

*A Collection of*

# NIDA NOTES

NATIONAL INSTITUTE  
ON DRUG ABUSE

*Articles That Address*



**RESEARCH  
ON COCAINE**

U.S. Department of Health and Human Services  
National Institutes of Health  
National Institute on Drug Abuse

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## Introduction

The National Institute on Drug Abuse (NIDA) supports most of the world's research on drug abuse and addiction. NIDA-funded research enables scientists to apply the most advanced techniques available to the study of every aspect of drug abuse, including:

- genetic and social determinants of vulnerability and response to drugs;
- short- and long-term effects of drugs on the brain, including addiction;
- other health and social impacts of drug abuse, including infectious diseases and economic costs;
- development and testing of medication and behavioral treatments for abuse and addiction; and
- development and evaluation of effective messages to deter young people, in particular, from abusing drugs.

Included in this document are selections of topic-specific articles reprinted from NIDA's research newsletter, *NIDA NOTES*. Six times per year, *NIDA NOTES* reports on important highlights from NIDA-sponsored research, in a format that specialists and lay readers alike can read and put to use. Selections like the current one are intended to remind regular *NIDA NOTES* readers and inform other readers of important research discoveries during the periods they cover.

We hope the information contained here answers your needs and interests. To subscribe to *NIDA NOTES* and for further information on NIDA's drug abuse and addiction research, please visit our Web site at [www.drugabuse.gov](http://www.drugabuse.gov).

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## Cocaine Locks Rats Into Unrewarding Behaviors

Brain circuits that guide behavior by registering consequences become less flexible after drug exposure.

By *NIDA NOTES* Staff

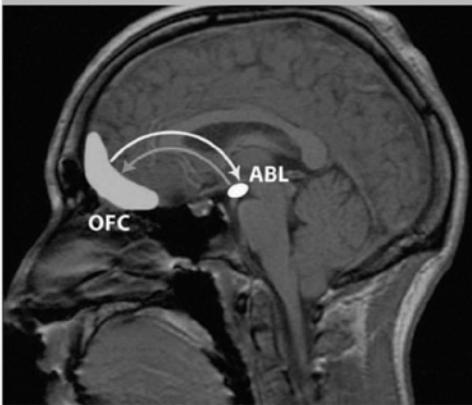
People initially take cocaine for pleasure, but for most chronic abusers, the high becomes progressively shorter and weaker, and negative social and economic consequences grow increasingly dire. Relationships hit the rocks, financial problems mount, and legal trouble follows, but the cocaine abuser often fails to adapt his or her behavior to avoid the accumulating personal disasters and instead remains stuck in self-damaging patterns.

New NIDA-funded research with rats indicates that cocaine may contribute to this inflexibility by impeding abusers' ability to associate warning signs with outcomes. The research links successful sign reading to two connected brain structures—the orbitofrontal cortex (OFC), located directly above the eye sockets, and the basolateral amygdala (ABL), deep in the brain. Cocaine appears to weaken neural signaling in these structures.

“Our findings may explain why cocaine abusers and cocaine-exposed animals have difficulty adapting their behavior to avoid negative outcomes,” says Dr. Geoffrey Schoenbaum, who led the University of Maryland School of Medicine studies. “Cocaine seems to disrupt the information-processing ability of neurons in a learning circuit that helps animals and people accommodate their behavior when the environment changes.”

### CRITICAL INFORMATION PROCESSING

Research indicates that cocaine weakens neural signaling in a learning circuit between the orbitofrontal cortex (OFC) and the basolateral amygdala (ABL).



### Learning To Use Cues

To test cocaine's impact on learning and adaptation, Dr. Schoenbaum and colleagues used a protocol called the two-odor go/no-go discrimination task (see box). The pro-

cedure consists of two parts. The first tests an animal's ability to link cues to desired and aversive outcomes. It challenges the animal to perform a task analogous to that of a person learning that right-hand faucets deliver cold water and left-hand ones, hot. In Dr. Schoenbaum's protocol, the counterparts to the faucets are odors. The researchers give a rat a whiff of one odor immediately before filling a well in the cage with a delectable sucrose-flavored drink, and they provide another odor when the well is about to be filled with a repugnant, quinine-flavored concoction. The rats have to learn to use both cues to obtain the sweet drink and shun the nasty one.

The second part of the go/no-go protocol tests rats' ability to adjust when cues change their meanings. The odor that formerly indicated the sweet drink now signals the bitter one, and vice versa. This put the animals into a situation analogous to that of a person whose inattentive plumber crossed the pipes leading to a sink's faucets. A person in this predicament must quickly learn to change expectations or risk repeated scaldings.

Dr. Schoenbaum's team ran two groups of rats through the go/no-go protocol. One group had been exposed to cocaine daily for 2 weeks one month prior to the protocol, and the other was drug-free. In the first part of the protocol, both groups readily learned to discriminate between the odor cues. After a dozen trials, both groups consistently—though not unerringly—went to the well following the cue for sweet and shunned it following the cue for bitter.

One observation during the first part of the protocol suggested that, despite their similar learning curves, the cocaine-exposed rats had reduced sensitivity to cues predicting negative experiences. The behavior of the rats in the two groups differed in those occasional instances where rats mistakenly went to the well following the cue for the bitter drink. The drug-naïve animals hesitated before setting off, suggesting that they had some inkling that the consequences might not be desirable. The drug-exposed animals, in contrast, rushed right to the well.

In the second part of the protocol, cocaine markedly reduced some rats' ability to adapt to the switched odor-drink pairings. The drug-naïve rats and half of the drug-exposed rats learned to reverse their responses to the cues

after an average of 28 trials. The other half of the drug-exposed rats, however, required 35 trials.

### Neuron Flexibility

The cocaine-exposed rats' poorer performance in the go/no-go protocols suggested that the drug impairs neurons in a brain circuit that links cues to the expectation of satisfaction or dissatisfaction. When a person or an animal responds to a cue—whether it be the position of a faucet or an odor—these neurons encode whether the experience that follows feels good or bad. In subsequent encounters with the cue, some neurons increase their firing rate if past responses led to a satisfying experience; others increase their firing rate if past responses caused aversive or disappointing outcomes.

“The firing of these neurons represents the linking of the cue to an expectation of an outcome, based on previous experience,” says Dr. Schoenbaum. “We believe that at the time an animal has to decide whether or how to respond, these expectations influence its decision.”

To test the hypothesis that cocaine exposure affects these outcome-expectant neurons, the research teams ran rats through go/no-go protocols while monitoring the animals' neuronal activity in two brain areas: the OFC and ABL.

The OFC is part of the brain's decisionmaking circuit; its neuronal activity has been associated with stimulant addiction and craving. The ABL is part of the brain's emotional circuit. In previous studies, people with a damaged OFC or ABL were slow to change response patterns after consequences had changed from rewarding to adverse. This behavior resembles that of chronic cocaine abusers—and also some of the cocaine-exposed rats in the team's earlier experiment.

In both cocaine-exposed and unexposed rats, electrode recordings taken during the first part of the protocol showed that about 19 percent of the neurons monitored in the OFC and 26 percent of those in the ABL developed outcome-expectant firing patterns. This finding is consistent with the observation that the two groups of animals learned equally well to use the initial cues to guide their drinking.

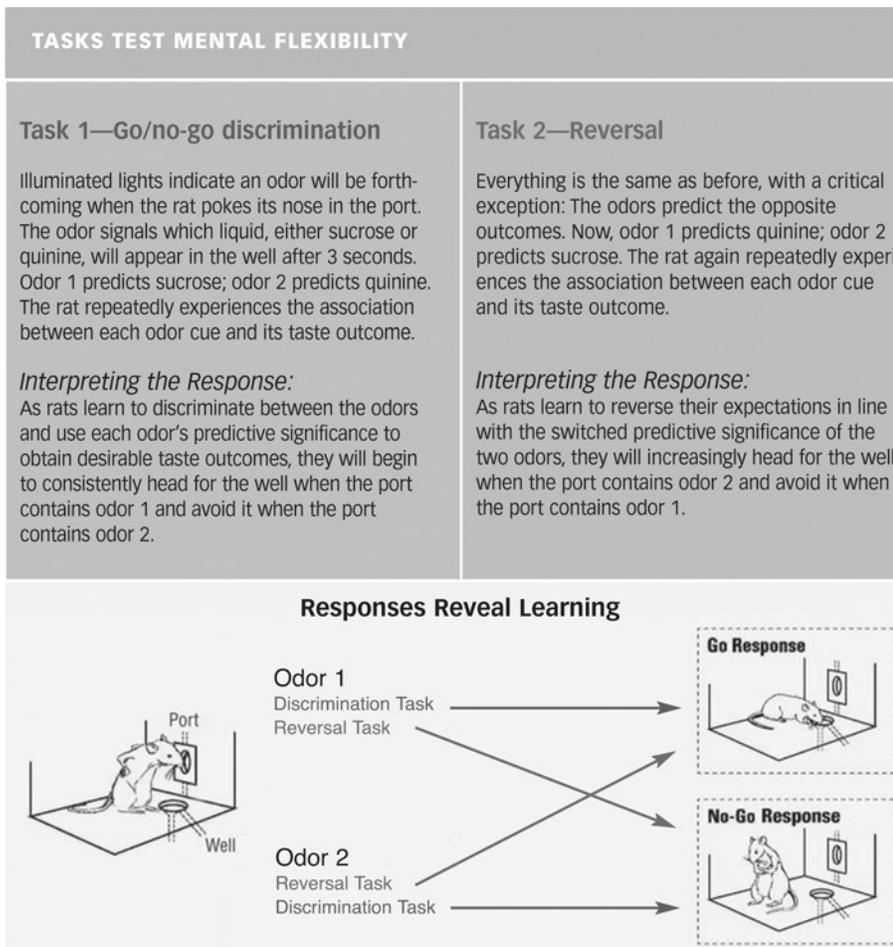
Nevertheless, the two groups' neuronal responses may help explain why, on those occasions when the rats mistakenly responded to the quinine cue, the cocaine-exposed rats went directly to the well while the unexposed rats hesitated. The recordings revealed that the exposed rats' OFC quinine-predicting neurons failed to activate in response to the odor.

In the second part of the go/no-go protocol, the cocaine-exposed animals' slower adaptation correlated with reduced flexibility of outcome-expectant neurons. When the researchers reversed the odor cues, neurons predicting sweet and bitter must switch their responses to continue to support decisions leading to happy drinking experiences.

Yet approximately 27 percent of those neurons in the ABL of the drug-exposed rats failed to make the switch—compared with only approximately 3 percent in the drug-free rats. The ABL neurons of the drug-exposed rats that initially signaled favorable expectations proved more inflexible than those that signaled unfavorable expectations.

### A Model for Decisionmaking

Dr. Schoenbaum's results led him to propose a model to explain how the ABL and OFC interact in cue response decisions. In this schema, when an individual encounters a familiar cue, ABL outcome-expectant neurons send the OFC a “good/go” or “bad/don't-go” message, or no message at all. The OFC combines this message with information



# Brain Activity Differs in Cocaine Abusers According to Gender

Cocaine abusers have reduced neural activity in the orbitofrontal cortex (OFC), a brain region that mediates decisionmaking. NIDA-funded researchers have discovered that gender determines where in the OFC the dampening occurs.

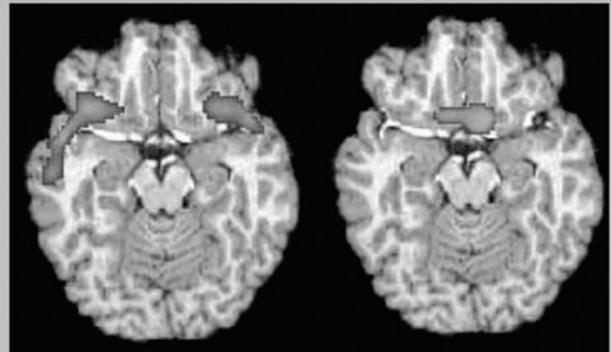
Dr. Bryon Adinoff and colleagues at the University of Texas Southwestern Medical Center and the Veterans Affairs North Texas Health Care System measured OFC neural activity, as indicated by blood flow, of 35 people who had used cocaine for 12 years, on average, but had been abstinent for 2 to 4 weeks. They compared the results with measurements from 37 people who had never used the drug. The researchers found that the OFC contributed a smaller portion of total brain activity in cocaine abusers than in nonabusers. However, the relative deficit was in the lateral OFC in men and in the medial OFC in women.

“One can hypothesize that sex differences in regional blood flow may give rise to contrasting behavioral responses,” says Dr. Adinoff. Such differences might arise because the areas most affected in each gender support different behaviors. For example, brain scans of people who do not use drugs have suggested that the lateral OFC is active when people refrain from doing something that they anticipate will have a bad outcome. In contrast, the medial OFC engages when people take action to try to achieve a desired result.

The depressed neural activity in the lateral OFC among men who abuse cocaine may lead to problems putting the brakes on behaviors with bad outcomes and so hinder their ability to abstain, says Dr. Adinoff. The less active medial area in women may reflect a blunted drug reward, he adds.

While his findings are likely to be relevant for individuals in early abstinence, Dr. Adinoff notes that they may not apply

**LOCAL LULLS** Abstinent cocaine abusers show gender-specific reduction of blood flow (blue) in the OFC. Below, differences between a male brain (left) and a female brain (right).



to individuals in later stages of recovery. “The participants in our study had only been abstinent 2 to 4 weeks,” he says. “Scientists need to examine whether the depressed neural activity we observed among cocaine abusers recovers with long-term abstinence.”

“Future research might examine whether regional differences influence treatment strategies and recovery success,” notes Dr. Harold Gordon of NIDA’s Division of Clinical Neuroscience and Behavioral Research.

Dr. Adinoff concurs, suggesting that through understanding these differences, treatment providers may eventually be able to tailor gender-specific therapies that promote abstinence.

**Source:** Adinoff, B., et al. Sex differences in medial and lateral orbitofrontal cortex hypoperfusion in cocaine-dependent men and women. *Gender Medicine* 3(3):206-222, 2006.

arriving from other brain areas to form a comprehensive picture of the likely consequences of acting.

**“By weakening the responses of these frontal cortex areas, chronic cocaine use may make people more prone to relapse and compulsive drug-seeking.”**

**—Dr. Geoffrey Schoenbaum**

This picture becomes the basis for a decision to respond to the cue or refrain. If the individual does respond, the OFC then compares the resulting consequences with the picture and notifies the ABL whether the latest data confirm or contradict the expectation. Completing the cycle, the ABL outcome-expectant neurons use this feedback to adjust their future responses to the cue.

The key to cocaine abusers’ persistent self-defeating behaviors is the drug’s interference with the last step in this cycle, Dr. Schoenbaum says. Feedback from the OFC is weakened by drug exposure; consequently, ABL outcome-

**COCAINE EXPOSURE REDUCED THE ABILITY OF ABL NEURONS TO CHANGE RESPONSE DURING A REVERSAL TASK** Researchers recorded effect on individual ABL neurons during the two-odor, go/no-go discrimination and reversal tasks.

	Changed Response	Failed to Change Response	Became Nonselective
Cocaine-exposed Rats	15%	27%	58%
Unexposed Rats	48%	3%	48%

expectant neurons fail to change their responses. Instead, they persist in established firing patterns, continuing to signal outdated information to the OFC, and become a hindrance rather than a help to good decisionmaking.

“Cocaine renders the OFC and other frontal cortex areas’ messages about likely outcomes less effective. Such signals both guide behavior and facilitate learning when things don’t go as expected. By weakening the responses of these frontal cortex areas, chronic cocaine use may make people more prone to relapse and compulsive drug-seeking,” says Dr. Schoenbaum.

“A person in drug abuse treatment is trying to change his or her behavior, yet these animal findings suggest that

cocaine exposure ossifies a neural circuit likely involved in these changes,” says Dr. Susan Volman of NIDA’s Division of Basic Neuroscience and Behavioral Research. “Scientists may someday develop medications that enhance neural flexibility and facilitate reengagement of cognitive circuits, which would help behavioral therapy lessons sink in.”

Dr. Elliot Stein of NIDA’s Intramural Research Program, who is performing brain imaging of cocaine abusers as they do reversal learning tasks, agrees: “If the drug-exposed brain lacks plasticity for new learning, then restoring

the functional integrity of the circuit may increase the effectiveness of behavioral interventions.”

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## Low Dopamine Receptor Availability May Promote Cocaine Addiction

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

By Lori Whitten, *NIDA NOTES* Staff Writer

In a study with rhesus monkeys, Dr. Michael Nader and colleagues at Wake Forest University recently showed that cocaine lowers availability of the dopamine D<sub>2</sub> 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 D<sub>2</sub> 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.

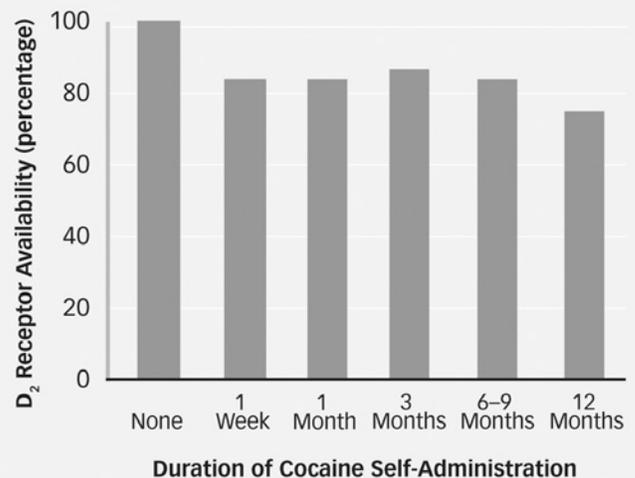
### Receptor Availability and Cocaine Exposure

The D<sub>2</sub> 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 D<sub>2</sub> 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 D<sub>2</sub> receptors a person has free affects how strongly he or she responds to the stimulus.

