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Rate and Duration of Drug Activity Play Major Roles in Drug Abuse, Addiction, and T

By Robert Mathias, NIDA NOTES Staff Writer

When smoked or taken intravenously, cocaine produces a fast, intense high that dissipates quickly, creat need to take the drug again. In this regard, cocaine provides a perfect illustration of the critical role that rate and duration of action play in drug abuse and addiction.

Rate of Action

The rate at which a psycho-active drug occupies, or binds to, the brain sites called receptors for that drug intensity of its rewarding effects and its abuse liability, according to a hypothesis discussed at several sc by Drs. George Uhl and David Gorelick of NIDA's Division of Intramural Research (DIR) in Baltimore Jeanne Kreek of the Rockefeller University in New York. The faster a drug such as heroin or cocaine oc brain receptors to produce a psychoactive effect, the greater the euphoria users experience, the more they and the more liable they are to abuse it, according to this "rate hypothesis."

Why Does Rate of Action Affect the Brain?

What makes a faster-acting psychoactive drug produce more euphoria than a slower-acting one?

"The brain has many adaptive mechanisms, and if you disturb the brain slowly, it often can catch up or compensate," explains Dr. George Uhl, who directs the Molecular Neurobiology Branch of

NIDA's Division of Intramural Research in Baltimore. "But, if you do things rapidly, often it can't." For example, going suddenly from a dark room into bright sunlight will result in a temporary loss of vision because the light sensitivity mechanisms of the eye and the brain cannot adapt that quickly, he says. But, if you proceed from dark to light slowly by stages, the mechanism works in a fairly automatic way, and you are able to see normally.

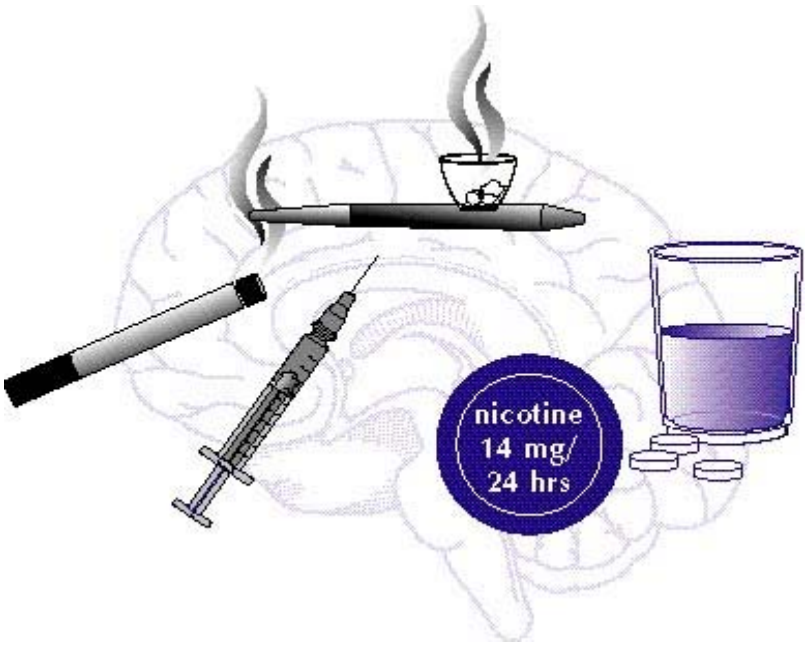
"If a drug acts slowly, the brain is able to compensate for the changes that the drug produces," says Dr. Uhl. However, when a drug's onset of action is very rapid, it may be able to overwhelm the brain's adaptive mechanisms, thus producing a bigger boost in its pleasure circuits, he says. Smoked and intravenous cocaine, for example, have fast rates of action. They reach the brain within seconds and rapidly flood the brain's "pleasure pathway" with excess dopamine, a brain chemical that helps transmit pleasurable feelings. If the brain's adaptive mechanisms cannot respond quickly enough to the sudden excess of dopamine, the euphoric rush ensues.

Conversely, the slower rate at which heroin treatment medications such as methadone and LAAM (l-alp methadol) occupy the same receptors targeted by heroin may be a critical factor in their effectiveness in addiction and their low abuse liability, according to these scientists. The fact that these slow-onset medi used to treat heroin, which has a fast rate of action, suggests that a compound that slowly occupies a suf the brain receptors targeted by cocaine might serve similarly and be effective in the treatment of cocaine researchers say.

The faster a drug such as heroin or cocaine occupies enough brain receptors to produce a psychoactive effect, the greater the euphoria users experience, the more they "like" the drug, and the more liable they are to abuse it.

"The rapid rate at which brain receptors are occupied may play an underrecognized role in determining t effects of cocaine and heroin. The slower rate of occupancy of heroin-treatment medications may play a appreciated role in their effectiveness in treating heroin addiction," says Dr. Uhl. Increasing evidence fr sources indicates that this concept offers "a promising, theory-based approach to developing a cocaine t medication," he says.

Method of Drug Administration Affect Rate of Action



The method of administering a drug can play a major role in the drug's rate of action, which in turn liability or potential as a treatment medication. Smoked drugs that are delivered through a "crack" p and injected drugs that are administered through a hyperdermic needle reach the brain very rapidly. is an important factor in the strong effect and high abuse liability of such drugs. Drug abuse treatme shown here in purple, are often administered orally or through a patch affixed to the skin and take lo brain. This slower rate of action is an important factor in the milder effect and low abuse liability medications.

Alhough there is clinical evidence that fast-acting drugs can have more of a euphoric effect than slow-ac "careful pharmacological studies demonstrating that different rates of cocaine and heroin administration effects have been sparse," Dr. Uhl says. However, recent research is now providing additional support fo hypothesis, he says.

