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Low Dopamine Receptor Availability May Promote Cocaine Addiction

Research Findings
Vol. 22, No. 3 (April 2009)

Reduced availability heightens reinforcing effects of cocaine in monkeys, and the drug drives this measure even lower.

BY LORI WHITTEN, *NIDA Notes* Staff

In a study with rhesus monkeys, Dr. Michael Nader and colleagues at Wake Forest University recently showed that cocaine lowers availability of the dopamine D₂ receptors in the basal ganglia—the brain region that includes key components of the reward system. The consequences may include addiction-promoting alterations in cognitive functioning and decisionmaking.

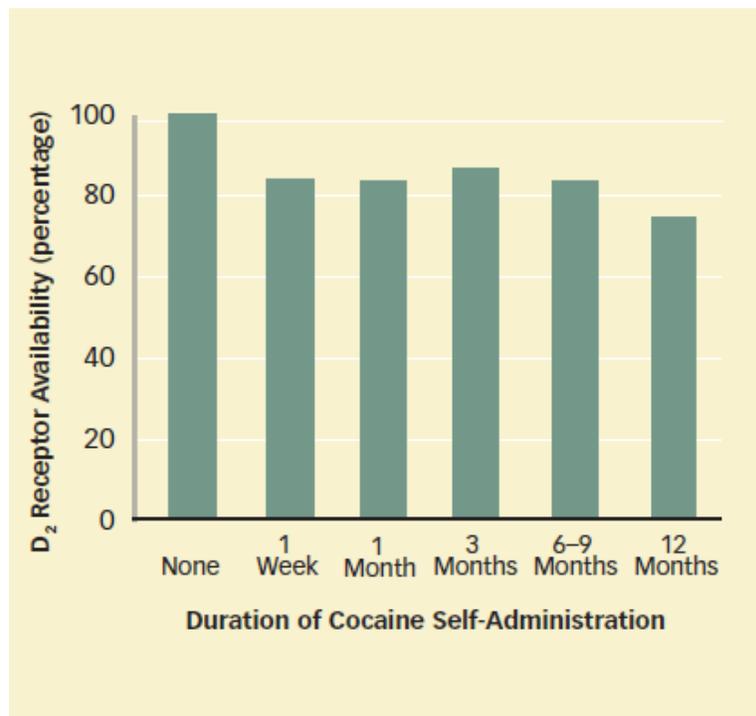
Dr. Nader's study also confirms previous findings that individual animals with lower D₂ receptor availability are especially responsive to cocaine's reinforcing effects.

In a promising finding for people trying to recover from cocaine addiction, receptor availability levels in some of the monkeys recovered after less than a year of abstaining from drug use.

RECEPTOR AVAILABILITY AND COCAINE EXPOSURE

The D₂ receptor resides in the outer membrane of brain cells that shape motivation and emotion, thought, and movement. The receptor protein enables the neurotransmitter dopamine to attach to these cells and affect their activity. At any given time, dopamine molecules occupy some of the D₂ receptors, while the rest of the receptors remain available until a stimulus—such as drug exposure—increases dopamine levels. One hypothesis holds that the proportion of D₂ receptors a person has free affects how strongly he or she responds to the stimulus.

COCAINE REDUCES AVAILABILITY OF D₂ RECEPTORS



Imaging studies of the human brain have found reduced levels of available D₂ receptors among abusers of cocaine. But that work could not distinguish between pre-existing differences in the proportion of available receptors and changes induced by drug use. The human studies also showed reduced availability of D₂ receptors among abusers of heroin, nicotine, amphetamine, and alcohol. Lower D₂ receptor availability has also been observed in other populations, such as the severely obese. So, findings on D₂ receptor availability may be relevant to a wide range of addictions and conditions.

To measure monkeys' D₂ receptor availability before cocaine exposure, Dr. Nader and colleagues injected each animal with a radiotracer that binds to the receptors. The radiotracer competes with dopamine for the receptor and provides a measure of D₂ function. Over the course of a 3-hour brain imaging study, the scientists used positron emission tomography (PET) to visualize and quantify the bound radiotracer.