Imaging studies of the human brain have found reduced levels of available D<sub>2</sub> 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 D<sub>2</sub> receptors among abusers of heroin, nicotine, amphetamine, and alcohol. Lower D<sub>2</sub> receptor availability has also been observed in other populations, such as the severely obese. So, findings on D<sub>2</sub> receptor availability may be relevant to a wide range of addictions and conditions.

To measure monkeys' D<sub>2</sub> 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 D<sub>2</sub> function. Over the course of a

COCAINE REDUCES AVAILABILITY OF D<sub>2</sub> RECEPTORS



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 D<sub>2</sub> receptor availability for a year.

The monkeys whose PET scans had revealed lower D<sub>2</sub> receptor availability at baseline testing before their initial cocaine exposure self-administered cocaine at higher rates. This finding suggests that lower D<sub>2</sub> 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 D<sub>2</sub> receptor availability, self-administered more cocaine than dominant monkeys, which have higher D<sub>2</sub> receptor availability.

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***This finding suggests that lower D<sub>2</sub> receptor availability increases vulnerability to cocaine reward.***

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“This result, as well as findings of other studies, indicates that low D<sub>2</sub> 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 D<sub>2</sub> receptors, and this augments the high.”

#### **Variable Recovery**

PET scans obtained at intervals throughout the trial revealed a rapid and marked suppressive effect of cocaine on D<sub>2</sub> 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, D<sub>2</sub> receptor availability returned to baseline values by the third week of abstinence.

The picture was more complex, however, in five monkeys that self-administered cocaine for a year. At that time, D<sub>2</sub> 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 D<sub>2</sub> 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 D<sub>2</sub> receptor availability and how often monkeys pressed the food lever. This suggests that low D<sub>2</sub> receptor availability disposes individuals to seek the cocaine experience specifically, rather than rewarding experiences in general.

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



A clue to why recovery is more difficult for some individuals than others may come from the two monkeys whose D<sub>2</sub> 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 D<sub>2</sub> receptor availability in response to cocaine,” says Dr. Nader.

The team’s findings and those of others suggest that therapies that elevate D<sub>2</sub> 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 D<sub>2</sub> receptors. “My colleagues and I are most intrigued by an environmental enrichment strategy for increasing D<sub>2</sub> 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 D<sub>2</sub> receptor availability

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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").

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 D<sub>2</sub> 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.

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## Aripiprazole Prevents Rats From Resuming Cocaine Seeking

A medication prescribed for schizophrenia and manic phases of bipolar disorder shows promise as a cocaine addiction treatment.

By Lori Whitten, *NIDA NOTES* Staff Writer

The antipsychotic medication aripiprazole appears to reduce cocaine craving in small studies of addicted individuals with schizophrenia and bipolar disorder. A recent NIDA-funded experiment suggests that aripiprazole may help not only those very-difficult-to-treat individuals, but others as well, to maintain abstinence from the stimulant.

Drs. Ronald See and Matthew Feltenstein of the Medical University of South Carolina found that rats treated with aripiprazole were less likely than untreated rats to resume cocaine self-administration after a period of abstinence. The finding indicates that the medication reduces cocaine seeking directly rather than as a byproduct of altering psychotic symptoms or processes. Therefore, the researchers speculate, cocaine abusers who do not have concurrent psychotic illness may also benefit from aripiprazole.

### Indifference to Cocaine With Few Side Effects

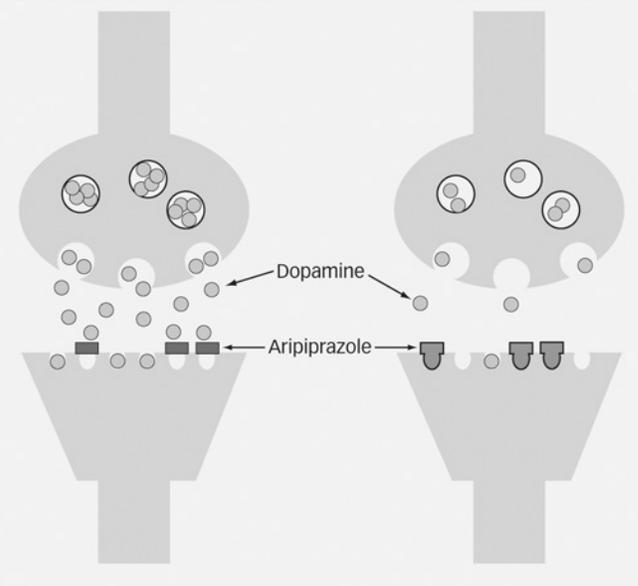
The researchers subjected rats to a protocol that simulates drug use, followed by the establishment of stable abstinence, and finally a test of the animals' vulnerability to relapse. Animals that are vulnerable respond to a relapse trigger—a cocaine-associated cue or a priming dose of the drug—by pressing a lever they previously used to self-administer the drug. The more vulnerable an animal is, the more often it will press the lever.

Rats given the lowest effective dose of aripiprazole (0.25 mg/kg) before the priming dose of cocaine pressed the lever associated with cocaine 50 percent as often as control rats did. The higher the dose of aripiprazole, the less the rats responded to the relapse triggers. For example, after the drug trigger, rats given the highest dose of aripiprazole (15 mg/kg) pressed the lever associated with cocaine only 9 percent as often as the rats receiving no aripiprazole.

To rule out the possibility that aripiprazole reduced the rats' cocaine seeking through general effects—such as sedation or lethargy—that would be undesirable in a medication, the investigators conducted further trials that showed:

- *Aripiprazole does not sedate animals to the point where they are too tired to approach and press levers for rewards.* During the protocol that mimicked relapse,

**ARIPIPRAZOLE ALLEVIATES DOPAMINE IMBALANCE THAT PROMOTES RELAPSE** According to researchers, cocaine relapse may be fostered by high dopamine concentrations in the nucleus accumbens, one of the brain's reward centers, and low concentrations in the prefrontal cortex. Aripiprazole simultaneously blocks dopamine receptors (left) in brain regions with high concentrations of the neurochemical and stimulates receptors (right) in regions where concentrations are low.



the lowest medication doses that attenuated lever pressing did not suppress locomotor activity. Higher doses (1 mg/kg and 5 mg/kg) reduced spontaneous and cocaine-induced locomotor activity only modestly. Furthermore, while aripiprazole-treated rats pressed the drug-linked lever less often, they continued to press another lever, which delivered nothing at all, as often as before.

- *Aripiprazole does not make rats indifferent to rewards from all activities, including natural, healthy ones.* Aripiprazole did not reduce the enthusiasm with which rats pressed levers to obtain food, so it did not seem to blunt their natural pleasure responses. In addition, when the researchers put animals through a protocol that simulates ongoing drug use, rather than recovery from an addiction, the animals pressed levers to obtain cocaine infusions just as avidly after receiv-

ing aripiprazole as after saline. This result indicates that while the medication may help individuals maintain abstinence, it is unlikely to diminish ongoing binge cocaine abuse.

“Aripiprazole’s minimal effect on rats’ motor activity and other behaviors is consistent with its good safety profile and general acceptance among patients as a psychiatric medication,” says Dr. See. “We find it encouraging that low doses block drug seeking and seem to have no other discernible effects on the animals. Taken together, our findings suggest that aripiprazole may selectively reduce drug-seeking behavior and is a promising candidate medication for preventing cocaine relapse.”

### A Selective Stabilizer

Dr. See and colleagues focused on aripiprazole for practical reasons: It is generally safe, it is already on the market, and its pharmacological action suggests the potential to reduce relapse. Aripiprazole preferentially binds to dopamine receptors D2 and D3, which are proteins on brain cell surfaces that mediate dopamine’s effects on cellular activity. The drug has different effects, depending on the amount of dopamine present. The overall effect is neurochemical modulation: Aripiprazole quiets hyperactive neurons and stimulates sluggish ones through both pre-synaptic and postsynaptic mechanisms, according to Dr. See. Such stabilization seems to account for the efficacy of aripiprazole as a psychiatric medication and may also underlie its benefit as a relapse-prevention agent.

“As a neurochemical stabilizer, aripiprazole most likely reduces excess dopamine activity in the mesolimbic reward

circuit brought about by drug abuse,” says Dr. See. “The medication also may simultaneously boost dopamine in the cortex, particularly the prefrontal circuits, thereby enhancing the ability to suppress the desire for drugs.” Although aripiprazole also acts at serotonin receptors, pharmacologists currently consider dopamine stabilization to be its main therapeutic action.

To evaluate the full extent of aripiprazole’s promise, it must still be determined whether the medication could be used to treat addiction to other psychostimulants besides cocaine, notes Dr. Cora Lee Wetherington of NIDA’s Division of Basic Neuroscience and Behavioral Research. Dr. See notes that his team plans to perform animal tests of the drug’s effect on methamphetamine.

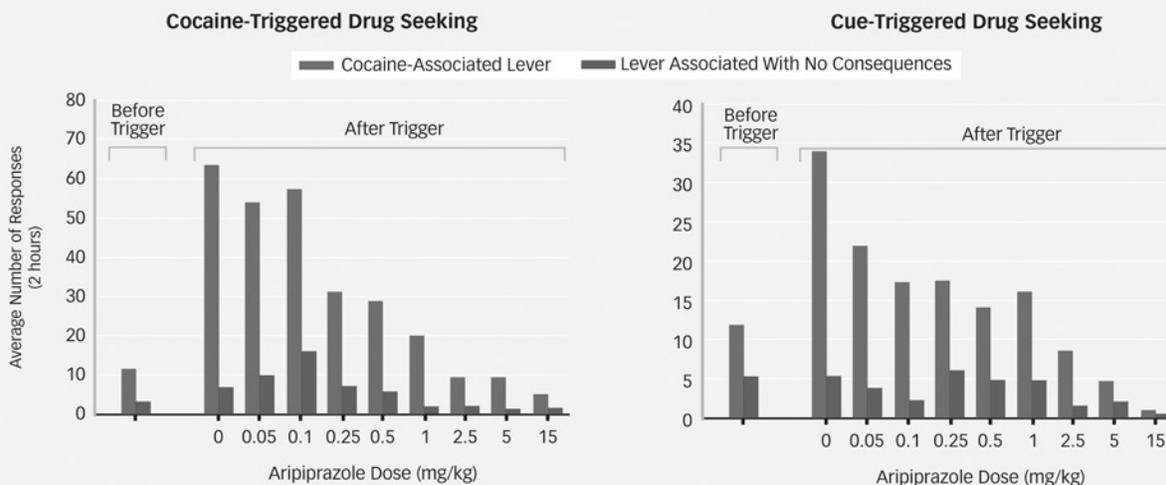
With regard to cocaine, Dr. Wetherington says, “the results of Dr. See’s animal study suggest that aripiprazole may help prevent relapse in cocaine abusers both with and without psychiatric conditions. The work lays the groundwork for future clinical research.”

Says Dr. See, “We hope to use brain imaging to examine aripiprazole’s effects on cocaine abusers’ responses to drug cues—to find out whether it dampens brain activity related to such cues. If so, that would also support the idea that the medication helps prevent relapse.”

### Source

- Feltenstein, M.W., Altar, C.A., and See, R.E. Aripiprazole blocks reinstatement of cocaine seeking in an animal model of relapse. *Biological Psychiatry* 61(5):582-590, 2007. [NN](#)

**ARIPIPRAZOLE ATTENUATES RETURN TO COCAINE SEEKING** To induce renewed drug seeking, rats were given either a small amount of cocaine or a cue of a light and sound they had previously learned to associate with the drug. The higher the dose of aripiprazole a rat received, the less often it pressed a lever that had delivered cocaine during training. Each test group contained 11 to 15 animals.



## Long-Term Cocaine Self-Administration Depresses Brain Activity

Neural activity of monkeys diminishes in regions linked with cognition and emotion.

By Lori Whitten, *NIDA NOTES* Staff Writer

Chronic exposure to cocaine depresses neural activity. Initially, the effect shows up mostly in the brain's reward areas. With longer exposure, however, neural depression spreads to circuits that form cognitive and emotional memories and associations, according to NIDA-funded research by Drs. Thomas J.R. Beveridge and Linda J. Porrino and colleagues at the Wake Forest University School of Medicine.

### Wider Effects With Longer Exposure

The researchers trained 14 male monkeys to press a lever for a reward. Six monkeys received banana-flavored food morsels, and eight received an infusion of cocaine (either 0.03 mg/kg or 0.3 mg/kg). Each monkey received up to 30 portions of food or infusions of cocaine daily for either 5 or 100 days. The 100-day trial, much longer than most other studies of drug use in primates, closely mimicked chronic cocaine abuse among people. For monkeys in the high-dose group, each session ended when they self-administered a dose equivalent to a person taking roughly 0.5-1.0 gram of cocaine per day. The researchers estimate that their experiment models a person heavily abusing cocaine daily for roughly 1 year.

After each monkey's final session, Dr. Porrino's team mapped its rate of cerebral glucose metabolism—the primary indicator of cerebral energy expenditure. The researchers injected a radiolabeled form of glucose (2-[14C]deoxyglucose; 2-DG) and, using autoradiography, obtained images that showed how much fuel different brain areas were utilizing (see image). Greater glucose metabolism indicates greater neural activity.

All the monkeys that had self-administered cocaine showed some localized depression of glucose metabolism. In the monkeys that self-administered cocaine daily for just 5 days, neural depression was largely restricted to pleasure and motivation areas, especially the reward circuit and areas that process expectations of rewards.

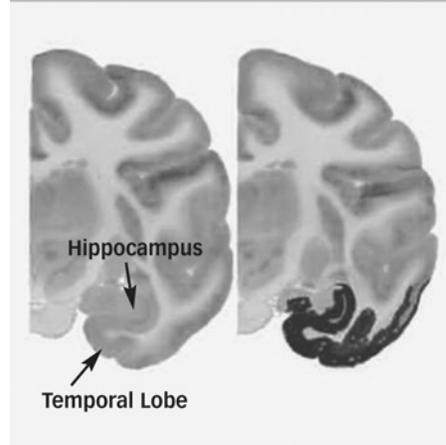
In the 100-day test, animals that had received the high dose of the drug revealed less neural activity in 40 of the 77 brain regions analyzed as compared with animals that had received only food morsels (see table). The high-dose monkeys incurred a 16 percent drop, on average, in overall cerebral glucose metabolism. The low dose of cocaine depressed metabolism in 14 of the regions, but not overall.

The tests suggest that with longer exposure to cocaine, reductions in neural activity expand within and beyond the pleasure and motivation centers, says Dr. Porrino. "Within the structure called the striatum, the blunting of activity spreads from the nucleus accumbens, a reward area, to the caudate-putamen, which controls behavior based on repetitive action," she says. Long-term cocaine use also depressed memory and information-processing areas.

The findings accord well with those of human imaging studies, which have found general depression in cerebral blood flow among chronic cocaine abusers compared with nonabusers. By using animals, however, Dr. Porrino eliminated two sources of uncertainty in those clinical studies: differences in metabolic rates that may have predated cocaine abuse and abuse of drugs other than cocaine. "My team can directly attribute to cocaine the depressed brain metabolism observed in the study," says Dr. Porrino.

"Our 100-day experimental protocol for rhesus monkeys gives a good picture of what might happen in the brains of cocaine abusers," she says. "Some addiction researchers believe that the shift in activity within the striatum may, in part, underlie the progression from voluntary drug taking to addiction. Moreover, human imaging research has linked drug craving with the amygdala and insula, temporal lobe areas depressed by cocaine in our study."

**LONG-TERM COCAINE EXPOSURE BLUNTS TEMPORAL LOBE AREAS IN MONKEYS** Blue coloring in these images represents areas of the temporal lobe that are less active after cocaine self-administration than after food self-administration. After 5 days of cocaine self-administration (left image), a monkey still shows normal activity in the temporal lobe area. In contrast, a monkey that self-administered cocaine for 100 days (right image) demonstrates lowered activity.



“The reduced activity of the temporal lobe indicates that this structure is somehow compromised,” says Dr. Nancy Pilotte of NIDA’s Division of Basic Neuroscience and Behavioral Research. “Some of these regions mediate the ability to connect emotionally, and cocaine’s blunting of them may induce a flattened affect similar to depression symptoms that are common among chronic cocaine abusers.”

“Dr. Porrino and her colleagues have identified key brain structures affected by long-term cocaine exposure and have provided a valuable set of observations that could serve as a basis for future research,” Dr. Pilotte says. For example, she adds, researchers might now focus on those regions when gauging the effectiveness of potential medications for cocaine addiction or when measuring recovery after abstinence.

### Sources

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- Porrino, L.J., et al. The effects of cocaine: A shifting target over the course of addiction. *Progress in Neuropsychopharmacology and Biological Psychiatry* 31(8):1593-1600, 2007. **NN**

COCAINE SELF-ADMINISTERED BY MONKEYS FOR 100 DAYS DEPRESSES NEURAL ACTIVITY IN SPECIFIC BRAIN AREAS.		
Name of area	Selected roles in behavior	Depression of metabolic activity* (percentage)
Nucleus accumbens (ventral striatum)	Processes reward and motivation	16–31
Caudate-putamen (dorsal striatum)	Controls behaviors based on repetitive action	10–23
Hypothalamus	Controls eating, fighting, mating, and sleep	18–22
Insula	Translates body signals into subjective feelings	17–19
Hippocampus	Consolidates memories and influences mood	15–23
Amygdala	Forms emotional and motivational memories, e.g., linking a cue and a drug to produce craving	13–19
Temporal cortex areas	Process emotional and cognitive information, e.g., recognition and short-term memory	17–22

\* Animals self-administering cocaine at either dose were compared with animals self-administering food.

## Methadone Reduces Rats' Cocaine Seeking

High-dose methadone undermines animals' motivation to acquire cocaine.

By *NIDA NOTES* Staff

Methadone may prove to be an effective treatment for cocaine as well as opioid abuse, if the results of a recent study with rats, funded by NIDA and the Canadian Institutes of Health Research, can be replicated and applied to people. The animals' cocaine seeking dropped in response to methadone given in doses that produce blood levels equivalent to those therapeutically effective for opioid addiction. Methadone at more than twice that dose abolished cocaine seeking.

