced sensitivity to alcohol that predicts the development of alcoholism.[22] Carriers of an allele of aldehyde dehydrogenase that encodes an isoenzyme with reduced activity are less likely to abuse alcohol owing to the presence of increased levels of acetaldehyde, which is responsible for aversive effects.[23] A Leu7Pro polymorphism of the neuropeptide Y gene has been correlated with increased alcohol consumption,[24] and single-nucleotide polymorphisms of the gene encoding the μ opioid receptor correlates with an increased likelihood of heroin abuse.[25] A deficiency in the cytochrome P-450 2D6 gene blocks the enzymatic conversion of codeine to morphine, thereby preventing codeine abuse.[26]

With regard to nicotine dependence, subjects with defective cytochrome P-450 2A6 *2 and *4 alleles, which impair the metabolism of nicotine,

smoke fewer cigarettes and are less likely to be dependent than subjects who are homozygous for these alleles.[27] A single-nucleotide polymorphism in the gene encoding fatty acid amide hydrolase, a major endocannabinoid-inactivating enzyme, has recently been associated with both an increased likelihood of recreational use of illegal drugs and problem use of drugs or alcohol.[28] The minor (A1) allele of the *Taq*IA D2 dopamine receptor gene has been linked to severe alcoholism; polysubstance, psychostimulant abuse or dependence; and opioid and nicotine dependence.[29] Advances in genomic scanning (for quantitative trait loci) will allow the identification of allelic variants that contribute to the vulnerability to addiction.[30]

DRUG EFFECTS AND MECHANISMS OF ACTION

OPIOIDS

Short-term administration of heroin or morphine produces euphoria, sedation, and a feeling of tranquility. Repeated administration rapidly produces tolerance and intense physical dependence. Overdose can cause lethal respiratory depression. Numerous reports have documented impairments in health related to long-term heroin use.[31,32]

Opioids activate specific receptors (μ, δ, and κ) that couple the G protein (Fig. 1 and 2). Knockout mice lacking the μ receptor neither exhibit the behavioral effects induced by opioids nor become physically dependent when given opioids (Table 2). The μ receptor has also been implicated in mediating or modulating the rewarding effect of other drugs of abuse (e.g., cannabinoids). Mice in which different receptors (CB_1 cannabinoid and D2 dopamine receptors) and transporters (dopamine) have been knocked out have been used to demonstrate the effect of systems other than the opioid on opioid-induced pharmacologic responses.[33]

CANNABINOIDS

The use of marijuana or hashish produces feelings of relaxation and well-being and impairs cognitive function and performance of psychomotor tasks. Overdose can induce panic attack and psychosis.[34] A high incidence of cannabis consumption has been reported among patients with schizophrenia.[35] Symptoms of withdrawal — restlessness, irritability, and insomnia — are subtle and appear in heavy consumers.[36] The long-term effects of high doses of cannabinoids is a complex and controversial subject. Although there is evidence that long-term use of cannabis impairs memory,[37,38] the cause of the marijuana amotivational syndrome — loss of energy and drive to work — remains unclear.[34]

G-protein–coupled cannabinoid CB_1 receptors (Fig. 1 and 2), which are richly distributed in basal ganglia and cerebral-cortex regions, are implicated in cannabinoid abuse and addiction. In contrast to other neurotransmitters, endocannabinoids act as retrograde messengers at many central synapses. They are released from postsynaptic neurons and activate CB_1 receptors on presynaptic neurons, inhibiting the release of neurotransmitters.[39] Natural ligands of CB_1 receptors (anandamide, 2-arachidonylglycerol, and noladin ether) have a shorter period of action than synthetic or plant-derived cannabinoids.[39] Selective synthetic agonists and antagonists of CB_1 receptors are currently being developed for medical purposes.[40,41]

ETHANOL

When ethanol is given at low doses or initially during acute ethanol intoxication, it is perceived as a stimulant owing to the suppression of central inhibitory systems, but as the plasma levels of ethanol increase, sedation, motor incoordination, ataxia, and impaired psychomotor performance appear.[42] The withdrawal syndrome (seizures and delirium tremens) may be severe and clinically challenging. The long-term effects of ethanol consumption have been extensively reviewed elsewhere.[43,44]

Ethanol modifies the activity of serotonin (5-hydroxytryptamine$_3$ [5-HT$_3$]) receptors, nicotinic receptors, γ-aminobutyric acid type A ($GABA_A$) receptors, and the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors. Ethanol acutely inhibits binding to the δ-opioid receptor, and long-term exposure to ethanol increases the density of μ and δ receptors.[45] Its actions on nearly all receptors are the result of a direct interaction with the receptor protein.[46]

COCAINE AND AMPHETAMINES

Short-term administration of psychostimulants such as amphetamine produces euphoria, a feeling of well-being, and alertness as well as increased arousal, concentration, and motor activity. These substances increase blood pressure and the pulse rate and induce the release of corticotropin-releasing factor, corticotropin, and cortisol.[47-49] Long-term use may cause irritability, aggressive and stereotyped behavior, and paranoid-like psychosis.

