Biological Components of Substance Abuse and Addiction

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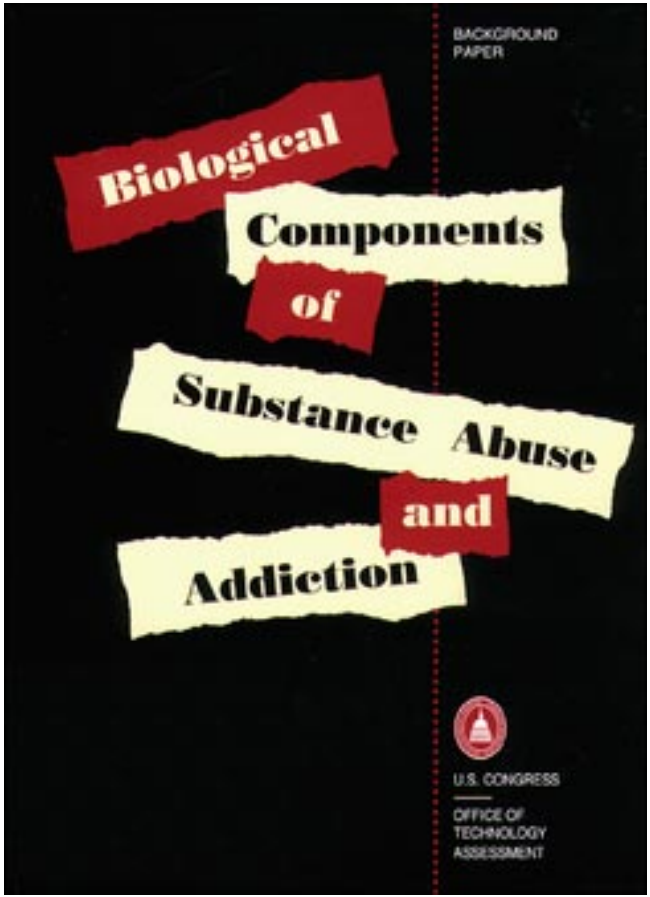

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Foreword

Substance abuse and addiction are complex phenomena that defy simple explanation or description. **A** tangled interaction of factors contributes to an individual's experimentation with, use, and perhaps subsequent abuse of drugs. Regardless of the mix of contributing factors, the actions and effects exerted by drugs of abuse underlie all substance abuse and addiction. In order to understand substance abuse and addiction it is first necessary to understand how drugs work in the brain, why certain drugs have the potential for being abused, and what, if any, biological differences exist among individuals in their susceptibility to abuse drugs.

This background paper is the first of two documents being produced by OTA as part of an assessment of *Technologies for Understanding the Root Causes of Substance Abuse and Addiction. The* assessment was requested by the House Committee on Government Operations, the Senate Committee on Governmental Affairs, and the Senate Committee on Labor and Human Resources. This background paper describes biological contributing factors to substance abuse and addiction. The second document being produced by this study will discuss the complex interactions of biochemical, physiological, psychological, and sociological factors leading to substance abuse and addiction.

OTA gratefully acknowledges the generous help of the Advisory Panel, contributors, and reviewers who gave their time to this project. OTA, however, remains solely responsible for the contents of this background paper.

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NOTE: OTA appreciates and is grateful for the valuable assistance and thoughtful critiques provided by the **advisory panel** *members. The panel does not, however, necessarily approve, "disapprove, or endorse this report. OTA assumes full responsibility for the report and the accuracy of its contents.*

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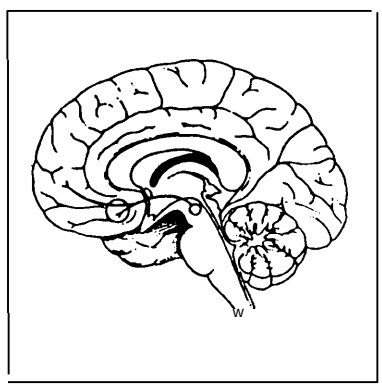
Executive Summary 1

Substance abuse and addiction are complex phenomena that defy simple explanation or description. A tangled interaction of factors contributes to an individual's seeking out, using, and perhaps subsequently abusing drugs. Since more individuals experiment with drugs than eventually develop substance abuse problems, great interest persists in understanding what differentiates these groups. Factors that can play a role in drug abuse susceptibility include a person psychological makeup (e.g., self-esteem, propensity to take risks, irnpulsivity, depression), biological response to drugs and environmental situation (e.g., peer groups, family organization, socioeconomic status), and the availability of drugs. The exact combination of elements that leads to substance abuse and addiction varies among individuals.

Regardless of the mix of contributing factors, the actions and effects that drugs of abuse exert underlie all substance abuse and addiction. In order to understand substance abuse and addiction one must first understand how drugs work in the brain, why certain drugs have the potential for abuse, and what, if any, biological differences exist among individuals in their susceptibility to abuse drugs. While numerous factors ultimately contribute to an individual's drug-taking behavior, understanding the biological components is crucial to a better comprehension of substance abuse and addiction. In this background paper, the Office of Technology Assessment (OTA) describes the biological components of substance abuse and addiction.



Two biological factors contribute to substance abuse and addiction: the effects drugs of abuse exert on the individual, and the biological status of the individual taking drugs. The former

Box l-A–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 (figure l-l). The molecules of the neurotransmitter move across the synapse and attach, or bind, to proteins called receptors in the outer membrane of an adjacent ceil. Once a neurotransmitteractivates a receptor, it unbinds from the receptor and is removed from the synapse. This is done either by the neurotransmitter being taken backup into the neuron that released it or by its being chemically broken down.

For each neurotransmitter in the brain, there are several specific receptors to which it can attach. Binding by the neurotransmitter activates 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. while receptors are specific foa neurotransmitter, there maybe a variety of receptor subtypes, linked to different cellular mechanisms and to different neuronal circuits, that all respond to the same neurotransmitter. In this way one neurotransmitter can have diverse effects indifferent areas of the brain. Many chemicals have been identified as neurotransmitters. Sores are of particular relevance to the rewarding properties of drugs of abuse. These include dopamine, norepinephrine, serotonin, opioids and other neuropeptides, gamma amino butyric add (GABA), and glutamate.

A neuron can have thousands of receptors for many different neurotransmitters. Some neurotransmitters activate neurons (excitatory neurotransmitters), while others decrease neuron activity (inhibitory neurotransmitters). Sometimes a receptor for one neurotransmitter can affect a receptor for another neurotransmitter. In such cases, 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. *Such* receptors are acted on by the neuron's own neurotransmitter to regulate the release of the neurotransmitter. Thus, these so-called autoreceptors act as a feedback mechanism to regulate a neuron's activity. The activity ofa neuron will be determined by the cumulative activity of all of its various receptors.

Drugs that work in the brain, including drugs of abuse, alter normal neuropharmacological activity through a varietyofdifferent mechanisms. They can affect the production, release, or reuptake of a neurotransmitter, they can mimic or block the action of a neurotransmitter at a receptor, or they can interfere with or enhance the activity of a membrane or cellular mechanism associated with a receptor. Prolonged drug use has the potential to alter each of these processes.

SOURCE: office of Technology Assessment, 1993.

relates to the acute mechanisms of action of drugs of abuse in the brain and the long-term effects that occur after chronic exposure. The latter pertains to an individual's biological constitution, most importantly the presence of inherited characteristics, which affects that person's response to a drug.

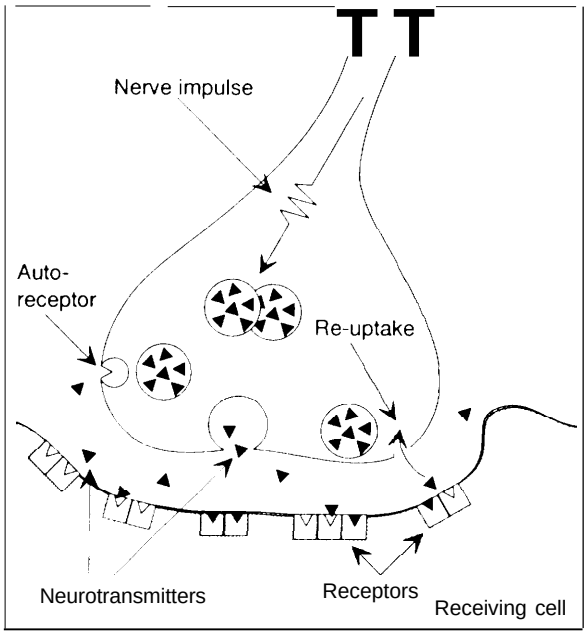
DRUG ACTION

I Acute Actions

Drugs of abuse alter the brain's normal balance and level of biochemical activity (box l-A). What separates drugs of abuse from other psychoactive drugs is that most of these drugs act, at least in part, on those areas of the brain that mediate feelings of pleasure and reward (box l-B).

The ability to induce activity in the so-called brain reward systems gives drugs of abuse positive reinforcing actions that provoke and support their continued use and abuse. *Reinforcement* is defined as the likelihood that the consequences of taking the drug will increase the behavior directed toward seeking that drug. Put more simply, individuals who use drugs experience some effect, such as pleasure, detachment, or relief from distress, that initially establishes and then maintains drug self-administration. The **con-**

Figure I-I—The Synapse and Associated Structures



SOURCE: Office of Technology Assessment, 1993.

sequence of taking the drug enhances the prospect that it will continue to be used for some real or perceived effect and eventually compulsive self-administration. In fact, the capacity of a drug to support self-administration in experimental animals is a measure of the drug's strength as a reinforcer.

While growing evidence indicates that the brain reward system likely plays a role in the reinforcing properties of most drugs of abuse, the precise mechanisms involved in all drugs of abuse have yet to be completely described. The rewarding properties of stimulant drugs such as cocaine and amphetamines are due to a direct increase in the activity of the neurotransmitter dopamine in the mesocorticolimbic dopamine pathway (see box l-B). Opiates, on the other hand, indirectly stimulate dopamine activity by activating other neurotransmitter pathways, which in turn increase dopamine activity in the mesocorticolimbic pathway (MCLP). Similarly, alcohol, barbiturates, and benzodiazepines also indirectly activate MCLP. All of these drugs have strong reinforcing properties. Phencyclidine (PCP) is also a strong reinforcer but its relationship, if any, to activity in MCLP has not been established. Other drugs are either weak reinforcers or have not been shown to support self-administration in animal experiments. Nicotine activates dopamine neurons in the mesocorticolimbic system. However, when compared with cocaine or amphetamine, this effect is modest. Likewise, caffeine is a weak reinforcer, but the precise mechanisms of its reinforcement are unclear. Finally, while cannabis and lysergic acid diethylamide (LSD) produce positive effects that clearly support their use, there is currently little empirical evidence that they act as reinforcers in controlled experiments.

Chronic Actions

Changes occur in the brain when it is exposed to drugs. Beyond their immediate, rewarding properties, drugs of abuse, when used on a chronic, long-term basis, can cause either permanent changes in the brain or alterations that may take hours, days, months, even years to reverse on drug cessation. These changes are adaptive responses related to the pharmacological action of a given drug that occur in the brain to counter the immediate effects of a drug.

Tolerance develops to a drug when, following a prolonged period of use, more of the drug is required to produce a given effect. Tolerance occurs with many types of drugs and is a common, but not necessary, characteristic of drugs of abuse. Tolerance can contribute to drug-taking behavior by requiring that an individual take progressively larger doses of a drug to achieve a desired effect.

Dependence occurs when, with prolonged use of a drug, neurons in the brain adapt to the drug's presence such that the use of the drug *is* now required to maintain normal function in the cells. On abrupt withdrawal of the drug, the neuron behaves abnormally and a "*withdrawal syn*drome" ensues, Generally, the withdrawal syn-

Box 1-B—The Brain Reward System

Eating, drinking, sexual, and maternal behaviors are activities essential for the survival of the individual and the species. Natural selection, in order to ensure that these behaviors occur, has imbued them with powerful rewarding properties. The brain reward system evolved to process these natural reinforcers.

