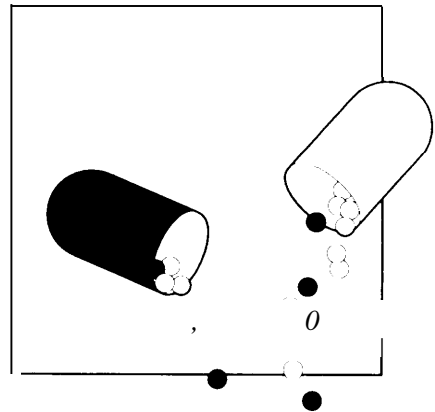


The Neuropharmacology of Drugs of Abuse | 3

Drugs of abuse interact with the neurochemical mechanisms of the brain. Some of these interactions are directly related to the reinforcing properties of a drug, while others are related to other effects associated with the drug. As in other areas of neuroscience, the level of understanding about these interactions and the mechanisms involved has increased tremendously over the last decade. The fundamentals of information processing in the brain and how psychoactive drugs can alter these processes are being elucidated. For drugs of abuse, certain commonalities have begun to emerge. While drugs of abuse have a wide range of specific individual actions in the brain, there is growing evidence that their reinforcing properties may result from a shared ability to interact with the brain's reward system. For each drug of abuse, this action, coupled with its actions in other areas of the brain, contributes to the overall behavioral effect the drug produces. In some cases, the relationship of a drug's neurochemical action and the behavioral effects it produces have been clearly elucidated, while in others much remains to be learned.

This chapter describes how drugs of abuse affect neurochemical activity and the mechanisms that may underlie the characteristics contributing to and determining a drug's abuse potential, namely, their reinforcing affects, the neuroadaptive responses associated with them, and the development of withdrawal symptoms. A brief summary of basic neuropharmacology is provided to give general background information on how drugs work in the brain.



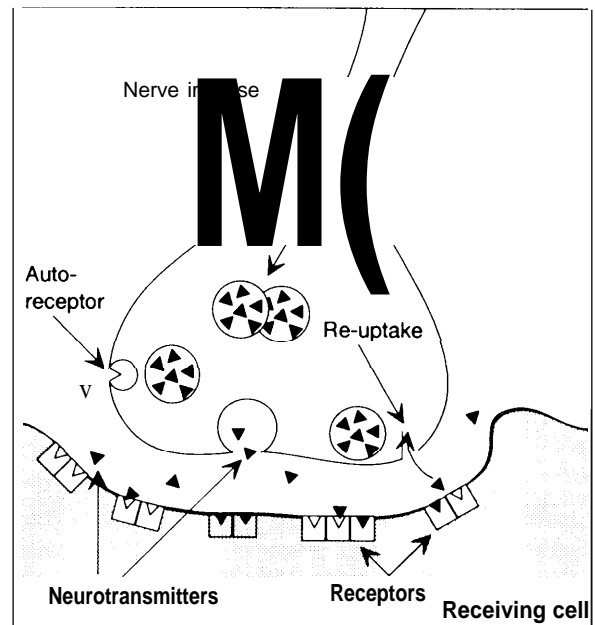
NEUROPHARMACOLOGY

Neurons are the cells that process information in the brain. Neurotransmitters are chemicals released by neurons to communicate with other neurons. When a neuron is activated it releases a neurotransmitter into the synapse, the gap between two neurons (see figure 3-1). The molecules of the neurotransmitter move across the synapse and attach, or bind, to proteins, called receptors in the outer membrane of an adjacent cell. Once a neurotransmitter activates a receptor, it unbinds from the receptor and is removed from the synapse. This is done either by the neurotransmitter being taken back up into the neuron that released it (a process called reuptake) or by being chemically broken down. Usually the axon terminal is the part of the neuron that releases neurotransmitters into the synapse, and the dendrites and cell body are the areas of the neuron that contain receptors that form synapses with the axons of other neurons.

For each neurotransmitter in the brain, there are specific receptors to which it can attach. Binding by the neurotransmitter activates the receptor, which can have different effects depending on the receptor. Receptors can be linked to a variety of membrane and cellular mechanisms that are turned on or off by the activation of the receptor. Some receptors open or close ion channels (i.e., for charged molecules such as potassium, sodium, calcium, or chloride) in the membrane of the cell. These channels regulate the flow of ions in and out of the cell. The relative concentration of ions between the inside and outside of a neuron is crucial in the activity of the neuron. Other receptors activate or inhibit intracellular mechanisms called second messengers. There are a number of different second messengers that control various aspects of cellular activity.

A neuron can have thousands of receptors for several different neurotransmitters. Some neurotransmitters activate neurons (excitatory neurotransmitters), while others decrease neuronal activity (inhibitory neurotransmitters). Sometimes

Figure 3-1—The Synapse and Associated Structures



SOURCE: Office of Technology Assessment, 1993.

a receptor for one neurotransmitter can affect a receptor for another neurotransmitter. In such case, the receptors are biochemically coupled: the activation of one modulates the function of the other, either increasing or decreasing its activity. A neuron can also have receptors for the neurotransmitter it releases; these are usually located near the site where the neurotransmitter is released into the synapse. Such receptors are acted on by the neuron's own neurotransmitter to regulate the release of the neurotransmitter. Thus, these autoreceptors, as they are called, act as a feedback mechanism to regulate a neuron's activity. The activity of a neuron will be determined by the cumulative activity of all of its various receptors. Activation of a neuron generates an electrical impulse inside the neuron that travels from the cell body, down the axon, to the axon terminal, where the impulse causes the release of neurotransmitter into the synapse.

While receptors are specific for a neurotransmitter, there may be a variety of receptor sub-

types, linked to different cellular mechanisms, that all respond to the same neurotransmitter. In this way one neurotransmitter can have diverse effects in different areas of the brain. In addition, neurons are connected to different circuits in the brain, further accounting for diverse effects. Many chemicals have been identified as neurotransmitters, among them dopamine, norepinephrine, serotonin, acetylcholine, various amino acids, and peptides. As discussed in chapter 2, some of these are of particular relevance to the rewarding properties of drugs of abuse.

Psychoactive drugs alter these normal neurochemical processes. This can occur at any level of activity including mimicking the action of a neurotransmitter, altering the activity of a receptor, acting on the activation of second messengers, or directly affecting intracellular processes that control normal neuron functioning.

In order to have these effects, a drug must enter the brain, by diffusing from the circulatory system into the brain. Routes of administration refers to the methods used to deliver a drug into the bloodstream. The route of administration affects how quickly a drug reaches the brain. In addition, the chemical structure of a drug plays an important role in the ability of a drug to cross from the circulatory system into the brain. The four main routes of administration for drugs of abuse are oral, nasal, intravenous, and inhalation. With oral ingestion, the drug must be absorbed by the stomach or gut, which usually results in a delay before effects become apparent, and must pass through the liver where it can be chemically broken down. Using the nasal route, effects are usually felt within 1 to 3 minutes, as the capillary rich mucous membranes of the nose rapidly absorb substances into the bloodstream. Intravenous administration produces effects in 1/2 to 2 minutes and is slowed only by detour back through the lungs that venous blood must take to reach the brain. Lastly, the inhalation method bypasses the venous system because the drug is absorbed into the arterial blood flow, which goes directly from the lungs to the heart and then to the

brain. As a result, effects are felt within 5 to 10 seconds, making inhalation the fastest route of administration. The route of administration of a drug can determine the potency and efficacy the drug will have on affecting brain activity. *In some cases, the* route of administration can also contribute to the abuse potential of a drug.