Next, the researchers allowed the monkeys to self-administer cocaine. Every day, they placed each monkey in an experimental chamber equipped with two levers—one that delivered banana pellets during the first 20 minutes of the test and another that provided the animal with an infusion of cocaine during the next 60 minutes. Then, the researchers put the animals through this sequence a second time. To describe the neurobiological effects of chronic cocaine exposure, the investigators continued the self-administration experiments and measured D₂ receptor availability for a year.

The monkeys whose PET scans had revealed lower D₂ receptor availability at baseline testing before their initial cocaine exposure self-administered cocaine at higher rates. This finding suggests that lower D₂ receptor availability increases sensitivity to cocaine reward. Similar findings have been reported in studies that compared drug abusers and people who do not abuse drugs. The results also complement those of a prior study by Dr. Nader, which showed that subordinate monkeys, having lower D₂ receptor availability, self-administered more cocaine than dominant monkeys, which have higher D₂ receptor availability.

"This result, as well as findings of other studies, indicates that low D₂ receptor

availability corresponds to increased vulnerability to cocaine abuse," says Dr.

Nader. "Perhaps an individual with low availability gets a

greater kick from cocaine because the drug-induced dopamine release stimulates a greater percentage of their receptors. Another possibility is that the drug prompts some individuals' brain cells to release dopamine in particularly high quantities that are sufficient to fill the great majority of vacant D₂ receptors, and this augments the high."

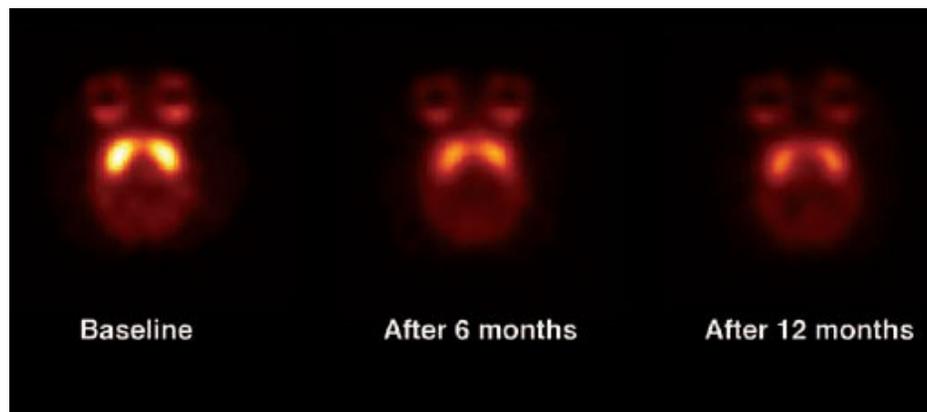
This finding suggests that lower D₂ receptor availability increases vulnerability to cocaine reward.

VARIABLE RECOVERY

PET scans obtained at intervals throughout the trial revealed a rapid and marked suppressive effect of cocaine on D₂ receptors. After 5 days of

self-administration, the monkeys' available receptors had dropped by 15 percent, on average. This effect was reversible: In three monkeys that were allowed to self-administer the drug for 1 week, D₂ receptor availability returned to baseline values by the third week of abstinence.

BRAIN SCANS Dopamine 2 receptor availability (yellow) in the basal ganglia falls dramatically after 6 and 12 months of cocaine self-administration.



The picture was more complex, however, in five monkeys that self-administered cocaine for a year. At that time, D₂ receptor availability was down 22 percent (see [graph](#)). When access to cocaine was then stopped, three of the monkeys showed strong recovery—93 percent, on average—of receptor availability a month after cocaine cessation. But two monkeys had recovered only 80 percent and did not recover further over 12 months of abstinence.

FOOD VERSUS DRUG

The researchers parsed the implications of the relationships between cocaine and D₂ receptors by comparing the monkeys' patterns of lever pressing for the drug and for food. In contrast to the cocaine self-administration results, there was no correlation between D₂ receptor availability and how often monkeys pressed the food lever. This suggests that low D₂ receptor availability disposes individuals to seek the cocaine experience specifically, rather than rewarding

experiences in general.

