The Biological Tangle of Drug Addiction

Alcohol and cocaine, a legal and illegal drug, affect the brain in different ways yet both are addicting—the question is why

This is the fifth in a series on addiction. Next: the National Institute on Drug Abuse.

RESEARCH ON DRUG ADDICTION is booming but hard facts on its biological underpinnings are spotty. For instance, no one can explain the relationship between alcohol's many effects on the brain and its potential to be addictive, and scientists are only beginning to understand this link in cocaine addiction. Researchers are accumulating a great deal of information associating genetic factors with alcohol abuse, but have yet to demonstrate a genetic predisposition for cocaine abuse. No one is discounting the contribution of social and cultural factors to drug addiction.

The way in which many researchers view addiction is changing as they learn more about how drugs alter normal brain function. In particular, they focus on a group of structures in the brain called the reward system. The system is not well defined in humans, but it probably extends from the forebrain through the midbrain and into the hindbrain (see box). Cocaine and alcohol differ in many respects, but the notion that they somehow stimulate a common brain reward system is very seductive, a 1950s concept that enjoys a revival today.

The gist of the theory is that a drug like cocaine stimulates the reward system directly, producing such intense pleasure that one wants to repeat the experience. In this sense, the drug is said to be reinforcing because animals or people will work to take it again. The effects of alcohol are different, however. It is much less clear that alcohol stimulates the brain's reward system, at least directly, and it often takes longer to become dependent on alcohol than on cocaine. Not everyone agrees that stimulating the brain's reward system is the key to addiction, even for cocaine abuse.

"From my point of view there does not seem to be a unifying theory of addiction," says Charles O'Brien of the University of Pennsylvania and the Veteran's Administration Medical Center in Philadelphia. "The diversity of response to a drug at the clinical level is impressive. Even the diversity seen in animal models of addiction is impressive." Monkeys, for example, become addicted to cocaine much more easily than to heroin. It is difficult to get a rat addicted to alcohol, but easy with either heroin or cocaine. Humans, of course, can become addicted to any of the three drugs.

To further complicate the issue, no one is certain what "addiction" really means. The American Psychiatric Association (APA) addresses the issue in terms of psychoactive substance dependence and abuse (24 June, p. 1731). Dependence and abuse do not always go hand in hand, however. For example, cancer patients can become dependent on morphine to relieve pain but not abuse the drug. Correspondingly, a person can abuse a drug without being dependent on it.

The evidence that cocaine stimulates certain structures in the brain reward pathway—the nucleus accumbens or the ventral tegmental area, in particular—comes largely from experiments with animals. Although researchers cannot experiment with people, they think the human brain's initial response to cocaine goes something like this: A person takes cocaine; if it is smoked, the drug reaches the brain within 15 seconds. The person feels high, euphoric. The euphoria probably occurs because cocaine blocks the sites on nerve cell terminals where dopamine is recycled back into the cell. This means that more dopamine than usual is available to stimulate other neurons in the reward pathway, an effect that is pleasurable and reinforcing.

Based on his studies with rats, James Smith of Louisiana State University Medical Center in Shreveport proposes that the initiation of cocaine reinforcement—which includes the brain phenomena that appear to drive repetitive drug-taking behavior—occurs in the prefrontal cortex. George Koob of the Research Institute of the Scripps Clinic in La Jolla, California, thinks that the nucleus accumbens of the rat brain sustains reinforcement. Michael Kuhar of the Addiction Research Center in Baltimore, Maryland, and his co-workers have new data that support both ideas. They report a strong correlation between cocaine's ability to bind to the dopamine reuptake sites in the prefrontal cortex and the nucleus accumbens, and its ability to induce monkeys to self-administer the drug.

Between cocaine binges, the chronic user is anhedonic, a pleasureless state that some researchers attribute to a functional depletion of the brain's supply of dopamine, a point of debate. In these people, the dopamine that normally triggers the brain reward pathway may be so low that they do not feel pleasure. Alternatively, Frank Gawin of Yale University proposes a more discrete mechanism for anhedonia. He thinks that chronic cocaine abuse induces an extreme sensitivity of dopamine receptors on nerve cells that release the transmitter, so that the system by which dopamine normally tunes itself down is working overtime. This would result in less available dopamine, less stimulation of the brain reward pathway, a reduced response to pleasurable stimuli, and a craving for cocaine—all of which typify the chronic abuser.