"Methadone is the primary drug used to treat opiate dependence worldwide, yet there is still so much to find out about it," says Dr. Francesco Leri of the University of Guelph in Ontario, Canada. "My colleagues and I are exploring the effects of maintaining relatively stable doses of methadone over time in rats to discover all of the benefits and properties of this valuable medication."

### Extinguishing Rats' Motivation

Clinical trials have shown that people who take high-dose methadone for heroin addiction and who are also addicted to cocaine decrease their abuse of both drugs. To Dr. Leri, that observation suggested that methadone might have unexploited potential as a medication to treat cocaine abuse in patients both with and without histories of opioid abuse. Accordingly, with colleagues at Concordia University in Montreal and

Rockefeller University in New York, Dr. Leri set out to better understand methadone's effect on cocaine seeking.

The team first tested whether methadone would suppress the normal tendency of rats to seek cocaine once they have been repeatedly exposed to the stimulant. To prepare their animals for the test, the researchers put some on methadone (20 or 55 mg/kg/day) via implanted mini-pumps and gave others saline by the same route. During these regimens, for 2 weeks, the researchers trained the animals to associate one designated chamber with cocaine injections and another with saline injections. Daily for 3 days, they injected each animal once with cocaine (1, 5, or 20 mg/kg) and once with saline. Immediately after

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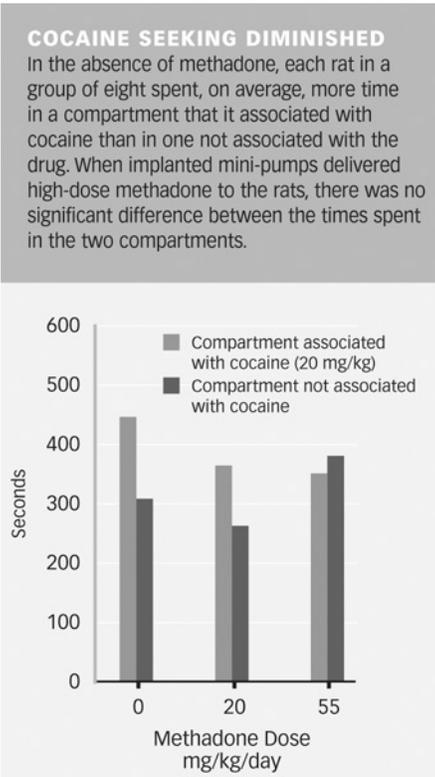
***"Overall, our results support the usefulness of high-dose methadone as a pharmacological tool to reduce severe cocaine abuse in opioid-dependent individuals."-Dr. Francesco Leri***

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each cocaine injection, they placed the animal in the first chamber; after each saline injection, they placed it in the second chamber.

On the day of the test, the researchers placed each rat between the two chambers without giving it any cocaine or saline, and monitored where it went. Among the animals given the highest dose of cocaine, those that received no methadone showed a strong preference for the cocaine-associated chamber; those that received the lower methadone dose showed less preference; and those maintained on the higher methadone dose, no preference at all, indicating a total loss of motivation to seek cocaine (see graph).

Another experiment by Dr. Leri's team assessed methadone's impact on cocaine seeking by measuring how hard rats will work to obtain the drug intravenously. They first trained rats to press a lever for cocaine, then implanted mini-pumps: Eight animals received 30 mg/kg/day of methadone, while another six received only saline. The



rats were allowed to self-administer cocaine, but the system was programmed to require progressively more presses before it would release each successive infusion. The eight methadone-treated animals gave up pressing the cocaine lever after six presses, on average, whereas the rats that did not receive methadone continued to press it more than 30 times to receive a single dose (see graph).

Some scientists have suggested that methadone-induced sluggishness saps individuals' initiative to seek cocaine. But Dr. Leri asserts that other behavioral tests by his team rule out this explanation. For example, methadone did not alter the animals' general activity, food consumption, or response to heat-generated pain.

"Overall, our results support the usefulness of high-dose methadone as a pharmacological tool to reduce severe cocaine abuse in opioid-dependent individuals and possibly in the management of addiction to only cocaine," Dr. Leri says.

Although the study found high-dose methadone to be effective in this regard, the highest doses of methadone tested in rats produced blood concentrations of the drug more than twice as high as those achieved in people undergoing standard methadone therapy. "To determine whether higher levels of methadone can be efficacious without producing adverse effects, we need clinical research on doses that are higher than customarily used in drug abusers," says Dr. Nancy Pilotte, of NIDA's Division of Basic Neuroscience and Behavioral Research.

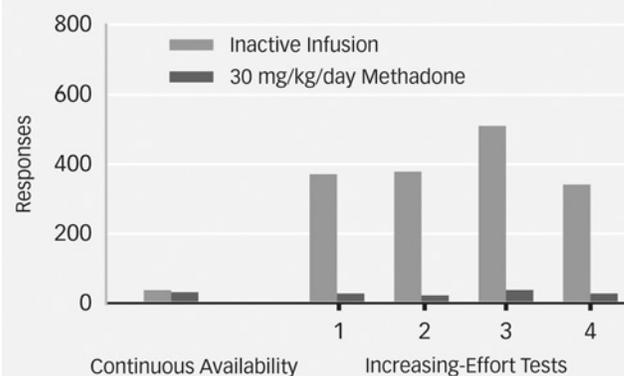
### Brain Correlates

Methadone helps heroin abusers abstain from opioids by partially stimulating the brain's mu-opioid receptors, an effect that keeps the symptoms of withdrawal at bay and also blocks the rewarding effects of other opioids. But it is not clear how methadone suppresses cocaine seeking. Methadone does not, for example, directly interact with the dopamine transporter, the brain protein that is primarily responsible for the cocaine high.

Dr. Leri suspects that the mu-opioid receptor, which is the site where methadone exerts its primary activity against opioid addiction, also plays a role in the medication's potentially therapeutic effect on cocaine addiction. In support of this idea, he and collaborators at Rockefeller University in New York City showed that cocaine increases production of the mu-opioid receptor in the nucleus accumbens, a key brain area involved in reward and addiction. Methadone, they also found, counteracts these increases.

In the experiments, rats exposed to three injections of 5 or 20 mg/kg doses of cocaine were found to have more mu-opioid receptor messenger RNA (mRNA)—an indicator of receptor production rates—than animals exposed

**RATS RECEIVING METHADONE EXPEND LITTLE EFFORT TO GAIN COCAINE** When rats were required to respond with more and more lever presses to receive cocaine, the six animals infused with an inactive substance dramatically increased their average number of responses, while the eight animals infused with methadone kept their responses at the same level as their earlier responses to continuously available cocaine.



to three injected doses of the drug at 1 mg/kg. These elevations were less pronounced, however, in rats that were being maintained on 20 mg/day of methadone at the time of the cocaine exposures. Moreover, rats exposed to cocaine while being maintained on 55 mg/kg/day of methadone had mu-opioid mRNA levels that were indistinguishable from those of rats that received no cocaine.

From these results, the researchers hypothesize that methadone probably blocks cocaine seeking by inhibiting cocaine-induced enhancement of mu-opioid receptor production. Other explanations may be possible, however, as enhancing receptor production is not methadone's only effect on brain chemistry. Among its other influences, it boosts the body's natural opioids, the endorphins. Dr. Mary Jeanne Kreek of Rockefeller University says, "We wonder whether people who are dependent on both heroin and cocaine respond well to methadone because methadone reduces the number of mu-opioid receptors in the reward system of their brains or whether they respond because cocaine depletes endorphins and methadone brings the endorphins back."

"Methadone and the mu-opioid antagonist, naltrexone, which blocks the mu receptor and its associated responses, can both be considered as treatments for cocaine abuse, as both decrease the availability of the mu-opiate receptor," says Dr. Pilotte. "Methadone may even be the better treatment as it does not force the client into an uncomfortable state of withdrawal as it decreases the incentive to take cocaine."

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## Sources

- Leri, F., et al. High-dose methadone maintenance in rats: Effects on cocaine self-administration and behavioral side effects. *Neuropsychopharmacology* 32(11):2290-2300, 2007.
- Leri, F., et al. Effects of high-dose methadone maintenance on cocaine place conditioning, cocaine self-administration, and mu-opioid receptor mRNA expression in the rat brain. *Neuropsychopharmacology* 31(7):1462-1474, 2006. **NN**

## Brain Proteins Differ in Cocaine-Overdose Victims

Scientists have found differences in protein concentrations in the brain pleasure centers of 10 people who died from cocaine overdose as compared with 10 people who did not abuse the drug. Dr. Scott Hemby and colleagues at Wake Forest University and the University of Miami Schools of Medicine used mass spectrometry to measure more than 1,400 proteins in post-mortem tissue samples from the nucleus accumbens. Levels of roughly 50 proteins were found to be either higher or lower in the cocaine abusers. These proteins participate in basic neurobiological processes such as forming cellular structures, strengthening neuronal connections, sending chemical messages between cells, deriving energy from glucose, and protecting cells from injury. Such information may point scientists toward new insights into the molecular mechanisms and consequences of cocaine addiction.

### Source

- *Molecular Psychiatry* 12(1):55-73, 2007. **NN**

## Fewer Young Adults Abuse Cocaine and Methamphetamine, National Survey Finds

The percentage of young adults who said they were abusing cocaine or methamphetamine dropped substantially from 2006 to 2007, according to the 2007 National Survey on Drug Use and Health (NSDUH), published in September 2008. Overall drug abuse, however, remained constant: According to the survey, an estimated 19.9 million Americans age 12 and over used an illicit drug in the previous month. That rate has held steady since 2002.

As in past years, young adults (aged 18-25) reported the highest rates of substance abuse. About 20 percent said they abused one or more illicit drugs; 16.4 percent said they abused marijuana, which topped the list of abused drugs in this cohort. Abuse rates for marijuana and most of the other drugs have changed little in the past 6 years. However, the decline in abuse of the stimulants cocaine and methamphetamine in this group runs counter to that pattern. In 2007, for example, 1.7 percent of the young adults reported cocaine abuse, a 23 percent decline from the previous year. Methamphetamine abuse in this age group dropped by a third, to 0.4 percent.

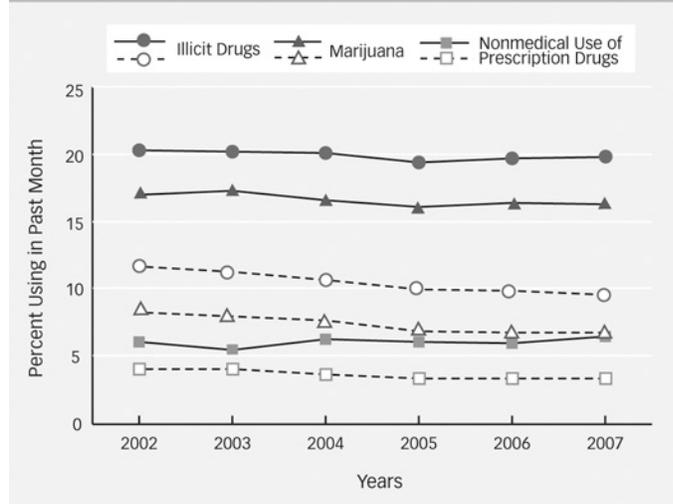
By contrast, 12- to 17-year-olds have reported a steady decline in overall illicit drug use, from 11.6 percent in 2002 to 9.5 percent in 2007. Driving the decline in this cohort has been an 18 percent drop in marijuana use, from 8.2 percent in 2002 to 6.7 percent in 2007. Inhalants are the only drug category that showed no decline among adolescents over that 6-year period, although rates for some drugs have leveled off since 2005.

Rates of drug abuse tend to decline steadily after the age of 25. However, as more baby boomers (people born between 1946 and 1964) enter the 50-59 age range, illicit drug use in that group has risen, jumping from 2.7 percent in 2002 to 5 percent in 2007. "Illicit drug use has historically been more prevalent in the baby boomer cohort. As its members age into the 50-59 age category, the prevalence increases relative to prior cohorts in this age group," says Dr. Marsha Lopez of NIDA's Division of Epidemiology, Services and Prevention Research.

Marijuana remains the most commonly used illicit drug across the survey, with an estimated 14.4 million past-month users. In 2007, roughly 2.1 million people smoked marijuana for the first time, and a similar number started

### ILLICIT DRUG USE AMONG YOUTHS AND YOUNG ADULTS

Youths (age 12 to 17) have lower rates of drug use than young adults (age 18 to 25). Youth rates (open symbols, broken lines) have fallen gradually, while the young adult (filled symbols, solid lines) rates have remained level.



using prescription painkillers for nonmedical purposes; these drugs drew more initiates last year than any other. Of the estimated 6.9 million people who used prescription psychotherapeutic drugs nonmedically, 5.2 million chose painkillers, representing a 16 percent rise in nonmedical use of these drugs since 2004. On a positive note, the 2007 survey found a significant 1-year decline in the non-medical use of prescribed stimulants.

In 2007, as in previous years, men reported higher rates of past-month illicit drug use than women (10.4 percent versus 5.8 percent). Among ethnic groups, American Indians/Alaska natives had the highest rate of illicit drug use (12.6 percent) of any racial/ethnic group, followed by multi-racial individuals (11.8 percent), African-Americans (9.5 percent), whites (8.2 percent), Hispanics (6.6 percent), and Asians (4.2 percent). No group had a significant change from the previous year.

The trends determined by NSDUH for adolescents and young adults are generally consistent with those reported by the NIDA-funded Monitoring the Future survey.

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(For more information, see *NIDA Notes*, Volume 21, Number 5, March 2008, page 15). The survey, based on the responses of 67,500 participants, is available online at [www.oas.samhsa.gov/NSDUH/latest.htm](http://www.oas.samhsa.gov/NSDUH/latest.htm). Hard copies can be ordered free by calling (800) 729-6686.

**Source**

- Substance Abuse and Mental Health Services Administration, 2008. Results from the 2007 *National Survey on Drug Use and Health: National Findings* (Office of Applied Studies, DHHS Publication No. SMA 08-4343). Rockville, MD: SAMHSA. **NN**

## 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.

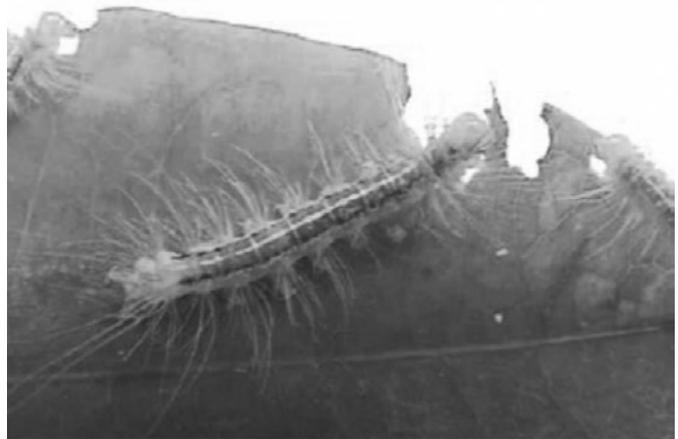
Scientists generally believe that cocaine produces its high by preventing DATs from regulating dopamine levels in the brain's reward system, resulting in a euphoria-producing buildup of the neurotransmitter in the nucleus accumbens (NAc). If an animal reliant on coca for nutrition were to be subject 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.

### 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

**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.



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.

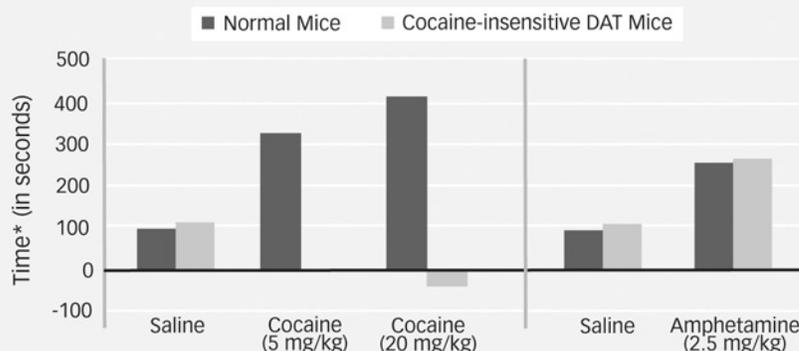
Dr. Gu's team is now seeking to identify a chemical compound that will prevent human DATs—like the mouse's altered DAT—from responding to cocaine. Such a compound would eliminate the drug high and limit the frequency and length of relapses. Yet it would not interfere with the DAT's ability to regulate 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.

#### 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).



\*Time indicates preference for the chamber where mice received the injections.

"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."

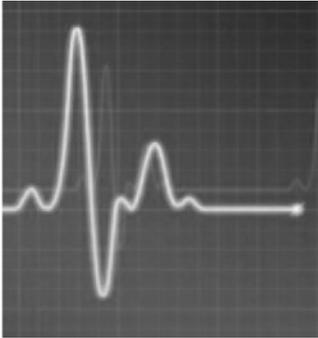
In light of their work with the mutants, the researchers now attribute the persistence of cocaine response in DAT-less mice to adaptation. "The brains of DAT knock-out mice seem to undergo significant adaptive neurobiological changes that alter how cocaine produces its effects," says Dr. Gu.

"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. **NN**

## Long-Term Cocaine Abuse Linked With Impaired Heart Function



Long-term regular cocaine abuse impairs cardiac left ventricular function in African-Americans, say NIDA-funded researchers Dr. Shenghan Lai and colleagues at The Johns Hopkins Medical Institutions. Magnetic resonance imaging of heart muscle contractions disclosed lower pumping efficiency in areas of the left ventricular wall among 32 African-Americans who abused cocaine compared with 14 nonabusers. The study participants, men and women aged 25 to 54, were all in good health with no signs of heart disease; the findings suggest that prolonged exposure to the drug may cause subclinical impairment that increases risk for cardiac events. Acute cocaine abuse has previously been associated with several cardiac complications, including arrhythmia, ruptured aorta, heart attack, and sudden death.