DRUGS OF ABUSE

I Stimulants

As the name implies, stimulant drugs have an energizing effect that promotes an increase in psychological and/or motor activity. Stimulants such as cocaine and the amphetamines have their most pronounced effect on the monoamine neurotransmitters (i.e., dopamine, serotonin, norepinephrine, and epinephrine) in the brain. They also stimulate the physiological mechanisms that are triggered in stressful situations (the “fight or flight” response) via activation of the sympathetic nervous system. These include increases in heart rate and blood pressure and the release of various hormones. The arousing and euphoric effects associated with these drugs are associated with these various actions. Other stimulant drugs are caffeine and nicotine. These drugs have various mechanisms of action, but their net effect is to stimulate central nervous system (CNS) activity.

COCAINE

Cocaine is found in the leaves of the Erythroxylon *coca* plant, a large shrub indigenous to South America. The compound is extracted from the leaves and is then processed into either paste, powder, or freebase form. The paste is the most rudimentary, unrefined form. Additional processing of the paste by adding hydrochloric acid produces cocaine powder (cocaine hydrochloride). Cocaine powder is often administered via nasal insufflation (i.e., snorting). Freebase cocaine is the pure cocaine base released from cocaine hydrochloride by further separation using simple chemicals such as ether or sodium hydrox-

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ide. This freebase cocaine is easily absorbed into the membranes of the relatively alkaline environment of the body. The well-known “crack” cocaine is simply baking soda and water mixed with the base to create a solid form of freebase cocaine which is immediately and completely absorbed by the body when smoked. The most common routes of administration for cocaine are smoking and snorting although the intravenous route is also used and is often preferred by those who also inject other drugs, such as opiates (45).

In humans, cocaine produces an elevation in mood and a sense of increased energy and alertness. This can include an improvement in concentration and attention, a reduction in the sense of fatigue and performance decrement caused by sleep deprivation, appetite suppression, and an increase in libido. The toxic effects of high doses of cocaine include delirium, seizures, stupor, cardiac arrhythmias, and coma. Seizures can result in sustained convulsions that stop breathing.

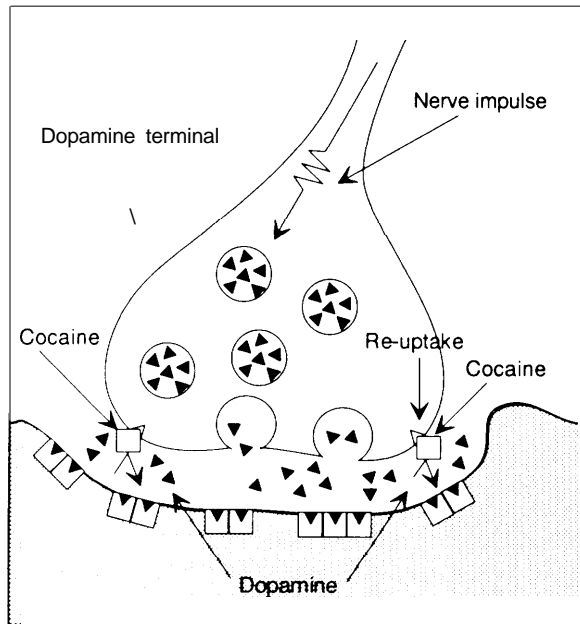
Acute administration—The most prominent pharmacological effect of cocaine is to block the reuptake of dopamine back into the presynaptic terminal once it has been released from a neuron terminal (61), resulting in increased levels of dopamine at its synapses in the brain (see figure 3-2). The specific uptake site for dopamine has been identified and cocaine’s actions on the mechanism that transports dopamine back into the neuron is an active area of research. Within the brain mesocorticolimbic pathway (MCLP), levels of dopamine increase in the synapses between the terminals of the neurons projecting from the ventral tegmental area and the neurons in the nucleus accumbens and medial prefrontal cortex (60,62). In addition to blocking dopamine reuptake, cocaine also blocks the reuptake of norepinephrine and serotonin (62).

The acute behavioral effects of cocaine are the result of these neurochemical actions. The acute reinforcing properties of cocaine are due to its capacity to enhance the activity of dopamine in MCLP. As with most neurotransmitters, dopa-

mine has a number of receptor subtypes distributed in different brain areas. The reinforcing properties of cocaine are mediated via dopamine activation of at least two of these, the D_1 and D_2 dopamine receptor subtypes (39,62), and more recently there is evidence for an action at D_3 receptors (12). The increase in dopamine activity via D_2 and D_1 receptors is also important in the other behavioral effects of cocaine (62). The role of cocaine’s actions on brain norepinephrine and serotonin uptake in its behavioral effects has not been clearly established (62).

Chronic administration—Chronic administration of cocaine activates a number of brain neurochemical compensatory mechanisms, the details of which are not completely understood. Both short- and long-term changes in the dynamics of neurotransmission following repeated cocaine administration have been observed in experiments. Results from animal studies indicate that continued administration results in a sustained increase in dopamine levels within the synapses of the nucleus accumbens (60). This is believed to be due to a decreased sensitivity of dopamine autoreceptors, which regulate the release of dopamine from the presynaptic terminal. In their normal state, these autoreceptors decrease the amount of dopamine released into the synapse. Changes also seem to occur in the number of postsynaptic receptors for dopamine, but the exact nature of these changes has yet to be characterized. Both increases and decreases in receptor numbers have been reported (62). The exact effects of chronic cocaine administration seem to vary among receptor subtypes and locations.

A number of changes in the intracellular mechanisms, including second messenger systems, involved in the activity of dopamine neurons in the ventral tegmental area and nucleus accumbens have been described following chronic cocaine administration (10). The changes are thought to be due to alterations in the expression of the genes that regulate and control the intracellular mechanisms. The net effect of these changes

Figure 3-2-Cocaine's Principal Action Mechanism

Cocaine's principal mechanism of action is to block the uptake of dopamine into the presynaptic terminal. (Compare to figure 3-1.)

SOURCE: Office of Technology Assessment, 1993.

is to reduce the capacity of ventral tegmental neurons to transmit dopamine signals to the neurons in the nucleus accumbens. This could represent a mechanism by which tolerance to the rewarding properties of cocaine could develop and could contribute to cocaine craving. Importantly, these changes are lacking in other dopamine pathways not involved in drug reward. Similar changes were observed following chronic morphine administration. These findings suggest that a common physiological response to chronic administration of these drugs of abuse may **exist**. Further investigations are necessary to completely characterize the changes that occur and to determine whether they are typical for other drugs of abuse.