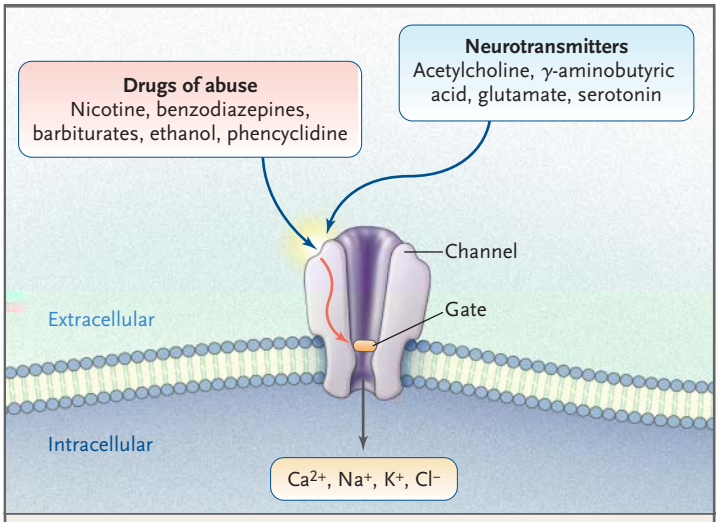

Figure 1. Ionotropic Mechanisms of Action of Drugs of Abuse.

Drugs of abuse are usually receptor agonists, such as endogenous neurotransmitters, that act on two different types of membrane receptors: ionotropic (shown in this figure) and metabotropic (shown in Fig. 2). Ionotropic receptors (ligand-gated ion channels) mediate fast synaptic transmission. The neurotransmitter or the drug binds to the receptor, which undergoes a conformational change, opening the gate and allowing ions to enter the cytoplasm and causing depolarization or polarization of the membrane and activation of various proteins. Nicotine binds to nicotinic cholinergic receptors, which contain a sodium channel. Benzodiazepines, barbiturates, and ethanol bind to γ-aminobutyric acid (GABA) type A receptors, facilitating the entry of chloride. Ethanol and phencyclidine inhibit *N*-methyl-D-aspartate–sensitive glutamate receptors, which contain calcium and sodium channels. Phencyclidine also acts as an antagonist.

Whereas signs of withdrawal can be mild (depression, lack of energy, and insomnia), craving is very intense.[50] So-called designer derivatives of amphetamine (3,4-methylenedioxymethamphetamine [MDMA], or "ecstasy") produce euphoria[51,52] and increased empathy (an "entactogenic" effect), but some derivatives have hallucinogenic effects. Acute intoxication with a psychostimulant can cause cerebral hemorrhage, hyperthermia and heat stroke, the serotonin syndrome, panic, and psychosis. The serotonin syndrome is characterized by altered mental status, autonomic instability, and neuromuscular abnormalities resulting in hyperthermia. So-called designer derivatives of amphetamine may have toxic effects on dopamine and serotonin neurons.[53,54]

Cocaine is a potent blocker of the dopamine-, norepinephrine-, and serotonin-uptake transporters. Amphetamines have a more complex mechanism of action. Amphetamines cause neuronal storage vesicles in the cytoplasm to release neurotransmitters to the synapse; inhibit the uptake of dopamine, norepinephrine, and serotonin by membrane transporters; and act as mild inhibitors of monoamine oxidase (Fig. 2). Amphetamine and methamphetamine seem to be more selective for dopamine and norepinephrine than for serotonin transporters, but MDMA and designer amphetamines are more selective for the serotonin transporter.[55]

OTHER ADDICTIVE SUBSTANCES

Nicotine binds to neuronal nicotinic acetylcholine receptors,[56] and barbiturates and benzodiazepines bind and modulate the ion-channel–gated $GABA_A$ receptors (Fig. 1 and 2).[57] The psychotomimetic actions of dissociative anesthesics (phencyclidine and ketamine) are mediated by their noncompetitive antagonism at the NMDA-sensitive glutamate receptor (ligand-gated ion channel).[58] Lysergide or mescaline (classic hallucinogens) are partial agonists at 5-HT_{2A} receptors,[58] whereas salvinorin A induces their effects through the activation of κ-opioid receptors.[59]