The reward system is made up of various brain structures. A key part of this system for drug reward appears to be the mesocorticolimbic pathway (MCLP) (figure 1-2). MCLP is made up of the axons of neuronal cell bodies in the middle part of the brain (i.e., ventral tegmental area) projecting to areas in the front part of the brain (i.e., the nucleus accumbens, a nucleus[1] in the limbic system, a network of brain structures associated with control of emotion, perception, motivation, gratification, and memory; medial prefrontal cortex, the front part of the brain involved with higher ordered thinking). Ventral tegmental neurons release the neurotransmitter dopamine to regulate the activity of the cells in the nucleus accumbens and the medial prefrontal cortex. Other parts of the reward system include the nucleus accumbens and its connections with other limbic structures, and other regions in the front part of the brain (i.e., substantia innominata-ventral palladium). The nucleus accumbens also sends signals back to the ventral tegmental area. Finally, other neuronal pathways containing different neurotransmitters regulate the activity of the mesocorticolimbic dopamine system and may also be involved in mediating the rewarding properties of drugs of abuse.

1 A nucleus is a collection of cells in the brain that share the same anatomical region and, to varying degrees, the same function.

SOURCE: G.F. Koob, "Drugs of Abuse: Anatomy, Pharmacology, and Function of Reward Pathways," *Trends in Pharmacological Sciences* 13:177-184, 1992; G.F. Koob, "thud Mechanisms of Drug Reinforcement," P.W. Kalivas, and H.H. Samson (eds.), *The Neurobiology of Drug and Alcohol Addiction, Annals of the American Academy of Sciences* 654:171-191, 1992.

drome is characterized by a series of signs and symptoms that are opposite to those of the acute effects of the drug. Withdrawal creates a craving or desire for the drug and plays a very strong role in recurrent patterns of relapse, in maintaining drug-seeking behavior to forestall the withdrawal syndrome, and in the need to reestablish some sense of normalcy.

Sensitization occurs when the effects of a given dose of a drug increase after repeated administration. Thus, sensitization is the opposite of tolerance. Sensitization to a drug's behavioral effects could play a significant role in supporting drug-taking behavior.

For example, while tolerance to some of the effects of cocaine and amphetamines develops, sensitization to other of their effects can also occur. Also, while it is unclear horn available data whether tolerance develops to cocaine's reinforcing effects, the notion is supported by some experimental evidence and anecdotal reports born cocaine users that the drug's euphoric actions diminish with repeated use. Tolerance also develops to the effects, including the reinforcing properties, of opiates and alcohol.

A withdrawal syndrome of varying severity is associated with most drugs of abuse. Barbiturates, alcohol, stimulants, opiates, and benzodiazepines produce pronounced and sometimes severe withdrawal symptoms, while those for nicotine and caffeine are less intense. **A mild withdrawal is** associated with cannabis use, while there is no evidence of a withdrawal syndrome related **to** LSD.

I Abuse Liability

The abuse liability of a drug is a measure of the **likelihood that its use will result in drug addic**tion. Many factors ultimately play a role in an individual's drug-taking behavior; nevertheless, the abuse potential of a drug is related to its intrinsic rewarding properties and/or the neu-

roadaptive responses that result from its prolonged use. Drugs can be tested and screened for their abuse liability using animals as models. The criteria that can be evaluated to classify a drug as having significant abuse potential are pharmacological equivalence to known drugs of abuse, demonstration of reinforcing effects, tolerance, and physical dependence. The capacity to produce reinforcing effects is essential to any drug with significant abuse potential, whereas tolerance and physical dependence most commonly occur but are not absolutely required to make such a determination.

SELF-ADMINISTRATION

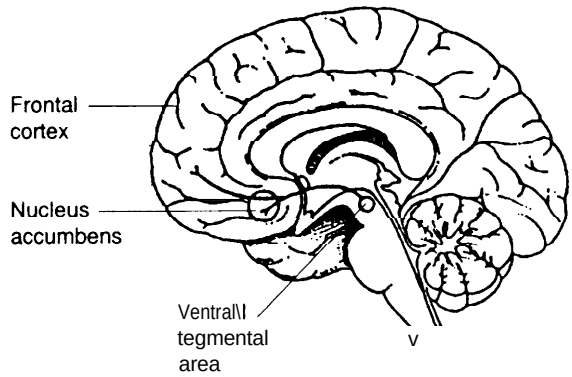
The predominant feature of all drugs with significant abuse potential properties is that they are self-administered. In fact, self-administration of a drug to the point when the behavior becomes obsessive and detrimental to the individual is the primary criterion that must be met to classify a drug as having significant potential for addiction. In addition to self-administration, another contributing factor to abuse liability is the notion of craving and the tendency of individuals to relapse to drug use during withdrawal. Although craving is a difficult term to quantify, once a drug is voluntarily or involuntarily withdrawn, the desire to take the drug can play a role in the relapse to substance abuse.

Animals can be readily trained to self-administer drugs. Animal models of self-administration provide a powerful tool that can give a good indication of the abuse liability of new or unknown drugs. These models also permit an examination of the behavioral, physiological, and biological factors that lead to sustained self-administration.

DRUG DISCRIMINATION

Another tool in the assessment of abuse liability of drugs is drug discrimination, which refers to the perception of the effects of drugs. Specifically, animals or humans trained to discriminate

Figure 1-2—The Mesocortlcolimbic Pathway



The mesocorticolimbic pathway from the ventral tegmental area to **the nucleus accumbens and the frontal cortex is a key component of the brain reward system for drug reinforcement.**
SOURCE: Office of Technology Assessment, 1993.

a drug from a placebo show a remarkable ability to distinguish that drug from other drugs with different properties. These procedures also permit a determination of whether the subject considers the drug to be the pharmacological equivalent of another drug. Pharmacological equivalence refers to the fact that drugs of a particular class, such as opiates, stimulants, and depressants, cause a series of effects on the brain and other organs that collectively constitute their pharmacological profile.

DEPENDENCE AND TOLERANCE

Dependence and tolerance can readily be induced in animals by chronic administration of drugs. Following abrupt withholding of a drug, a withdrawal syndrome will often develop and the motivation for self-administration of the drug may be increased. Thus, the capacity of a drug to induce neuroadaptive motivational changes can be assessed. Furthermore, since the understanding of the neuroadaptive changes that take place during the development of physical dependence and tolerance are poorly understood in humans, animal models offer a unique opportunity to carry out experiments designed to address these issues.

GENETIC FACTORS

Progress in understanding the genetics of various conditions and diseases has brought with it a realization that substance abuse and addiction probably involve a genetic component. That is, hereditary biological differences make some individuals either more or less susceptible to drug dependency than others. While it seems likely that inherited differences exist, a genetic component alone is insufficient to produce substance abuse and addiction.

Unlike disorders, such as Huntington's disease and cystic fibrosis, that result from the presence of alternations in a single gene, a genetic component of substance abuse is likely to involve multiple genes that control various aspects of the biological response to drugs or physiological predisposition to become an abuser. In addition, the complex nature of drug dependency, involving many behavioral and environmental factors, indicates that any genetic component acts in consort with other nongenetic risk factors to contribute to the development of substance abuse and addiction. Thus, the presence of a genetic factor does not ensure drug addiction nor does its absence guarantee protection from drug addiction.

Two questions arise when considering a genetic component to substance abuse and addiction: Do inherited factors exist? And, if so, what are they? To date, much of the work done in this field relates to alcoholism. Less is known about the genetic aspects of the abuse of other drugs.

I Do Inherited Factors Exist?

Results from family studies, twin studies, and adoption studies as well as extensive research on animal models indicate that heredity influences normal as well as pathological use of alcohol. Animal studies have established that genetic factors contribute to alcohol preference, the reinforcing actions of alcohol, alcohol tolerance, and alcohol physical dependence. While few studies have examined the genetic component of vulnerability to the addictive properties of other drugs of abuse, evidence from animal studies confirms the role of a genetic influence on the use and abuse of drugs other than alcohol. The study of nonalcoholic drug abuse in humans has been difficult due to substantially lower population prevalence and differences in availability and, hence, exposure to these agents. Investigation in this area is further hampered by the complexity of subjects' drug use: most drug abusers have used multiple agents. This has led researchers either to concentrate on one class of drug or to treat all illicit drug use as equivalent. The tendency to lump all illicit drugs into one category makes results difficult to interpret or compare.

I What Is Inherited?

While study results support the role of a genetic component in alcoholism and probably other drug abuse, they provide no information about what exactly is inherited. For example, do individuals with a family history of drug abuse have an increased susceptibility or sensitivity to the effects of drugs with reinforcing properties? If a susceptibility exists, what are its underlying biological mechanisms? Information about inherited biological mechanisms is most easily derived from studies of animals bred to have differing responses to various drugs. However, in humans, few studies have examined the relationship between inherited behavioral traits and the inherited biological mechanisms that might underlie them.

In the case of alcohol, studies suggest that low doses of alcohol are more stimulating and produce a stronger positive reward in rats bred to have a high preference for alcohol as compared with normal rats. Experimental data indicate that this may be due to inherited differences in the mesocorticolimbic dopamine system (see box l-B) and an inherited increased response of this system when exposed to alcohol. Also, alcohol-preferring rats have been found to have different levels of activity in other neurotransmitter systems that modulate activity in the mesocorti-

colimbic system. In humans, studies of college-aged individuals indicate that low initial sensitivity to alcohol may be a predictor for alcoholism later in life.

Studies using the technique of genetic linkage analysis[1] have attempted to identify genes that might be associated with alcoholism in humans. However, the findings of these studies are inconclusive. While some studies have reported a link between alcoholism and a gene that regulates the number of a type of dopamine receptor in the brain, others have not. The reason for this discrepancy is unclear, but one study has found a relationship between the presence of the gene not only in alcoholism, but also in other disorders such as autism, attention deficit hyperactivity disorder, and Tourette's syndrome. Thus, the presence of the gene may cause an alteration in the brain dopamine system that somehow exacerbates or contributes to alcohol abuse, but is not uniquely specific for alcoholism.

Fewer studies have focused on possible inherited biological mechanisms associated with the abuse of other drugs. For example, strains of rats and mice that differ in their sensitivity to the reinforcing effects of cocaine and in their cocaine-seeking behavior have also been observed to have differences in the number of dopamine-containing neurons and receptors in certain brain areas. Also, a comparison of one strain of rat that self-administers drugs of abuse at higher rates than another strain found that the higher self-administering strain exhibited differences in the intracellular mechanisms that control activity in some of the neurons in the brain reward system as compared with the low self-administering strain. Additional studies exploring the role of genes in drug response are needed to more fully understand the full range of biological factors associated with drug abuse. The recent development of new and more sensitive techniques to analyze brain activity and processes will facilitate these studies.

ROLE OF LEARNING

The learning that occurs when an individual takes drugs is an important contributing force in the continued use and craving of drugs. Drugs of abuse produce positive or pleasurable feelings in the user and have reinforcing properties. In addition to these effects, drugs of abuse produce changes in numerous organ systems such as the cardiovascular, digestive, and endocrine systems. Both the behavioral and physiological effects of a drug occur in the context of an individual's drug-seeking and drug-using environment. As a result, environmental cues are present before and during an individual's drug use that are consistently associated with a drug's behavioral and physiological effects. With repetition the cues become conditioned stimuli, that on presentation, even in the absence of the drug, evoke automatic changes in organ systems and behavioral sensations that the individual experiences as drug craving. These associations are difficult to reverse. In theory, repeated presentation of the environmental cues, absent the drug, should extinguish the conditioned association. Animal studies indicate that extinction is difficult to achieve and does not erase the original learning, As a result, even once established, the extinction is readily reversed.