### Source

- *American Journal of Cardiology* 97(7):1085-1088, 2006. **NN**

## Cocaine Can Mobilize Stored Dopamine

Cocaine increases dopamine levels primarily by preventing the neurochemical from being transported back into its releasing cell, leaving more outside the neuron, where it contributes to the drug's euphoric effects. Dr. R. Mark Wightman and colleagues of the University of North Carolina at Chapel Hill and Dr. George Augustine of Duke University have recently shown that cocaine also can tap into an intracellular dopamine reserve pool. As far back as the 1970s, some researchers suspected this could occur, but they could not confirm it. Now, thanks to advances in molecular genetics and techniques to study neurotransmission, scientists have learned in studies with mice that proteins called synapsins, under the control of three genes, lock up the reserve pool by tethering its vesicles to the neuron's internal structural framework. When the cell is called upon to release extraordinary amounts of the neurotransmitter, a chemical reaction relaxes the synapsin's grasp on reserve pool vesicles, allowing them to join the releasable pool. "Although this extra mechanism is definitely not the most important action of cocaine, it points to a way that the drug can switch dopamine cells into a sustained-release mode, promoting the activation that dopamine exerts on its target neurons," says Dr. Wightman.

### Source

- *The Journal of Neuroscience* 26(12):3206-3209, 2006. **NN**

## Chronic Cocaine Abusers Have Occult Insomnia in Early Abstinence

Patients in early treatment may not recognize their own sleep impairment or its impact on their performance.

By Lori Whitten, *NIDA NOTES* Staff Writer

Chronic cocaine abusers may feel they are sleeping better and better during early abstinence, but objective measures show the opposite happens. A team of NIDA-funded addiction and sleep researchers at the Yale and Harvard Schools of Medicine found evidence of insomnia, with learning and attentional deficits, on days of taking the drug and after 2.5 weeks of abstinence. The researchers believe cocaine may impair the brain's ability to gauge its own need for sleep, and patients' ability to benefit from early treatment may suffer as a result.

"Problems in memory and attention are linked with increased treatment dropout and likely affect patients' ability to 'take in' lessons from drug abuse counseling," says Dr. Robert Malison of Yale, a co-investigator on the study. If the results are confirmed, clinicians and patients may want to consider addressing sleep disorders in early therapy, perhaps with the use of medications or behavioral treatments.

The researchers recruited 10 men and two women aged 24 to 49 who, on average, had abused cocaine for 17 years and had used \$500 worth of the drug per week. All the participants declined an offer of drug abuse treatment. Urine tests indicated that cocaine was the only drug any of them had abused during the week before the study.

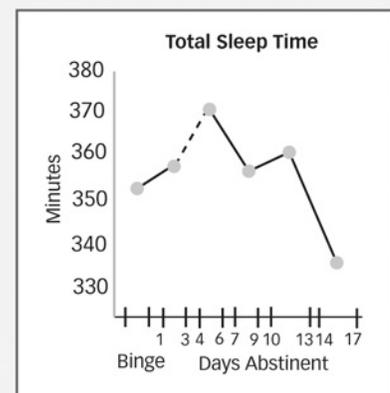
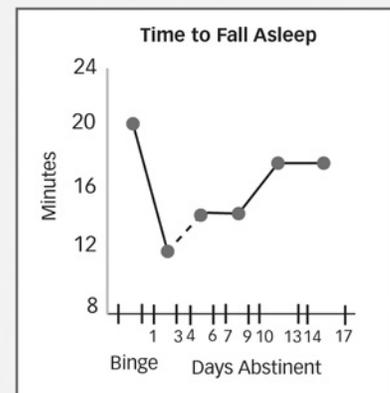
At the outset of the study, participants self-administered cocaine from a pump under physician oversight, building up to a dose of 32 mg/kg of body weight over 1.5 hours, then repeating this dose essentially at will, but no less than 5 minutes apart, for another 1.5 hours. Subsequently, they self-administered the higher dose with the same minimal restriction for 2 hours on each of three consecutive days, either on days 4-6 or 18-20. This schedule simulated chronic cocaine abusers' typical bingeing pattern of drug abuse and allowed

researchers to monitor each participant's sleep and cognitive performance for 17 days after a binge.

Research staff made sure the participants stayed awake from 7:45 AM to 9:30 PM, and let them sleep through the night. At night, the participants wore Nightcap sleep monitors, a bandana-like device that records eye and body movements that indicate whether someone is awake, asleep and dreaming, or sleeping dreamlessly. On most nights participants also wore polysomnographic (PSG) devices that continuously assessed brain activity with electroencephalography (EEG) and measured eye and muscle movements associated with different sleep stages.

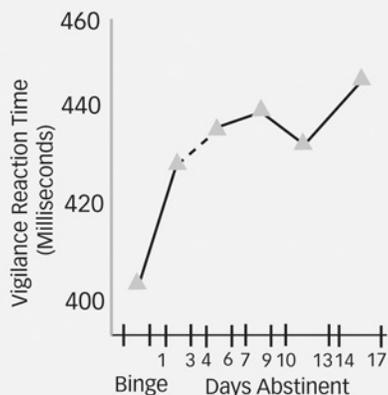
### OBJECTIVE MEASURES BELIE PATIENTS' IMPRESSIONS OF SLEEP IMPROVEMENT

Patients thought their sleep was better (left), but objective measures (right) showed that after an initial improvement they started to need longer to fall asleep and their total sleep time went down.



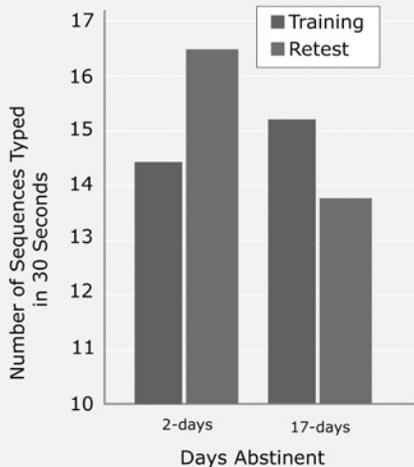
### ALERTNESS IMPAIRMENTS PARALLEL SLEEP DEFICITS

In the Digital Vigilance Test, participants were required to press a button when they saw a target number on the right side of the screen while viewing a rapidly changing number sequence in the middle of the screen. Poor performance on the task corresponded with sleep deficits at 14-17 days of abstinence.



### PERFORMANCE DECLINES WITH SLEEP QUALITY

In the Motor-Sequence Task, participants typed a five-digit sequence of four keys with their non-dominant hand, a skill that improves after a night's sleep. Cocaine abusers showed improvement after two but not 17 days of abstinence.



Combining the information gathered by these measures with participants' responses to daily questionnaires on their sleep experience and with cognitive testing, the researchers demonstrated that the participants had:

- *Sleep deficits*—After 14 to 17 days of abstinence, the study group exhibited sleep deficits on several

measures, relative to healthy, age-matched peers who participated in prior studies. For example, they had less total sleep time (336 versus 421-464 minutes) and took longer to fall asleep (19 versus 6-16 minutes).

- *Declines in sleep quantity and quality*—The time participants took to fall asleep and their total time asleep transiently improved during the first week of abstinence, but then reverted to the patterns recorded on days of cocaine taking. On abstinence days 14-17, participants took an average of 20 minutes to fall asleep (from a low of 11) and slept for 40 minutes less than their minimum. Slow-wave sleep—a deep sleep that often increases following sleep deprivation—rose during the binge and on abstinence days 10-17.
- *Lack of awareness of their sleep problems*—In contrast to the evidence of objective measures, the study participants reported steadily improving sleep from the beginning to the end of their days of abstinence.
- *Impairments in learning and attention*—As with sleep quality, participants' performance on tests of alertness and motor-skills learning initially improved and then deteriorated. On abstinence day 17, they registered their lowest scores on alertness and ability to learn a new motor skill.

### Increased Risk of Relapse

“Unlike most people with chronic insomnia, including alcoholics, cocaine abusers do not perceive sleep problems and may not ask clinicians for treatment to improve sleep,” says Dr. Malison. The problem often goes unaddressed and persists as a result, and the accompanying impairments in attention and learning may affect how well they respond to drug abuse treatment (see “Cocaine Abusers’ Cognitive Deficits Compromise

Treatment Outcomes”). Clinical studies have shown that poor objective sleep during the first 2 weeks of abstinence predicts relapse to alcohol 5 months after treatment.

In fact, the insidious nature of cocaine-related insomnia may directly trigger relapse, suggests Dr. Peter Morgan, lead investigator of the study. “Addicted people may take cocaine to improve sleep-related cognitive functioning deficits—unaware that they are abusing, in part, to ‘solve’ these problems.”

Dr. Morgan adds, “Cocaine abusers who recognize their cognitive problems often report that it takes them 6 months to a year to turn the corner—a clinical observation that points to the need for longer term studies of sleep and treatment outcomes among this population.” In addition to studies with larger numbers of participants, the investigators say there is a need to investigate possible gender differences in cocaine-related sleep problems. Dr. Morgan and his team are currently testing two medications, tiagabine and modafinil, to see if they can improve cocaine abusers' sleep and restore cognitive performance.

“Experts believe that not getting enough sleep is an unmet public health problem in the general population. These findings highlight this important problem in cocaine abusers,” says Dr. Harold Gordon of NIDA's Division of Clinical Neuroscience and Behavioral Research.

### Source

- Morgan, P.T., et al. Sleep, sleep-dependent procedural learning and vigilance in chronic cocaine users: Evidence for occult insomnia. *Drug and Alcohol Dependence* 82(3):238-249, 2006. **NN**

## Neuropeptide Promotes Drug-Seeking and Craving in Rats

Orexin emerges as a link in the chain of brain mechanisms regulating appetite for rewards.

By Lori Whitten, *NIDA NOTES* Staff Writer

Orexin, a neuropeptide that stimulates eating and regulates wakefulness, also fosters animals' drug seeking and craving responses to drugs, according to two NIDA-funded studies. The research teams, led by Drs. Glenda Harris and Gary Aston-Jones at the University of Pennsylvania and Drs. Stephanie Borgland and Antonello Bonci at the University of California, San Francisco (UCSF), used different experimental procedures and studied different drugs. Their findings, however, point to the same conclusion: Augmenting orexin increases drug seeking, while blocking it has the opposite effect.

Orexin, also called hypocretin, is produced by neurons in the hypothalamus—a brain structure that regulates hunger, thirst, sleep, and other processes essential to survival. Scientists recently discovered that people with narcolepsy lack orexin-producing neurons. The finding suggested an explanation for a striking observation made in the mid-1970s: People with narcolepsy rarely became addicted to the potent stimulants used to treat the disorder at the time. Perhaps, some scientists speculated, orexin contributes to the development of drug abuse.

### Orexin and Drug Seeking

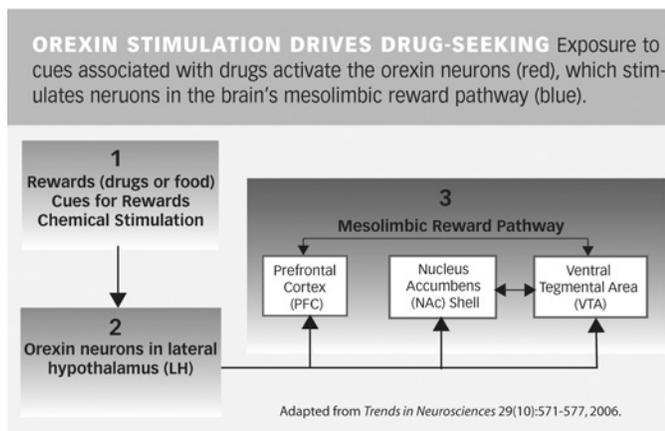
An observation in animals by Drs. Harris and Aston-Jones also seemed to suggest a possible connection. They noted that lateral hypothalamus (LH) cells in the same area as orexin neurons were activated during drug seeking using a behavioral assay called conditioned place preference (CPP; for more on CPP, see "Animal Experiments in Addiction Science"). After repeated morphine injections in one

chamber of a test cage and saline in the other, rats gravitate to the drugpaired area in an effort to re-experience the opiate effects. The time they spend in the area—their morphine place preference—indicates how intensely the drug motivates drug seeking. When Drs. Harris and Aston-Jones determined that the LH neurons activated during drug seeking produce orexin, they conducted further experiments.

The Pennsylvania researchers first demonstrated that activation of orexin neurons in the LH was tightly coupled with rats' place preferences for morphine, cocaine, and sweet food. Next, they gave a different group of rats morphine for 3 days to establish place preference, then stopped the drug and injected some rats with a compound (SB334867) that prevents orexin from interacting with brain cells. Following treatment with SB334867, rats spent 58 percent less time in the morphine-associated cage area—indicating a halving of their drug seeking. Rats given inert vehicle showed no significant change in drug seeking.

The investigators also tested orexin's impact on the tendency of a new group of rats to revert to drug seeking after CPP waned following extended testing without drug administration (extinction). In contrast to the first experiment, this time the investigators injected a compound (rat pancreatic polypeptide, rPP) that stimulates orexin neurons into the LH of some animals. These rats quickly resumed CPP—indicated by the difference in time spent in the morphine versus saline chambers—as marked as that of another group that received a morphine priming injection (353 seconds and 424 seconds for rPP and morphine, respectively). Rats that received a vehicle injection did not renew morphine CPP.

To establish that stimulation of orexin neurons by rPP, and not some other unidentified factor, was responsible for the effects in their second experiment, the investigators repeated the procedure. This time they blocked the extinction of orexin by giving the rats SB334867 prior to rPP. These rats did not resume CPP. Finally, the researchers infused orexin directly into rats' ventral tegmental area (VTA), the origin of the dopamine-rich reward pathway, and observed a resumption of drug-seeking behavior.



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## Drugs May Unsurp Feeding System

The results, although in animals, suggest that orexin promotes drug abusers' desire for drugs and their risk for relapse. "It makes sense, anatomically and physiologically, that orexin might play a role in reward-seeking and craving," says Dr. Harris, now at the Centre de Regulacio Genomica in Spain. "Neurons in this part of the brain stimulate eating; intense cravings for food and water originate here. Our findings suggest that orexin from the lateral hypothalamus affects the reward pathway. Perhaps drugs take over the brain system for feeding and craving just as they usurp neural systems for reward."

"These behavioral findings extend the team's important anatomical work differentiating two populations of orexin-producing neurons in the hypothalamus. One population, located in the lateral hypothalamus, is involved in feeding, reward, and drug seeking, while the other regulates sleep and arousal," says Dr. Susan Volman of NIDA's Division of Basic Neuroscience and Behavioral Research. "The findings identify new neural pathways involved in drug abuse, craving, and relapse, and may ultimately help scientists find more effective therapies."

## A Role in Cocaine Craving?

Drs. Borgland and Bonci and colleagues at the UCSF Ernest Gallo Clinic and Research Center demonstrated orexin effects on cocaine-related behaviors remarkably consistent with those the Pennsylvania team showed with respect to drug-related behaviors. They also provided evidence that orexin produces these effects at least in part by altering neurons in the VTA. The UCSF team used behavioral sensitization to evaluate orexin's impact on rats' responses to cocaine. Scientists generally think animals' behavioral sensitization—increased locomotor activity following repeated exposure to a drug—reflects drug-induced neural changes and corresponds to human craving for the drug. In the UCSF experiment, rats pretreated with an orexin blocker displayed only half as much increase in locomotor activity (138 percent) following five daily cocaine infusions (15 mg/kg) as rats pretreated with an inert vehicle (257 percent).

To explore the cellular bases for their behavioral observations, the UCSF group measured orexin's effects on the electrophysiological properties of dopamine-producing cells in brain slices removed from the VTA of rats. The results showed that orexin increased the number of receptors for neural excitation on the surfaces of these cells. Such strengthening of intercellular connections occurs during learning. Scientists believe it may foster the development of drug craving. When the researchers pretreated the rats with an orexin blocker, cocaine lost its ability to alter dopamine-producing cells in the VTA, suggesting that orexin may be necessary for cocaine-induced neuroplasticity and its behavioral consequences.

"Our findings point to a key role for orexin in the neural changes in the reward pathway that underlie craving and relapse," says Dr. Borgland. "The physiological alterations we observed likely influence those cells' dopamine release, perhaps affecting the activity of the reward pathway in a way that increases the likelihood of relapse. One implication of our findings is that addiction medication development efforts might do well to target orexin receptors," she says. The work of the Pennsylvania and UCSF teams points to orexin involvement in reward-seeking in general. Researchers studying the effects of orexin-blocking compounds in animal models of alcoholism and obesity have reported preliminary but promising findings. Both teams are currently determining whether giving such compounds to animals reduces self-administration of cocaine, say Dr. Bonci and Dr. Aston-Jones, the latter now at the Medical University of South Carolina.

## Sources

- Harris, G.C., Wimmer, M., and Aston-Jones, G. A role for lateral hypothalamic orexin neurons in reward seeking. *Nature* 437(7058):556-559, 2005.
- Borgland, S.L., et al. Orexin A in the VTA is critical for the induction of synaptic plasticity and behavioral sensitization to cocaine. *Neuron* 49(4):589-601, 2006. **NN**

## Gene Experiment Confirms a Suspected Cocaine Action

Building on knowledge from developmental and cancer biology, addiction researchers are learning how acute and chronic cocaine exposure regulates certain genes.

By Lori Whitten, *NIDA NOTES* Staff Writer

Cocaine produces the long-term brain changes that underlie addiction in part by activating certain genes. Dr. Eric Nestler and colleagues at the University of Texas Southwestern Medical Center and Harvard Medical School have shown that the drug achieves this activation at least in part through a process called chromatin remodeling.

