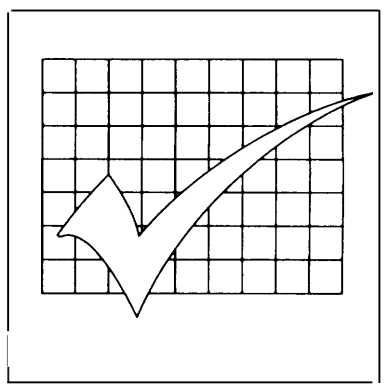
Basic Concepts 2

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.

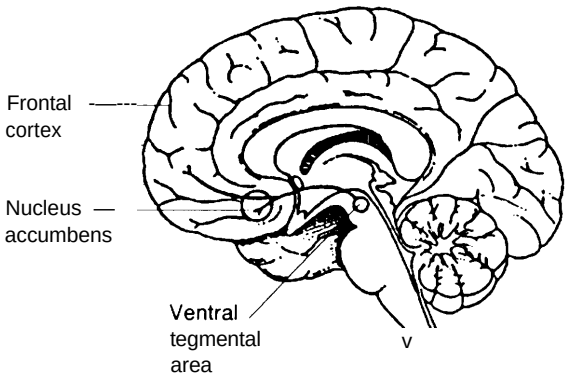
Studies have shown that direct stimulation of the areas of the brain involved in the reward system, in the absence of any goal-seeking behavior, produces extreme pleasure that has strong reinforcing properties in its own right (17). Such stimulation activates neural pathways that carry natural rewarding 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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