Finally, animal studies have shown that repeated administration of cocaine causes changes in the levels of other neurotransmitters, most notably some of the peptide neurotransmitters.

These changes may result from alterations in dopamine transmission that effect other areas of the brain. These secondary responses indicate that the neurochemical adaptive response to repetitive cocaine administration involves a complex interaction between multiple neuronal pathways and neurotransmitter systems (62).

Matching the pharmacological profile, the behavioral response to repeated cocaine administration is also complex. Results from animal studies suggest that how the drug is administered can affect whether sensitization or tolerance occurs. Intermittent administration of cocaine can trigger sensitization to some of its specific motor effects, such as stimulating levels of activity (61,62). Conversely, tolerance to these motor effects develops when the drug is given continuously (62). While it is unclear whether tolerance develops to cocaine's reinforcing effects, experimental evidence suggests that it does and subjective reports from cocaine users that the euphoric actions of the drug diminish with repeated use support the notion (45,62). Increasingly, experimental evidence suggests that chronic cocaine administration increases drug craving (36,42).

A withdrawal reaction occurs with the abrupt cessation of cocaine administration after repeated use. This reaction is marked by prolonged sleep, depression, lassitude, increased appetite, and craving for the drug (61). In animal studies, cocaine withdrawal results in an increase in the level of electrical stimulation necessary to induce a rat to self-stimulate the brain reward system (40). This indicates that during cocaine withdrawal, the brain reward system is less sensitive. While the precise pharmacological mechanism underlying this withdrawal is unknown, it is suspected that it relates to some hypoactivity in dopamine functioning within the brain reward system (40). Changes in the expression of genes that control intracellular mechanisms (10) represent a possible mechanism that could account for this change and could contribute to the drug craving associated with chronic cocaine use. Avoidance of the withdrawal reaction can be

another important determinant in continued cocaine use.

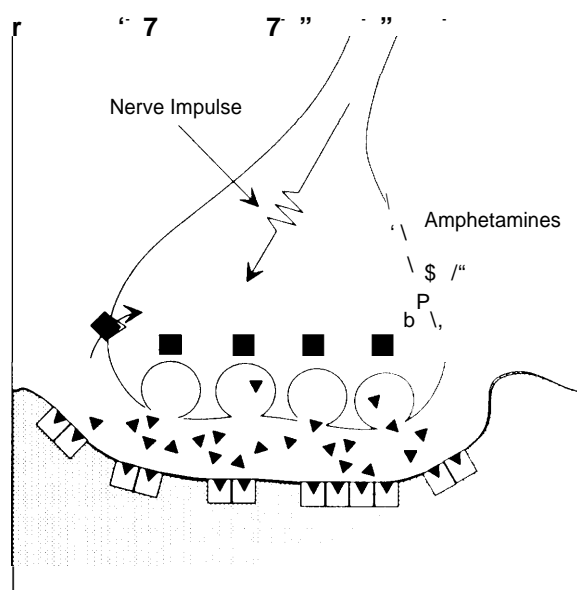
AMPHETAMINES

Amphetamines (i.e., dextroamphetamine, methamphetamine, phemetrazine) produce effects similar to cocaine (20). Amphetamine users describe the euphoric effects of the drug in terms indistinguishable from those used by cocaine users and in the laboratory, subjects cannot distinguish between the subjective effects of cocaine and amphetamine (36). This is not to suggest that cocaine and amphetamine have identical mechanisms of action or that under properly selected experimental conditions differences between their effects cannot be demonstrated. For example, cocaine effects are relatively brief after intravenous injection, whereas those of methamphetamine may last for hours (36). Oral ingestion is the most common route of administration of amphetamines, although intravenous injection, smoking, and nasal insufflation are also used.

Acute administration—Like cocaine, acute amphetamine administration results in mood elevation and increased energy. In addition, the user may experience feelings of markedly enhanced physical strength and mental capacity. Amphetamines also stimulate the sympathetic nervous system and produce the physiological effects associated with sympathetic activation. High doses of amphetamine produce a toxic syndrome that is characterized by visual, auditory, and sometimes tactile hallucinations. There are also feelings of paranoia and disruption of normal thought processes. The toxic reaction to amphetamines is often indistinguishable from an episode of the mental disorder schizophrenia.

Not surprisingly, action of amphetamines is similar to cocaine. The reinforcing properties of these drugs is due to their ability to enhance dopamine action in MCLP. However, while amphetamines also block dopamine reuptake, their most significant action is to directly stimulate the release of dopamine from neurons (61) (figure 3-3). Thus, unlike cocaine, which blocks

Figure 3-3-Amphetamines' Principal Action Mechanism



Amphetamines' principal mechanism of action is to stimulate the release of dopamine from the presynaptic terminal. (Compare to figure 3-1.)

SOURCE: Office of Technology Assessment, 1993.

dopamine reuptake following normal release of the transmitter from the terminal, the amphetamine increase in dopamine activity is independent of neuronal activity (61). As a result of this difference, amphetamines are more potent than cocaine in increasing the levels of dopamine in the synapse. Amphetamines also directly stimulate the release of norepinephrine, epinephrine, and serotonin from neurons. Among the amphetamines, the balance between their actions on these different neurotransmitter systems vary. For example, methylenedioxymethamphetamine (MDMA) has a particularly potent effect on the serotonin system, which imbues this drug with a psychedelic effect.

Chronic administration—As with cocaine, both sensitization and tolerance to different effects of amphetamines occur. Animal studies have shown that intermittent administration of

amphetamines results in sensitization to the motor stimulating effects (61). This sensitization is thought to be due to an augmentation of dopamine release after intermittent, repeated drug administration. Tolerance to the euphoric effects of amphetamine develops after prolonged, continuous use (45). Such tolerance is believed to be caused by depletion of stored neurotransmitters, especially dopamine, in the presynaptic terminals as a result of the continued stimulation of release from the stores by the drug. Drug craving is increased with continued amphetamine use (36,42). Finally, a withdrawal syndrome, similar to cocaine's, is produced with the cessation of amphetamine administration after prolonged use.

CAFFEINE

Caffeine is the most widely used psychoactive substance in the world (28,33). Surveys indicate that 92 to 98 percent of adults in North America regularly consume caffeine, mostly in coffee or tea (28). Caffeine belongs to a class of compounds called methylxanthines, which act as CNS stimulants (49). The stimulating effects of caffeine are due to its ability to block the receptors for the inhibitory neurotransmitter adenosine (49). Caffeine blocks both the A₁ and A₂ adenosine receptor subtypes, having its more potent effect on the A₁ receptor (49). Adenosine inhibits the release of various neurotransmitters, in particular the excitatory amino acid glutamate. Therefore, caffeine blockade of adenosine receptors results in increased glutamate activity. Caffeine also increases the levels of norepinephrine and serotonin, which contributes to the drug's CNS stimulating effects (49). Caffeine's effects on dopamine are unclear in that increases, decreases, or no change in the release of dopamine have been observed following caffeine administration in various experiments (49).