Also, it has long been known that conditioning occurs in relation to the withdrawal effects of drugs. This phenomenon, termed conditioned withdrawal, results from environmental stimuli acquiring the ability, through classical conditioning, to elicit signs and symptoms of pharmacological withdrawal. The emergence of withdrawal symptoms as a result of exposure to conditioned cues can contribute to drug use relapse by

[1] Genetic linkage studies establish an association between an area of a specific chromosome and the expression of a trait. Linkage analysis uses specific markers that identify the area on a chromosome that might contain the gene of interest. If the marker consistently occurs in association with the expressed trait, then it is likely that the gene of interest is in that chromosomal region.

motivating an individual to seek out and use drugs.

Thus, exposure to environmental cues associated with drug use in the past can act as a priming force to motivate voluntary drug-seeking behavior. Drug conditioning can help explain the fact that many drug abusers often return to environments associated with drug use, even after being counseled not to. The effects of the environmental stimuli can be similar to the priming effects of a low dose of the drug or result in withdrawal symptoms. In either case these stimuli can occasion further drug use even after successful detoxification.

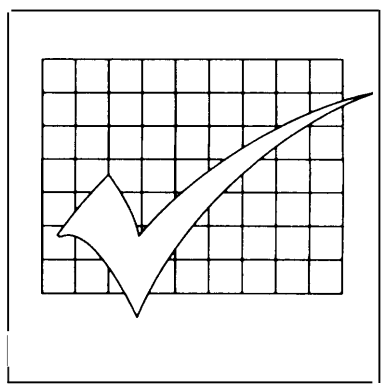
The complexity of human responses to drugs of abuse, coupled with the number of drugs that are abused, complicates understanding of the role of biology in drug use and abuse. Nevertheless, scientists know the site of action of many drugs in the brain, and sophisticated new devices are expected to improve that understanding. A genetic component to drug use and abuse is likely, but it has not been fully characterized.

Basic Concepts 2

Similar to other psychoactive drugs, drugs of abuse alter the brain's normal balance and level of biochemical activity. This can include mimicking the action of naturally occurring neurotransmitters (chemicals in the brain that send messages from one nerve cell to another), blocking neurotransmitter action, or in other ways altering the normal chemical actions that mediate the transmission of information within the brain. The ultimate effect is to either elevate or depress activity in different brain regions (see ch. 3).

What separates drugs of abuse from other psychoactive drugs is that these drugs act, at least in part, on those areas of the brain that mediate feelings of pleasure and reward. Inducing activity in the so-called brain reward system gives drugs of abuse positive reinforcing actions that provoke and support their continued use and abuse.

Beyond their immediate, rewarding properties, drugs used on a chronic, long-term basis can cause either permanent changes in the brain or alterations that may take hours, days, months, even years, to reverse on drug cessation. These changes are adaptive responses that occur in the brain to counter the immediate effects of a drug. When drug taking is stopped, these changes are often manifested as effects that are opposite to the initial pleasurable drug response. The continued administration of drugs to avoid the aversive effects of drug cessation also contributes to an individual's addiction to a drug.



Their immediate and long-term effects imbue drugs of abuse with reinforcing properties. Reinforcement is defined as the likelihood **that the** consequences of taking the drug will increase the behavior directed toward seeking that drug (6). Put more

simply, individuals who use drugs experience some effect, such as pleasure, detachment, or relief from distress, that initially establishes and then maintains drug use. Thus, the consequence of taking the drug enhances the prospect that it will continue to be used for some real or perceived effect and also establishes a need state, hence, engendering compulsive self-administration.

In addition to their reinforcing effects, drugs of abuse can have a variety of pharmacological actions in other areas of the brain and the body. The ultimate effect of a drug will also be shaped by other factors including the dose of the drug, the route of administration, the physiological status of the user, and the environmental context in which the drug is taken. The subjective experience of the drug user and his or her overt behavior is the result of a combination of these factors and the drug's pharmacological action.

THE BRAIN REWARD SYSTEM

Eating, drinking, sexual, and maternal behaviors are activities essential for the survival of the individual and the species. Natural selection, in order to ensure that these behaviors occur, has imbued them with powerful rewarding properties. The brain reward system evolved to process these natural reinforcers.

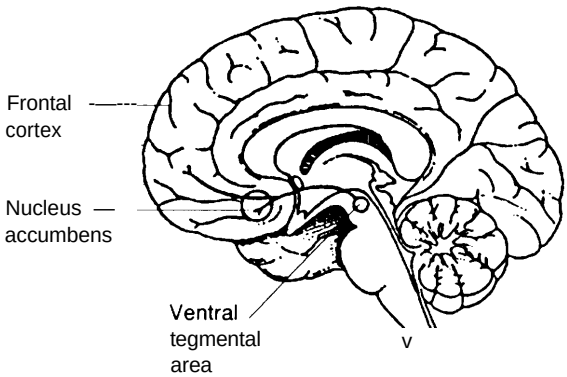
Studies have shown that direct stimulation of the areas of the brain involved in the reward system, in the absence of any goal-seeking behavior, produces extreme pleasure that has strong reinforcing properties in its own right (17). Such stimulation activates neural pathways that carry natural rewarding stimuli. Animals with electrodes implanted in these areas in such a way that electrical impulses produce a pleasurable sensation will repeatedly press a bar, or do any other required task, to receive electrical stimulation. The fact that animals will forego food and drink to the point of death or will willingly experience a painful stimulus to receive electrical stimulation of the reward system attests to the powerful reinforcing characteristics of the reward system.

Most drugs of abuse, either directly or indirectly, affect the brain reward system. This is evident by the fact that administration of most drugs of abuse reduces the amount of electrical stimulation needed to produce self-stimulation responding (28).

The reward system is made up of various brain structures. The central component is a neuronal pathway that interconnects structures in the middle part of the brain (i.e., hypothalamus, ventral tegmental area) to structures in the front part of the brain (i.e., frontal cortex, limbic system) (15,16). A key part of this drug reward pathway appears to be the mesocorticolimbic pathway (MCLP) (figure 2-l). MCLP is made up of the axons of neuronal cell bodies in the ventral tegmental area projecting to the nucleus accumbens, a nucleus in the limbic system. The limbic system is a network of brain structures associated with control of emotion and behavior, specifically perception, motivation, gratification, and memory. MCLP also connects the ventral tegmental area with parts of the frontal cortex (medial prefrontal cortex). Ventral tegmental neurons release the neurotransmitter doparnine to regulate the activity of the cells in the nucleus accumbens and the medial prefrontal cortex. Other parts of the reward system include the nucleus accumbens and its connections with other limbic structures like the amygdala and hippocampus, as well as to other regions in the front part of the brain (i.e., substantial innominata-ventral palladium). There are also connections from the nucleus accumbens down to the ventral tegmental area. Finally, other neuronal pathways containing different neurotransmitters (i.e., serotonin, opioids, gamma amino butyric acid (GABA), glutamate, peptides) regulate the activity of the mesocorticolimbic doparnine system and are also involved in mediating the rewarding properties of drugs of abuse.

These structures and pathways are thought to play a role in the reinforcing properties of many drugs of abuse, although the precise mechanisms involved in all drugs of abuse lack a thorough description. The mesocorticolimbic dopamine

Figure 2-l—The Mesocorticolimbic Pathway



The mesocorticolimbic pathway from the ventral tegmental area to the nudeus accumbens and the frontat cortex is a key component of the brain reward system for drug reinforcement.
SOURCE: **Off Ice of Tdnobgy Assessment, 1993.**

pathway appears to be critical in the rewarding properties of stimulant drugs such as cocaine and amphetamines (15,16,29). Also, both the ventral tegmental area and the nucleus accumbens appear to be important for opiate reward (7,15,16), while these same structures and their connections to other limbic areas, like the amygdala, may play a role in the rewarding properties of barbiturates and alcohol (15,16,20). Further details about the brain areas involved in the rewarding properties of various drugs of abuse are provided in chapter 3.

NEUROADAPTIVE RESPONSES

Exposure to drugs causes changes in the brain. These changes are alterations in neurochemical mechanisms related to the pharmacological action of a given drug. Often the change represents a compensatory adjustment in the brain to return the balance of activity back to normal after initial exposure to the drug. Most drugs of abuse involve complex actions in the brain resulting in a variety of behavioral effects. Often, the type of neuroadaptive response that occurs to a drug is opposite to its acute effects. Thus, the positive reinforcing properties of drugs are replaced by the negative reinforcing properties of withdrawal. This indicates that neuroadaptive responses can have motivational consequences that contribute and play a role in an individual's subsequent drug-taking behavior. The specific details of the biological mechanisms that underlie these phenomena are not completely understood, but recent advances in neuroscience research have begun to unravel how neuroadaptive responses manifest themselves for various drugs of abuse. As with the immediate rewarding properties of these drugs, some evidence suggests that there may be common underlying mechanisms to the neuroadaptive responses related to reward mechanisms of various drugs of abuse (2). What follows is a general description of neuroadaptive responses. Specific details of possible biological mechanisms associated with the neuroadaptive responses of various drugs are provided in chapter 3.

| Tolerance

Tolerance develops to a drug when, following a prolonged period of use, more of the drug is required to produce the same effect (10,14). Tolerance occurs with many types of drugs. It is a common, but unnecessary, characteristic of drugs of abuse. There are two types of tolerance: dispositional (pharmacokinetic) and pharmacodynamic.

DISPOSITIONAL

Dispositional tolerance develops when the amount of drug reaching active sites in the brain is reduced in some way. Generally, this arises from an increased breakdown of the drug or a change in its distribution in the rest of the body. Thus, more drug must be taken to achieve the same blood levels or concentrations at the active sites in the brain.

PHARMACODYNAMIC

This form of tolerance represents a reduced response of the brain to the same level of drug. It develops during the continued and sustained presence of the drug. It may be that the mechanism of adaptation may differ from drug to drug and depend on the original mechanism of action

of a given drug. The net effect is that more drug is required to overcome this new neuronal adaptation to produce an equivalent pharmacologic effect.

Although dispositional tolerance represents a component of tolerance to some drugs (e.g., alcohol, barbiturates), in most cases much or all of the tolerance that develops to drugs with significant abuse potential can be attributed to pharmacodynamic tolerance (10,14). Tolerance can contribute to drug-taking behavior by requiring that an individual take larger and larger doses of a drug to achieve a desired effect.

Dependence

Like pharmacodynamic tolerance, dependence also refers to a type of neuroadaptation to drug exposure. Dependence differs in that, with prolonged use of a drug, cells in the brain adapt to its presence such that the drug is required to maintain normal cell function. On abrupt withdrawal of the drug, the neuron behaves abnormally and a withdrawal syndrome ensues. Generally, the withdrawal syndrome is characterized by a series of signs and symptoms that are opposite to those of the acute effects of the drug. For example, on withdrawal, sedative drugs produce excitation and irritability. Conversely, stimulants produce profound depression on withdrawal.

The magnitude of the withdrawal syndrome varies from drug to drug. With some drugs very mild withdrawal occurs, whereas with others (e.g., alcohol, barbiturates) the withdrawal syndrome can be so severe that it is life-threatening. No matter the severity of the withdrawal syndrome, its existence can create a craving or desire for the drug and dependence can play a very strong role in recurrent patterns of relapse, in maintaining drug-seeking behavior to forestall the withdrawal syndrome, and in the need to reestablish some sense of normalcy.

Residual Tolerance and Dependence

In general, expression of tolerance and dependence has been considered to be rate-limited in that tolerance to most drugs gradually dissipates with time as the brain readapts to the disappearance of the drug and withdrawal peaks within hours or days after discontinued use and then dissipates. However, substantial evidence indicates that there may be persistent or residual neuroadaptation that lasts for months or years (10,27). For example, craving and drug-seeking behavior have been reported to last for years with nicotine, alcohol, and cocaine suggesting some residual effect of drug use that may or may not dissipate with time. Moreover, there is a phenomenon that characterizes drug-dependent individuals. Specifically, with repeated cycles of abstinence and reinitiation of drug use, the time required to elicit drug dependence grows shorter and shorter. Furthermore, there is evidence that the administration of naloxone, a drug that blocks the actions of opiates, may elicit a withdrawal syndrome in individuals who have abstained from use for extensive periods of time. These data indicate that some residual neuroadaptive changes induced by drugs persist for as yet undefined periods of time. Little information is available about the mechanisms involved in this effect, but it is clear that residual neuroadaptive changes may persist for extended periods of time in former drug users and that they may account for the striking relapses that occur in long-term abstinent drug-dependent individuals.