NEUROBIOLOGY

ANIMAL MODELS

Various animal behavioral paradigms have been used to study the neuronal substrates involved in addiction, especially euphoria and rewarding effects, including self-stimulation, self-administration, and conditioned place-preference models (Fig. 3).[60] In the place-preference model, the rewarding properties of a compound are associated with the particular characteristics of a given environment (place); after conditioning, the animal prefers to spend more time in the environment associated with the drug. Molecular studies have identified regulatory processes that occur after drug administration at the level of receptors, membrane transporters, and their associated signaling proteins. Useful strains of mice have been developed by genetically disrupting drug targets (receptors and transporters) or proteins in the pathways of these targets. Genetic alterations are generally present throughout development in these mice. Therefore, when the phenotypes of interest are absent, the effect of a drug could actually reflect compensatory changes in other neurobiologic systems.[33,61] To avoid this limitation, conditioned and tissue-specific knockout animals have been developed.[62]

For some drugs, the risk of abuse in humans can

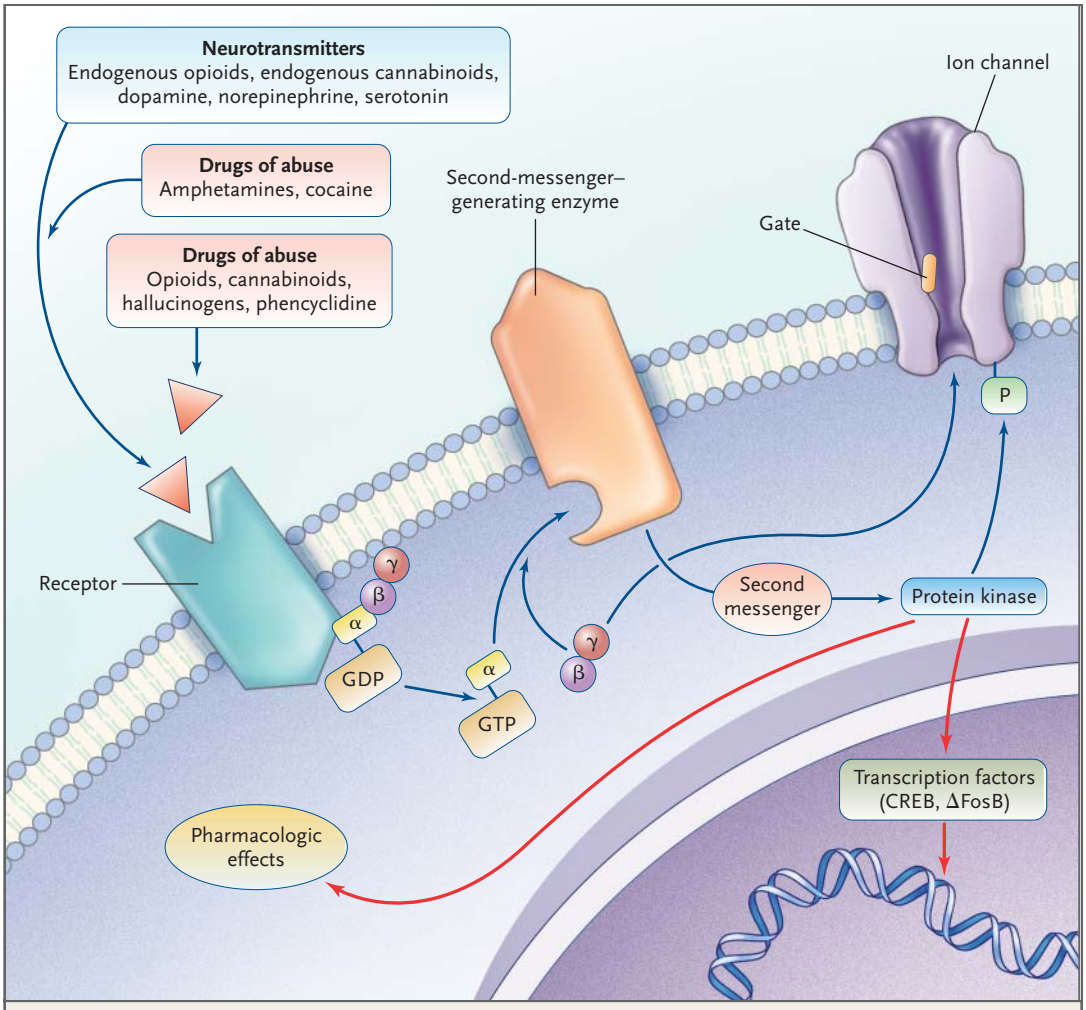

Figure 2. Metabotropic Mechanisms of Action of Drugs of Abuse.