In humans, caffeine has a general alerting affect, and it has been shown to increase locomotor activity in laboratory animals (49). However, experimental evidence indicates that in humans

there is **great** individual variability in caffeine's effects (49). These differences are linked to differences in rates of caffeine absorption from the gastrointestinal system and metabolism in the body. Age also seems to affect the response to caffeine, in that older people show an increased sensitivity to caffeine's stimulating effects (49). This is particularly true of caffeine's disruptive effects on sleep.

Acute administration-caffeine exhibits, at most, weak reinforcing effects in animal self-administration experiments (28,33). The level of responding induced by caffeine is much less than that seen with other stimulants such as amphetamine and cocaine (33). In humans, experiments demonstrate that caffeine's reinforcing actions are also minimal and dose-dependent (28,33). Low doses are mildly reinforcing with subjects reporting positive subjective effects, while higher doses produce adverse effects. The results from human studies indicate that reinforcement occurs only under certain conditions and not across all individuals (28). The mechanism of caffeine's reinforcing actions is unknown.

Chronic administration—Humans can develop tolerance to many of the physical manifestations of caffeine's actions such as increased heart rate and higher blood pressure and there is evidence that tolerance develops to its behavioral consequences including alertness and wakefulness (28,33,49). In animals, tolerance develops to some of caffeine's behavioral effects such as the stimulation of locomotor activity (49).

A withdrawal syndrome has clearly and repeatedly been demonstrated after the cessation of chronic caffeine consumption (28,33,49). Changes in mood and behavior can occur with lethargy and headache being the two most common symptoms of caffeine withdrawal (28). These changes may be the result of a compensatory increase in adenosine receptors resulting from the chronic blockade by caffeine. However, more studies are needed to confirm this possibility (49).

NICOTINE

It is generally accepted that while people smoke tobacco for many reasons (e.g., social, cultural), the majority of people who smoke tobacco do so in order to experience the psychoactive properties of the nicotine contained in the smoke (4,56). Furthermore, a significant proportion of habitual smokers become dependent on nicotine and tobacco smoking has all the attributes of drug use considered to be addicting (4,38). Nicotine activates one of the receptor subtypes for the neurotransmitter acetylcholine (38,56). As a result, this receptor is called the nicotine receptor. The psychological effects of nicotine are fairly subtle and include mood changes, stress reduction, and some performance enhancement (7).

When tobacco is smoked, nicotine is readily absorbed by the lungs. Studies of smoking patterns have shown that habitual smokers tend to smoke more efficiently, because they inhale longer, have shorter intervals between puffs, and take a greater number of puffs per cigarette thus increasing the dose of nicotine they receive (38). Smokeless tobacco involves either chewing tobacco leaves or placing tobacco between the cheek and gums. The blood nicotine level achieved using smokeless tobacco can be comparable to that achieved by smoking cigarettes. Because of the route of administration, however, blood nicotine levels remain higher longer (45). Evidence indicates that the diseases related to the use of tobacco may be caused by different constituents of tobacco or tobacco smoke. For example, cardiovascular effects are related to carbon monoxide in the smoke, and the effects on the heart and various cancers are probably due to carcinogens in the tobacco (36).

Acute administration—Nicotine stimulates the release of dopamine from dopamine neurons in the MCLP (4,56). This results from activation of nicotine receptors that stimulate activity in dopamine neurons in the ventral tegmental area. However, when compared to the effects of cocaine or amphetamine, the nicotine increase in

dopamine release is modest, and as a result, nicotine is a comparatively weak reinforcer in animal experiments (4,56). Nonetheless, nicotine reinforcing properties are thought to be the result of this action. Animal study results indicate that activation of nicotine receptors also stimulates the release of noradrenaline from neurons in the locus ceruleus and may reduce serotonin activity in the hippocampus (4). However, the exact nature of these changes and the role they may play in the behavioral effects of nicotine is unclear.

Chronic administration—Tolerance develops to many of the effects of nicotine and a withdrawal syndrome marked by irritability, anxiety, restlessness, and difficulty in concentrating develops when tobacco use stops (4,36,45). In addition, a craving for tobacco, which may subside in a few days, occurs (36). The pharmacological mechanisms underlying these changes are unknown. Although animal studies have suggested that chronic administration of nicotine increases the number of nicotine receptors, the mechanism that mediates this increase and the possible involvement it plays in the tolerance and withdrawal associated with nicotine remains to be clarified (4,56).

| Phencyclidine

Phencyclidine (PCP) is representative of a unique class of abused drugs that includes the anesthetic ketamine and other drugs similar to PCP. PCP was developed as an injectable anesthetic in the 1950s. However, PCP anesthesia is quite dissimilar to that produced by typical general anesthetics (6,8). It produces a dissociative state in which patients are generally unresponsive and perceive no pain. Patients are amnesic for the surgery and CNS depression seen with other general anesthetics is absent. Delirium that often occurs on emergence from PCP anesthesia curtailed PCP's use as an anesthetic in humans. It is still sometimes used as a veterinary anesthetic but is no longer marketed in the United States.

At nonaesthetic doses PCP produces behavioral effects in common with several other drugs including amphetamines, barbiturates, opiates, and psychedelics (13). Given its wide range of behavioral effects, PCP'S broad neurochemical action in the brain is not surprising. PCP antagonizes the actions of the excitatory amino acid neurotransmitter glutamate at the N-methyl-D-aspartate (NMDA) receptor, one of the receptor subtypes for glutamate (8,37). Glutamate is found throughout the brain and increases the flow of calcium ions into cells to cause excitatory actions. The NMDA receptor controls the calcium ion channel acted on by glutamate and binding of PCP to the receptor blocks calcium entry into the cell. It is likely that the diverse behavioral effects of PCP are due to the fact that glutamate is widely distributed in the brain and regulates the activity of a number of other neurotransmitter systems. PCP also affects brain dopamine systems in ways similar to amphetamine (37).

The subjective effects of PCP administration can vary dramatically depending on a user's personality and a user may experience vastly different reactions during different drug-taking episodes (13). In most cases, low doses produce euphoria, feelings of unreality, distortions of time, space, and body image, and cognitive impairment. Higher doses produce restlessness, panic, disorientation, paranoia, and fear of death. As with its use as an anesthetic, PCP often causes amnesia to occur beginning immediately after the drug is taken until its effects begin to wear off. PCP is often associated with violent behavior in users but laboratory studies indicate that it does not increase aggressive behavior in animals (6). In fact, the bulk of evidence indicates that PCP decreases aggression at most doses under most experimental conditions (6). The violence often associated with PCP use is likely to be due to a combination of its multiple effects including its ability to block pain and its stimulant and psychedelic actions.

Acute administration—In animal studies, PCP has been shown to be a highly effective reinforcer

(6,13). From clinical reports of human PCP use and from animal studies, route of administration appears to affect the self-administration rate. Intravenously delivered PCP has been established as a reinforcer in rats, dogs, and primates. Oral PCP is rapidly established as a reinforcer in primates but not in rats (13). In humans, the most common route of administration of PCP is smoking.