Cocaine paraphernalia.

William B. Folsom/Uniphoto

In addition to its effect on dopamine transport, cocaine also blocks the reuptake of serotonin and noradrenaline into brain neurons. At high concentrations it is a local anesthetic, probably because it blocks the ion channels that allow sodium ions to flow into nerve cells. Cocaine is a powerful constrictor of blood vessels, an effect that may lead to death from a heart attack if the blood supply to the heart is cut off. And new evidence indicates that cocaine may bind to the same site as phencyclidine, also known as angel dust. But none of these actions is linked specifically to its addictive properties.

Unlike cocaine, which acts as a stimulant, alcohol often depresses brain function and can induce sedation. In one area of alcohol research, several groups of investigators are trying to link the addictive effects of the drug to a particular brain pathway or neurotransmitter system. According to Floyd Bloom, also of Scripps, the list of brain neurotransmitters affected by alcohol includes gamma-aminobutyric acid (GABA), serotonin, dopamine, noradrenaline, somatostatin, acetylcholine, and vasopressin. Intoxicating doses of alcohol may affect the metabolism of steroid hormones in the brain. New evidence suggests that alcohol alters the interaction of certain membrane proteins and lipids, which in turn affects intracellular processes regulated by cyclic adenosine monophosphate. And recent data indicate that alcohol may stimulate the brain reward system directly—by triggering dopamine release from the nucleus accumbens.

The overall effect of alcohol on the brain therefore becomes impossible to predict on the basis of its interaction with any one neurotransmitter system. Other complicating factors are that the acute effects of alcohol may differ from its chronic effects and that different doses of alcohol may have different effects. "The basis of the reinforcing action of alcohol is not clear," says Bloom. "It's a lot easier to explain what being intoxicated is than to explain why being intoxicated is reinforcing."

Perhaps the clearest link between the biological actions of alcohol on brain neurons and behavioral responses to the drug involve the inhibitory neurotransmitter, GABA. "It turns out that most of the effects of alcohol—reducing anxiety and causing sedation and motor incoordination—are related to the GABA system in the brain," says Maharaj Ticku of the University of Texas Health Science Center in San Antonio.

Data from several laboratories, including Ticku's, indicate that alcohol enhances the function of the GABA receptor complex, where barbiturates, benzodiazepines such as Valium, and many convulsants also act. Ticku does not know precisely how alcohol