Smoked and intravenous cocaine act faster and produce greater euphoria than snorted cocaine, which in turn, acts faster and generates more euphoria than oral cocaine.

This research includes DIR animal studies that indicate that rapid infusion of cocaine and heroin produc than slower infusion does. In addition, DIR studies examining the effects of different methods of admini indicate that smoked and intravenous cocaine act faster and produce greater euphoria than snorted cocai turn, acts faster and generates more euphoria than oral cocaine.

The link between the effect of a drug and its rate of receptor occupancy also has been buttressed in recer cloning of the gene for the mu opiate receptor, the principal site in the brain where heroin works to prod

effects. Using the cloned mu opiate receptor, NIDA researchers have determined that opiate treatment m as methadone and LAAM work through the same receptor that heroin works through to produce euphori some researchers had suggested that because these medications produce effects that are so different from they might work through different receptors than heroin does, says Dr. Uhl. Now, it appears that the dra in effects produced by the abused substance and its treatment medication stems from the fact that heroin receptors within seconds and produces a brief, intense "rush," whereas methadone occupies the same rec more slowly, producing only a very modest rewarding effect, he says.

While the fast rate at which cocaine acts on the brain plays a major role in its rewarding effects, it is cocaine's extremely rapid removal from the brain that both promotes and enables its frequent reuse and abuse.

Duration of Action

Duration of action, or how long the drug occupies a receptor once it gets there, also plays an important r and treatment. For example, cocaine has both a fast rate of action that produces euphoria and a rapid off duration of action, that allows frequent abuse.

Compounds with these traits may foster craving for more drug and stronger conditioning of the drug-tak according to a hypothesis proposed by Dr. Nora Volkow of Brookhaven National Laboratory in Upton, imaging studies conducted by Dr. Volkow indicate that while the fast rate at which cocaine acts on the b major role in its rewarding effects, it is cocaine's extremely rapid removal from the brain that both prom its frequent reuse and abuse.

Conversely, a long, sustained duration of action is important in determining the potential usefulness of a compound, says Dr. Kreek. First, longer-lasting medications such as methadone are more practical beca given every 24 hours, whereas shorter-lasting medications require more frequent doses. Second, because dissipate slowly, long-duration medications appear to be particularly useful in normalizing physiologica as regulation of hormonal activity and behaviors that have been disrupted by the rapid "on-off" effects p abused drugs, she says.

Clinical experience with both methadone and LAAM indicates that these medications have a much lowe than heroin has, Dr. Kreek says. They prevent withdrawal symptoms and reduce craving, thereby decrea eliminating heroin abuse. And they stabilize patients physiologically and psychologically, she points out taking methadone have been stabilized at a therapeutically appropriate dose, "their behavior is essentiall from that of any other healthy human being, and they are able to get an education or a job and improve t relationships," she says.

Developing a Cocaine Treatment Medication

Several rate-based approaches to developing a potential cocaine treatment medication are possible, says acting director of NIDA's Medications Development Division. One approach is to search for compounds

onset of action than cocaine that produce less euphoria and have a longer duration of action. Another is t slow onset compounds that would probably produce only subtle effects. To determine their treatment po compounds "that meet these parameters would need to be tested to see if they could block cocaine's effe chronic craving while they were active, Dr. Vocci says.

"We're starting to see some compounds now in our cocaine medication discovery program that have ver days as opposed to minutes or hours, to reach peak levels," Dr. Vocci says.

Some of these compounds may enter the brain very slowly, but once they are there, they may hang onto a long time. Others may be compounds that are slowly activated and gradually accumulate on brain rece is also possible to modulate a compound's onset of action pharmaceutically by manipulating its rate of a body with transdermal patches or controlled-release forms of administration, Dr. Vocci points out.

How Does Method of Administration Influence Rate of Action?

Many complex factors affect a compound's rate of action in the human body. These factors include the compound's structure and properties, how quickly the body absorbs it and transports it to the brain, and how rapidly it crosses the blood-brain barrier and binds to a sufficient number of targeted brain sites called receptors to produce its effects. Because the method of administering a drug affects a number of these factors, it can play a major role in the drug's rate of action and abuse liability.

By using different methods of administering a compound, scientists can slow its rate of action and produce milder effects that may substitute for the stronger effects of an abused substance. Such a compound may be an effective medication for patients in treatment.

The effect that method of administration has on rate of action may be best illustrated by the transdermal nicotine patch, which uses the abused substance itself-nicotine-to ease withdrawal symptoms and aid smoking cessation. However, unlike smoking a cigarette, which delivers an almost instantaneous burst of nicotine-laden blood to the brain, administering nicotine through a patch affixed to the skin slows its rate of action and produces more sustained, lower peak levels of nicotine in the blood. This lower, slower dose of nicotine has proven to be effective in short-term treatment of nicotine dependence and aiding smoking cessation.

To increase the potential usefulness of rate-based approaches in the development of a cocaine treatment and extramural researchers are attempting to answer basic questions about the rate at which cocaine brai need to be occupied and the degree of occupancy that is required to either produce or block cocaine's rev Dr. Gorelick says. "At this point, we don't really know the minimum level of receptor occupancy we nee cocaine's euphoria, but that information should come from ongoing studies," he says.

"We're starting to see some compounds now in our cocaine medication discovery program that have very slow onsets, days as opposed to minutes or hours, to reach peak levels."

Once scientists have that information in hand, they can attempt to develop a compound that achieves the action and degree of receptor occupancy that is needed to produce a milder effect and longer duration of cocaine. Such a compound, the rate hypothesis suggests, should be effective in reducing cocaine-seeking normalizing physiological functions that are disrupted by long-term cocaine abuse.

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