The mechanism of action of PCP'S reinforcing effects are unclear. Part of PCP'S behavioral effects are similar to dopamine-stimulating drugs like amphetamine (37) and its administration potentiates the sedating properties of alcohol and barbiturates (6,13). As previously mentioned, PCP blocks the action of glutamate at the NMDA receptor. All of these actions may be relevant to the production of its reinforcing effects.

Chronic administration—Repeated PCP administration has been shown to produce tolerance to many of its effects in animals (6,13). The magnitude of the tolerance, however, is less than what is seen with most other drugs of abuse (13). Systematic studies of PCP tolerance in humans have been few, but chronic PCP users report that after regular use they increase the amount of PCP smoked by at least twice (13). Some evidence from animal studies also suggests that sensitization may develop to PCP under certain conditions (13).

A withdrawal syndrome occurs in animals that have been chronically administered PCP (13). It is characterized by signs of CNS hyperexcitability such as twitches, tremors, and increased susceptibility to seizures. Although PCP withdrawal syndrome can be reliably produced in animals, a withdrawal syndrome in humans has yet to be clearly identified (13). Symptoms of depression, drug craving, increased appetite, and increased need for sleep have been reported to occur between 1 week and 1 month after termination of chronic PCP use (57). The lack of clear evidence of a PCP withdrawal syndrome in humans may be due to the fact that the drug is usually not taken in large enough quantities

and/or not frequently enough to produce symptoms (13).

The neurochemical mechanisms underlying PCP tolerance and withdrawal are unknown. Both, direct PCP-induced alterations in NMDA receptors and secondary changes in other neurotransmitter systems as a result of altered glutamate activity could play a role.

| Sedatives

Alcohol, barbiturates, and benzodiazepines are drugs that inhibit CNS activity. Many of the abuse inhalants appear to produce similar effects to these sedative/depressant drugs. Although all these drugs have different specific mechanisms of action in the brain, they all share the ability to enhance the activity of the inhibitory amino acid neurotransmitter gamma amino butyric acid (GABA). In some cases activation of inhibitory pathways in the brain, in turn, hampers other inhibitory pathways. The effect of inhibiting an inhibitory pathway is often the net activation of a brain region. This mechanism of interfering with other inhibitory pathways is thought to play a role in the abuse potential of these drugs.

ALCOHOL

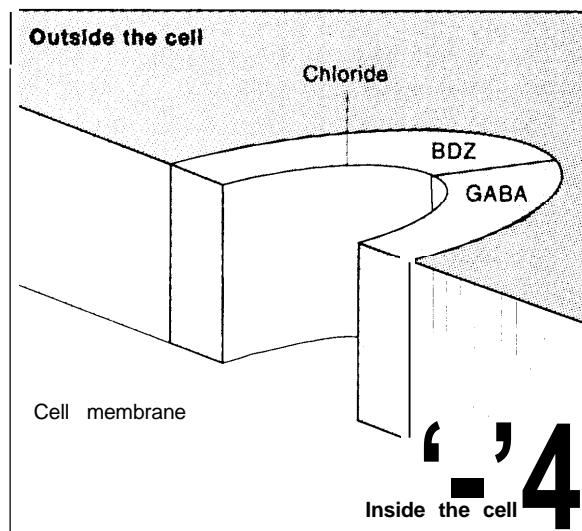
Alcohol differs from most other drugs of abuse in that it has no known receptor system in the brain (52). Alcohol affects a number of different neurotransmitter systems through its action on the membranes of neurons and the ion channels, particularly those for calcium and chloride, that lie within them (43). In general, alcohol inhibits receptors for excitatory neurotransmitters and augments activity at receptors for inhibitory neurotransmitters (52). For example, alcohol enhances the activity of GABA by affecting ion channels that are related to a subpopulation of the GABA_A receptor subtype (figure 3-4) and decreases the action of the excitatory amino acid neurotransmitter glutamate, through inhibition of the NMDA receptor (43,52,55). The net effect of alcohol is to depress activity in the brain producing its characteristic sedating and intoxicating

effects. A similar spectrum of effects is seen with barbiturates and benzodiazepines.

Acute administration—In humans, acute consumption of alcohol produces a sense of well being and mild euphoria and studies have shown that animals will orally self-administer alcohol. Several lines of evidence have implicated dopamine, serotonin, GABA, and opioid peptides in alcohol reinforcement.

Results from several types of studies indicate that dopamine is involved in the acute reinforcing effects of alcohol. Drugs that block the activity of dopamine reduce alcohol self-administration in rats (40,53). Also, depending on the dose, alcohol may stimulate locomotor activity and produce an increase in dopamine levels in the nucleus accumbens (60). Finally, data from genetic models of alcohol preference, in which a strain of rats is bred to have a higher than normal preference for self-administering alcohol, indicate that alcohol-induced release of dopamine is higher in the alcohol-preferring rats than in nonpreferring rats (60). These data suggest that activation of the MCLP is involved in the reinforcing actions of alcohol. However, the precise mechanisms of this activation are unclear.

Alcohol also is thought to enhance GABA activity in specific parts of the brain. GABA enhancement has been linked to the reinforcing effects of alcohol by the observation that drugs that block GABA activity also decrease alcohol intake in alcohol-preferring rats, while drugs that increase GABA activity act as a surrogate for alcohol, maintaining alcohol preference during alcohol withdrawal (27). In addition, an increase in the number of GABA containing fibers has been observed in the nucleus accumbens of alcohol-preferring rats as compared with nonpreferring rats (34). Part of alcohol's reinforcing effects possibly are due to an increase of GABA inhibition on other inhibitory neurons that decrease the activity of the dopamine neurons in the ventral tegmental area. This chain of action would have the ultimate effect of increasing the activity of the dopamine neurons (27). However, the

Figure 3-4-The GABA_A Receptor Complex

The GABA_A receptor complex is made up of a chloride ion channel surrounded by a GABA receptor (GABA) and a benzodiazepine receptor (BDZ). Activation of the GABA_A receptor complex increases the flow of chloride into a cell, thereby inhibiting the activity of the cell.

SOURCE: Office of Technology Assessment, 1993.

experimental evidence supporting this idea is equivocal (27). While it is clear that both GABA and dopamine are involved in the reinforcing effects of alcohol, the relationship between these systems in this action is yet to be defined (27).

Some experimental evidence implicates serotonin in the reinforcing effects of alcohol, although that involvement is not as clear as for dopamine and GABA. Alcohol-preferring rats show a relative deficit in brain serotonin levels as compared to nonpreferring rats (48) and evidence suggests that alcoholic patients have lower levels of serotonin than nonalcoholics (5). In animal studies, drugs or experimental manipulations that increase the levels of serotonin in the brain reduce voluntary intake of alcohol (40). These results would seem to indicate that part of the reinforcing effects of alcohol is due to its inhibitory effect on the serotonin system. However, a variety of studies using animals with experimentally depleted serotonin levels has found that this manip-

ulation decreased alcohol consumption (40). Thus, while serotonin seems to be involved in alcohol's acute reinforcing effects the exact mechanisms that may be involved still need to be clarified. The discrepancies observed in experiments may ultimately be explained by differential effects of alcohol on serotonin receptor subtypes in various brain regions.