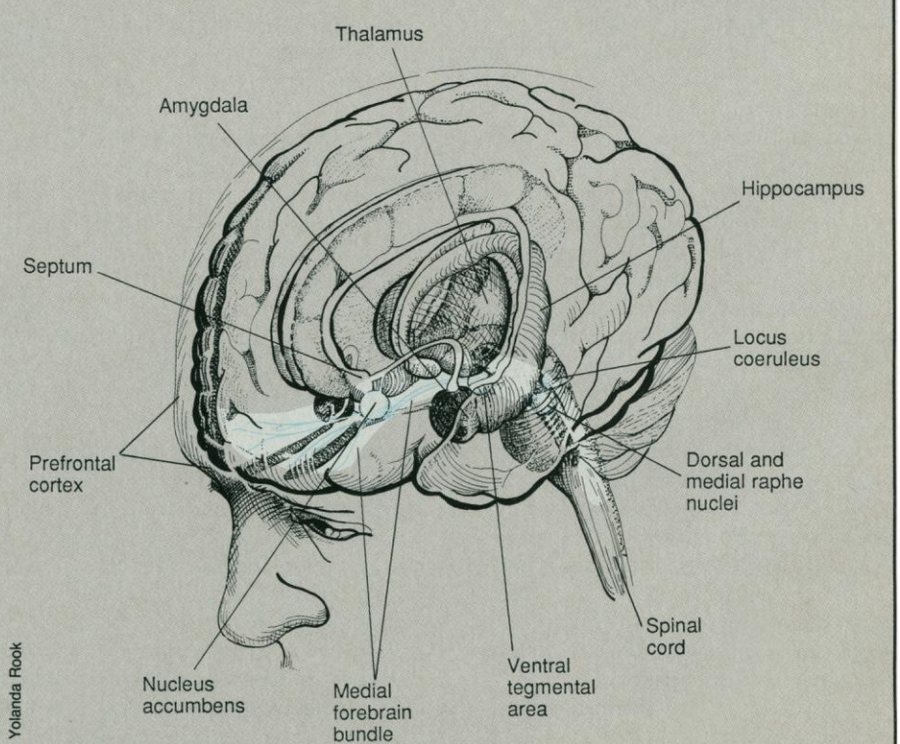
Drug Reward in the Brain

The human brain has a reward system that is both primitive and powerful. It is so primitive in evolutionary terms that a similar system exists in rats. It is so powerful that an animal will take a drug that stimulates the system until it dies. Exciting the brain reward pathway apparently causes intense feelings of pleasure, leading some to argue that brain hedonism may be the biological basis of addiction.

No one is certain what structures the human reward system consists of, but in rats it probably includes the medial forebrain bundle, a pathway from the frontal cortex to the ventral tegmental area (VTA), says Roy Wise of Concordia University in Montreal, Quebec. Fibers branch off this pathway toward the dorsal and medial raphe nuclei, groups of neurons in the hindbrain that use acetycholine as the primary neurotransmitter. These neurons synapse onto dopamine neurons in other parts of the reward pathway and indirectly increase their activity.

George Koob of the Research Institute of the Scripps Clinic in La Jolla, California, focuses on different structures. He sees the dopamine pathway from the VTA to the nucleus accumbens as most critical for brain reward and says the olfactory tubercles and frontal cortex—parts of the limbic system—are also important. Two closely associated roles of the reward system in rats are to motivate and direct movement, he says. For instance, the neural pathways leading into the nucleus accumbens from the amygdala are associated with emotion and motivation. The circuit leading out of the nucleus accumbens to the ventral pallidum helps control motor behavior.

"The question that gets complicated is where does pleasure come in," says Koob. Rats in which the nucleus accumbens has been removed or dopamine transmission to it cut off will cease to work for cocaine, presumably because they no longer feel pleasure from the drug. Whereas in rats dopamine transmission in the nucleus accumbens and VTA seems to be important for the rewarding properties of cocaine, in humans no one is certain which brain structures are most important for the pleasurable effects of drugs. But the pharmacology of the rat and human brain is similar, and researchers who study the reward pathway think that the process of drug addiction may also be similar. ■ **D.M.B.**



The brain reward system *(in blue) is closely associated with structures of the limbic system.* [*Adapted from F. E. Bloom, Ed.*, Brain, Mind and Behavior *(Freeman, New York, 1988), with special assistance from L. Porrino and E. Palombo*]

works, "but it may act on a lipoprotein domain associated with the chloride ion channel regulated by GABA," he says. It remains to be seen if alcohol has the same effect on human brain neurons as it does on the cultured mouse spinal cord cells that Ticku studies.

A commonly cited difference between cocaine and alcohol addiction is that it often takes much longer to become addicted to alcohol. One reason for this, says Boris Tabakoff of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in Bethesda, Maryland, is that people must learn to tolerate the unpleasant effects of alcohol, such as a bad taste, feeling drowsy, or having a hangover after drinking too much, before they develop a habitual drinking pattern.

It is also much more difficult to train a rat to give itself alcohol than cocaine because the animal must also develop tolerance to the drug. "With alcohol it's a long, slow process and a striking contrast to cocaine," says Harold Kalant of the University of Toronto and the Addiction Research Foundation in Toronto. Data from his laboratory and Tabakoff's research group indicate that a serotonin system in the brain, which goes from the medial raphe nucleus in the brainstem to the hippocampus, and the brain's noradrenergic system must be intact for an animal to become tolerant to the unpleasant effects of alcohol. "What all of this means to me is that the reinforcement model projected for addiction to cocaine is not a general reinforcement model that can explain the abuse of all drugs by humans," says Kalant.

A second area of alcohol research is identifying genetic factors that may predispose a person to alcohol abuse. "We are actually inheriting varying capacities to direct our behavior," says Robert Cloninger of Washington University in St. Louis, Missouri. "Some people are more predisposed to anxiety, which alcohol alleviates, so they drink." Cloninger finds that these people often have "passive-dependent" or "anxious" personalities and he terms them type I alcoholics. Type II alcoholics, in contrast, want the stimulating effects of alcohol. They seek novel experiences and apparently drink for different reasons. "These individuals have primarily antisocial personality traits," he says. They often develop a habitual pattern of heavy drinking before the age of 25 and may get into trouble with the law when they drink. Cloninger also contends that certain brain systems and neurotransmitters—norepinephrine, dopamine, and serotonin, in particular—influence behavior and personality.