Sensitization

Sensitization occurs when the effects of a given dose of a drug increase after repeated administration. Thus, sensitization is the opposite of tolerance. Sensitization to a drug's behavioral effects can play a significant role in supporting drug-taking behavior.

ABUSE LIABILITY

The abuse liability of a drug is a measure of the likelihood that its use will result in drug addiction. While many factors ultimately play a role in an individual's drug-taking behavior, the abuse potential of a drug is related to its intrinsic rewarding properties and the neuroadaptive responses that result from prolonged use. Drugs can be tested and screened for their abuse liability. The conceptual framework to screen drugs for their abuse potential is virtually the same for all drugs: opiates, stimulants, depressants, hallucinogens, and inhalants (l). The criteria that can be evaluated to classify a drug as having significant abuse potential are: pharmacological equivalence to known drugs of abuse, demonstration of reinforcing effects, tolerance, and physical dependence. The capacity to produce reinforcing effects is essential to any drug with significant abuse potential, whereas tolerance and physical dependence most commonly occur but are not absolutely required to make such a determination.

Testing new pharmaceuticals for their abuse potential is an important step in new drug development. The emphasis of many major pharmaceutical firms today is on the development of new and safer drugs for pain reduction and in the development of psychoactive compounds to treat brain disorders. In particular, scientific strides in understanding the brain, neurological disease, psychiatric disturbances, and aging are fueling research into treatment of brain disorders. As such psychoactive compounds become available, they must be screened for abuse potential. The abuse liability assessment of new products is not simply at the discretion of the manufacturer. As discussed in appendix A, various Federal regulatory laws mandate such testing and Federal regulatory agencies are charged with seeing that testing is carried out.

Animal models are generally used to screen for the abuse potential of new drugs in earlier stages of drug development or to evaluate abuse potential in drugs that cannot be readily studied in humans (l). Laboratory methods for abuse potential evaluation in humans are also well developed, and this is an area of active research(8). However, factors such as the heterogeneity of drug using populations, the use of multiple drugs, and the other biological, social, and environmental factors involved in human drug use make human studies complex.

At first glance, it would seem impossible to mimic in an animal the highly complex syndrome of drug abuse in humans. However, paradoxically, the apparent limitations of animal models are actually their strengths. Specifically, the simplicity of an animal model obviates the problems inherent in the complexity of humans: the experimenter has strict control of environmental factors, drug use experience and patterns, and individual differences that permit study of the pharmacological and biological mechanisms associated with the development of addiction potential. Thus, the use of animal models permits the highly complex syndrome of human drug addiction to be dissected into separate components without the intrusion of a series of confounding variables found in humans.

In terms of the validity of animal models as a means of studying human drug addiction, an excellent correlation exists between predicting the abuse liability of specific classes of drugs in animals and humans (12). However, it must be recognized that animal models are not perfect and, in fact, there are examples of drugs that proved to have significant abuse potential in humans, whereas the preclinical testing in animals revealed relatively minimal abuse potential (6,10,14). Thus, the ultimate answer to the issue of whether a drug has significant abuse potential is long-term experience with the drug once it has become available, either legally or illegally. Nevertheless, animal models serve as the only practical means of initially screening drugs for abuse liability and have proven to be the most effective means of detecting whether there is likely to be a problem in humans.

Self=Administration

The predominant feature of all drugs with significant addiction-producing properties is that they are self-administered (3,5,9,11). In fact, self-administration of a drug to the point when the behavior becomes obsessive and detrimental to the individual is the primary criterion for classifying a drug as having significant potential for addiction. In addition to self-administration, another predictor of drug addiction is the notion of craving and the tendency to relapse or increase use during withdrawal (6, 10,14). Although craving is a difficult term to quantify, once a drug is voluntarily or involuntarily withdrawn, the desire to take it can play a role in the relapse to substance abuse. As previously mentioned, the reinforcing properties of the drug underlying craving maybe shifted from the pattern established during the initial, early phase of drug addiction. Specifically, the drug may have initially been self-administered for its pleasurable effects but may eventually be self-administered to relieve the discomfort associated with withdrawal. Thus, the primary motivation for using the drug can be that the individual needs the drug to function normally.

Animals can be readily trained to self-administer drugs (6). Which experimental technique is used depends on the class of compounds, a drug's normal route of administration in humans, and methodological concerns (e.g., solubility of the drug). While the reasons animals initiate drug-seeking behavior are dictated by the experimental situation, rather than intrinsic dispositional factors as in humans, the pattern of use once established fulfills all of the criteria of drug addiction: compulsive drug-seeking behavior to the point of detrimental effects on the animal and enhanced attempts of self-administration during withdrawal.

The technique of self-administration is a powerful tool and provides a good indication of the abuse liability of new or unknown drugs (l). For example, substitution studies can be used to determine whether, and over what dosage ranges, drugs have reinforcing effects. In addition, the efficacy of drugs as reinforcers can be evaluated using the amount of work animals will perform to obtain drug injections or how they make selections between drug reinforcers. By making comparisons of the self-administration rates of unknown compounds with known standard reference drugs, it is often possible to estimate the reinforcing property of the drug relative to the standard. Thus, by using self-administration techniques, one can assess the relative reinforcing strengths of a drug and also examine the behavioral, physiological, and biological factors that lead to sustained self-administration.

I Drug Discrimination

Drug discrimination is another tool used in the assessment of abuse liability of drugs in animals (3,6). Drug discrimination refers to the perception of the effects of drugs. Specifically, animals or humans trained to discriminate a drug from placebo show a remarkable ability to distinguish between the effects of the drug from other drugs possessing different properties. The procedures also permit a determination of whether the animal considers the drug to be the pharmacological equivalent of another drug. Pharrnacologicalequivalence refers to the fact that drugs of a particular class, such as opiates, stimulants, and depressants, produce a unique series of effects on the brain and other organs that collectively constitute their pharmacological profile. Thus, although drugs may vary considerably in their chemical structure, similar pharmacological effects indicate specifically how they actually interact with and influence the behavior of the intact organism. While animals cannot express whether a drug's subjective effects are similar or dissimilar to another, various behavioral experiments can be used to determine whether an animal perceives drugs to be pharmacologically dissimilar or equivalent. For example, animals can clearly distinguish opiates from stimulants or other

depressants, but may be unable to distinguish one opiate of the same type from another.

| Dependence and Tolerance

Dependence and tolerance can readily be induced in animals by either volitional or passive means (13,14). Specifically, using a self-administration model, animals often will develop tolerance and dependence characterized by increased amounts of drug self-administration and/or enhanced rates of self-administration. Following abrupt withdrawal of the drug, a withdrawal syndrome will often develop and, if given the opportunity, self-administration rates will be increased. Alternatively, it is often easier to induce tolerance and physical dependence passively by injecting large amounts of drug into animals for prolonged periods of time. In this case, neuroadaptation occurs quickly and predictably. This technique has the advantage that the experimenter can exercise complete control of doses and times required to produce tolerance and dependence. In either case, it is possible to induce neuroadaptation in animals that can then be experimentally manipulated. Furthermore, since the understanding of the neuroadaptive changes that take place during the development of tolerance and physical dependence are poorly understood in humans, animal models offer a unique opportunity to carry out experiments designed to address these issues.

I Interpretation of Results in Animals and the Concept of Thresholds

Once a drug has been classified as having significant abuse potential, two central questions remain: first, does this information pertain to humans; and, second, can one rate the relative abuse potential of drugs in animals (e.g., Does drug A have five times the abuse liability of drug B?). with regard to the frost point, results from animal testing generally have been excellent predictors of abuse liability of drugs in humans, but a small number of exceptions mandate that final drug testing be carried out in humans. Nevertheless, animal testing is an accepted predictor of abuse potential in humans and must be carried out to provide the basis for additional screening in humans.

In terms of rating the abuse liability of drugs in animals, the degree of abuse liability that can be expected from a drug of abuse can be determined using the animal testing procedures outlined above. For example, by comparing the degree to which a drug satisfies the criteria outlined above, such as the amount of work that will be performed to self-administer the drug and the strength of the physical dependence, general conclusions about the abuse potential of an unknown drug by either comparison to drugs of a similar class or different classes of drugs can be made.

while tests show that a drug has abuse potential, the problem it poses in humans ultimately depends on the overall effects of the drug and the extent to which self-administration of the drug represents a problem to the individual or society. Relative abuse potential and its severity must be considered in terms of the consequences not only to the person, but also in the societal and environmental context in which it occurs.

ROLE OF LEARNING

Another significant contributing force in drug abuse is the learning that can occur during an individual's drug-taking activity (18,23).

In addition to producing pleasant feelings in the user and having rewarding properties, drugs of abuse produce changes in numerous organ systems such as the cardiovascular, digestive, and endocrine systems. Both the behavioral and physiological effects of a drug occur in the context of an individual's drug-seeking and drug-using environment. As a result, there are environmental cues present before and during an individual's drug use that are consistently associated with a drug's behavioral and physiological effects. With repetition the cues become conditioned stimuli, that on presentation, even in the

absence of the drug, evoke automatic changes in organ systems and behavioral sensations that the individual may experience as drug craving. This is analogous to Pavlov's classical conditioning experiments in which dogs salivate on the cue of a bell, following repeated pairing of food presentation with a ringing bell. Evidence for this effect is seen in numerous studies showing that animals seek out places associated with reinforcing drugs and that the physiological effects of drugs can be classically conditioned in both animals and humans (12). Thus, exposure to environmental cues associated with drug use in the past can act as a stimulus for voluntary drug-seeking behavior. If the individual succeeds in finding and taking the drug, the chain of behaviors is further reinforced by the drug-induced rewarding feelings and the effects of the drug on other organ systems (18). Drug conditioning can help explain the fact that many drug abusers often return to environments associated with drug use, even after being counseled not to. The effects of the environmental stimuli can be similar to the priming effects of a dose of the drug.

Also, it has long been known that conditioning occurs in relation to the withdrawal effects of drugs (26). It was observed that opiate addicts who were drug free for months and thus should not have had any signs of opiate withdrawal, developed withdrawal symptoms (e.g., yawning, sniffling, tearing of the eyes) when talking about drugs in group therapy sessions. This phenomenon, termed conditioned withdrawal, results from environmental stimuli acquiring the ability, through classical conditioning, to elicit signs and symptoms of pharmacological withdrawal. Conditioned withdrawal can also play a role in relapse to drug use in abstinent individuals. The emergence of withdrawal symptoms as a result of exposure to conditioned cues can motivate an individual to seek out and use drugs.

Studies have also demonstrated that, once established, conditioned associations are difllcult to reverse (23). In theory, repeated presentation of the environmental cues, without the drug, should extinguish the conditioned association. Animal studies indicate that extinction is difficult to achieve and does not erase the original learning. As a result, once established, the extinction is easily reversed. Animal studies examining drug conditioning have found that various aspects of extinguished responses can either be reinstated with a single pairing of the drug and environmental cue, can be reinstated with a single dose of drug in the absence of the environmental cue, or can spontaneously recover (23).

The biological mechanisms underlying conditioned drug effects are just beginning to be described. Recent evidence links the mesocorticolimbic system to these effects. Studies have found increased release of dopamine in the nucleus accumbens associated with anticipated voluntary alcohol consumption (18,19,24,25). Other studies have presented evidence that destruction of MCLP blocks the conditioned reinforcing effects of opiates (4,21,22). The excitatory amino acid neurotransmitters may also play a role in drug conditioning effects. As the name implies, excitatory amino acids are a class of neurotransmitter that act to stimulate neuronal activity in the brain. These amino acids have been implicated in learning and memory. Injection of a drug that blocks the activity of the excitatory amino acids has been shown to block the development of conditioned amphetamine effects (23). Finally, there is evidence that genetic factors may play a role in the conditioning phenomena associated with drug use (see ch. 4).