In animal studies alcohol self-administration is decreased by drugs that block the action of the opioid peptide neurotransmitters and is enhanced by drugs that mimic their action, suggesting a role for these neurotransmitters in alcohol reinforcement (40). However, drugs that block opioid peptide activity also suppress food and water intake indicating that their action is not specific for alcohol but is related to an inhibition of consummatory behavior in general (40). Nevertheless, as a result of this experimental work naltrexone, an opioid peptide blocking drug, has been tested in alcohol dependent humans, where it has been demonstrated to be a promising adjunct to behavioral relapse prevention treatment (50,59).

Chronic administration—Repeated administration of alcohol results in tolerance to many of its effects. Tolerance to the motor, sedative, antianxiety, and anesthetic effects of alcohol has been shown in animal studies and tolerance in humans is indicated by the fact that dependent individuals increase their consumption over time. How alcohol tolerance develops is not clearly understood, but since alcohol affects the activity in a wide range of neurotransmitter systems, it may involve mechanisms common to many or all of them. In particular, an adaptation in membrane channels for the calcium ion following chronic exposure to alcohol may play a significant role in alcohol tolerance (43). Dispositional tolerance also plays a role.

Alcohol withdrawal in animals is characterized by CNS hyperexcitability. In humans this hyperexcitability results in anxiety, anorexia, insomnia, tremor, disorientation, and sometimes hallucinations. In severe withdrawal a syndrome called

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delirium tremens, marked by vivid hallucinations, disorientation with respect to time and place, and outbursts of irrational behavior, may develop.

In humans, the craving for alcohol during periods of abstinence has often been considered a prime factor underlying excessive alcohol use. However, there is no evidence of a correlation between development of physical dependence and a specific craving for alcohol in experimental animals (52). This same result has been noted in human alcoholics in an experimental laboratory situation (44). While avoidance of withdrawal symptoms plays a role in continued alcohol use in humans, the relationship between the development of the withdrawal syndrome and alcohol **craving** during abstinence needs to be clarified (52).

The CNS hyperexcitability associated with alcohol withdrawal is thought to be related to alcohol-induced alterations in the sensitivity of GABA and glutamate receptors (40,43). Experimental evidence indicates that prolonged alcohol exposure decreases the sensitivity of GABA receptors (47) and increases the sensitivity of glutamate receptors (24). With the cessation of alcohol intake, these changes are manifested throughout the brain as a decrease in the overall activity of the inhibitory neurotransmitter GABA and an increase in the activity of the excitatory amino acid neurotransmitter glutamate.

BARBITURATES

Barbiturates are a class of drugs that depress CNS activity. First introduced in the early 1900s, barbiturates were widely prescribed as anti-anxiety agents and sleep aids, and to treat other psychiatric conditions. However, their lethal overdose potential and high abuse potential, coupled with the advent of the safer benzodiazepine compounds curtailed their use starting in the 1960s (46).

Barbiturates' sedative effects result from their ability to increase GABA activity (54). Their mechanism of action is through an augmentation of the activity of one of the receptor subtypes for

GABA, the GABA_A receptor (see figure 3-4). The GABA_A receptor is linked to a chloride ion channel. Stimulation of the receptor by GABA opens the channel and increases the flow of chloride into the neuron, which acts to inhibit the cell's activity. Barbiturates increase the amount of time the chloride channel stays open thus increasing the inhibitory effects of GABA.

Acute administration—The reinforcing properties of barbiturates have been clearly demonstrated in both animal and human studies (46). Animals readily self-administer barbiturates in a variety of different experimental paradigms. In humans, studies using self-report measures have demonstrated that drug-experienced subjects, blind to the identity of the drug, consistently give barbiturates high rankings when asked to rate a series of drugs as to 'liking' or 'would you take this drug again?' Also, in controlled studies, human subjects will work to receive barbiturates and will do more work to receive the drug if the available dosage is increased (46). The mechanism of barbiturate reward is unclear. Since one of its major effects is to enhance GABA activity, barbiturates, like alcohol, may increase GABA inhibition of other inhibitory neurons that decrease the activity of the dopamine neurons in the ventral tegmental area. Further studies are necessary to confirm this possibility.

Chronic administration—With continued use some tolerance develops to most effects of the barbiturates (46). Little tolerance develops to the lethal dose. Unlike most other drugs of abuse, both dispositional and pharmacodynamic tolerance are important in the development of barbiturate tolerance. Barbiturate withdrawal is marked by a severe and sometimes life-threatening withdrawal syndrome (46). Both anxiety and depression are common features, and with heavy, prolonged use, the development of severe grand mal tonic epileptic seizures can occur. The neurochemical changes responsible for the pharmacodynamic tolerance and withdrawal syndrome have yet to be clearly established. Some experimental evidence suggests that tolerance is

the result of the GABA_A receptors becoming less sensitive to the effects of barbiturates (54). With drug cessation, the barbiturate stimulation of GABA activity ceases and the action of the desensitized receptors manifests itself as an overall decrease in GABA activity, resulting in withdrawal symptoms. Again, the hyperexcitability that results is similar to what occurs in alcohol withdrawal.

BENZODIAZEPINES

Benzodiazepines are a class of drugs introduced in the 1960s as antianxiety agents (25). They rapidly replaced barbiturates, which have significant abuse potential, to treat anxiety and other psychiatric conditions. Like barbiturates, benzodiazepines have a general inhibitory effect in the brain by enhancing GABA activity. But unlike barbiturates' nonspecific effect on chloride ion channels, benzodiazepines act by binding to a specific benzodiazepine receptor (21,54). The presence of a benzodiazepine receptor in the brain indicates the presence of a naturally occurring endogenous neurotransmitter that normally interacts with the receptor. An endogenous benzodiazepine-like neurotransmitter has yet to be identified.

The benzodiazepine receptor is coupled with the GABA_A receptor (figure 3-4). Stimulation of the benzodiazepine receptor increases the frequency of chloride ion channel opening in response to GABA binding to the GABA_A receptor (21). Also, benzodiazepines enhance the binding of GABA to its receptor and the presence of GABA enhances benzodiazepine binding. The net effect of benzodiazepines is to augment GABA activity at the GABA_A receptor and enhance GABA action. The antianxiety and other sedative effects of the benzodiazepines are due to this action.

Acute administration—Most benzodiazepines support only modest levels of self-administration, much below the levels observed with barbiturates, when given intravenously in animal studies (25,46). When given orally, benzodiazepines do not induce self-administration in

animal studies (46). In humans, self-report studies, similar to those used to examine barbiturates, have demonstrated that benzodiazepines yield modest rankings of liking and that given a choice, subjects consistently prefer barbiturates over benzodiazepines (25,46). Since benzodiazepines act selectively on GABA activity it is probable that their mild reinforcing properties are due to activation of GABA mechanisms similar to those described for alcohol.