"The idea that something about the vulnerability to alcoholism is inherited is supported by an overwhelming amount of evidence from studies of population genetics," says Enoch Gordis, director of NIAAA. "But the question is, what is inherited—certainly not a gene with alcohol on it." Research to identify what complement of genes may predispose a person toward alcohol abuse is still in the planning stages.

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A third area of alcohol research is identifying biological factors that may mark a future alcoholic. Marc Schukit of the University of California School of Medicine and the Veteran's Administration Hospital in San Diego compares the 18- to 25-year-old sons of alcoholic fathers to the sons of nonalcoholic fathers. The sons of alcoholics show smaller "increases in body sway and hormone levels, and changes in electroencephalogram (EEG) patterns," says Schukit. These men also report feeling less sleepy, dizzy, or high than their counterparts when they take either a low dose of alcohol that corresponds roughly to three drinks or a high dose that corresponds to five. Both groups show changes in their responses but the sons of alcoholics show less of a change.

Schukit, Eric Gold, also of UCSD, and their colleagues find no difference between the two groups in "baseline factors" such as personality types, performance on certain cognitive tests, or electrical activity in the brain. A follow-up study of the population, to conclude in 1995, should answer whether diminished responses to alcohol, which occurs in about 40% of the sons of alcoholics, identifies individuals who are more likely to become alcoholics.

In their recent studies, Henri Begleiter and Bernice Porjesz of the State University of New York Health Science Center in Brooklyn also find biological differences in the young sons of alcoholics that may predict future alcohol abuse. The researchers randomly present flashes of light, from a very dim to a very bright intensity to three different groups of boys—controls, sons with a family history of alcoholism that spans at least two generations and in which at least three members are alcoholic, and sons with only fathers who are alcoholic.

"We find that the group with a multigenerational history of alcoholism shows a very large response to intense stimuli that varies considerably from the control group," says Begleiter. Unlike Schukit, Begleiter monitors EEG activity in boys who have never had any alcohol to drink. His data suggest that the problem of alcoholism involves the frontal cortex and limbic system, brain regions also implicated in chronic cocaine abuse.

Experiments with animals lend further support to the notion that alcohol abuse may have a genetic component, and it also constitutes a fourth major area of research. Ting-Kai Li of the Indiana University School of Medicine and the Veteran's Administration Medical Center in Indianapolis and his colleagues select rats that have a high preference for drinking alcohol (given free choice and available food and water) and breed them. Similarly, they breed animals that do not like alcohol. "We get two lines of animals that show different responses to alcohol," says Li. "The alcohol-preferring animals find low to moderate concentrations of alcohol to be rewarding."

To determine why the rats behave so differently, Li, William McBride, and Lawrence Lumeng, also of Indianapolis, study neurochemical differences between the two groups. "The brains of alcohol-preferring rats are about 20% lower in the neurotransmitters serotonin and dopamine," says Li. Cloninger compares the preferring rats to human type II alcoholics who seek novelty and the stimulating effects of the drug. It is this group in which alcoholism seems to be the most heritable, says Cloninger, and he would expect them also to be low in brain serotonin and dopamine levels.

Despite the vast amount of recent information on how cocaine and alcohol alter brain function, no one is willing to say that addiction can be explained on the basis of these effects. "Cocaine can gradually gain control over behavior, but the concept that the drug changes behavior because it induces changes in nerve cells is not clear," says Jerome Jaffe of the Addiction Research Center in Baltimore, Maryland. "Memory may be the real biological basis of drug dependence," he says. "It is a loss of innocence in some respects."

The question of what causes drug addiction will not be answered solely by explanations of how drugs affect the brain. Many researchers emphasize that habitual drug-taking constitutes a powerful form of behavioral conditioning that is very difficult to disrupt in chronic users. They also see social pressures and acceptance of drug use—particularly with alcohol—as contributing to the problem of addiction.

■ DEBORAH M. BARNES