Metabotropic (G-protein–coupled) receptors mediate slow synaptic transmission. G proteins are trimeric structures composed of two functional units: an α subunit that catalyzes GTPase activity (converting guanosine triphosphate [GTP] to guanosine diphosphate [GDP]), and a β–γ dimer that interacts with the α subunit when bound to GDP (inactive state). The binding of the agonist activates a nearby G protein. The α subunit bound to GTP subsequently dissociates from its β and γ subunits. Both can activate or inhibit enzymes (adenylyl cyclase or phospholipase C) that synthesize second messengers such as cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate, inositol triphosphate, and diacylglycerol. In addition, the β and γ subunits directly regulate calcium-, sodium-, and potassium-ion channels. Second messengers also regulate ion channels by activating protein kinases, which phosphorylate (P) such channels. Protein kinases induce pharmacologic effects and produce changes in transcription factors such as cAMP-responsive element–binding protein (CREB) and ΔFosB. Opioids bind to opioid receptors (which reduce cAMP levels), and cannabinoids bind to cannabinoid receptors. Classic hallucinogens are partial agonists of serotonin receptors. Amphetamines and cocaine have an indirect action on receptors, increasing the synaptic levels of dopamine, norepinephrine, and serotonin (facilitating release and inhibiting reuptake, respectively). These neurotransmitters activate different subtypes of dopaminergic, adrenergic, and serotonergic receptors.

be predicted with the use of tests based on behavioral paradigms in animals. These methods, however, are not systematically used during the development of centrally acting drugs,[63] probably because the methods are not required by regulatory agencies.

NEUROANATOMICAL SUBSTRATES

The neuronal pathways of drug addiction are components of the mesocorticolimbic dopamine systems that originate in neurons in the ventral tegmental area (Fig. 4).[64] All drugs of abuse act on this

Table 2. Inactivation of Opioid Receptors in Knockout Mice.

Opioid Receptor That Is Knocked Out	Withdrawal Syndrome	Self-Administration Model*	Place-Preference Model*	Analgesia
μ Receptor	No	No	No	No
δ Receptor	Yes	Unknown	Unknown	Yes
κ Receptor	Yes (reduction in symptoms)	Unknown	Yes	Yes

* The model is defined in Figure 3.

system at different levels. The mesolimbic circuit includes projections from cell bodies of the ventral tegmental area to limbic structures, such as the nucleus accumbens, amygdala, and hippocampus. This circuit has been implicated in acute reinforcing effects, memory, and conditioned responses linked to craving and the emotional and motivational changes of the withdrawal syndrome. The mesocortical dopamine circuit includes projections from the ventral tegmental area to the prefrontal cortex, orbitofrontal cortex, and anterior cingulate. It is involved in the conscious experience of the effects of drugs, drug craving, and the compulsion to take drugs. The mesolimbic and the mesocortical dopamine circuits operate in parallel and interact with each other and with other areas — forming the so-called extended amygdala — by means of projections from the GABA neurons of the nucleus accumbens to the ventral tegmental area and prefrontal cortex and glutamatergic projections from the prefrontal cortex to the nucleus accumbens and ventral tegmental area.[11,12,64]

THE LEADING ROLE OF THE DOPAMINE PATHWAY

Both natural rewards (food, drink, and sex) and addictive drugs stimulate the release of dopamine from neurons of the presynaptic ventral tegmental area into the nucleus accumbens, causing euphoria and reinforcement of the behavior. In the case of natural rewards, there is a very rapid adaptive change, or habituation, after a few experiences, and the novelty or unexpectedness of the reward seems to play a major part in the initial response. The response to addictive drugs is not influenced by habituation, and each dose of the drug stimulates the release of dopamine.[65] Moreover, dopamine mediates the hedonic consequences of a reinforcing stimulus, promoting associative learning about the stimulus or anticipating its rewarding effects.[65] During the withdrawal syndrome associated with opioids, cannabinoids, ethanol, psychostimulants, and nicotine, there is a substantial decrease in dopamine levels in the nucleus accumbens.[66]

Dopamine binds to a G-protein–coupled receptor with two main subtypes, D1-like receptors (D1 and D5) and D2-like receptors (D2, D3, and D4). D1-like receptors activate adenylyl cyclase, whereas D2-like receptors inhibit the enzyme (Fig. 1 and 2). A membrane dopamine transporter moves the released neurotransmitter from the extracellular space back into the presynaptic neuron (uptake). Animals can be taught to self-administer D1-like and D2-like receptor agonists.[55,67]