Chronic administration—Prolonged exposure to benzodiazepines results in tolerance to their therapeutic and other effects (19,21). This tolerance maybe due to a reduction in the functional activity of GABA as a result of a desensitization of the benzodiazepine receptor caused by prolonged exposure to the drug (21). As with alcohol and barbiturates, a withdrawal syndrome occurs following benzodiazepine drug cessation due to a decrease in GABA activity. In general, the characteristics of benzodiazepine withdrawal are similar to barbiturate withdrawal, but at typical benzodiazepine therapeutic doses the magnitude of the symptoms are less severe than seen in barbiturate withdrawal. Nonetheless, since benzodiazepines are widely prescribed, their ability to induce physical dependence at therapeutic doses indicates that care must be given in their administration (25).

| Opiates

The poppy plant, *Papaver somniferum*, is the source of naturally occurring opium. This natural substance contains more than 20 alkaloid compounds, including the drugs commonly known as morphine and codeine. Illicit drugs such as heroin and other semisynthetic opiates are derived by altering morphine (20). Opiates are drugs, natural or synthetic, which have opium- or morphine-like activity. These drugs, when administered into the body, mimic the body's endogenous, or self-produced, opioid peptide neurotransmitters (endorphins, enkephalins, and dynorphins). The opioid peptide neurotransmitters are involved in

three major functions: modulation of pain perception and response to painful stimuli; reward; and regulation of homeostatic functions such as food, water, and temperature regulation (39). The main types of opioid receptors have been identified in the brain— mu, delta, and kappa (18), all of which are linked to second messengers in the cell (14). In general, the opioid peptide neurotransmitters have an inhibitory effect on the activation of neurons (18). Since morphine is selective for the mu receptor, it is thought that the activation of this receptor is responsible for the reinforcing characteristics of opiates (18,39,40,41). The overall acute and chronic effects of opiate drugs in the brain involve many interactive brain systems (39). Related to the function of endogenous opioid neurotransmitters, opiate drugs produce a profound sense of euphoria and well-being coupled with sedation, relaxation, and increase in pain threshold in humans.

Acute administration-Opiates have an immediate reinforcing effect and are readily self-administered by humans and animals in experimental situations (40). The weight of experimental evidence favors a role for dopamine in the rewarding effects of opiates, while other systems may also be involved (18). Animal studies have shown that opiates increase the activity of dopamine neurons in the ventral tegmental area (18,39,40,41). This increase is via an indirect mechanism (18). Within the ventral tegmental area neurons contain the inhibitory neurotransmitter GABA. Those GABA containing neurons have mu receptors on them and form synapses with the dopamine neurons. Since opioids also inhibit neural activity, when the mu receptors are activated by opiates, the GABA receptors release less GABA, which decreases the inhibition on the dopamine cells, causing the dopamine neurons to become more active. The net effect of this disinhibition is to increase activity in the ventral tegmental neurons, which release dopamine in the nucleus accumbens. This increase in dopamine activity results in the rewarding and motor stimulating properties of opiate drugs. In addition to the

dopamine-dependent mechanism of opiate reinforcement, there appears to be another component not involving dopamine (40,41). This second component is thought to involve opiate activity on the neurons of the nucleus accumbens and their connections to other areas in the front of the 'brain (41).

Chronic administration—In general, repeated administration of opiates results in the development of marked tolerance to their effects including their reinforcing effects (15,18). While the precise mechanism of opiate tolerance is unclear, one hypothesis is that chronic exposure causes a desensitization of opioid receptors (15,58). Repeated activation of the receptors by the drug causes an uncoupling of the receptor from the internal cellular mechanisms that are activated when the receptors are stimulated normally (58). Experimental evidence also suggests that chronic exposure to opiate drugs may decrease the levels of endogenous opioid neurotransmitters, contributing to the development of tolerance (58). The decrease is believed to be due to an over activation by the opiate drugs of mechanisms that normally regulate the levels of neurotransmitter (58).

Craving and withdrawal are two prominent characteristics of chronic opiate administration. In humans withdrawal is characterized by depression, irritability, insomnia, nausea, and weakness (18,36). Chronic morphine administration, like chronic cocaine administration, has been shown to produce changes in the expression of genes involved in a number of intracellular mechanisms within neurons in the ventral tegmental area and nucleus accumbens (10). These changes may contribute to the craving and feelings of dysphoria associated with withdrawal.

The locus ceruleus, a nucleus in the brainstem, has been implicated in the physical signs of opiate withdrawal (15,39,40). The locus ceruleus is composed mainly of neurons containing noradrenaline. These neurons send fibers to numerous brain structures including the cortex, hippocampus, and other structures in the front of the brain

and receive fibers from various structures, including a strong excitatory input from other areas in the brainstem. The activity of locus ceruleus neurons is inhibited by opioid neurotransmitters via activation of mu receptors (15). Animal studies have shown that direct electrical stimulation of these neurons produces symptoms similar to those seen in opiate withdrawal (15). Locus ceruleus neurons become tolerant to the effects of opiates after chronic exposure (15,39). An increased stimulation of the neurons in the locus ceruleus via their brainstem excitatory inputs is thought to occur during opiate withdrawal, resulting in the enhanced noradrenaline release at the many brain sites that receive inputs from the locus ceruleus (15).

| Cannabis

The different types of drugs made from *Cannabis sativa* are distinguished by the plant parts used in preparing the drug. Marijuana consists mainly of dried plant material such as cut leaves, stems, seeds, and the flowering tops of the plants. Hashish is the dried resin made from the flower tops and sinsemilla is a variety of marijuana selected for its particularly potent effects and harvested before seed formation. Cannabis is most frequently smoked, resulting in the rapid delivery of the drug into the bloodstream, such that effects may be felt within minutes and last for 2 to 3 hours. Cannabis may also be administered orally. However, the plasma concentration is lower and takes about an hour to peak.

Cannabis sativa contains psychoactive cannabinoids. The primary psychoactive component of *Cannabis sativa* is the cannabinoid delta-9-tetrahydrocannabinol (THC). Most of the other cannabinoids are either inactive or weakly active. In addition, smoking marijuana produces hundreds of other compounds (2). While most research has concentrated on evaluating the molecular and biochemical mechanisms of THC that underlie the actions of the cannabinoids, these other compounds can also play a role in the

acute and long-term consequences of marijuana use (2).

It has only been in the last few years that a specific receptor for THC has been identified in the brain (16,30). This receptor is linked to a second messenger (14) and is localized to specific brain regions including the hippocampus, cerebral cortex, cerebellum, and the axon terminals of fibers that arise in the basal ganglia (a brain structure in the front of the brain involved with movement) and terminate in the globus pallidus (a structure in the front of the brain involved in movement and closely connected with the basal ganglia) and substantia nigra (located in the midbrain, next to the ventral tegmental area, it contains dopamine neurons that send fibers to the basal ganglia) (29,30). The characteristic cognitive (e.g., memory impairment) and motor (e.g., decreased motor coordination) effects of THC are thought to be the result of its action on these receptors (29). As with benzodiazepines, the identification of a specific receptor for THC suggests that there may be a naturally occurring endogenous neurotransmitter in the brain that normally interacts with the receptor. While not positively identified, several candidates have been proposed, including the chemical anandamide (16).