A clue to why recovery is more difficult for some individuals than others may come from the two monkeys whose D₂ receptor availability failed to recover completely following year-long cocaine self-administration. Throughout the year of cocaine self-administration, these animals exhibited a reduced attraction to food, Dr. Nader says. When given the opportunity to press a lever for banana pellets, these animals did so only half as often as the monkeys whose receptors returned to baseline after long-term cocaine self-administration. "Although the findings are preliminary, we believe that these individuals may find rewards other than cocaine devalued," Nader says. "If it is not cocaine, it is just not rewarding to them." That trait may presage an unusually long-lasting influence of the drug.

TOWARD TREATMENT

"Predisposition seems to play a role in addiction, as does the dopamine system's rapid and robust reduction in D₂ receptor availability in response to cocaine," says Dr. Nader.

The team's findings and those of others suggest that therapies that elevate D₂ receptor availability may help prevent and treat cocaine abuse. According to Dr. Nader, the medications that appear most likely to accomplish this without deleterious side effects do so indirectly by altering neurotransmitters other than dopamine—either by increasing serotonin or gamma aminobutyric acid. Dr. Nader and his colleagues plan to test this strategy in monkeys.

In prior research, Dr. Nader has shown that enriching individuals' environments also can prompt the brain to generate additional D₂ receptors. "My colleagues and I are most intrigued by an environmental enrichment strategy for increasing D₂ receptor levels," Dr. Nader says. "This approach is based on the most profound result that my colleagues and I have ever observed: Adult monkeys that have a high level of control over the social environment show enhanced D₂ receptor availability and markedly diminished response to cocaine's rewarding effects" (see "[Social Environment Appears Linked to Biological Changes in Dopamine System, May Influence Vulnerability to Cocaine Addiction \(Archives\)](#)").

Other researchers have reported that, in rodents, environmental enrichment reverses the rewarding effects of cocaine. Dr. Nader and his team are preparing to test whether enhancing monkeys' environments—for example, by reducing stress, providing novel objects, and increasing peer interaction—can increase receptor availability and curb cocaine self-administration.

If the enrichment is successful, analogous provisions for people—improved living conditions, broad recreational choices, stress management techniques, and rewarding activities—might reduce vulnerability to cocaine abuse.

"A question for further research is whether animals whose D₂ receptor availability levels remain low during abstinence are more likely to exhibit behaviors akin to relapse, compared with those whose receptors recover," says Dr. Cora Lee Wetherington of NIDA's Division of Basic Neuroscience and Behavioral Research. Dr. Nader says his team plans to adapt its current experimental protocol to explore this question in rhesus monkeys.

SOURCES

Nader, M.A., et al. Positron emission tomography imaging studies of dopamine receptors in primate models of addiction. *Philosophical Transactions of the Royal Society of London, Series B* 363 (1507):3223-3232, 2008. [[Abstract](#)]

Nader, M.A., and Czoty, P.W. Brain imaging in nonhuman primates: Insights into drug addiction. *Institute for Laboratory Animal Research Journal* 49(1):89-102, 2008. [[Abstract](#)]

Nader, M.A., et al. PET imaging of dopamine D₂ receptors during chronic cocaine self-administration in monkeys. *Nature Neuroscience* 9(8):1050-1056, 2006. [[Abstract](#)]

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Research Findings
Vol. 21, No. 6 (June 2008)

Mice With Genetic Alteration Eschew Cocaine

A South American caterpillar inspired a successful 10-year quest to desensitize the dopamine transporter to the drug.

BY LORI WHITTEN, *NIDA Notes* Staff Writer

NIDA researchers have desensitized mice to cocaine by genetically altering their dopamine transporters—proteins that are a key target of cocaine—to resemble ones found in the brains of some insects. If investigators can identify a compound that alters these transporters in the same manner, they might be one step closer to developing medications to treat cocaine addiction.