Dopamine and Opioids

Opioids release dopamine mainly by an indirect mechanism that decreases the activity of GABA-inhibitory interneurons in the ventral tegmental area. Rodents can be taught to self-administer μ-receptor agonists into both the ventral tegmental area and the nucleus accumbens. Stimulation of κ receptors decreases dopamine levels in the nucleus accumbens and produces aversive responses. Rodents will continue to self-administer opioid into the nucleus accumbens even in the presence of dopaminergic lesions or after a dopamine antagonist has been given. Reward and physical dependence on opioids are mediated by the activation of μ receptors (Table 2), since reinforcement is blocked by selective receptor antagonists. Mice in which the μ receptor has been knocked out do not exhibit place preference or withdrawal signs after the administration of morphine.[68]

Dopamine and Cannabinoids

Δ^9-Tetrahydrocannabinol and other cannabinoids increase the efflux of dopamine in the nucleus accumbens and cell firing in the ventral tegmental area by their actions on CB_1 receptors in glutamatergic and GABA-ergic neurons associated with the nucleus accumbens and ventral tegmental area.[69] Laboratory animals cannot be taught to self-administer Δ^9-tetrahydrocannabinol, and spontaneous symptoms of withdrawal do not appear after such drugs are stopped. Highly potent, short-acting synthetic cannabinoid agonists (e.g., Win 55,212-2) induce self-administration behavior in rodents.[70] Selective cannabinoid antagonists (e.g., SR 141716A) precipitate a withdrawal syndrome in cannabinoid-dependent animals, but at doses that are difficult

to extrapolate to the consumption of plant-derived cannabis in humans.[71]

Dopamine and Ethanol

Ethanol raises dopamine levels in the nucleus accumbens by an indirect mechanism: it increases the firing of dopamine neurons in the ventral tegmental area by activating $GABA_A$ receptors or by inhibiting NMDA receptors. Alcohol administration induces specific, long-lasting adaptive changes in the composition of NMDA receptor subunits, which enhances the function of NMDA receptors. These findings are the basis of the experimental and clinical use of NMDA antagonists for treating the ethanol-withdrawal syndrome and reducing alcohol intake and relapse rate.[43,72] Opioid and serotonin receptors seem to have a role in the reinforcing effects of ethanol. In rats, naltrexone decreases the rate of self-administration of ethanol, and selected $5\text{-}HT_3$ antagonists block the release of dopamine induced by ethanol and reduce alcohol consumption.[45,72]

Dopamine and Cocaine and Amphetamines

Cocaine and amphetamines increase synaptic dopamine levels by inhibiting the activity of dopamine transporters. Imaging of the brain has shown that cocaine and amphetamines increase extracellular dopamine levels in the striatum and that euphoria is related to the occupancy of dopamine transporters by cocaine and amphetamines.[73] Lesions in dopamine pathways, inhibition of dopamine synthesis, and dopamine antagonists markedly attenuate the rate of self-administration of cocaine in rats. Dopamine-transporter–knockout mice are insensitive to the locomotor stimulatory effects and are less sensitive than normal mice to the behavioral effects of psychostimulants, but they will still self-administer cocaine and amphetamine. This effect may indicate a contribution of the serotonin and norepinephrine systems to the maintenance of the rewarding properties of cocaine.[55,61]

Dopamine and Nicotine

Nicotine exerts its positive reinforcing effects by acting on $\alpha 4\beta 2$ nicotinic acetylcholine receptors located on the somatodendritic membranes of the dopamine cells of the ventral tegmental area and possibly by sensitizing $\alpha 7$ nicotinic acetylcholine receptors located on glutamate terminals. Experiments with mutant mice lacking $\beta 2$ nicotinic acetylcholine receptors confirm the primary role of this receptor in promoting the self-administration of nicotine.[74,75]