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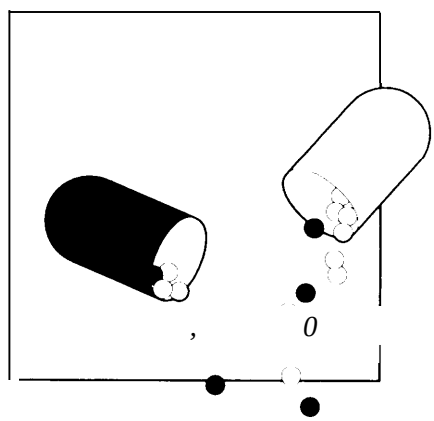
The Neuropharmacology of Drugs of Abuse

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.



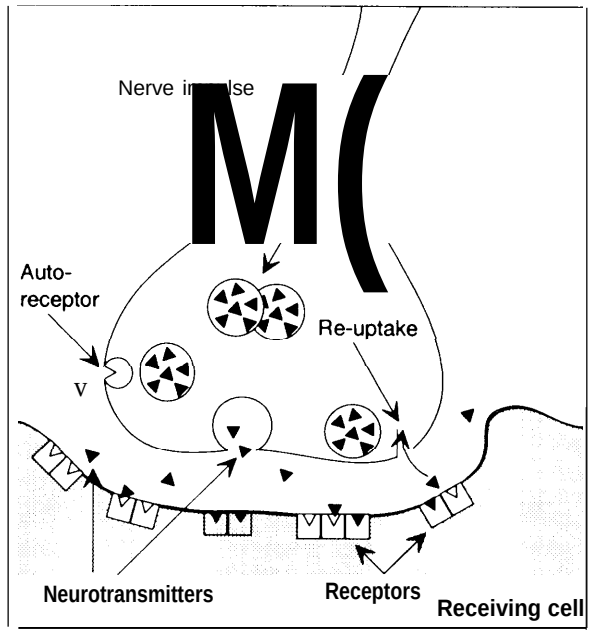
NEUROPHARMACOLOGY

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-l). 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-l—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 affects, 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 epenephrine) 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-

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.

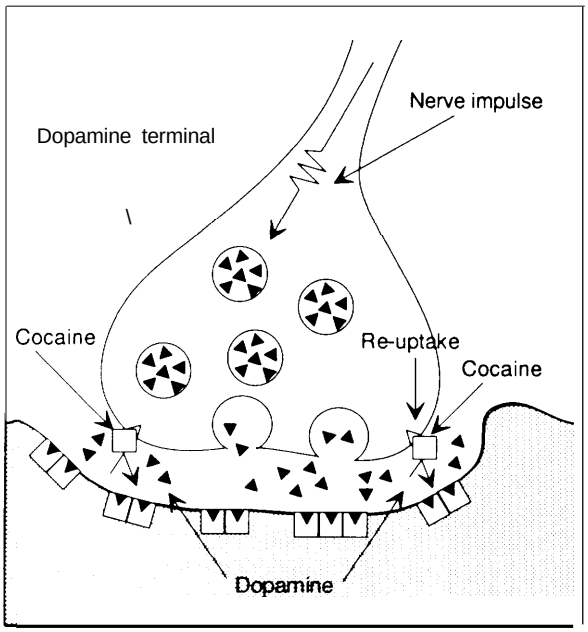
Acute administration—The most prominent pharmacological effect of cocaine is to block the reuptake of dopamine back into the presynaptic terminal once it has been released from a neuron terminal (61), resulting in increased levels of dopamine at its synapses in the brain (see figure 3-2). The specific 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, dopamine 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



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

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.

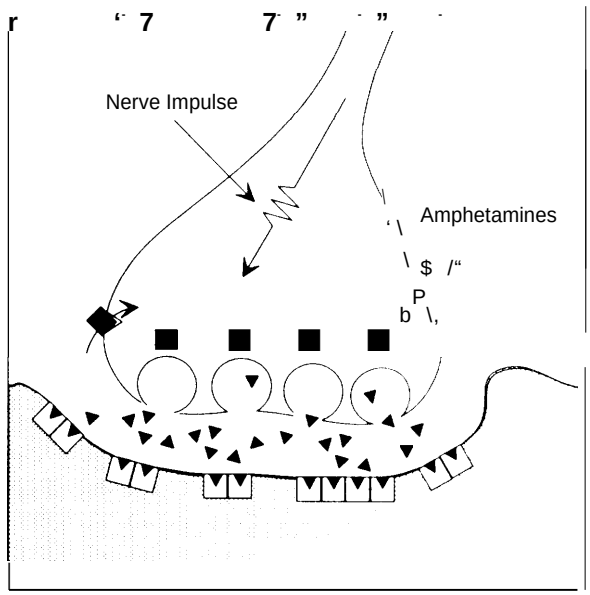
AMPHETAMINES

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 amphetarnines 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 mechanismism 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

amphetamine es 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 Al and A2 adenosine receptor subtypes, having its more potent effect on the A 1 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 potentates 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

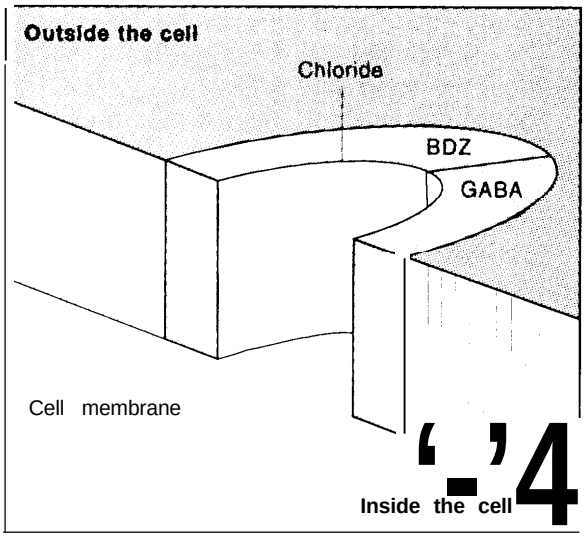
Alcohol differs from most other drugs of abuse in that it has no known receptor system in the brain (52). Alcohol affects a number of different neurotransmitter systems through its action on the membranes of neurons and the ion channels, particularly those for calcium and chloride, that lie within them (43). In general, alcohol inhibits receptors for excitatory neurotransmitters and augments activity at receptors for inhibitory neurotransrnitters (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-administraticm 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 affects 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 manipulation 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 neurotransrnitter 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

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 antianxiety 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 phaxmacodynamic 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 affect 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 (2 1). 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 neurotransrnitter 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 doparnine 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 desensitivity 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 neurotransrnitters 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 t0 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 substantial 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

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 imitability 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 diethyklamide (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 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 (l). 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 phenomenon 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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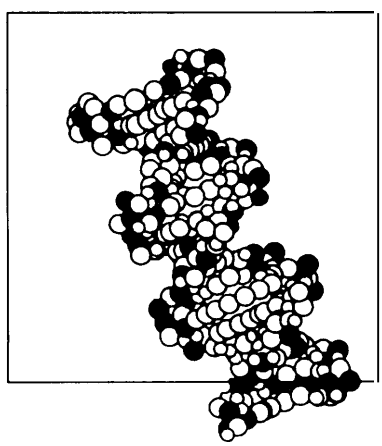
Genetics 4

Why does one person become dependent on drugs while another, exposed to the same environment and experiences, does not? As progress in understanding the role of genetics in various conditions and diseases increases, there has been a realization that there is likely to be a genetic component to substance abuse and addiction. That is, inherited differences among individuals affect their response to drugs. To date, much of the work done in this field is related to alcoholism, less is known about the genetics of other drugs of abuse.

Studies in both humans and animals contribute to the understanding of genetic factors in substance abuse and dependence. Human studies shed light on the question of whether drug dependency is transmitted between generations. In addition, the study of individuals with substance abuse problems as well as animal studies provide information about what is actually inherited. For example, are there genetic differences in sensitivity and responsiveness to drugs? And, if yes, are the differences drug-specific, or are they related to general mechanisms associated with the actions of all abused drugs? Finally, the tools of modern molecular biology can be used to identify the specific genes that control various cellular and biochemical functions possibly involved in an inherited component of substance abuse and addiction.



While the existence of inherited differences seems likely, a genetic component alone probably is insufficient to precipitate substance abuse and addiction. Unlike disorders such as Huntington's disease and cystic fibrosis, which result from the presence of alterations in a single gene, substance abuse is likely

to involve multiple genes that control various aspects of the biological response to drugs. In addition, the complex nature of drug dependency, involving many behavioral and environmental factors, indicates that any genetic component acts in consort with other nongenetic risk factors to contribute to the development of substance abuse and addiction. Thus, neither the presence nor absence of a genetic factor ensures development of, or protection from, drug addiction.

DO INHERITED FACTORS EXIST?

A number of confounding factors complicates the study of genetic transmission of substance abuse liability in humans. One is the high incidence of psychiatric conditions among substance abusers (104), which raises questions about the role of psychiatric comorbidity in liability to illicit drug addiction. In particular, antisocial personality disorder (ASPD) is often associated with substance abuse. One study shows that 84 percent of individuals with ASPD also have some form of substance abuse during their lifetimes (104). Other psychiatric conditions that may be associated with substance abuse are depression, anxiety disorders, manic-depression, and schizophrenia.

Another issue related to studies of the genetics of liability to abuse of specific drugs is that many drug abusers engage in multiple drug use, so examining any familial trends in the use of a particular drug becomes difficult. Finally, rates of illicit drug use show strong secular trends. Even assuming a vulnerability to drug-specific addictions, there might be tremendous variations in expression of addiction, simply because of differences in drug availability over time: No matter how vulnerable an individual might be, addiction requires exposure. Such issues often hamper studies on the genetic transmission of drug liability.

I Family Studies

ALCOHOLISM

References to a familial tendency or hereditary ‘‘taint’ of alcoholism date back to classical times (44); an observation repeatedly confirmed by family studies. While not all cases axe familial, the risk of alcoholism consistently has been found to be higher among frost-degree relatives (i.e., parents, siblings, children) of alcoholics as compared to the general population (79). Moreover, while family studies can establish that a disorder (or liability to a disorder) is transmitted; in general, they are unable to distinguish between biological and cultural transmission (though this issue can be evaluated in large family studies by analyzing multiple classes of relatives with differing degrees of genetic relatedness).

Results of numerous family studies indicate that alcoholism segregates within families, with male first-degree relatives of alcoholics having a higher incidence (ranging from 27 to 54 percent) than female first-degree relatives (6 to 17 percent) as compared to first-degree relatives of nonalcoholics (20 percent of males, 4 percent of females) (49,103,133). In fitting models of inheritance to family data, researchers concluded that observed patterns of inheritance were consistent with the hypothesis that familial factors predisposing to alcoholism were the same in men and women, but that nonfamilial environmental factors exerted more influence in the development of alcoholism in women (20). Familial alcoholics (those with at least one relative with alcoholism) appear to have earlier onset, more antisocial symptoms, more social complications of alcohol use, and worse treatment outcome than nonfamilial alcoholics (38,93,111).

Familial is not identical to genetic, and in the case of alcoholism, the familial patterns of inheritance are not consistent with those of a purely genetic condition (58,109). In addition, evidence suggests that the transmissibility of alcoholism has increased over time (102). Thus, any genetic factors promoting the development of

alcoholism are significantly moderated by nongenetic influences.

OTHER DRUGS

Fewer family studies have been conducted on the genetic transmission of liability to other drugs of abuse. Nonetheless, the evidence available suggests that, as in the case of alcohol, addiction to other psychoactive substances appears to run in families.