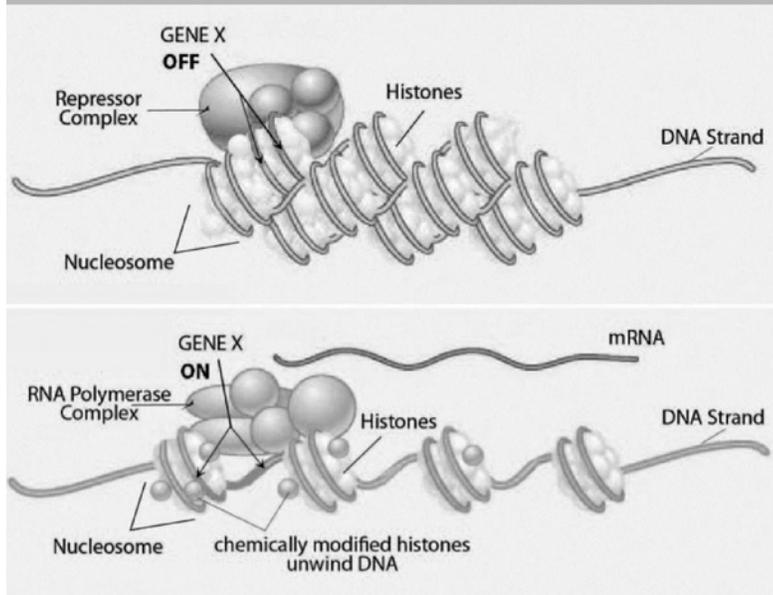
The finding opens up a new avenue for potential therapies for addiction. “Our research suggests that testing chemical compounds that reverse chromatin remodeling is a promising approach to seeking treatments for drug abuse. This is already a major strategy for cancer therapy development,” says Dr. Nestler.

### Genes Regulate Crucial Proteins

Cocaine activates the genes that provide the templates for building the proteins cFos,  $\Delta$ FosB, BDNF, and Cdk5, among others. Researchers have linked the resulting higher brain levels of some of these proteins with long-term consequences of chronic drug abuse. For example, accumulation of long-lasting  $\Delta$ FosB correlates with cocaine craving and drug self-administration in animals, and may contribute to longlasting structural changes in cocaine abusers’ brain reward systems. As researchers continue to trace out the consequences of cocaine-induced gene activation, Dr. Nestler and colleagues pursued a related inquiry: How does it happen? Their candidate explanation was chromatin remodeling, a basic mechanism cells use to alter levels of the body’s vast array of proteins to suit new circumstances and challenges (see “Experience Restructures Chromatin”).

Chromatin consists of the deoxyribonucleic acid (DNA) double helix that carries an organism’s genes wrapped around complexes of histone proteins. The unit of chromatin is called the nucleosome, and chemical processes control how tightly packed nucleosomes are. Chromatin remodeling occurs when this packing becomes more or less compact. As the nucleosomes bunch up or spread out, some genes move into positions that increase—and others into positions that decrease—their ability to interact with RNA polymerase, the enzyme that executes the first step

**CHROMATIN AND DNA HELIX FORM CHROMOSOMES** Nucleosomes slide apart during chromatin remodeling, increasing transcription factors’ access to a gene and thereby activating it. The DNA will then make mRNA, the blueprint for protein production.



in protein building. This helps determine how much of the protein blueprint by each gene will be made.

To test their hypothesis that cocaine activates genes by inducing chromatin remodeling, Dr. Nestler and his team compared tissue taken from the striatum of rats exposed to the drug and others given saline. Specifically, they assayed the tissue for the end products of two chemical reactions known to modify chromatin’s shape: acetylation and phosphoacetylation of its primary molecular components, histone 3 (H3) and histone 4 (H4). Both of these reactions remodel chromatin in ways that increase gene expression.

The findings bore out the hypothesis. Within 30 minutes of a single injection, the chromatin associated with the cFos gene in the cocaine-exposed animals contained twice as much acetylated H4 than that in the control animals, and phosphoacetylated H3 also was higher. The time course of these effects jibed with previous observations that cocaine induces a rapid, transient increase in levels of the cFos protein. They were no longer present in tissues taken 3 hours after the injection, and they stopped occur-

ring when animals were given repeated cocaine doses over an extended period. These data support scientists' conception of the *cFos* gene as an early responder to acute neural disruptions, with little or no direct role in situations of recurrent disruption.

As with *cFos*, a single cocaine injection elevated acetylated H4 in chromatin linked to the *FosB* gene, but the levels returned to baseline within 3 hours. Repeated cocaine did not induce H4 acetylation in *FosB* gene-associated chromatin, but did cause H3 acetylation. The researchers say that the switch from H4 acetylation after a single cocaine exposure to H3 acetylation after chronic exposure may mark a turning point in developing addiction.

"More research is needed to identify the specific molecular basis of this switch," says Dr. Nestler. "However, prior work in my laboratory and with collaborators is starting to fill in a picture of why H3 acetylation and *FosB*'s activation and subsequent triggering of  $\Delta$ FosB after chronic cocaine might be important. We believe that this series of molecular events, and probably others, mediate the long-term behavioral and neural changes that underlie the transition from drug abuse to addiction," says Dr. Nestler. The experiments and assays also showed:

- A single cocaine injection did not affect *BDNF* or *Cdk5* gene-associated chromatin, but chronic exposure induced H3 acetylation of both. Once initiated, the effects were long-lasting. The quantities of modified H3 in *BDNF* gene-associated chromatin in exposed animals increased from 3-fold of those of saline-treated animals at day 1 to 14-fold at day 7. Acetylated H3 related to the *Cdk5* gene were more than two-fold those of saline 1 day after the last injection, and started to return to control levels only 7 days after cocaine cessation. Such persistent and robust gene activation long after the last dose of cocaine is striking in contrast with the relatively short-lived activation observed for *cFos* and *FosB*.
- Elevations in the  $\Delta$ FosB protein selectively activated *Cdk5*—the only gene examined in the study that was turned on in this way. This finding suggests that  $\Delta$ FosB may influence histone modifications by recruiting the chemical agents of chromatin remodeling to some target genes.

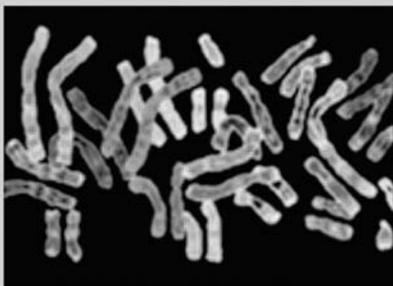
"Understanding how cocaine turns on these genes could help addiction researchers develop potential treatments that counteract the effects of drug abuse at the molecular level. Agents that reverse chromatin remodeling are available, and we are examining whether they block cocaine's cellular effects," says Dr. Nestler.

"Taken together with other studies showing that drugs induce long-term structural changes to brain cells, Dr. Nestler's findings show that chromatin remodeling is one way that such neural modification might occur. Such alterations are not necessarily permanent, and studies are needed to determine whether abstinence or other behavioral modifications further restructure chromatin to a state similar to that seen prior to drug exposure," says Dr. Joni Rutter of NIDA's Division of Basic Neuroscience and Behavioral Research. Whether nonstimulant drugs of abuse also act through chromatin remodeling is another important area for future research, she says.

### A Connection With Cocaine-Related Behavior

In other experiments, Dr. Nestler and colleagues linked chromatin remodeling to cocaine's behavioral effects by examining its role in a laboratory stand-in for human cue-induced drug seeking called conditioned place preference (CPP). By exhibiting CPP—lingering in a part of a cage where it has received a drug—an animal indicates that it is seeking more of the drug (see "Animal

## Experience Restructures Chromatin



Chromosomes (pictured) are very long, continuous pieces of DNA that contain genes that help determine an individual's identity. Humans have 23 chromosome pairs with an estimated 30,000 genes. The DNA sequence wraps around proteins that give the chromosome a structure; together, they form chromatin. Cocaine and other external agents and experiences can alter the configurations of these proteins. Depending

on the type of chemical change, the chromatin either bunches up or stretches out, activating or silencing genes along the DNA sequence.

Chromatin reshaping seems to underlie healthy adaptations such as learning and memory as well as disease processes—including cancer, seizures, schizophrenia, and depression. In another study, for example, Dr. Nestler's team found that social stress turned on a particular gene in the brains of mice through chromatin remodeling, a long-lasting change that corresponded with a behavioral indicator of depression. Antidepressant medication reversed both the behavioral sign of depression and the elevated gene activity, underscoring a key point about the modifications: experience and chemical agents can alter gene expression through chromatin remodeling, but such changes are reversible.

**COCAINE TURNS ON GENES BY ALTERING CHROMOSOMAL PROTEINS** The researchers found chemical modifications to histone 3 (H3) and histone 4 (H4)—major proteins that form the structure of chromosomes—at areas linked with four genes. Acetylation of H3 and H4 and phosphoacetylation of H3 alter the proteins' chemical structure, facilitating gene activation.

Experiment	Gene	Results					
		30 min.	1 hr.	90 min.	3 hr.	1 day	7 days
<b>Acute Cocaine</b> Rats received a single injection, either saline or cocaine (20 mg/kg).	<b>cFos</b>	Acetylated H4 Phosphoacetylated H3		Normal Histones	Normal Histones	----	
	<b>FosB</b>	Acetylated H4					
	<b>BDNF</b>	No change			No change		
	<b>Cdk5</b>	No change			No change		
<b>Chronic Cocaine</b> Rats received an injection of either saline or cocaine (20 mg/kg) daily for 7 days.	<b>cFos</b>	No change			No change		
	<b>FosB</b>	Acetylated H3	Normal Histones				
	<b>BDNF</b>	Acetylated H3				Normal Histones	
	<b>Cdk5</b>	Acetylated H3				Normal Histones	
<b>Cocaine Withdrawal</b> Rats received an injection of either saline or cocaine (20 mg/kg) daily for 7 days and did not receive the drug again.	<b>cFos</b>	Effects too transient to examine					
	<b>FosB</b>	Effects too transient to examine					
	<b>BDNF</b>	Acetylated H3: Levels rise to 3-fold those associated with saline injection after 1 day, and to 14-fold after 7 days.					
	<b>Cdk5</b>	Acetylated H3: Levels rise to 3-fold those associated with saline injection after 1 day, and return to normal after 7 days.				Normal Histones	

The investigators administered cocaine to mice daily for 4 days. Before each administration, they treated one group with a drug that enhances histone acetylation (trichostatin A, TSA) and another with a virus that expresses an enzyme that blocks this particular modification (herpes simplex virus, HSV). When placed back in the test cage on day 5, the group given TSA doubled the time spent in the drug-associated cage, on average, relative to the control group. In contrast, the group given the HSV vector lingered in the test cage for one-third of the time spent by its control group.

The findings suggest a causal link between histone acetylation in the striatum and sensitivity to cocaine's behavioral effects.

“The team had already demonstrated that chromatin remodeling plays a role in the rewarding aspects of cocaine abuse by including a group of animals that self-administered the drug in the study. Their CPP experiment further strengthens the connection between histone restructuring and behavioral aspects of addiction and suggests that agents that reverse chromatin restructuring hold promise as potential therapies,” says Dr. Rutter.

**Source**

• Kumar, A., et al. Chromatin remodeling is a key mechanism underlying cocaine-induced plasticity in striatum. *Neuron* 48(2):303-314, 2005. **NN**

Experiments in Addiction Science” *NIDA Notes*, Vol. 20, No. 5). The researchers hypothesized that augmenting or preventing histone modifications during drug administration sessions would increase or decrease CPP, respectively.

## Impacts of Drugs on Neurotransmission

The defining features of drug intoxication and addiction can be traced to disruptions in cell-to-cell signaling.

By Carl Sherman, *NIDA NOTES* Contributing Writer



Drugs of abuse alter the way people think, feel, and behave by disrupting neurotransmission, the process of communication between brain cells. Over the past few decades, studies have established that drug dependence and addiction are features of an organic brain disease caused by drugs' cumulative impacts on neurotransmission. Scientists continue to build on this essential

understanding with experiments to further elucidate the physiological bases for drug abuse vulnerability as well as the full dimensions and progression of the disease. The findings provide powerful leads to new medications and behavioral treatments.

This second article in our *NIDA Notes Reference Series* discusses the central importance of studying drugs' effects on neurotransmission and describes some of the most common experimental methods used in this research. As with other articles in the series, we provide illustrative references from articles published in *NIDA Notes*.

### What Is Transmission?

A person reads. The words on the page enter the brain through the eyes and are transformed into information that is relayed, from cell to cell, to regions that process visual input and attach meaning and memory. When inside cells, the information takes the form of an electrical signal. To cross the tiny intercellular gap that separates one cell from the next, the information takes the form of a chemical signal. The specialized chemicals that carry the signals across the intercellular gaps, or synapses, are called neurotransmitters.

The ebb and flow of neurotransmitters—neurotransmission—is thus an essential feature of the brain's response to experience and the environment. To grasp the basic idea of neurotransmission, compare the brain to a computer. A computer consists of basic units (semiconductors) that are organized into circuits; it processes information by relaying electric current from unit to unit; the amount of current and its route through the circuitry determine

the final output. The brain's corresponding basic units are the neurons—100 billion of them; the brain relays information from neuron to neuron using electricity and neurotransmitters; the volume of these signals and their routes through the organ determine what we perceive, think, feel, and do.

Of course, the brain, a living organ, is much more complex and capable than any machine. Brain cells respond with greater versatility to more types of input than any semiconductor; they also can change, grow, and reconfigure their own circuits.

### The Basic Research Questions

Neuroscientists seeking to understand why a drug is abused and the consequences of that abuse focus on two issues:

- Which neurotransmitter or neurotransmitters does it affect?
- How does it alter neurotransmission?

### Which Neurotransmitter or Neurotransmitters Does the Drug Affect?

A person's experiences when abusing a drug reflect the functional roles of the particular neurotransmitter whose activity it disrupts. Each individual neuron manufactures one or more neurotransmitters: dopamine, serotonin, acetylcholine, or any one of a dozen others that scientists have discovered to date. Each neurotransmitter is associated with particular effects depending on its distribution among the brain's various functional areas. Dopamine, for example, is highly concentrated in regions that regulate motivation and feelings of reward, accounting for its importance in compulsive behaviors such as drug abuse. A neurotransmitter's impact also depends on whether it stimulates or dampens activity in its target neurons.

Some drugs primarily disrupt one neurotransmitter or class of neurotransmitters. For example, opioid drug abusers experience changes that are similar to—but more pronounced than—those that accompany normal fluctuations in the brain's natural opioid-like neurotransmitters, endorphin and enkephalin: increased analgesia, decreased alertness, and slowed respiration (see table). Other drugs interact with more than one type of neurotransmitter. Cocaine, for example, attaches to structures that regulate dopamine, thereby producing euphoria; however, cocaine

also produces changes in norepinephrine and glutamate, which are the sources of its stimulant effects.

Because a neurotransmitter often stimulates or inhibits a cell that produces a different neurotransmitter, a drug that alters one can have secondary impacts on another. In fact, the key effect that all abused drugs appear to have in common—a dramatic increase in dopamine signaling in the nucleus accumbens (NAc), leading to euphoria and a desire to repeat the experience—is in many cases an indirect one. For example, nicotine stimulates dopamine-releasing cells directly by stimulating their acetylcholine receptors, and also indirectly by triggering higher levels of glutamate, a neurotransmitter that acts as an accelerator for neuron activity throughout the brain.<sup>1</sup>

### How Does the Drug Alter Neurotransmission?

Neurotransmission is a cyclic process that transpires in several steps utilizing specialized components of the sending and receiving cells (see “Getting the Message Across”). Identifying the precise step that a drug disrupts, and how, provides crucial insight into its impact on abusers and is key to identifying medical and behavioral interventions to inhibit, counter, or reverse the disruption.

Some drugs mimic neurotransmitters. Opioid drugs such as heroin and OxyContin, for example, chemically resemble the brain’s natural opioids sufficiently to engage and stimulate their specialized receptors. Since heroin stimulates many more receptors than the brain uses in the normal cycle of endorphin and enkephalin release and uptake, the result is a massive amplification of opioid activity. Marijuana and hashish mimic cannabinoid neurotransmitters, the most important of which is anandamide. Nicotine attaches to receptors for acetylcholine, the neurotransmitter for the cholinergic system.

Some drugs alter neurotransmission by interacting with molecular components of the sending and receiving process other than receptors. Cocaine, for example, attaches to the dopamine transporter, the molecular conduit that draws free-floating dopamine out of the synapse and back into the sending cell. As long as cocaine occupies the transporter, dopamine cannot reenter the cell by this route. It builds up in the synapse, stimulating receiving cell receptors more copiously and producing much greater dopamine impact on the receiving cells than occurs naturally. “Cocaine’s Dopamine

Connections” enumerates some of cocaine’s interactions with the mechanisms of dopamine signaling, and how they motivate abuse and contribute to dependence and addiction.

Finally, some drugs alter neurotransmission by means other than increasing or decreasing the quantity of receptors stimulated. Benzodiazepines, such as diazepam or lorazepam, enhance receiving cells’ responses when the neurotransmitter gamma-aminobutyric acid (GABA) attaches to their receptors. Benzodiazepines’ relaxation effects result from this increased sensitivity to GABA’s inhibitory impact on cellular activity.

### What Changes Occur With Chronic Drug Abuse?

During the early phase of an individual’s drug experimentation, neurotransmission normalizes as intoxication wears off and the substance leaves the brain. Eventually, however, drugs wreak changes in cellular structure and function that lead to long-lasting or permanent neurotransmission abnormalities. These alterations underlie drug tolerance, addiction, withdrawal, and other persistent consequences.