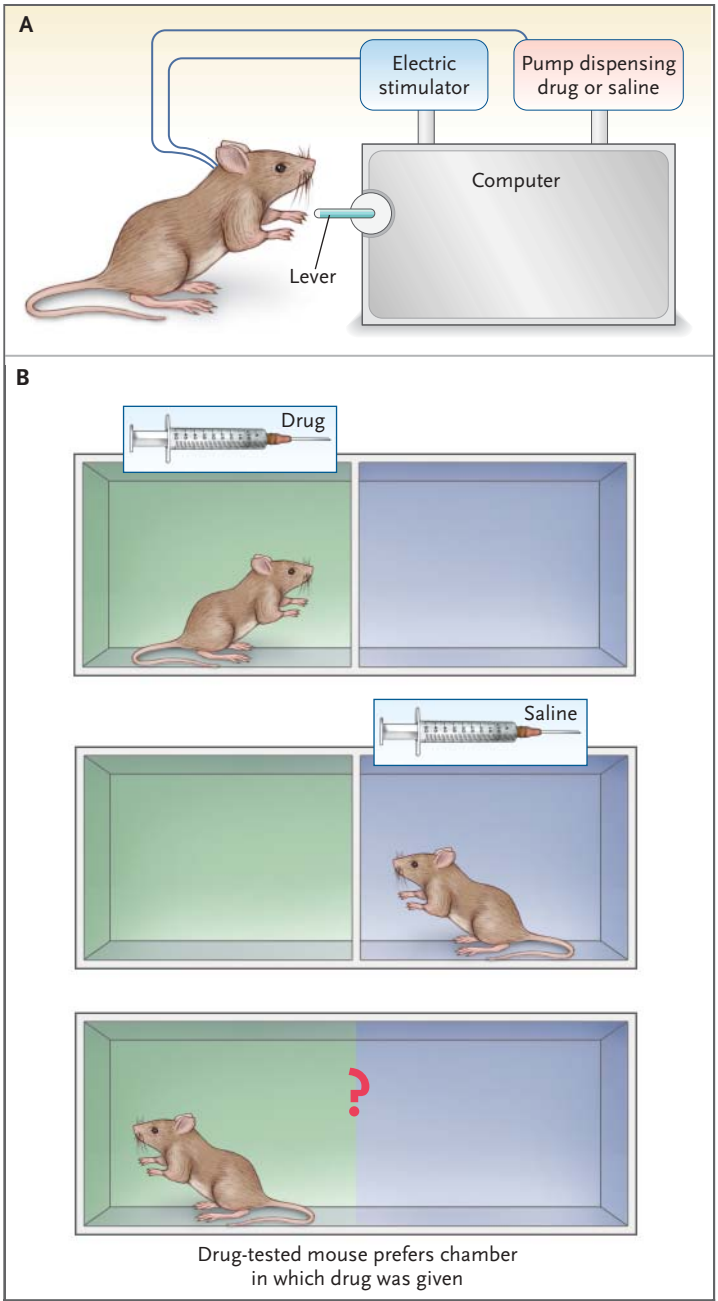

Figure 3. Animal Behavioral Paradigms Used to Study Positive Reinforcing (Rewarding) Actions of Drugs.

In Panel A, animals are trained to press a lever to obtain a drug or saline (self-administration) or to receive intracranial current in brain-rewarding loci (self-stimulation). In Panel B, mice are placed in a box with two discrete chambers, or environments, and are then repeatedly injected with a drug in one environment and with saline in the other environment. In a drug-free state, the animal is allowed access to both environments, and the amount of time spent in each environment is recorded. A positively reinforcing effect of the drug is apparent if the mouse spends more time in the environment in which the drug was administered (place preference) than in the one in which saline was administered.

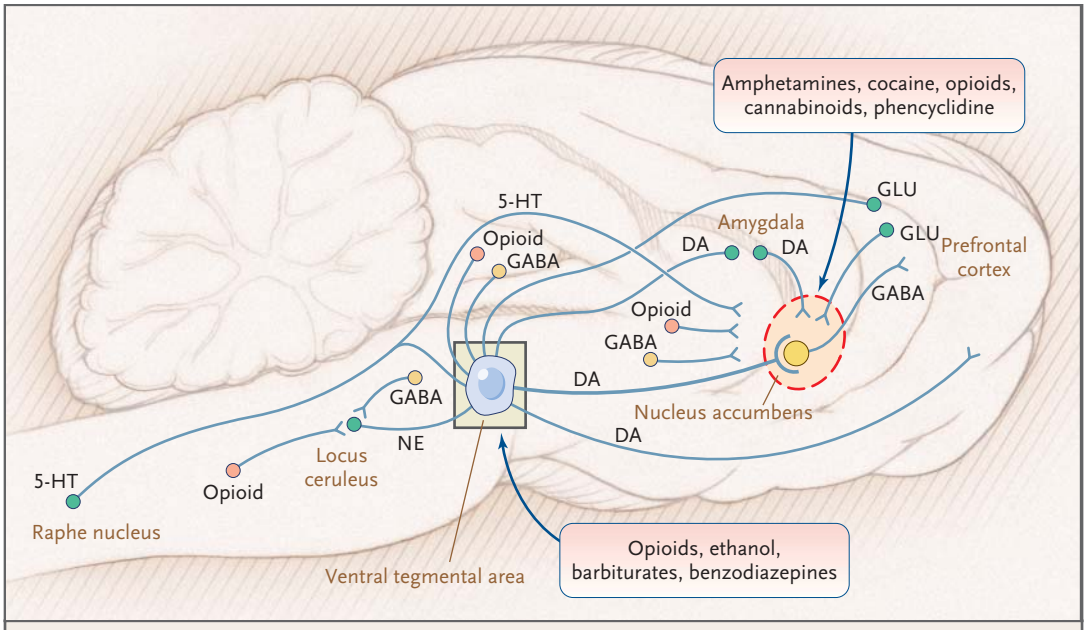

Figure 4. Neural Reward Circuits Important in the Reinforcing Effects of Drugs of Abuse.