One study found evidence for familial aggregation of drug use, based on family history obtained from individuals admitted for substance abuse treatment (78). However, this study also combined use of all illicit drugs into one category and relied on self-reports by the subject on his or her drug use as well as that of family members. In a large family interview study comparing 201 opiate addicts and 82 normal controls, as well as interviews of 1,398 first-degree relatives of these subjects, the relatives of opiate users had elevated rates of drug addiction as compared with the controls (105). In addition there was an association between opiate use and the presence of ASPD. Further analysis of these data revealed that the incidence of both drug abuse and ASPD was higher among the siblings of the opiate subjects than among their parents (69,70).

Some studies note a familial association between opiate addiction and alcoholism (65). However, another family history study (51), comparing families of 32 alcoholics, 72 opiate addicts, and 42 individuals addicted to both substances, found that while both opiate addiction and alcoholism clustered within families, co-occurrence of the disorders within families occurred no more frequently than expected by chance, thus supporting the hypothesis of independent transmission. However, a later study of 201 opioid addicts and 877 of their first-degree relatives also showed familial aggregation of both alcoholism and depressive illness suggesting a possible co-occurence of the disorders (64).

Little research has been done to test hypotheses regarding familial transmission of liability to addiction to specific substances other than opiates or alcohol. One study involving 350 treated drug abusers and 1,478 relatives, found that alcoholism was equally common among relatives of individuals who preferentially abused opiates, cocaine, or sedative-hypnotics (27 percent, 31 percent, and 24 percent of male relatives, respectively), whereas relatives of sedative-hypnotic users were subject to diagnoses of other substance abuses (2 percent of male relatives, versus 11 percent of male relatives of opiate abusers and 16 percent of male relatives of cocaine abusers) (80).

I Twin and Adoption Studies

While family studies can establish that a disorder (or liability to a disorder) runs in a family, they generally are unable to distinguish between biological and cultural transmission. However, two other methods are used to help disentangle the effects of genetic and nongenetic factors. Adoption studies compare the presence of a trait among biological versus adoptive family members or other control groups. In this way individuals that share the same environment but different genetic heritages, or vice versa, can be compared. Twin studies, by contrast, involve siblings raised in the same environment, but compare how often identical twins, who are genetically identical, and fraternal twins,[1] who are not, are similar, or concordant, for a trait. A high concordance rate for a trait among identical twins versus fraternal twins usually indicates a genetic component for the trait.

TWIN STUDIES

Evidence fromn twin studies suggests genetic influences on drinking patterns as well as alcohol-related problems. Results from twin studies demonstrate genetic influences on measures of alcohol consumption such as abstention, average

[1] Fraternal twins share the same in utero environment but are genetically no more similar than any two siblings,

alcohol intake, and heavy alcohol use (50,60,92). Twin studies also indicate an inherited risk for smoking (24).

When evaluating how alcoholism develops, twin studies generally support the existence of genetic influences on the development of the disorder. One study found a higher concordance rate for alcohol abuse between identical twins (54 percent) versus fraternal twins (28 percent) (57), while two subsequent studies found no such relationship (48,92,). A 1991 study (94) examined 50 male and 31 female identical twin pairs and 64 male and 24 female fraternal twin pairs, with 1 member of the pair meeting alcohol abuse or dependence criteria. The study found that identical male twins differed fromn fraternal male twins in the frequencies of both alcohol abuse and dependence as well as other substance abuse and/or dependence. On the other hand, female identical and fraternal twins were equally likely to abuse alcohol and/or become dependent on other substances, but identical female twins were more likely to become alcohol dependent. Another study of 356 twin pairs also found higher identical than fraternal rates of concordance for problems related to alcohol and drug use as well as conduct disorder (77). The same study also noted that among men, heritability was greater for early rather than late onset of alcohol problems, whereas no such effect was seen for women. Finally, a study of 1,030 female twin pairs found evidence for substantial heritability of liability to alcoholism, ranging from 50 to 60 percent (61).

Thus, twin studies provide general agreement that genetic factors influences certain aspects of drinking. Most twin studies also show genetic influence over pathological drinking, including the diagnosis of alcoholism, which appears (like many psychiatric disorders) to be moderately heritable. Whether genetic factors operate comparably in men and women, and whether severity of alcoholism influences twin concordance is less clear. How psychiatric comorbidity may affect heritability of alcoholism also remains to be studied.

ADOPTION STUDIES

Adoption studies have supported the role of heritable factors in risk for alcoholism (1 1,18,1 17). The results from a series of studies conducted in Denmark during the 1970s are typical. Of 5,483 nonfamily adoption cases from the copenhagen area between 1924 and 1947, the researchers studied 55 male adoptees, and later compared 20 adoptees with 30 nonadopted brothers. They also studied 49 female adoptees, comparing them with 81 nonadopted daughters of alcoholics. Comparisons also were made with matched control adoptees. The Copenhagen study revealed that adopted-away sons of alcoholic parents were four times as likely as adopted-away sons of nonalcoholics to have developed alcoholism; evidence also suggested that the alcoholism in these cases was more severe. The groups differed little on other variables, including prevalence of other psychiatric illness or "heavy drinking." Being raised by an alcoholic biological parent did not further increase the likelihood of developing alcoholism. That is, rates of alcoholism did not differ between the adopted-away children and their nonadopted brothers. In contrast, daughters of alcoholics were not at elevated risk of alcoholism. Among adoptees, 2 percent had alcoholism (and another 2 percent serious drinking problems), compared with 4 percent of alcoholism among the adopted controls and 3 percent among nonadopted daughters (44).

Another analysis examined factors promoting drug abuse as well as alcoholism (17). In this study, all classes of illicit drug use were collapsed into a single category of ''drug abuse. " Most of the 40 adopted drug abusers examined had coexisting ASPD and alcoholism; the presence of ASPD correlated highly with drug abuse. Among those without ASPD, a biological background of alcoholism (i.e., alcoholism in a biological parent) was associated with drug abuse. Also, turmoil in the adoptive family (divorce or psychiatric disturbance) was also associated with increased odds for drug abuse in the adoptee.

Finally, results from other adoption studies suggest two possible forms of alcohol abuse (12,19). The two forms have been classified as "milieu-limited" or type 1 alcohol abuse and "male-limited" or type 2 alcohol abuse (21). Type 1 alcohol abuse characterized by mild alcohol problems and minimal criminal behavior in the parents, is generally mild, but occasionally severe, depending on presence of a provocative environment. Type 2 is associated with severe alcohol abuse and criminality in the biological fathers. In the adoptees, it was associated with recurrent problems and appeared to be unaffected by postnatal environment.

In summary, adoption studies of alcoholism clearly indicate the role of biological, presumably genetic, factors in the genesis of alcoholism. They do not exclude, however, a possible role for nongenetic, environmental factors as well. Moreover, evidence suggests more than one kind of biological background conducive to alcoholism. In particular, one pattern of inheritance suggests a relationship between parental antisocial behavior and alcoholism in the next generation. Thus, adoption studies, like other designs, suggest that even at the genetic level, alcoholism is not a homogeneous construct.

WHAT IS INHERITED?

Although studies indicate that genetics contributes to alcoholism and probably other drug abuse, they lack information about what exactly is inherited. For example, do individuals with a family history of drug abuse have an increased susceptibility or sensitivity to the effects of drugs with reinforcing properties? If a susceptibility exists, what are the biological mechanisms that underlie it? To understand what might be inherited, both individuals who have a substance abuse problem and animals models of substance abuse are studied. Various types of information can be derived from these studies. As with family, twin, and adoption studies, much more information is available about alcoholism as compared with other drugs of abuse.

First, specific inherited risk markers for alcoholism and other substance abuse can be identified. A risk marker is a biological trait or characteristic that is associated with a given condition. Thus, if an individual is found to have an identified marker for substance abuse, he or she is at risk for developing a drug dependency. To date, no biological characteristic has been clearly identified as being a risk marker for either alcoholism or substance abuse, although evidence suggests some possible candidates. The identifcation of a valid and reliable risk marker could provide important information about the fundamental mechanisms underlying substance abuse and addiction and would be an invaluable aid in diagnosis and treatment.

Second, inherited differences in biochemical, physiological, and anatomical processes related to differences in drug responses might be identified and studied. Thorough biological assays can be performed using animal models of substance abuse. Animal models of substance abuse consist of strains of animals (usually rodents) that have been selectively bred to either exhibit a preference for taking a drug, exhibit a preference for not taking a drug, or differ in some way in their behavioral or physiological response to a drug. Thus, such differences represent inherited traits related to drug-taking behavior, and these animals can be studied to determine what biological mechanisms are involved in the expression of such traits.

Finally, the genetic technique of linkage analysis can narrow the area on a chromosome where a gene may be located. It can lead to the identification of the gene itself, which, in turn, can improve the understanding of the molecular events that underlie the expression of the gene. There have been few genetic linkage studies related to substance abuse since few specific biological traits associated with drug dependency have been identified. Some studies in humans have been carried out related to alcoholism but the

findings of these studies are contradictory and inconclusive (see later discussion).

Specific Risk Markers

ELECTROPHYSIOLOGICAL ACTIVITY

Attempts to correlate distinctive patterns of spontaneous electrical activity of the brain with alcoholism and substance abuse have been equivocal. A few studies have found distinctive electroencephalograph (EEG) patterns in individuals at risk for alcoholism (32,39), but others have not (31,59,101). Similarly, the use of alcohol challenge (i.e., giving the subject alcohol and then recording EEG) on subjects at high risk for alcoholism has likewise yielded inconclusive results. The rationale for challenge studies rests on the observation that alcohol has been shown to affect resting EEG, and thus might have a differential effect on those at low and high risk for alcoholism (100). Again, some studies have seen distinctive responses (100,101), while other have not (39,59).

A logical extension of studying resting EEG activity is examining event-related potentials (ERPs). ERPs are patterns of brain electrical activity produced in response to a particular stimulus (e.g., auditory, visual); they can reflect a variety of sensory and cognitive processes. Since ERPs may reflect heritable differences in cognitive function or capability that may in turn contribute to liability to alcoholism, some have suggested that ERP changes may allow discrimination between those at low and high genetic risk for alcoholism. The results of these studies have also been equivocal. Some have found characteristic responses among individuals at risk for alcoholism (3,4,33,52,53,89,90,125) while others have not (95,96,97,98). In addition to being equivocal, the specificity for alcoholism of such findings is unclear. In particular, it is not yet known whether similar findings might be identified in subjects with (or at risk for) illicit drug abuse.

Currently, both EEG and ERP findings seem best viewed as possible markers. Further studies **are** needed to confirm or refute the positive results that have been observed. In addition, while ERP findings in particular might relate to aspects of sensory, perceptual, or cognitive functioning that may differ among those at risk for alcoholism, how such differences contribute to risk for alcoholism and perhaps substance abuse is not well understood.

BIOCHEMICAL ASSAYS

Serotonin—Results over the last two decades from both human and animal studies have supported a relationship between low levels of central nervous system (CNS) (i.e., brain and spinal cord) serotonin and impulsive and violent behavior (130,131). Since problematic use of alcohol (as well as other drugs) has long been associated with a wide range of violent behavior, scientists have examined the relationship between alcoholism and serotonergic abnormalities. While a consistent relationship between alcoholism and low CNS levels of serotonin and its metabolizes is lacking, mounting evidence supports the presence of such abnormalities in a subgroup of alcoholics with early-onset problems and a history of violence (16,67,68,107,130).

Because measures of serotonin activity are difficult to obtain, researchers have used pharmacologic probes of serotonin function, such as hormonal response to drugs that affect serotonin. These indirect measures have also indicated a relationship between impulsivity, substance abuse, and abnormal serotonin function (37,42,71,83).

For alcoholism, given that early-onset alcoholism and ASPD overlap substantially (16), the specificity of the serotonin findings is unclear, especially as similar results have been found in substance abusers with ASPD (71). However, at least one report has indicated that, even after controlling for the presence or absence of ASPD and illicit drug abuse, other neurochernical findings remained significantly associated with alcoholism (106). While further work might delineate

the relationship between decreased CNS serotonin levels and Specific psychiatric syndromes, current evidence suggests relatively specific biological differences may exist between early- and late-onset alcoholics; raising the possibility of defining biologically homogeneous subgroups.