A South American caterpillar started the researchers on their path to the discovery. Larvae of the *Eloria noyesi* moth have a particular appetite for leaves of the coca plant. This preference has captured the interest of drug-control authorities, who view the caterpillar as a potential tool for eradication of coca crops. To Dr. Howard Gu at Ohio State University (OSU), however, the caterpillar's apparent immunity to the psychoactive properties of the coca leaf suggested something else: Perhaps cocaine's target protein in the caterpillar's brain—the dopamine transporter (DAT)—does not respond to the leaf. If so, he reasoned, an understanding of how the insect's DAT functions might provide a template for pharmacological agents to block the effects of the coca leaf's potent derivative, cocaine.

Scientists generally believe that cocaine produces its high by preventing DATs from regulating dopamine levels in the brain's reward system, resulting in a euphoria-producing buildup of the neurotransmitter in the nucleus accumbens (NAc). If an animal reliant on coca for nutrition were to be subject to this effect, however, surges of euphoria would occur whenever it ate and presumably be very disruptive of its functioning. "Because the caterpillar is interested in coca leaves as a food source, we hypothesized that its DATs might not interact with cocaine," Dr. Gu says.

FOOD NOT DRUG A coca leaf—the source of cocaine—is just food to the South American caterpillar *Eloria noyesi*. Like some other insects, its dopamine transporters are much less sensitive to cocaine than those of mice.



A SURPRISING TWIST

Dr. Gu undertook a 10-year project that ultimately established a mutated form of DAT that is cocaine-insensitive. But he encountered several surprising twists—and frustrating letdowns—along the way.

Chief among these, Dr. Gu was disappointed to find that the DAT from *Eloria* is not substantially less sensitive to cocaine than the DAT from other insects they tested, such as a silkworm that does not eat coca leaves. He quickly recognized that there was nothing unique about the *Eloria* caterpillar in this regard and was forced by that evidence to relinquish the elegant evolutionary theory he had held about how its insensitivity to the stimulating effects of the coca leaf might have developed.

But what he learned in the process was more important than a busted theory: Dr. Gu discovered that the DATs from a number of insect species are just 5 percent as sensitive to cocaine as is mouse DAT. "I seized on the difference to generate clues about how to alter the mouse DAT to be cocaine-insensitive like the insects'," he says.

As a first step, Dr. Gu switched fragments of insect DAT sequences with mouse DAT sequences and identified key regions that affect how tightly cocaine binds to the DAT protein. He then randomly generated a large number of alterations in these regions of the mouse DAT sequence. Working with cultured cells, he tested them one by one to see if the changes they introduced would desensitize mouse DAT to cocaine. Through this laborious process, he eventually identified the sequence changes that make the transporter cocaine-resistant.

Dr. Gu created mutant mice with the same DAT sequence changes. The mutant mice produced cocaine-resistant DAT. But were the animals truly immune to the rewarding sensations of the drug? Dr. Gu joined with colleagues at OSU and the University of Tennessee College of Medicine to answer this question.

SELECTIVE INDIFFERENCE

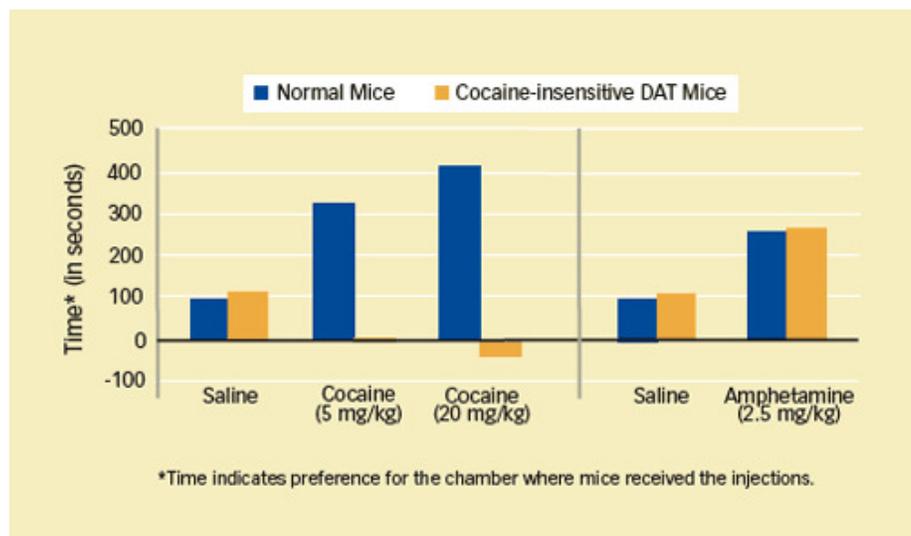
When normal mice are exposed to cocaine in one compartment of a split cage, they demonstrate liking for the drug by later spending the bulk of their time in that compartment. The proportion of time the animals spend in the drug-associated compartment provides a quantitative behavioral measure of the intensity of the drug's rewarding effects. In Dr. Gu's trials, the mutant mice spent no more time in a cage area where they received the injections of cocaine (5 mg/kg or 20 mg/kg) than they did in a compartment where they were given saline injections—a clear demonstration that they were not experiencing cocaine's rewarding effects ([see graph, left panel](#)).