As shown in the rat brain, mesocorticolimbic dopamine (DA) systems originating in the ventral tegmental area include projections from cell bodies of the ventral tegmental area to the nucleus accumbens, amygdala, and prefrontal cortex; glutamatergic (GLU) projections from the prefrontal cortex to the nucleus accumbens and the ventral tegmental area; and projections from the γ-aminobutyric acid (GABA) neurons of the nucleus accumbens to the prefrontal cortex. Opioid interneurons modulate the GABA-inhibitory action on the ventral tegmental area and influence the firing of norepinephrine (NE) neurons in the locus ceruleus. Serotonergic (5-HT) projections from the raphe nucleus extend to the ventral tegmental area and the nucleus accumbens. The figure shows the proposed sites of action of the various drugs of abuse in these circuits.

THE OPIOID PATHWAY

The opioid system is another pathway in the brain involved in the rewarding effects of addictive drugs.[71] The importance of this system in addiction to cannabinoids was brought out by studies in which opioid-receptor antagonists were found to attenuate the self-administration of cannabinoids and precipitate behavioral signs of withdrawal in rats treated with cannabinoid agonists for long periods.[76] Opioid antagonists reduce the consumption and self-administration of ethanol in animals, but naltrexone does not reduce the rate of relapse or alcohol consumption in patients with alcoholism.[77] By contrast, μ-receptor–knockout mice cannot be induced to self-administer alcohol.[72] The opioid system also inhibits the self-administration of nicotine in animals. Indeed, naloxone precipitates withdrawal in rats that receive nicotine for long periods and reduces cigarette consumption in smokers.[74] In addition, nicotine-induced conditioned place preference is abolished in μ-receptor–knockout mice.[78]

LONG-TERM DRUG USE AND NEUROADAPTATION

TOLERANCE AND WITHDRAWAL

Tolerance leads to modifications of drug use to obtain desired effects, by increasing the dose, reducing the intervals between doses, or both. Withdrawal compels addicts to resume drug use to prevent or reduce physical symptoms and dysphoria. Both tolerance and withdrawal increase compulsive drug-seeking and drug-taking behavior and are essential in maintaining the addiction. Sensitization, however, is also important. Molecular adaptations related to tolerance and dependence have been studied extensively in animal models of opioid and cocaine addiction, and the results can be extrapolated to other substances.[12,79,80]

Opioid Tolerance

Short-term administration of opioid activates the μ-opioid $G\alpha_{i/o}$-coupled receptor, which inhibits

adenylyl cyclase, lowers cyclic adenosine monophosphate (cAMP) levels, decreases cAMP-dependent protein kinase A activity, and reduces phosphorylation of cytoplasmic and nuclear targets, including cAMP–responsive element–binding protein (CREB), a transcription factor. Activation of μ receptors can also cause the phosphorylation of some mitogen-activated protein kinases, which in turn phosphorylate CREB and other transcription factors.[12,79,81,82] Decreases in the number of opioid receptors have been related in some reports to the development of opioid tolerance. Continuous stimulation desensitizes opioid receptors, which become phosphorylated by G-protein–coupled receptor kinases; β-arrestins then bind to the receptors, causing them to be internalized by the neuron.[83] Other studies, however, have found that opioids that cause internalization of the opioid receptors are inefficient in initiating tolerance.[84]

Opioid Withdrawal

Chronic activation of opioid receptors produces effects opposite to those of acute activation. It up-regulates cAMP signaling pathways by increasing the activity of adenylyl cyclases (subtypes I and VII), cAMP-dependent protein kinase A, and tyrosine hydroxylase. In addition, chronic activation of opioid receptors increases the phosphorylation of CREB and ΔFosB, factors regulating gene transcription.[66,79,85] These changes correlate with the manifestations of the withdrawal syndrome.