Aldehyde and alcohol dehydrogenase enzymes-Many Asians rapidly develop a prominent facial flush following ingestion of a small amount of alcohol. Continued drinking leads to nausea, dizziness, palpitations, and faintness. This reaction is due to inactivity in individuals' aldehyde dehydrogenase, an enzyme that helps metabolize (i.e., break down) alcohol in the body. Ineffective enzyme activity results in a buildup of the chemical acetaldehyde in the blood following alcohol consumption. Clinicians have taken advantage of the aversive properties of acetaldehyde buildup by using the drug Antabuse to inhibit aldehyde dehydrogenase, thus inducing a severe form of the adverse reaction in abstinent alcoholics who begin to drink (30,135).

Alcohol dehydrogenase is another enzyme involved in the metabolism of alcohol. A mutant form of alcohol dehydrogenase also produces a transient increase in the acetaldehyde concentration after alcohol ingestion. This form of the enzyme also has been reported in Asian populations.

The two enzymes, aldehyde and alcohol dehydrogenase, probably interact in some individuals to amplify the adverse reaction to alcohol consumption (129). Since this reaction discourages heavy drinking, the observation that it commonly occurs in some populations where alcoholism is relatively rare suggests that alcohol and aldehyde dehydrogenase mutations might be a major determinant of alcohol consumption, abuse, and dependence. This would seem to hold true for Taiwan and Japan where the reaction occurs in 30 to 50 percent of individuals.

The genetics of the aldehyde and alcohol dehydrogenases are well described. The production of the different forms of these enzymes is caused by variations of their normal genes. The presence of these gene variations in an individual accounts for variations in the metabolism of alcohol (54). Thus, the presence of these genes can also effect alcohol consumption. For example, the gene variations that code for the ineffective form of aldehyde dehydrogenase is not only less common in alcoholics, but also is rare in Japanese patients with alcoholic liver disease (27, 121,135). Despite identification of such genes, the relationship between their inheritance and the familial transmission of alcoholism remains unstudied.

Alcohol challenge-A number of studies have been conducted investigating the effect of administering alcohol to young adult sons of alcoholics (99). These studies indicate that, despite similarity of blood alcohol levels, sons of alcoholics demonstrate less intense subjective responses to alcohol, as well as less intense upper body sway (110,111,113,114). Thus, one mechanism by which alcoholism might develop is that since these individuals have less of a reaction to alcohol, they would find it more difilcult to self-regulate alcohol consumption, thus increasing the risk of developing dependence. In conjunction with these findings, other studies have found that sons of alcoholics demonstrate slightly lower levels of certain hormones (i.e., prolactin, cortisol, adrenocorticotropin hormone (ACTH)) after ingesting alcohol as compared to controls (82,1 14,115,116,1 18). The relationship, if any, of these decreased hormonal levels to alcohol consumption is unclear.

COGNITIVE DIFFERENCES

Study of high-risk populations (e.g., sons of alcoholics) has revealed temperamental, as well as biological, differences between high-risk and control subjects, leading to the suggestion that vulnerability to alcoholism can be conceptualized from a behavior-genetic perspective (127). Heritable, constitutional differences, in other words, might affect temperament and, hence, risk for alcoholism and addiction to other drugs. In particular, these differences might influence cog-

nitive styles, learning ability, and capability to control one's own behavior.

In general, it appears that sons of alcoholics demonstrate group differences from low-risk populations in that the former tend to have impairment on tests of cognitive development, academic achievement, and neuropsychological function (34,12,8). However, the magnitude of these differences may depend greatly on how the population is ascertained. To date, little is known of what specific psychological, temperamental, or cognitive factors might distinguish between high-risk subjects who actually go on to develop alcoholism from those who do not (128).

I Biological Mechanisms

Animals that have been bred for specific characteristics are a valuable tool in drug use and abuse research. For example, certain strains of rodents differ in their response to the analgesic and body temperature regulating effects of morphine, the motor activating effects of stimulant drugs, and the convulsant producing properties of benzodiazepines (28,122). Since the essential characteristic of human drug abuse and addiction is persistent drug-seeking behavior, the most salient models are those of genetic differences in drug self-administration and the factors associated with it (e.g., tolerance). While there are some genetic models of self-administration or preference for different drugs (i.e., alcohol, opiates, cocaine) (28,41), more information is available about the hereditary biological mechanisms that underlie the self-administration of alcohol than other drugs.

ALCOHOL

A general working hypothesis is that alcoholics are sensitive to the low-dose rewarding properties of alcohol, are less sensitive to the high-dose actions of ethanol (i.e., have a higher aversive threshold) and develop tolerance to the aversive effects of alcohol. The fact that rats can be selectively bred to have such alcohol drinking characteristics supports a genetic link to these traits.

Dopamine and alcohol intake-Studies of dopamine content in the brains of two different strains of rats bred for either preference or nonpreference for alcohol have found 25 to 30 percent lower levels of dopamine in the nucleus accumbens and the olfactory tubercle of the alcohol-preferring rats (45,74,86). No other differences in dopamine content have been observed in other brain areas. These data suggest an abnormality in the dopamine system projecting from the ventral tegmental area to limbic regions (nucleus accumbens and/or olfactory tubercle) of the alcohol-preferring rats. Since this system is thought to be involved in mediating the actions of various drugs of abuse (see ch. 2) and alcohol is thought to increase dopamine levels in the system (see ch. 3), it may indicate that an abnormal functioning of the mesocorticolimbic dopamine system might be involved in promoting high alcohol drinking behavior. That is, the alcohol preference may be related to the ability of alcohol to compensate for the abnormality. The nature of this abnormality is unknown but may be due to one or more of the following factors: decreased dopamine synthesis, a lower number of dopamine neurofibers, and/or reduced functional activity of dopamine neurons.

Some evidence exists that the mesocorticolimbic dopamine system may respond to systemic ethanol administration to a greater degree in the alcohol-preferring strains than in the nonpreferring strains. Studies have found that levels of dopamine metabolizes were higher in areas of this system (i.e., caudate nucleus, medial prefrontal cortex, and olfactory tubercle) after ingestion of alcohol in alcohol-preferring rats as compared to nonpreferring rats (35,36). Also, one study has reported that the oral self-administration of alcohol, under experimental conditions where the animal was allowed to receive alcohol as a reward for performing a task, increased the synaptic levels of dopamine significantly more in the nucleus accumbens of these alcohol-preferring

rats than in nonpreferring rats (132). It was also established that the alcohol-preferring strain of rats will self-administer alcohol directly into the ventral tegmental area (73,74). These studies suggest that the mesocorticolimbic dopamine system is involved in regulating alcohol drinking behavior and that alcohol may be a stronger positive reinforcer in alcohol-preferring rats than in the nonpreferring rats.

Differences in dopamine receptor populations have also been reported. Two genetically determined high-alcohol seeking lines of rats have been reported to have fewer of one type of dopamine receptor (i.e., the D_2 receptor) in their limbic system compared with the nonalcoholic rats (74,124), Twenty percent fewer D_2 receptors were observed in the olfactory tubercle and nucleus accumbens of these rats. These studies, along with genetic linkage studies (see later discussion), provide support for the involvement of the D_2 receptor in alcohol-preference.

Serotonin and alcohol intake--Examination of alcohol-preferring and nonpreferring rats has indicated a relationship between high alcohol preference and a deficiency in the CNS serotonin system. A number of studies have reported 10 to 30 percent lower levels of serotonin and its metabolizes in the brains of alcohol-preferring rats as compared with alcohol nonprefening rats (45,66,74,84,85,86). Only one study, using a strain of rats not used in any of the others, did not find lower brain serotonin levels (63). Areas of the brain found to have low serotonin levels include the cerebral cortex, frontal cortex, nucleus accumbens, anterior and corpus striatum, septal nuclei, hippocampus, olfactory tubercle, thalamus, and hypothalamus.

Since several of these CNS regions may be involved in mediating the rewarding properties of drugs of abuse, including alcohol, these findings suggest a relationship between lower contents of serotonin in the brain and high alcohol preference. Evidence suggests that the serotonin system is involved in regulating the activity of the dopamine mesocorticolimbic system (136). Also, some of the areas found to have low serotonin levels (i.e., hypothalamus, hippocampus) may be involved in mediating the aversive effects of alcohol. Since the development of tolerance to the aversive actions of alcohol is one possible characteristic of alcoholic abuse, a deficiency in serotonin in these areas may be an innate factor promoting tolerance to the aversive effects of ethanol in alcohol-preferring lines of rodents.

Further study of one of the rat strains used in these studies showed that low serotonin in the alcohol-preferring line compared with the nonpreferring line was due to fewer serotonin containing axons (137). This study found fewer serotonin presynaptic fibers forming synapses in the nucleus accumbens, frontal cortex, cingulate cortex, and hippocampus of alcohol-preferring rats. These results suggest that the low serotonin is the result of structural differences in the CNS serotonin system rather than lower production of serotonin. Examination of this same strain of rats found that there were increased numbers of one type of post-synaptic serotonin receptor in areas of the frontal cortex and hippocampus (73,76,134). This increase in the number of serotonin postsynaptic receptors may represent a compensation for the lower number of presynaptic serotonin fibers. No such increase in receptors was found in the strain of rats with normal levels of brain serotonin activity discussed earlier (62).

Overall, the animal data favors an inverse relationship between the functioning of the CNS serotonin system and alcohol drinking behavior. Thus, innate low functioning of the serotonin system may be associated with high alcohol preference. In support of this concept, some studies have found lower cerebrospinal fluid serotonin metabolize concentrations in alcoholics than in various control populations (2,14).

GABA and the actions of alcohol—Evidence indicates that alcohol can exert some of its antianxiety and intoxicating effects by potentiating the actions of the neurotransmitter gamma *amino* butyric acid (GABA) at the $GABA_A$ receptor (see ch. 3) and that this receptor might be

involved in mediating alcohol drinking behavior of alcohol-preferring rats (75). However, little has been published that indicates an innate abnormality may exist in the GABA system that could be associated with alcohol preference. A recent study examined the densities of GABA containing fibers in the nucleus accumbens and other brain areas of two different strains of alcohol-preferring and nonprefering rats (55). The results of this study indicated a higher density of GABA fibers in the nucleus accumbens of the alcohol-preferring rats compared with the nonpreferring rats. There were no differences between the respective lines in the other regions. These results suggest alcohol preference may involve an innate, abnormal GABA system within the nucleus accumbens.

The experimental drug RO 15-4513 binds to the $GABA_A$-BDZ-Chloride channel receptor complex (see ch. 3) and is known to block the actions of alcohol at this receptor (126). The administration of RO 15-4513 reduced alcohol but not water intake in a study using one of the alcohol-preferring line of rats (75). The blocking effect of RO 15-4513 on alcohol intake could itself be blocked by administration of a drug that blocks the benzodiazepine receptor. These results indicate that the $GABA_A$-BDZ-chloride channel receptor complex may be involved in mediating the reinforcing actions of ethanol that promote alcohol drinking behavior in these rats. The observation that RO 15-4513 blocks oral self-administration of alcohol supports this idea (56,108). Furthermore, treatment with a drug that activates the $GABA_A$ receptor was shown to markedly increase the acquisition of voluntary ethanol consumption in laboratory rats (123). Also, $GABA_A$ receptor function is enhanced by alcohol in animals selected for sensitivity to alcohol intoxication, but alcohol has little effect on $GABA_A$ receptors of animals selected for resistance to alcohol intoxication (28). Overall, these results are consistent with the involvement of the $GABA_A$ receptor in regulating alcohol consumption. (See also ch. 3).