Neurotransmitter	Distribution in the Central Nervous System	Functions Affected	Drugs That Affect It
Dopamine	Midbrain, Ventral tegmental area (VTA), Cerebral cortex, Hypothalamus	Pleasure and reward Movement, Attention, Memory	Cocaine, Methamphetamine, Amphetamine. In addition, virtually all drugs of abuse directly or indirectly augment dopamine in the reward pathway
Serotonin	Midbrain, VTA, Cerebral cortex, Hypothalamus	Mood, Sleep, Sexual desire, Appetite	MDMA (ecstasy), LSD, Cocaine
Norepinephrine	Midbrain, VTA, Cerebral cortex, Hypothalamus	Sensory processing, Movement, Sleep, Mood, Memory, Anxiety	Cocaine, Methamphetamine, Amphetamine
Endogenous opioids (endorphin and enkephalin)	Widely distributed in brain but regions vary in type of receptors, Spinal cord	Analgesia, Sedation, Rate of bodily functions, Mood	Heroin, Morphine, Prescription painkillers (Oxycodone)
Acetylcholine	Hippocampus, Cerebral cortex, Thalamus, Basal ganglia, Cerebellum	Memory, Arousal, Attention, Mood	Nicotine
Endogenous cannabinoids (anandamide)	Cerebral cortex, Hippocampus, Thalamus, Basal ganglia	Movement, Cognition and memory	Marijuana
Glutamate	Widely distributed in brain	Neuron activity (increased rate), Learning, Cognition, Memory	Ketamine, Phencyclidine, Alcohol
Gamma-aminobutyric acid (GABA)	Widely distributed in brain	Neuron activity (slowed), Anxiety, Memory, Anesthesia	Sedatives, Tranquilizers, Alcohol

Some longer term changes begin as adjustments to compensate for drug-induced increases in neurotransmitter signaling intensities. For example, drug tolerance typically develops because sending cells reduce the amount of neurotransmitter they produce and release, or receiving cells withdraw receptors or otherwise dampen their responsiveness. Scientists have shown, for example, that cells withdraw opioid receptors into their interiors (where they cannot be stimulated) when exposed to some opioid drugs; when exposed to morphine, however, cells appear instead to make internal adjustments that produce the same effect—reduced responsiveness to opiate drugs and natural opioids.<sup>2</sup> Over time, this and related changes recalibrate the brain's responsiveness to opioid stimulation downward to a level where the organ needs the extra stimulation of the drug to function normally; without the drug, withdrawal occurs.

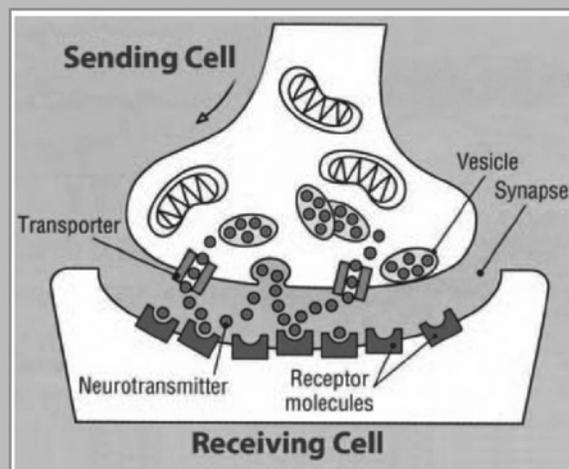
The drug-related mechanisms producing cumulative changes in neurotransmission sometimes are genetic in nature. While a drug cannot change a person's genes, drugs can prod some genes to increase their production of proteins, leading to changes in cell function or even actual reshaping of the physical structure of cells. For example, in rats, cocaine and amphetamine stimulate genes that produce the proteins used to build dendrites, branch-like cell structures that contain neurotransmitter receptors.<sup>3</sup> Brains normally sprout new dendrites as they register new learning; the accelerated dendrite formation stimulants induce may partially account for these drugs' unusual hold on an abuser's attention.

Some drugs are toxic to nerve cells, and the effect accumulates with repeated exposures. For example, the club drug methylenedioxymethamphetamine (MDMA, ecstasy) damages axons that release serotonin; the result is disruption of serotonin neurotransmission that likely underlies the long-lasting memory problems experienced by abusers.<sup>4</sup> Similarly, methamphetamine, over time, damages enough dopamine-sending cells to cause significant defects in thinking and motor skills; with abstinence, dopamine function can partially recover, but it is unclear whether cognitive and motor capabilities come back as well.<sup>5</sup>

### Experimental Methods

To determine whether or how a drug affects a particular neurotransmitter, researchers typically will compare individuals who have a history of drug exposure with others who do not. If researchers are investigating links between a drug's impact on neurotransmission and a drug-related behavior or symptom, they may compare individuals who exhibit the behavior or symptom with others who do not. The subjects in these experiments may be animals or people. In the case of animals, drug exposure often takes place under laboratory conditions designed to mimic

## Getting the Message Across



The task in neurotransmission is to convey a signal from a sending cell to a receiving cell across an open space known as a *synapse*. All brain cells accomplish this in approximately the same way.

The sending cell manufactures neurotransmitter molecules and stores them in packets called *vesicles*. When stimulated appropriately, the cell generates an electric signal and causes some vesicles to migrate to the cell membrane, merge with it, open up, and release their contents into the synapse. Some molecules drift across the synapse and link up, lock-and-key fashion, with molecules called *receptors* on the surface of the receiving cell. Receptors bridge the receiving cell's membrane; they have one facet on the outside and one on the inside of the cell. When the neurotransmitter links up with the exterior facet, the interior facet precipitates an electrical response in the cell membrane or inside the cell. The result may be increased production of some cell product or—often—a repeat of the process just described, so that the message gets relayed in turn to the next cell in the circuit.

At this point, cell-to-cell communication is complete. The neurotransmitter molecules drop off the receptors. Loose again in the synapse, they meet three fates:

- Some attach to another receptor;
- Some encounter an *enzyme*, a chemical that breaks them apart; and
- Some reenter the sending cell via a special pathway through the axon membrane, called a *transporter*. Once back inside the cell, they are available for re-release in future neurotransmission episodes.

Normally, when drugs are not present, the cycle of release, breakup, and cell re-entry maintains the amount of neurotransmitter in the synapse, and hence neurotransmission, within certain limits. In most cases, when an abused drug enters the brain, it causes neurotransmission to increase or decrease dramatically beyond these limits.

human drug consumption. Studies can be divided into those in which measurements are made in living animals or people and those in which animal brain tissue is removed and examined.

### Brain Tissue Assays

With removed tissue, scientists may perform chemical assays to quantify the presence of a neurotransmitter, receptor, or other structure of interest. In a recent experiment, scientists assayed brain tissue from 35-day-old rat pups and found that those that had been exposed to nicotine *in utero* had fewer nicotine receptors in the reward system than unexposed rats.<sup>6</sup>

A second experimental method using removed brain tissue—*in vitro*, literally, *in glass*, a historical term referring to the containers for the tissue and solution—enables researchers to view a drug's effects on neurotransmission in action. Scientists place the tissue in a laboratory solution of nutrients that enables the cells to continue to carry out some of their living functions. The researchers may then, for example, add the drug being investigated to the solution and monitor whether the cells respond by increasing their release of neurotransmitters. Alternatively, they may measure cell membrane or electrical properties that stimulate or inhibit the release of neurotransmitters.

In both *in vitro* experiments and in living animals, the techniques for measuring neurotransmitter quantities and fluctuations include microdialysis and fast-scan cyclic voltammetry (FSCV). Microdialysis involves taking a series of samples of the intercellular fluid containing the neurotransmitter through a microscopic tube inserted into the tissue or living brain. FSCV, recently developed by NIDA-funded scientists, monitors neurotransmitter fluctuations at tenth-of-a-second intervals by measuring electrical changes related to neurotransmitter concentrations.<sup>7</sup>

## Cocaine's Dopamine Connections

Research on cocaine illustrates that many dimensions may be involved in a single drug's interaction with the activity of a single neurotransmitter. Studies show that cocaine alters dopamine neurotransmission with effects on:

### Reward

- Cocaine causes the pleasurable feelings that motivate drug abuse by raising dopamine concentrations in the synapses of the reward system.<sup>a</sup>
- Besides keeping dopamine in the synapses by blocking the transporters, cocaine can indirectly promote release of additional dopamine into the synapses by mobilizing a supply that the sending cells normally hold in reserve.<sup>b</sup>
- Cocaine's yield of pleasurable feelings arises largely through the activity of one particular set of dopamine receptors, called D3 receptors.<sup>c</sup>

### Addiction

- Some studies indicate that the transition from casual cocaine abuse to addiction begins with the abuser's very first doses. For example, a single exposure to cocaine causes some cells in the brain's reward system to increase their responsiveness to subsequent stimulations.<sup>d</sup>
- In living animals with minimal exposure to cocaine, the drug alters the dopamine responsiveness for at least a week.<sup>e</sup>
- After chronic cocaine abuse dopamine ticks up in the reward system when the abuser encounters a cue associated with the drug.<sup>f</sup>
- Brains normally sprout new neurotransmitter receiving structures in the process of turning new experience into learning. Cocaine accelerates this process, which may help account for the drug's unusual hold on an addicted individual's attention.<sup>g</sup>

### Vulnerability to Abuse

- A young person's marked taste for novelty may be an indication that dopamine activity in his or her brain's reward system is especially sensitive to cocaine.<sup>h</sup>
- An individual's attraction to cocaine's dopamine-stimulating effects also may relate to his or her social circumstances.<sup>i</sup>

a "Brain Scans Open Window to View Cocaine's Effects on the Brain," *NIDA Notes* 13-2.

b Venton, B.J., et al. Cocaine increases dopamine release by mobilization of a synapsin-dependent reserve pool. *The Journal of Neuroscience* 26(12):3206-3209, 2006. Article will be featured in *NIDA Notes* 21-5.

c "Animal Studies Suggest D3 Receptors Offer New Target for Treatment Medications," *NIDA Notes* 18-4.

d "Altered Cellular Activity May Be First Step in Progression to Cocaine Addiction," *NIDA Notes* 16-5.

e "Even Modest Cocaine Use May Cause Brain Changes That Could Contribute to Addiction," *NIDA Notes* 16-3.

f "In Chronic Drug Abuse, Acute Dopamine Surge May Erode Resolve to Abstain," *NIDA Notes* 19-1.

g "Stimulant Drugs Limit Rats' Brain Response to Experience," *NIDA Notes* 19-3.

h "Behavioral Response to Novelty Foreshadows Neurological Response to Cocaine," *NIDA Notes* 21-2.

i "Social Environment Appears Linked to Biological Changes in Dopamine System, May Influence Vulnerability to Cocaine Addiction," *NIDA Notes* 17-5.

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## Live Studies

Studies with living animals or people are essential for tying drugs' effects on neurotransmitters to behaviors or symptoms. A common design for experiments with either animals or people is to give study subjects a chemical that has a known effect on a particular neurotransmitter, and then observe the impact on their behavior. Typically, the chemical is either an *agonist* (promoter) or *antagonist* (blocker) of signaling by the neurotransmitter.

In a recent experiment, for example, a research team administered a glutamate agonist to rats and showed that the resulting increased levels of the neurotransmitter correlated with a reduction in the animals' cocaine seeking.<sup>8</sup> Another team using the same strategy implicated glutamate in nicotine withdrawal.<sup>9</sup> Such studies are a staple of testing compounds to identify medication classes with potential for treating abuse or addiction.

Researchers also genetically alter animals to have special characteristics, such as producing less or more than the normal amounts of a particular neurotransmitter, or lacking receptors for a neurotransmitter. Researchers expose such animals to a drug and observe whether the animals' display of some particular drug-related behavior—for example, pacing restlessly after being given a stimulant—increases or decreases.

## Brain Scans

Brain imaging techniques enable neuroscientists to directly assess neurotransmission in people and living animals. With positron emission tomography (PET), researchers can compare groups of drug-abusing and nonabusing individuals, quantifying differences in their levels of a particular neurotransmitter molecule (e.g., dopamine) or neurotransmission component (e.g., a receptor or transporter). With PET, researchers also can correlate a drug's transit through the brain with fluctuations in a target neurotransmitter. They can elicit a drug-related behavior or symptom (e.g., craving) and relate neurotransmitter fluctuations to the rise and fall in its intensity.

One recent PET study, for example, showed that smokers have less of the neurotransmitter-degrading enzyme monoamine oxidase-B (MAO-B) throughout their bodies than nonsmokers.<sup>10</sup> The relative deficit of MAO-B may help explain why smokers are at higher risk for hypertension and other chronic diseases.

Researchers use both PET and functional magnetic resonance imaging (fMRI) to monitor metabolic activity in selected regions of the brain. Because each neurotransmitter has a unique distribution among the regions of the

brain, information on locations of heightened or decreased activity provides clues to which neurotransmitter is affected under the conditions of the study.

## Summary

By altering neurotransmission, addictive drugs produce effects that make people want to continue to abuse them and induce health problems that can be longlasting and profound. The effects are drug-specific: Each drug disrupts particular neurotransmitters in particular ways. Some important effects, however, are shared by all: initial pleasurable feelings, and subsequent dependence and addiction, resulting from disruption of the dopamine neurotransmitter system.

Scientists use a wide variety of experimental tools and techniques to study drugs' effects on neurotransmission, and their consequences, in both animals and people. Their findings enhance our understanding of the experiences of drug abusers and the plight of addicts, point the way to new behavioral and medication treatments, and provide potential bases for prevention strategies and monitoring progress in treatment.

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<sup>1</sup>“Nicotine’s Multiple Effects on the Brain’s Reward System Drive Addiction,” *NIDA Notes* 17-6.

<sup>2</sup>“Genetic Engineering Studies May Lead to Development of More Effective Pain Relievers,” *NIDA Notes* 15-3.

<sup>3</sup>“Stimulant Drugs Limit Rats’ Brain Response to Experience,” *NIDA Notes* 19-3.

<sup>4</sup>“Ecstasy Damages the Brain and Impairs Memory in Humans,” *NIDA Notes* 14-4.

<sup>5</sup>“Methamphetamine Abuse Linked to Impaired Cognitive and Motor Skills Despite Recovery of Dopamine Transporters,” *NIDA Notes* 17-1.

<sup>6</sup>“Nicotine Alters the Developing Rat Brain,” *NIDA Notes* 21-2.

<sup>7</sup>“Microscopic Probe Detects Changes in Brain Chemistry as They Occur,” *NIDA Notes* 19-1.

<sup>8</sup>“Brain Glutamate Concentrations Affect Cocaine Seeking,” *NIDA Notes* 19-3.

<sup>9</sup>“Nicotine Withdrawal Linked to Disrupted Glutamate Signaling,” *NIDA Notes* 19-6.

<sup>10</sup>“Smoking Decreases Key Enzyme Throughout Body,” *NIDA Notes* 19-1. **NN**

## Serotonin System May Have Potential as a Target for Cocaine Medications

By targeting specific receptors of the neurochemical serotonin, investigators hope to advance the development of potential relapse prevention agents.

By Lori Whitten, *NIDA NOTES* Staff Writer

NIDA-supported researchers have weakened rats' behavioral responses to environmental cocaine cues by manipulating the neurotransmitter serotonin. Moreover, such manipulation can make the drug seem less stimulant-like to the rats. The findings suggest that medications that act on the serotonin system might help recovering cocaine abusers sustain abstinence, say Dr. Kathryn Cunningham and colleagues at the Center for Addiction Research at the University of Texas Medical Branch in Galveston and the Polish Academy of Sciences in Krakow.

While cocaine makes its primary pharmacological impact on the neurotransmitter dopamine, it also increases levels of other chemical messengers, including serotonin (5-HT). Previous research with animals has shown that 5-HT<sub>2C</sub> and 5-HT<sub>2A</sub> receptors—two proteins on brain cell surfaces that mediate serotonin's effects on cellular activity—regulate behavioral responsiveness to cocaine. For example, activating the 5-HT<sub>2C</sub> receptor reduces the animals' typical behavioral responses to cocaine—including hyperactivity, self-administration, and return to drug-seeking following abstinence. Dr. Cunningham's studies showed that the 5-HT<sub>2C</sub> receptor affected responsiveness to cocaine-associated environments, and that both receptors affected the animals' experience of the drug.

### Hyperactivity and Discrimination

Dr. Cunningham and colleagues first examined the effect of manipulating 5-HT<sub>2C</sub> receptors on a behavior called conditioned hyperactivity: When researchers repeatedly move an animal from its home cage and give cocaine in a test cage, the drug-paired environment comes to evoke the same behavioral effect as the stimulant itself when saline is administered, so that the animal starts moving about restlessly as soon as it finds itself in the cage. Experience has shown that compounds that inhibit conditioned hyperactivity usually also reduce behaviors that are laboratory stand-ins for human relapse.

Dr. Cunningham and colleagues administered cocaine (15 mg/kg) to rats daily for 7 days in a test cage. Two days later, they gave some of the rats a compound that activates the 5-HT<sub>2C</sub> receptor (MK 212), some a compound that blocks it (SB 242084), and others saline, and returned the animals to the test cage. Compared with the saline-treated animals, who showed the usual conditioned hyperactivity, rats given the 5-HT<sub>2C</sub>-receptor-stimulating compound moved around less (by about 40 percent), while those that received the blocker showed an exaggerated hyperactive response (by 25 percent) to the test cage. A separate group of animals was given cocaine only in their home cage and saline in the test cage. These animals showed normal activity when tested 2 days later, which was unaffected by the 5-HT<sub>2C</sub> receptor compounds. These data strengthen the conclusion that the 5-HT<sub>2C</sub> receptor is important in the cocaine-environment link.

In another study, Dr. Cunningham's team used an experimental protocol called drug discrimination to determine whether compounds that act at the 5-HT<sub>2C</sub> and 5-HT<sub>2A</sub> receptors would alter the way cocaine made the rats feel (see textbox, below). Prior research had indicated that the

## The Drug Discrimination Protocol

In their second experiment, Dr. Cunningham and colleagues used a drug discrimination procedure to determine whether the test compounds changed how cocaine felt to the animals. To each rat, they first gave randomly alternating infusions of cocaine and saline. After each infusion, the rat could obtain a water reward by pressing Lever A if it had received cocaine or Lever B if it had received saline. After numerous repetitions, the rat regularly pressed the correct lever—demonstrating that it had learned the challenge, wanted the reward, and could discriminate between the experiences produced by cocaine and saline. Next, the researchers observed the rat's performance when it was given a receptor blocker prior to cocaine:

- Rats given a 5-HT<sub>2A</sub> receptor blocker no longer went as reliably to Lever A, indicating that they were less able to distinguish cocaine from the placebo;
- Rats given a 5-HT<sub>2C</sub> receptor blocker pressed more on Lever A, indicating enhanced cocaine-like effects.

two receptors oppose each others' effects on the cocaine response, and the researchers hypothesized that blocking the 5-HT<sub>2A</sub> receptors would make cocaine feel less stimulant-like to the rats, whereas inhibiting 5-HT<sub>2C</sub> receptors would enhance the drug's effects. Rats given a compound that blocks 5-HT<sub>2A</sub> receptors (SR 46349B) prior to cocaine reduced their pressing on the lever associated with cocaine's effects compared with one linked with saline. Animals pretreated with a compound that blocks 5-HT<sub>2C</sub> receptors (SDZ SER-082) increased their pressing on the cocaine lever over the saline lever. The results bore out the hypothesis.