Up-regulation of cAMP is a homeostatic response to the inhibition of the locus ceruleus by opioids and a key mechanism in withdrawal. The locus ceruleus is a noradrenergic nucleus that regulates arousal, responses to stress, and the activity of the autonomic nervous system. Tolerance to the inhibitory effects of opioids occurs in the locus ceruleus during long-term administration. When opioid levels fall, the firing rates of neurons in the locus are unopposed and lead to adrenergic overactivation. A direct relation between overactivity of the locus ceruleus neurons and the somatic expression of opioid withdrawal has been demonstrated.[86] Mechanisms other than noradrenergic neurons may also participate in opioid withdrawal because destruction of the locus ceruleus does not alter naloxone-precipitated or spontaneous opioid withdrawal.[87]

In the nucleus accumbens, a similar up-regulation of the cAMP pathway, including activation of CREB, occurs after long-term administration of opioids, ethanol, or cocaine. CREB increases the production of dynorphin, which activates κ receptors in the neurons of the ventral tegmental area and decreases the release of dopamine in the nucleus accumbens. These changes contribute to the negative emotions (dysphoria and anhedonia) present during the early phases of abstinence.[66,79]

Stress Systems

Drug administration and withdrawal activate central and peripheral stress systems.[88] Short-term administration elevates peripheral glucocorticoid levels and central corticotropin-releasing factor levels. These hormonal elevations have been related to the rewarding properties of drug use. During withdrawal, an increase in corticotropin-releasing factor in the amygdala has been related to stress and negative effects of abstinence.[47,80]

MOLECULAR MECHANISMS OF SENSITIZATION AND RELAPSE

Long-term administration of addictive drugs produces alterations in the brain that increase vulnerability to relapse and facilitate craving even months or years after successful detoxification. Factors involved in relapse and craving include acute reexposure to the drug or drug-priming, exposure to environmental stimuli previously paired with drug use or conditioned drug cues, and exposure to environmental stressors (Table 1). The extent of sensitization varies with different drugs and is responsible for responses, craving, and relapse.

Functional Changes

Repeated administration of opioids, psychostimulants, or nicotine sensitizes laboratory animals to the stimulant or rewarding effects, or both, of these addictive substances. Behavioral sensitization is associated with marked and long-lasting alterations in the functional activity of the mesocorticolimbic dopamine system, particularly in glutamate and dopamine transmission in the nucleus accumbens.[12,67] Elevated levels of the R1 subunit of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) subtype of glutamate receptors seems to be involved in sensitization and relapse.[89] Stress or a single dose of addictive substances with different molecular mechanisms of action (cocaine, amphetamine, morphine, ethanol, or nicotine) produces similar degrees of enhancement in the strength of glutamate excitatory synapses (AMPA-sensitive glutamate receptors) on dopamine neurons in the ventral tegmental area. The administra-

tion of a glucocorticoid antagonist blocked the actions of stress but not those of addictive substances. These changes can have a role in behavioral sensitization.[90]

Sensitization is associated with long-lasting adaptive changes in the patterns of expression of genes of the terminal mesolimbic dopamine systems,[79] in particular the activation of proteins belonging to the family of transcription factor activator protein 1, such as Fos proteins. In self-administration models, long-term treatment with morphine, cocaine, or nicotine increases the expression of the family of Fos-related transcription factors, particularly the extremely stable isoforms of ΔFosB. The persistent increase in the expression of Fos genes in mesolimbic structures is in part a consequence of the activation of the cAMP cascade through D1 dopamine receptors in the ventral tegmental area.[85,91,92]

Structural Changes

Exposure to addictive drugs can cause long-lasting structural changes in neurons. Opioids decrease the size and the caliber of dendrites and soma of dopamine neurons of the ventral tegmental area.[93] Repeated use of cocaine or amphetamine increases the number of dendritic branch points and spines on both medium spiny neurons in the nucleus accumbens and pyramidal neurons in the medial prefrontal cortex.[94] Neurotrophic factors seem to be responsible for these changes. Modifications in the density of dendritic spines and neurotrophic factors have also been implicated in long-term potentiation and long-term depression by AMPA-sensitive glutamate receptors.

The glutamate system of the brain is responsible for the long-term plasticity associated with learning and memory. It is therefore not surprising that the same glutamatergic mechanisms also underlie addiction-related behavior.[12,66,79,95,96] Behavioral sensitization can persist for weeks or months and is augmented by environmental cues (e.g., people, places, or paraphernalia associated with past drug use).[12] These cues and sensitization contribute to relapse. Interestingly, the processes involved in sensitization overlap the neuronal substrates and pathways involved in the rewarding properties of drug abuse.[7,9]

COMMENTS

Advances in the neurobiology of drug addiction have led to the identification of neuronal substrates responsible for the rewarding effects of prototypical drugs of abuse, which are crucial to the addictive process. There is increasing evidence that prolonged exposure to drugs of abuse produces long-lasting effects in cognitive and drug-rewarding circuits. For this reason, addiction should be considered a chronic medical illness.[97,98] Symptoms of withdrawal can be treated, and maintenance therapy is available for most drugs of abuse,[43,98-101] but the development of long-term strategies based on medication, psychosocial support, and continued monitoring[97,98] is a challenging clinical goal.

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