Since smoking marijuana results in the inhalation of many potentially psychoactive compounds in addition to THC, the subjective effects of marijuana vary somewhat among individuals (2). The behavioral response to marijuana may vary as a function of dose, setting, experience, and expectation of the user, the cannabinoid content of the sample, and the compounds that are produced as the marijuana is burned. Nevertheless, several behavioral effects are generally ascribed to marijuana use (32). The most prominent feature is an initial period of euphoria. The euphoria is often followed by a period of drowsiness and sedation. Perception of time is altered and there is a dissociation of ideas, and distortions in hearing and vision. Some studies have documented impairment on a variety of cognitive and

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performance tasks involving memory, perception, reaction time, learning, and motor coordination (2). An amotivational syndrome, characterized by apathy, dullness and impairment of judgment, concentration and memory, along with loss of interest in pursuit of conventional goals, has been described in the literature, and evidence shows that this syndrome is a result of chronic intoxication (35).

Acute administration—While marijuana produces a feeling of euphoria in humans, in general, animals will not self-administer THC in controlled studies (29). Also, cannabinoids generally do not lower the threshold of the amount of electrical stimulation needed to get animals to self-stimulate the brain reward system, as do other drugs of abuse; although one series of studies has shown that in the inbred lewis rat, THC not only lowers the threshold for electrical self-stimulation but also enhances the release of dopamine in the nucleus accumbens (22). The enhancement of dopamine release was blocked by drugs that block endogenous opioid activity (22) indicating that endogenous opioids can regulate this response. The fact that these results have been observed in an inbred strain of rat indicates that they have some inherited variation related to the mechanism of THC. Since THC receptors are not directly associated with dopamine neurons (29) and the dopamine response that has been observed is modulated by opioids, it is likely that the effects of cannabinoids on dopamine circuits involved in reward are indirect and different from those of drugs, such as cocaine and morphine that directly affect dopamine levels and produce craving and drug-seeking behavior (29). Nonetheless, the observation that the ability of animals to recognize the intoxicating effects of THC can be mimicked by drugs that selectively activate the THC receptor indicates that these effects are mediated through the THC receptor (9,23).

Chronic administration—Tolerance readily develops to the behavioral and pharmacological effects of THC in both humans and animal experimental models (2,5 1). In humans, tolerance

develops to the mood, memory, motor, and performance effects of the drug (51). The mechanism of this tolerance is thought to be a desensitization of the THC receptor, perhaps by some alterations in its interaction with the second messenger (2,51).

Cessation of cannabinoid administration does not give rise to an intense withdrawal syndrome (2,51). Only a few animal studies show that any withdrawal symptoms result. Changes that have been observed include increased motor and grooming activity in rats, altered susceptibility to convulsion induced by electric shock in mice, and increased aggressiveness in monkeys (51). In humans, withdrawal signs are relatively mild (2,51) and consist of changes in mood and sleep, increased irritability and restlessness, anorexia, and mild nausea. As with all drugs the relative intensity of the withdrawal syndrome is dependent on the quantity, frequency, and duration of drug use. While a severe physical dependence phenomenon is not associated with cannabis withdrawal, the probability of developing a form of craving is high (2). The mechanism for these various withdrawal effects is unknown, but it is likely related to the unmasking of the desensitized receptors on drug cessation. Also, both the tolerance and withdrawal phenomena may be related to alterations in the as yet unidentified endogenous neurotransmitter that interacts with the THC receptor (5 1).

| Lysergic Acid Diethylamide

Lysergic acid diethylamide (LSD) is *one* of a broadly defined class of drugs known as psychedelics. Other psychedelics include mescaline and psilocybin. The effects of the psychedelics are similar, but LSD is the most potent (13). These drugs distort the perception of space and time, and produce exaggerated sensory phenomena in vision, hearing, and touch. The subjective effects associated with psychedelic use are strongly determined by a number of factors such as setting, expectations, user's personality, and dose. In

some cases, adverse psychiatric effects occur including 'bad trips', panic reactions, and even psychotic episode during intoxication. While these drugs are some of the most powerful psychoactive drugs known and can have adverse consequences, their dependence potential, as measured by their reinforcing properties and neuroadaptive response, is low as compared with the other drugs discussed in this report. Psychedelic use has undergone cycles of popularity, such as during the 1960s, and serves as an example of how extrinsic societal factors can affect drug use, in addition to the intrinsic pharmacological actions of a drug.

Acute administration—LSD's psychedelic properties are a result of its actions on the serotonin neurotransmitter system (1,26). LSD is thought to stimulate the various receptor subtypes for serotonin, and has particular potency in activating the serotonin autoreceptor (3). A similar activation of the serotonin system is seen with MDMA, which is a derivative of amphetamine and has both dopamine and serotonin stimulating properties. Unlike LSD, MDMA stimulates serotonin neurotransmission by blocking its reuptake into the presynaptic terminal (1). This action on serotonin gives MDMA psychedelic properties in addition to its amphetamine-like stimulating properties. To date, no evidence confirms that LSD supports self-administration in animal studies (13).

Chronic administration—Tolerance develops rapidly to LSD and other psychedelics when they are repeatedly administered and the extent of the tolerance is greater than what is observed with other drugs such as PCP or alcohol (13). The mechanism of LSD tolerance is unclear. Since LSD stimulates serotonin receptors and a typical response of receptors to continued activation is a desensitization process, it is possible that serotonin receptor desensitization plays a role.

Currently, there is no evidence that a withdrawal syndrome is associated with termination of chronic hallucinogen use (13). The phenome-

non of flashbacks, in which the perceptual changes associated with LSD spontaneously appear after drug cessation, are reported to occur in about 23 percent of regular users (31). It unclear whether flashbacks represent a withdrawal syndrome and are related to, or predictive of, hallucinogen dependence (13).

SUMMARY

Studies of the pharmacological actions of drugs of abuse indicate that their reinforcing properties may be due to actions on a common neural circuit. While the mechanisms involved for all drugs of abuse have not been completely described, many, either directly or indirectly, activate MCLP. Such drugs include cocaine, amphetamines, opiates, sedatives, and nicotine. For other drugs of abuse the precise relationship, if any, to the brain reward system is unclear.

Repeated administration of all drugs of abuse is associated with neuroadaptive responses. In general, tolerance develops to at least some of their effects although the specific details of the biological mechanisms underlying these changes are not completely understood. In terms of promoting substance abuse, an important action is the development of tolerance to the reinforcing properties of a drug. Available evidence suggests that tolerance develops to the reinforcing properties of cocaine, alcohol, PCP, and opiates. A withdrawal syndrome is associated with most drugs of abuse, though the severity varies. Barbiturates, alcohol, stimulants, opiates, and benzodiazepines produce pronounced and sometimes severe withdrawal symptoms, while those for nicotine and caffeine is less intense. A mild withdrawal is associated with cannabis use; while there is no evidence of a withdrawal syndrome related to LSD. Certain aspects of withdrawal, such as changes in mood and motivation, induced by the chronic drug state may be key factors to relapse and drug-seeking behavior.

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