Alcohol withdrawal severity—Animal models have been developed for differential genetic susceptibility to alcohol withdrawal. For example, withdrawal seizure-prone mice display a higher incidence of convulsions than do seizure-resistant mice when exposed to identical alcohol concentrations (29). Other studies suggest that this alcohol withdrawal reaction is mediated by an increased sensitivity of channels for calcium ions, coupled to receptors for excitatory amino acids (46,47). Several results have emerged in studies of these mouse lines that are potentially important for understanding drug abuse. For example, studies indicate that independent genetic factors control alcohol sensitivity, tolerance, and dependence, suggesting that these features of drug abuse are maintained by different neurobiological mechanisms (28). In addition, the alcohol withdrawal seizure-prone mice have more severe withdrawal to other depressant drugs (i.e., diazepam, phenobarbital, nitrous oxide) (6,7,8) suggesting that a group of genes acts to influence drug withdrawal severity not only to alcohol, but also to a number of other depressant drugs.

OTHER DRUGS

A variety of strains of rats and mice has been developed that exhibit genetic variations in their sensitivity to the reinforcing effects of drugs of abuse and in their drug-seeking behavior (28). In addition, genetic differences in various biological and neurochemical mechanisms have been observed in these animals.

For example, strains of rats and mice that differ in their sensitivity to the reinforcing properties of cocaine and in their cocaine-seeking behavior have also been observed to have differences in the number of dopamine containing neurons and receptors in certain brain areas (120). While the role of these biological findings in the expression of the behavioral traits is unclear, given that dopamine is the key neurotransmitter in cocaine's action, it is likely that a link may exist. Other studies have shown that the development of nicotine tolerance is genetically related. Strains of

mice that differ in the rate at which they develop tolerance to nicotine have also been found to differ in nicotine receptor changes following chronic administration of the drug (72). Thus, inherited differences in nicotine receptor mechanisms may underlie inherited differences in the development of nicotine tolerance.

A recent study indicates that inherited differences in the intracellular mechanisms of the neurons in the mesocorticolimbic pathway could contribute to a genetic predilection to drug addiction (87). In a comparison of rats with either high or low rates of self-administering drugs of abuse, the higher self-administering strain exhibited differences in the intracellular mechanisms that control activity in the neurons of the ventral tegmental area and nucleus accumbens (5).

The further examination of causative relationships between inherited neurochemical alterations and inherited behavioral traits would produce valuable information about the biological mechanism that underlies genetic factors related to substance abuse and addiction. The recent development of new and more sensitive techniques to analyze brain activity and processes will facilitate such studies.

I Linkage Studies

Genetic linkage studies establish an association between an area of a specific chromosome and the expression of a trait. Linkage analysis uses specific markers that identify the area on a chromosome that might contain the gene of interest. If the marker consistently occurs in association with the expressed trait, then it is likely that the gene interest is in chromosomal region.

In the area of substance abuse and addiction, genetic linkage studies have purported to show a linkage between the gene for the dopamine D_2 receptor and alcoholism. The gene for the D_2 receptor has two forms associated with two markers, the A 1 and A2 alleles. The Al allele occurs in about 20 percent of the population, while the AZ allele is found in the remaining 80 percent (l). Two separate studies (9,10) reported that the frequency of the Al allele for the D_2 dopamine receptor was significantly greater in severe alcoholics compared with nonalcoholics. Furthermore, another study (88) found that individuals with the Al allele had fewer D_2 receptors than those with the A2 allele. In agreement with these findings, another study (91) observed a significant association between the Al allele of the D_2 receptor and alcoholism. An association of the Al allele with alcoholism and decreased numbers of D_2 dopamine receptors implies a role for an inherited deficit in the dopamine system in alcoholism. However, in contrast to these results, other studies have not found an association between the frequency of the Al allele of the D_2 receptor and alcoholism (13,26,40,1 **19). The** discrepancies between these studies has called into question the validity of the association of the Al allele with alcoholism.

Moreover, the report of a higher prevalence of the Al allele not only in alcoholics, but also in other disorders such as autism, attention deficit hyperactivity disorder, and Tourette's syndrome (25), suggests that the presence of the Al allele is not specific for alcoholism, but that it has a more diffuse effect that can contribute to the occurrence of other conditions. Also, recent findings indicate that the frequency of the Al allele varies markedly among different populations (e.g., it is high in some Native Americans) but there does not appear to be an association with its increased frequency and the occurence of alcoholism (43). This complexity, coupled with the heterogeneous and complex nature of alcoholism, could account for the disagreements among these studies. Such complexity makes construction of appropriate control groups difficult, which in turn can affect study results. Additional research is needed to unravel the disagreement and establish the importance of these findings. It might be that the presence of the Al allele is not unique to alcoholism, but rather, causes a general alteration

in the brain dopamine system that then exacerbates or contributes to alcohol abuse.

SUMMARY

The existence of heritable influences on normal and pathological consumption of alcohol is supported by results from family studies, twin studies, and adoption studies as well as research on animal models. Animal studies have established that alcohol preference and the reinforcing actions of alcohol are influenced by genetic factors. While there have been fewer studies examining the genetic component of vulnerability to the addictive properties of other drugs of abuse, evidence from animal studies supports a genetic influence on the use and abuse of drugs other than alcohol. The study of nonalcohol drug abuse in humans is more difficult because of substantially smaller populations that use or abuse these drugs and marked changes in availability and, hence, exposure to these agents. Investigation in this area is further hampered by the complexity of subjects' drug use: Most drug abusers have used multiple agents. This has led researchers either to concentrate on one class of drug or to treat all illicit drug use as equivalent. The tendency to lump all illicit drugs into one category makes results difficult to interpret or compare.

In the case of alcohol, studies indicate that low doses of alcohol are stimulating and produce a strong positive reward in animals susceptible to the addictive properties of alcohol. Another component of excessive alcohol consumption might be that alcoholics have a high threshold to the aversive effects of ethanol. This could be a result of an innate low sensitivity to medium and high doses of alcohol and/or acute tolerance to its aversive effects. Results from animal studies suggest an association between high alcohol preference and acute tolerance to the medium-and high-dose effects of ethanol. These animal experiments need to be extended and consideration should be given to related studies in humans. Findings with animals selectively bred for alcohol preference need to be extended to studies of sensitivity, tolerance, and preference for other drugs of abuse.

Neurobiological evidence points to common pathways mediating the positive reinforcing actions of alcohol and other drugs of abuse. Most evidence is consistent with the involvement of the mesocorticolimbic dopamine system in drug reinforcement mechanisms. Other neuronal pathways that regulate the activity of the mesocorticolimbic dopamine system may also be involved in mediating the rewarding properties of ethanol and other drugs of abuse. In the case of serotonin, innate, genetically determined factors appear to reduce CNS activity of serotonin, which is associated with heavy alcohol drinking. In addition, animal and human studies suggest an inherited difference in dopamine response to alcohol consumption and possibly an anomaly in the D_2 receptor for Dopamine associated with alcohol abuse. Additional studies with animals and humans are needed to clarify these differences and to explore the relationship of other neurobiological mechanisms related to the inherited components of other drugs of abuse.

Alcoholism and drug abuse are complex conditions that are the result of multiple causal factors. Alcoholism and other forms of addiction represent entities that have a genetic component but require specific (but as yet poorly understood) environmental influences to manifest. Thus, consideration of the impact of genetic factors must also take into account general social conditions such as availability and cost of substances, acceptability of use, and specific environmental influences on initiation of use, maintenance or cessation of use, and development of use-related problems. A major goal of addiction research in clinical populations is to determine who is vulnerable under what conditions. Understanding this interaction might lead to better prediction of relapse as well as improved matching of patients and treatments.

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Appendix A: The Drug Evaluation Committee of the College on Problems of Drug Dependence

The Comprehensive Drug Abuse Prevention and Control Act (PL 91-513) and the Psychotropic Substances Act of 1978 (PL 95-633) gives exclusive authority to the Secretary of the Department of Health and Human Services to determine the abuse liability of substances and to make recommendations concerning their regulation and other drug policy decisions. Although the Secretary receives advice from the Drug Enforcement Agency (DEA), the Food and Drug Administration (FDA), and various other regulatory agencies, these laws explicitly state that the National Institute on Drug Abuse (MDA) must provide to the secretary information relevant to the abuse potential of suspected drugs of abuse and all information relevant to an assessment of their abuse potential. On the basis of this information from NIDA, and information from FDA and DEA, the secretary makes a judgment as to the dependence potential of new drugs.

NIDA's role in providing information relevant to the dependence liability of potential substances of abuse has placed enormous demands on the Institute. The agency supports a variety of activities in commercial and private laboratories around the country to provide this information. One of its principal sources of information comes from the College on Problems of Drug Dependence (CPDD) and, specifically, its Drug Evaluation Committee (DEC). The relationship between NIDA and CPDD is both formal and informal: NIDA provides over 98 percent of the funds required to assess the dependence liability of compounds in CPDD-sponsored testing facilities, NiDA is an official liaison member of CPDD, and CPDD provides direct input as requested in all NIDA decisions regarding the dependence potential of drugs.

Established in 1929, CPDD is the longest standing group in the country concerned with drug dependence and abuse. It is an independent body, affiliated with most scientific societies concerned with the dependence potential of abused substances and with regulatory and governmental agencies such as the World Health Organization (WHO), MDA, the National Institute on Alcoholism and Alcohol Abuse, DEA, and FDA. Each of these agencies has formal ties with CPDD via liaison membership. In turn, CPDD provides liaison representation to FDA and all other agencies on request.

CPDD has three major functions: to assess the abuse liability of psychoactive drugs; to hold an annual scientific meeting to review the status of the dependence liability of drugs; and, to seine as a consultant to the private sector and various governmental agencies on all drug-related matters and policies.

DEC oversees all aspects of CPDD'S dependence liability testing program. DEC is devoted to research on drugs of abuse and the determination of the dependence potential and abuse liability of specific classes of drugs: analgesics, stimulants, and depressants. Governmental and regulatory agencies, such as NIDA, DEA, and FDA have relied on DEC for information on the abuse liability of opiate-like compounds and stimulant and depressant drugs, In addition, CPDD is a collaborating center to WHO and provides information about the abuse potential of pharmaceuticals and scheduling worldwide. Producing this information is generally beyond the capabili-

ties of third world countries. Finally, CPDD provides the pharmaceutical industry and academic investigators information on new and novel compounds in the design and development phase. Thus, the information provided plays an important role in scheduling drugs, drug policy making decisions, and the facilitation of new drug development.

Approximately 50 to 60 drugs per year are submitted by industry, academic institutions, National Institutes of Health (NIH) laboratories, NIDA, WHO, and DEA (generally as a result of confiscation). A computerized list of submitted compounds is maintained at NIH; the code is broken only when testing is complete testing.

Appropriate quantities of the compounds are distributed for testing to the various laboratories that work under the auspices of CPDD. The test results are released as soon as practical, but at most within 3 years of receipt of the compound. Information about the drugs is confidential until one of three conditions is satisfied: the submittee grants explicit permission to release the data; 3 years have elapsed or, Federal and/or regulatory organizations request CPDD to provide information concerning the compound for the public welfare (e.g., a determination of whether the compound should be scheduled under the Controlled Substances Act prior to its marketing and distribution to humans).

Two university-based groups are involved with DEC'S evaluation of the analgesic types of drugs, and three with evaluation of the stimulants and depressants. The Medical College of Virginia, Virginia Commonwealth University, and the University of Michigan Medical School examine analgesics, using different methods to discern the physical dependence potential and abuse liability of presumed analgesics. Those two academic centers, along with the Mississippi Medical Center test stimulants and depressants.

'The programs' testing determines dependence liability of drugs and, on request, carries out more detailed studies to examine specific aspects of dependence liability, such as tolerance. For the last 30 years, this program has been largely responsible for obtaining basic scientific information on specific classes of compounds and the mechanisms involved in their acute and chronic pharmacological effects. DEC receives new compounds that are generally unavailable to other testing groups and provides scientific data on the pharmacology and abuse potential of new compounds. Thus the program contributes to the development of new drugs and the understanding of the mechanisms underlying the abuse liability of drugs.

Appendix B
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