"Taken together, the findings of these studies support the idea that the serotonin 5-HT<sub>2C</sub> receptor plays a role in linking environmental cues and the experience of cocaine, as well as the subjective effects of the drug. The 5-HT<sub>2A</sub> receptor also influences these behaviors, but in the opposite direction," says Dr. Cunningham. "From the medication development perspective, a drug with dual action at both receptors—that is, one that simultaneously stimulates the 5-HT<sub>2C</sub> receptor and blocks the 5-HT<sub>2A</sub> receptor—might be effective in reducing cue-induced craving. We know of no such compound, and our team is working to develop one." She adds that agents that stimulate 5-HT<sub>2C</sub> or inhibit 5-HT<sub>2A</sub> receptors do not fully mimic cocaine or affect other behaviors, suggesting limited side effects.

"It is not really surprising that serotonin is implicated in addiction given its importance to essential behaviors—including sleep, eating, mood, cognitive processes, and self-regulation—and its influence on dopamine," says Dr. Minda Lynch of NIDA's Division of Basic Neuroscience and Behavioral Research. "Serotonin influences dopamine in the brain's reward pathway and cortex, so examining the behavioral effects of serotonin-influencing compounds in animals is a reasonable approach in the investigation of potential pharmacotherapies," says Dr. Lynch. She agrees that a dual-action compound that operates on the serotonin 5-HT<sub>2C</sub> and 5-HT<sub>2A</sub> receptors might eventually help prevent relapse. "However, a great deal of further testing in animals is needed. A good next step would be to confirm the findings in

animal protocols that mimic cue-induced relapse," says Dr. Lynch.

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## More Data Point to Serotonin

Dr. Janet Neisewander and colleagues at Arizona State University confirmed the therapeutic potential of compounds that act on the two serotonin receptors (5-HT<sub>2A</sub> and 5-HT<sub>2C</sub>) that Dr. Cunningham's team examined. Using a self-administration-extinction-trigger-exposure model of testing for relapse (see "Animal Experiments in Addiction Science," *NIDA Notes* Vol. 20, No. 5), the researchers found that:

- Ketanserin—a compound that blocks the 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors—attenuated cue-induced relapse to cocaine, but not drug-triggered relapse. Because ketanserin blocks both receptors, the investigators did not know which might have been responsible for preventing cue-induced relapse. By combining data from this experiment and the one described below, the researchers were able to zero in on the 5-HT<sub>2A</sub> receptor.
- SB 242084, a selective blocker of 5-HT<sub>2C</sub> receptors, did not affect cue-induced or cocaine-triggered drug-seeking. The findings suggested that the results seen with ketanserin most likely were due to its ability to block the 5-HT<sub>2A</sub> receptor. The researchers concluded that blocking the 5-HT<sub>2A</sub> receptor might help prevent relapse triggered by environmental cues associated with taking cocaine, the same inference as Dr. Cunningham's team.

In another experiment, Dr. Neisewander's team found that SB 242084 interfered with the ability of a drug that augments serotonin, *d*-fenfluramine, to prevent cue-induced cocaine seeking. Because blocking the 5-HT<sub>2C</sub> receptor made *d*-fenfluramine ineffective, the investigators concluded that stimulating the receptor may help prevent cue-induced relapse.

The compounds tested by Dr. Neisewander's team will not necessarily be developed as medications to prevent cocaine relapse, but the results of the study do suggest that drugs that act on serotonin may be potential pharmacotherapy candidates. The findings add to a growing number of studies that suggest the promise of a dual-action pharmacotherapeutic approach for relapse prevention—that is, a drug that simultaneously blocks 5-HT<sub>2A</sub> receptors and stimulates 5-HT<sub>2C</sub> receptors.

"Recent evidence suggests that serotonin is involved in motivation for various pleasurable experiences, including food. Researchers developing medications for obesity also are studying the effect of stimulating the 2C receptor, which may be a point of intersection for several addictions," says Dr. Cunningham.

**Source:** Burmeister, J.J., et al. Differential roles of 5-HT receptor subtypes in cue and cocaine reinstatement of cocaine-seeking behavior in rats. *Neuropsychopharmacology* 29(4):660-668, 2004.

## Brain Changes Accompany Cocaine Withdrawal



Rats repeatedly exposed to cocaine and then withdrawn from it exhibit neural changes in the lateral amygdala, a part of the brain involved in responding to pleasurable and aversive stimuli. Such changes may mediate the negative emotional effects that accompany drug withdrawal, say the researchers who documented the effect in a recent study. Dr. Vadim Bolshakov and colleagues at Harvard Medical School have shown that long-term potentiation (LTP), a process underlying learning and memory, occurs in the lateral amygdala when cocaine-exposed rats no longer have access to the drug. They found a clear link between LTP and enhanced levels of the neurotransmitter glutamate in the lateral amygdala and signs of

withdrawal in the rats. The findings suggest that amygdala circuits might contribute to drug modulation of motivational states and influence addictive behaviors.

### Source

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## Cocaine Craving Activates Brain Reward Structures; Cocaine “High” Dampens Them

A study documented changing emotional and neurobiological responses to cocaine with successive doses during a single session of drug taking.

By Lori Whitten, *NIDA NOTES* Staff Writer

NIDA-funded researchers mapped the dynamic of drug-induced brain activity and emotional responses that occur during a cocaine abuser’s typical binge-like pattern of self-administration. Dr. Robert Risinger and colleagues at the Medical College of Wisconsin found that craving corresponds with increased activity in key brain areas underlying reward and motivation, while the cocaine-induced “high” is linked with decreased activity in these same regions. “Our results suggest that, as one takes multiple ‘hits’ of cocaine, pleasure accumulates with each successive dose, but lasts for a shorter time—a pattern that would compel people to keep abusing,” he says.

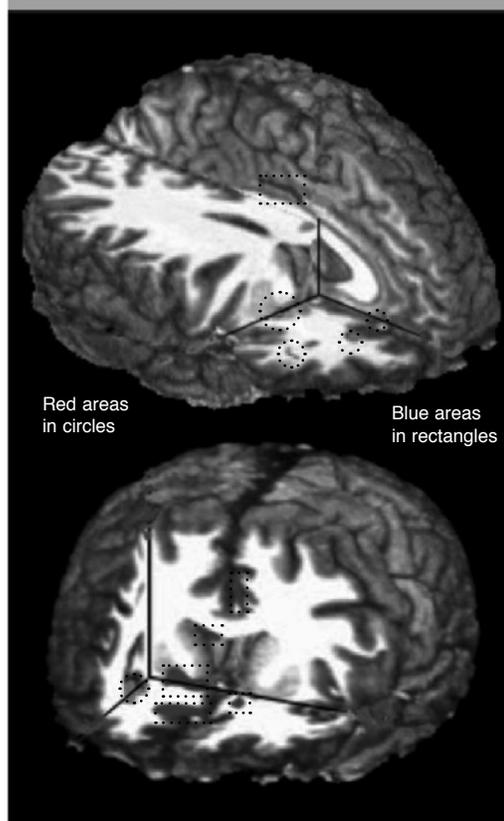
“My colleagues and I wanted to know what cocaine does to the brain to compel drug-seeking behavior in addicted people—particularly, why taking a small amount of the drug can lead to a binge. Understanding this could help identify interventions to stop such abuse,” says Dr. Risinger.

Dr. Risinger’s team recruited six cocaine-addicted men who were not seeking treatment. The men, aged 23 to 41, had abused crack cocaine for 11 years, on average. They completed a medical examination, received counseling on the health consequences of cocaine abuse, and were offered (but all declined) addiction treatment before the study.

Each man participated in two 1-hour sessions of cocaine self-administration. At the beginning of the first session, he learned how to press a joystick button to receive infusions of cocaine through an intravenous catheter. After a 5-minute baseline period, he saw a computer-displayed signal that the joystick was activated, and for the next 55 minutes he pressed the button at will. Each press delivered a 20 mg/70 kg of body weight dose of the drug—except that, for safety reasons, doses could not be repeated at intervals of less than 5 minutes, and total doses over the course of the hour were limited to six. Meanwhile, in response to prompts on a computer display, the volunteer used a joystick to rate his cocaine craving, high feelings, and other sensations once per minute. During the second session, the researchers used functional magnetic resonance imaging (fMRI) to obtain brain scans synchronized with the subjective reports. After each session, each man underwent a brief physical examination and left the facil-

### COCAINE CRAVING AND “HIGH” CORRESPOND WITH OPPOSITE PATTERNS OF BRAIN ACTIVATION

Cocaine craving was linked with activation (red areas, top panel), and euphoria with deactivation (blue areas, bottom panel) of the same brain regions according to an fMRI study in which cocaine-addicted participants reported subjective responses during a 1-hour self-administration session. The brain regions affected by craving and high are involved in reward anticipation, emotional response, and control over actions. The insula—a brain structure that seems to translate bodily sensations into emotions—was activated during cocaine-induced euphoria (red area, bottom panel).



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ity once his vital signs returned to baseline levels and he no longer showed drug effects or reported craving.

### **Behavioral Results**

Participants administered 4.5 injections a session, on average, spacing the doses about 7.4 minutes apart. Only two administered the maximum six doses. “For many patients, the amount of cocaine consumed during a self-administration session was less than they typically abused,” says Dr. Risinger.

As anticipated, the men’s feelings of being high decreased before and increased after cocaine administration. From the first through the fourth injection, the intensity of each successive high was greater, and its duration shorter. Craving peaked about 1 minute before each injection and decreased to a low point about 2 minutes after cocaine administration, before rising again during minutes 3 to 4. Absolute levels of craving decreased with each successive injection, but the preadministration increase in craving rose more sharply.

Dr. Risinger says the participants’ reports match other abusers’ accounts of their feelings during binges: “People often talk about ‘chasing the high.’ They abuse the drug several times in an episode, feel increasingly high with the first few hits, and experience a rapid dropoff in the duration of pleasure with repeated use—which may explain consuming larger amounts and more frequently over a session. Consuming cocaine satisfies craving only briefly, and then the feeling increases again before another administration, which may also contribute to the binge pattern.”

“It is not clear whether the subjective feeling of craving was directly responsible for driving the participants to self-administer, or whether some other process, perhaps response-outcome learning, was responsible for initiation of self-administration,” says Dr. Steven Grant of NIDA’s Division of Clinical Neuroscience and Behavioral Research.

### **Imaging Findings**

Cocaine-induced craving was associated with increased neural activity in brain areas involved in reward anticipation, emotional response, and control over actions: the nucleus accumbens (NAc), the orbitofrontal cortex, and the anterior cingulate cortex. The findings accord well with those of cue-induced craving studies, which generally indicate that the anticipation of a reward is accompanied by activation of the dopamine-rich mesolimbic pathway—a neural circuit involved in reward, motivation, and directing attention to stimuli. Such a neural response is thought to “set up” the brain to experience reward and to drive goal-directed behavior.

The researchers also found that cocaine-induced euphoria depressed activity in the areas activated by craving (see figure, page 4). In prior studies, Dr. Risinger’s team has observed NAc suppression in participants who reported experiencing a cocaine-induced high. Although researchers do not yet fully understand the neurobiological mechanisms underlying the high, some have speculated that suppression of NAc firing may be an important component, perhaps reflecting altered receptor sensitivity or weakened stimulation from other brain structures. Another research team found that participants who reported feeling high after receiving a single researcher-controlled dose of cocaine exhibited increased activity in the NAc. The

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***The study represents an important step in correlating drug-induced craving and high with neural activity in specific regions of the human brain.***

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different findings may reflect the teams’ divergent experimental methods.

The study represents an important step in correlating drug-induced craving and high with neural activity in specific regions of the human brain. “It provides insight into the neurobiology involved in drug-taking binges, a very common and dangerous behavior associated with the disease of addiction,” says Dr. Risinger.

“Dr. Risinger’s study is a good example of translational research, which applies a well-established technique in animal research to people. Although the results need replication in a larger number of participants, the findings are provocative because they raise good questions about the relationship between the various neurobiological responses—the fMRI signal and dopamine release, for example. We currently do not have a complete picture of how neurochemical responses and neural activation patterns exactly relate to the entire drug-taking experience, but this issue can be addressed in reverse translational research—animal imaging studies of self-administration and passive cocaine delivery,” says Dr. Grant. NIDA-funded investigators are developing such techniques, he adds.

### **Source**

- Risinger, R.C., et al. Neural correlates of high and craving during cocaine self-administration using BOLD fMRI. *NeuroImage* 26(4):1097-1108, 2005. **NN**

## Cocaine Abusers' Pretreatment Cue Responses Predict Recovery Success

In the future, patients' brain scans may help clinicians tailor addiction treatment to improve therapeutic outcomes.

By Lori Whitten, *NIDA NOTES* Staff Writer

A recent NIDA study strengthens prospects that brain imaging may one day help clinicians assign individual patients to treatment models that maximize their personal chances of a successful outcome. The study, conducted by Dr. Thomas Kosten and colleagues at Yale University School of Medicine, the University of Arkansas for Medical Sciences, and the Massachusetts Institute of Technology, correlated cocaine-addicted patients' regional brain responses to drug cues with their outcomes in subsequent treatment. The patients whose brain scans revealed rapid and strong activation in sensory, motor, and cognition- and emotion-processing brain areas were more likely to drop out of treatment and fail to achieve stable abstinence.

"A test that predicts treatment outcomes, especially vulnerability to relapse, could help guide individualized treatment. For example, a clinician might recommend an extended stay in residential treatment or more intense behavioral intervention for patients with a propensity for relapse," says Dr. Kosten, now at Baylor College of Medicine.

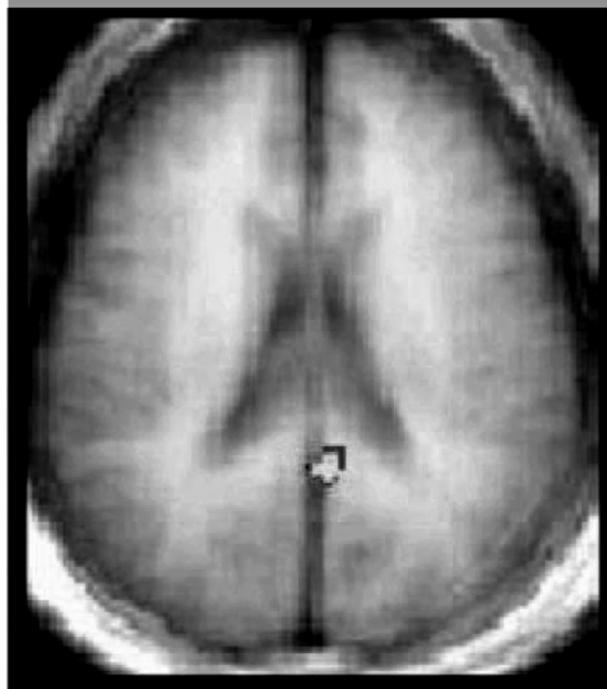
Dr. Kosten and colleagues pursued the implications of an intriguing finding made in a prior study of cocaine cue responses: In some patients, strong, rapid activation of brain areas associated with emotion and sensing preceded the onset of craving. Although craving itself does not generally predict relapse, Dr. Kosten's team speculated that cue-induced brain activation that occurs quickly and reflexively, below awareness, might do so. They hypothesized that patients who showed such responses during the first 30 seconds of cue exposure would also demonstrate poorer treatment outcomes.

To test their hypothesis, the investigators recruited 17 men and women who were participating in a trial of an antidepressant—sertraline—that is being evaluated as a possible treatment for cocaine addiction. The participants reported abusing cocaine 20 days, on average, during the month before the study. All met standard clinical criteria for cocaine addiction and had abused the drug for 6 years, on average. Most were new to treatment.

After being cocaine-free for 5 days, on average, each participant underwent functional magnetic resonance imag-

### fMRI TRACKS CUE-INDUCED BRAIN ACTIVITY

When cocaine-addicted patients watched a drug-related videotape, activation of the posterior cingulate cortex (highlighted in the brain image) occurred more quickly in those who subsequently relapsed.



ing (fMRI) while watching two 4-minute videotapes. The first minute of each tape reported on vegetable prices, and the participants' brain activity while hearing this emotionally neutral information served as a baseline for comparison. During the last 3 minutes, an actor pretended to smoke cocaine and experience a "rush." Immediately after viewing the tapes, each participant rated peak cocaine craving intensity on a scale from 0 to 10. After the imaging session, participants began taking either sertraline or a placebo daily and completed 2 weeks of residential treatment. During the 10-week outpatient phase of the trial, they were to continue their medication regimen, receive weekly individual cognitive-behavioral therapy, and submit urine samples three times a week.

## Interplay Within Cingulate Cortex?

Nine of the 17 participants relapsed, defined by the investigators as submitting fewer than 15 of a possible 30 cocaine-free samples during the study and not completing outpatient treatment. Participants taking sertraline were just as likely as those taking the placebo to relapse. Relapsers and nonrelapsers reported cue-induced cravings of comparable intensity. The two groups differed, however, on brain activation during the first 30 seconds of the cocaine-cue videotapes. Relapsers showed greater cue-induced activation than nonrelapsers in several areas of the cortex: the left precentral (movement control), right superior temporal (auditory processing), right lingual and right inferior occipital (visual processing), and the left posterior cingulate cortices. The cingulate cortex is integral to attention, response inhibition, emotional regulation, and decisionmaking (see chart).