To ensure that the mutant mice retained normal responses to stimuli other than cocaine, the researchers gave them amphetamine. This stimulant triggers dopamine surges by mechanisms different from those that cocaine triggers. The researchers found that both mutant and normal mice developed elevated extracellular dopamine in the NAc after amphetamine exposure. In addition, the mutants exhibited as much behavioral evidence of amphetamine reward as did a comparison group of normal mice ([see graph, right panel](#)).

"The mutants' response to amphetamine demonstrated that the neural machinery works properly in these animals, and they are not generally deficient in drug-induced reward," says Dr. Gu.

MICE WITH MUTATED DOPAMINE TRANSPORTERS GET NO KICK FROM COCAINE Normal mice spent more time in a chamber where they had received cocaine injections than in one where they had received saline.

But mice with a cocaine-insensitive dopamine transporter (DAT) showed no preference (left panel). In contrast, both normal mice and those with an insensitive DAT lingered in the amphetamine-paired chamber longer than saline-treated animals (right panel).



Dr. Gu's team is now seeking to identify a chemical compound that will prevent human DATs—like the mouse's altered DAT—from responding to cocaine. Such a compound would eliminate the drug high and limit the frequency and length of relapses. Yet it would not interfere with the DAT's ability to regulate dopamine, which produces feelings of reward and motivation vital for life-promoting activities, such as eating. NIDA is supporting research to screen for such compounds with a protocol and cell lines provided by Dr. Gu.

A THEORY BOLSTERED

Beyond yielding leads for medication development, Dr. Gu's findings alleviate doubts that have arisen about the strategy of selective DAT desensitization to reduce cocaine reward. In some studies, animals continued to exhibit dopamine surges and behavioral responses to cocaine despite having been genetically altered to lack DAT.

"The results from mice without DAT represented a milestone in cocaine research—it was remarkable that these mice still experienced a high from cocaine," explains Dr. Gu. "In view of that observation, it is reasonable to question the approach of finding compounds that prevent cocaine from binding to the DAT as a therapeutic strategy for cocaine abuse. The results from our mutant mice, however, indicate that DAT altering can block cocaine reward."

In light of their work with the mutants, the researchers now attribute the persistence of cocaine response in DAT-less mice to adaptation. "The brains of DAT knock-out mice seem to undergo significant adaptive neurobiological changes that alter how cocaine produces its effects," says Dr. Gu.

"Dr. Gu and colleagues have verified decisively that cocaine's inhibition of DAT is necessary for its behavioral effects, answering an important question in addiction research," says Dr. Nancy Pilotte of NIDA's Division of Basic Neuroscience and Behavioral Research. She notes, however, that the strong confirmation of DAT's role in cocaine reward does not rule out the idea of redundant systems. "If the dopamine system is damaged, as it is in the DAT-less mice, the brain may 'train' norepinephrine and serotonin neurons to take over reward and other functions," she says.

SOURCE

Chen, R., et al. Abolished cocaine reward in mice with a cocaine-insensitive dopamine transporter. *Proceedings of the National Academy of Sciences* 103(24):9333-9338, 2006. [[Full Text](#)]

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