The relapsers' greater activation of the posterior cingulate cortex (PCC) was the most notable of the findings. Also significant was the lack of any difference between the outcome groups in activation of the neighboring anterior cingulate cortex (ACC). This contrasts with findings from previous studies, in which ACC activation and craving were associated in patients who had longer abstinence (average 14-28 days) and were imaged for periods longer than 30 seconds after being shown cues.

Taken together Dr. Kosten says, these results suggest that an interplay occurs between the PCC and ACC following exposure to cocaine cues and changes with increasing stability of abstinence. In patients highly vulnerable to cues, intense PCC activation occurs within 30 seconds of cue

***“If researchers can determine changes in brain activity that predict responses to particular treatments, then clinicians could match therapy with individuals’ scan results or even monitor progress in therapy.”***

exposure and is positively associated with risk for relapse. In less vulnerable patients, early PCC activation is less intense, and these patients are able to activate the ACC to counter the association with relapse risk.

Dr. Kosten's findings highlight the promise of imaging linked to behavioral assessments as a tool for guiding the treatment of addictions and other psychiatric disorders. They parallel a previous NIDA-funded study in which brain activity patterns during a decisionmaking task predicted treatment outcomes among patients addicted to methamphetamine (see “Brain Activity Patterns Signal Risk of Relapse to Methamphetamine,” *NIDA NOTES*, Vol. 20, No. 5).

“If researchers can determine changes in brain activity that predict responses to particular treatments, then clinicians could match therapy with individuals’ scan results or even monitor progress in therapy,” says Dr. Kosten. More generally, studies that examine biological and behavioral predictors of treatment response elucidate the physiology underlying addiction—particularly the neural circuitry integrating stress, craving, and the propensity to relapse. New tools—for example, scanners that highlight brain areas that are working together—are expected to reveal more about these physiological processes. “With such functional connectivity imaging, one could examine how the anterior and posterior cingulate ‘talk’ to each other during a drug cue or other experience,” says Dr. Rajita Sinha, an investigator in the Kosten study.

“Eventually, researchers will integrate the findings of such studies into a complete picture that will specify therapeutic pathways or help in the development of targeted medications to reduce relapse probability,” adds Dr. Harold Gordon of NIDA’s Division of Clinical Neuroscience and Behavioral Research.

### WHAT RESEARCHERS KNOW ABOUT THE CINGULATE CORTEX AND BEHAVIOR

The cingulate cortex connects to both the limbic systems (emotion and motivation) and the prefrontal cortex (planning and control of behavior) and seems to integrate emotion and cognition. The anterior and posterior regions of the cingulate are connected to different brain areas and differ functionally.

Anterior Cingulate Cortex (ACC)	Posterior Cingulate Cortex (PCC)
<p>Paying attention—The ACC monitors inputs from the senses (competing options) and selects what we attend to.</p> <p>Making decisions—Influenced by past experience, the ACC assesses risk, reward, and conflict. It works with areas of the frontal cortex to select a response.</p> <p>Inhibiting responses—The ACC integrates input from the prefrontal cortex and detects and corrects errors in behavior.</p> <p>Detecting and controlling emotions—The ACC monitors what is going on inside (feelings, pain, and bodily arousal) and controls voluntary suppression of these sensations.</p>	<p>Responding reflexively—The PCC integrates sensory and movement information with established behavior patterns and acts “below awareness.” The PCC responds to reward and positive feedback.</p> <p>Reacting emotionally—The PCC processes emotion-related autobiographical memories and the emotional perspective of self and others. Its activity correlates with internal physiological responses (heart rate, anxiety, and arousal level).</p>

## Source

- Kosten, T.R., et al. Cue-induced brain activity changes and relapse in cocaine-dependent patients. *Neuropsychopharmacology* 31(3):644-650, 2006. [NN](#)

# Stress Cues Also Signal Relapse Risk

Exposing patients to stress cues at the beginning of cocaine addiction treatment triggers craving and measurable biological responses that may predict drug abuse outcomes during early recovery. NIDA-funded researchers found that stress-induced craving was associated with a shortened interval to relapse following inpatient treatment, while hormonal responses to stress predicted the amount of cocaine the patients consumed during relapse.

The findings were reported in a followup to prior research conducted by Dr. Rajita Sinha and colleagues at Yale University School of Medicine. In the previous study, patients who listened to tapes reminding them of a stressful experience and a drug-related experience demonstrated an elevated biological stress response and increased cocaine craving compared with their response to tapes of relaxing experiences (see "Cocaine-Related Environmental Cues Elicit Physiological Stress Responses," *NIDA NOTES*, Vol. 20, No. 1).

Dr. Sinha and colleagues followed up with 49 of the 54 patients 3 months after completion of inpatient behavioral treatment. They found that patients who had experienced more intense cocaine craving while revisiting their stressful experiences via audiotape tended to relapse sooner. The probability of relapse 3 months after treatment was 56 percent among patients who reported no craving. Each unit increase on a craving intensity scale of 0 to 10 was associated with a 31 percent rise in the likelihood of relapse during the followup period.

Participants who released high levels of the stress hormones adrenocorticotrophic hormone (ACTH) and cortisol in response to the stressful tapes consumed more cocaine than low-level responders during the followup. Three months after treatment, high-level responders had consumed about 8g of cocaine cumulatively over their cocaine abuse periods, while low-level responders consumed about 3g.

The findings of the study suggest that different components of the stress response are associated with various aspects of relapse: craving with reinitiating abuse and hormonal responses with the ability to control intake after reinitiating abuse. "Greater

hormonal release during stress may 'prime' higher cocaine consumption or bingeing after return to abuse, perhaps by altering the rewarding effects of the drug," Dr. Sinha says.

Dr. Sinha and colleagues did not find a link between drug cue-induced craving and relapse outcomes, a result that is consistent with previous studies. However, because the drug cue imagery produced physiological reactions similar to those triggered by the stress cues, the researchers speculated that studies using a larger sample or exposure to actual drug cues, rather than just images of them, may show such an association.

Prior studies that did not find a link between cue-induced craving and relapse generally assessed only one or two dimensions of craving, Dr. Sinha points out. Studies that address multiple components—wanting the drug, feelings about the drug and about wanting it, drug-seeking behaviors, coping reactions, physiological arousal, and stress hormone levels—may better indicate vulnerability to relapse, she says.

"For people who are not addicted, knowing that you want a particular thing probably defines craving. Our findings suggest that for addicted people, craving is a 'state'—a multidimensional experience—comprised, in part, of stress-like arousal. In this state, desire becomes pathological, and people cannot delay gratification or divert their attention," says Dr. Sinha.

The results of Dr. Sinha's study suggest that stress-induced drug craving and physiological responses may be used as a diagnostic indicator of relapse propensity and might one day help clinicians tailor their interventions toward regulating stress and coping with stress-induced craving. "Research on each component and the role that it plays in continued drug abuse is just beginning, but such studies ultimately may improve our ability to help people attain long-term recovery," she says. ■

## SOURCE

Sinha, R., et al. Stress-induced cocaine craving and hypothalamic-pituitary-adrenal responses are predictive of cocaine relapse outcomes. *Archives of General Psychiatry* 63(3):324-331, 2006.

## Behavioral Response to Novelty Foreshadows Neurological Response to Cocaine

Young rats' engagement with novel objects correlates with cocaine-induced dopamine release, shedding light on the mechanisms of drug abuse vulnerability.

By Lori Whitten, NIDA NOTES Staff Writer

NIDA-supported researchers Dr. Cheryl Kirstein and Ms. Kirstie Stansfield at the University of South Florida have found that higher scores on tests of impulsivity and some behavioral responses to novelty correlate with a heightened biological response to cocaine in adolescent, but not adult, rats. The findings accord well with scientists' widely shared view that developmental differences in brain systems that use the neurotransmitter dopamine underlie age differences in susceptibility to drug abuse.

Dr. Kirstein and Ms. Stansfield conducted a series of behavioral assays to rate rats' relative responsiveness to novelty, then compared these results with measures of dopamine release in the reward pathway after an injection of cocaine. First, they put adolescent rats (34 days old, which is roughly equivalent to adolescence in people) and fully mature rats (59 days old, equivalent to human young adulthood) through four behavioral protocols. The tests measured activity in a new environment (how much the rat moved around when put into a new cage); impulsivity (how quickly it approached a new object placed into its cage); exploratory drive in response to a new object (how many times it approached the object in a given period of

time); and attraction to new objects (what percentage of a given time interval was spent close to the object).

The researchers then injected the animals with saline and then, 2 hours later, with cocaine 20 mg/kg. Every 10 minutes, starting immediately after the saline injection and continuing until 2 hours after administering the cocaine, they measured the concentrations of the neurotransmitter dopamine and its major metabolite in the rats' nucleus accumbens (NAc). The measurements were made using the technique of *in vivo* microdialysis. By the time of the last measurement, the drug had cleared the animal's system.

### On Most Tests, Age Matters

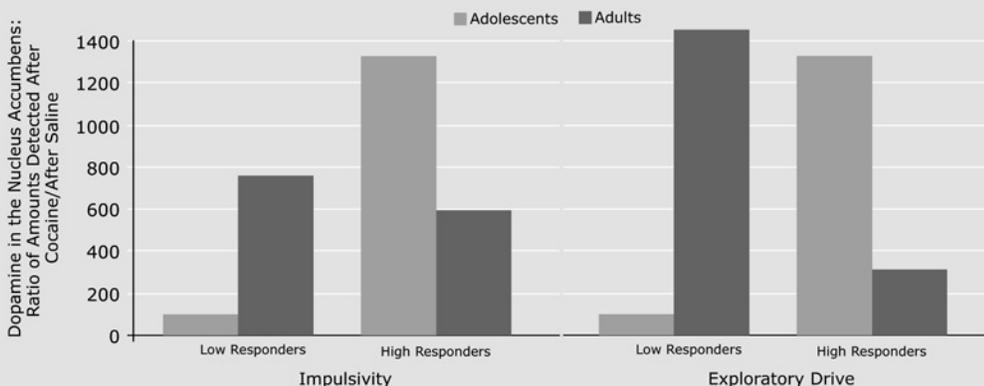
In their analysis, the researchers compared cocaine-induced dopamine release in animals that had responded above the mean level on each test (high responders, HR) to those who had scored below the mean (low responders, LR). The results revealed that among both the adult and adolescent rats, those that exhibited greater activity in a new environment also demonstrated enhanced dopamine release following a cocaine injection. This was the only test, however, in which age did not influence

cocaine-induced dopamine release. The other behavioral assays revealed interactions between age and the response to novelty on cocaine-induced dopamine release in the NAc:

- Impulsivity—Adolescent rats with above-the-mean impulsivity scores released more dopamine in response to cocaine than their age mates who were LR. Mature rats exhibited no clear relationship between impulsivity and cocaine-induced dopamine response.
- Exploration of a new object—Adolescent rats

### COCAINE-INDUCED DOPAMINE RELEASE VARIES WITH AGE AND RESPONSE TO NOVELTY

Among adolescents, high responders—rats that demonstrated above-the-mean scores on impulsivity and exploratory drive in tests of response to novelty—released more dopamine after an injection of cocaine than low responders. Adult rats showed no clear relationship with impulsivity and cocaine-induced dopamine response, and those with high exploratory drives released less dopamine after an injection of cocaine than age mates who were low responders.



with above-the-mean scores on this measure released more dopamine in response to cocaine than their age mates who were LR. Adult rats showed the opposite pattern: Animals with above-the-mean scores showed attenuated cocaine-induced dopamine release compared with age mates who were LR.

- Attraction to a new object—Adolescent rats exhibited no clear relationship between reactivity on this assay and cocaine-induced dopamine release. Mature rats with above-the-mean scores released less dopamine in response to cocaine compared with their age mates who were LR.

Dr. Kirstein's finding that for all the animals, greater activity in a new environment corresponded with increased sensitivity to stimulants is consistent with earlier research. Her team's mixed findings on the impulsivity and other novelty response tests indicates, she says, that those behaviors arise from different physiological mechanisms than does locomotor activity. "My colleagues and I think locomotor activity may reflect primarily dopamine activity in a brain circuit involved with generating and controlling movement. Novelty may instead differentially stimulate mesolimbic dopamine—a pathway implicated in attention as well as reward and motivation," says Dr. Kirstein.

### Inhibition Develops Later

The findings on the three tests where age affected the relationship between behavior and cocaine-induced dopamine release may reflect maturation of the brain's reward circuit. When rats are adolescents, dopamine-producing and releasing cells in this circuit may be particularly sensitive both to novelty and to pharmacological stimulation. As part of normal neurological development, areas of

## In Vivo Microdialysis

The investigators used in vivo microdialysis to measure dopamine each animal released from its nucleus accumbens (NAc) in response to cocaine. They implanted a probe into the shell area of the NAc. The probe is a fine tube, about the size of a sewing needle, connected to a mini-pump that continuously perfuses it with artificial cerebrospinal fluid. The membrane tip of the probe captures dopamine and its metabolites. The samples collected by the needle are then analyzed using techniques, such as chromatography, that are able to isolate dopamine and its metabolites from other molecules.

the brain that dampen the activity of this circuit come "online" later, explaining the age-related differences observed in Dr. Kirstein's study. "The mesolimbic pathway and the cortical areas that inhibit it to regulate dopamine release are not yet fully matured in the adolescent, and this may explain why the adolescent brain responds to drugs differently than the adult brain," says Dr. Kirstein.

"The results of Dr. Kirstein's study, along with other animal research on the interaction of drugs and developmental stage, indicate that the adolescent brain is more responsive to drugs than the adult brain—both neurochemically and behaviorally," says Dr. Nancy Pilotte of NIDA's Division of Basic Neuroscience and Behavioral Research. Studies that identify the physiological and behavioral processes underlying age-related susceptibility to addiction complement epidemiological work on the individual and social factors contributing to adolescent vulnerability to substance abuse.

### Source

- Stansfield, K.H., and Kirstein, C.L. Neurochemical effects of cocaine in adolescence compared to adulthood. *Developmental Brain Research* 159(2):119-125, 2005. **NN**

## Methylphenidate for Comorbid Cocaine Abuse, ADHD

In an inpatient study with 14 non-treatment-seeking volunteers, Columbia University researcher Dr. Stephanie Collins and colleagues reported that a regimen of 40-60 mg/day of sustained-release methylphenidate (SR-MPH) reduced ratings on scales of “feel high,” “good drug effect,” and other measures of cocaine’s reinforcing effects among seven abusers affected by attention deficit hyperactivity disorder (ADHD). The medication increased the cardiovascular effects seen with cocaine alone, but not to dangerous levels. Although preliminary, the findings suggest that a therapeutic approach of using slow-acting

stimulants to reduce craving for cocaine—parallel to the use of methadone or buprenorphine in opiate addiction—may be possible for cocaine-addicted patients with ADHD. Although the researchers did not formally assess SR-MPH’s effects on participants’ ADHD symptoms, they did not note any obvious benefits.

### Source

- Drug and Alcohol Dependence 82(2):158-167, 2006.  
**NN**

## Brain Mechanism Turns Off Cocaine-Related Memory in Rats

An exploration of memory’s molecular basis suggests potential novel therapeutic approaches to cue-induced craving.

By Patrick Zickler, *NIDA NOTES* Contributing Writer

Scientists at the University of California, Irvine, have added to evidence that a brain enzyme controls key memory processes that link drug experiences, the surroundings in which they take place, and the urge to repeat them. In a series of experiments, inhibiting the enzyme attenuated a rat behavior that is a laboratory stand-in for human cue-induced drug-seeking. The findings suggest that in the future, therapeutically manipulating levels of the enzyme might cut addicted individuals’ vulnerability to environmental triggers for drug craving and abuse.

The NIDA-funded scientists, Drs. Courtney Miller and John Marshall, focused on the enzyme in an attempt to elucidate the ways cellular activities promote cue-induced drug-seeking. “Although studies have established that nerve cells in the core of the nucleus accumbens are critically involved,” Dr. Miller says, “we haven’t had much information about the molecular mechanisms that transform environmental cues into an urge to repeat drug-associated behavior.” One likely candidate for a role in the process, however, was extracellular signal-regulated kinase (ERK). This enzyme is known both to foster the new cellular connections that register emotional and object recognition memories in the brain and to be affected by cocaine.

The researchers explored ERK’s role in a behavior called conditioned place preference (CPP). By exhibiting CPP—lingering in a part of a cage where it has had a drug experience—an animal indicates that it remembers the experience, associates it with the preferred cage area, and is seeking to have it again (for more on CPP, see “Animal Experiments

in Addiction Science,” *NIDA Notes*, Vol. 20, No. 5). In previous research, blocking ERK activity in the nucleus accumbens (NAc) prior to exposing rats to drugs prevented them from developing CPP. Drs. Miller and Marshall reasoned that if blocking ERK forestalls initial formation of the memory links underlying CPP, it might also weaken links that had already been formed. The potential therapeutic implications would be significant if this were so; they would suggest that manipulating ERK might be a means to disrupt drug-environment associations that are already established by the time patients begin therapy.

To test their hypothesis, the researchers administered cocaine to rats daily for 9 days, after which the rats exhibited CPP whenever they were placed back in their test cage. The researchers then conducted a series of trials and assays that showed:

- CPP involves activation of ERK: Rats that lingered in the cocaine-associated area of the test cage had higher ERK levels in the core area of the NAc than a group of rats that had not been exposed to cocaine or a third

**ENZYME BLOCKAGE DISRUPTS DRUG-SEEKING** In experiments with rats, researchers used a compound called U0126 to block ERK, an enzyme that facilitates memory formation and consolidation.

Days 1-9	Day 10	Day 11	Day 26	Conclusions
 <p>Researchers trained rats to associate cocaine with a specific setting. The animals signaled their successful conditioning by exhibiting conditioned place preference—spending more time in a chamber where they had received cocaine injections over 9 days.</p>	<b>Group 1</b> Rats received infusions of U0126 or a control vehicle. After 30 minutes, they were tested for CPP.  Rats given U0126 showed no preference for a cocaine-associated chamber. Control rats did show preference for the cocaine-associated chamber.	Rats given U0126 still exhibited no CPP.  Control rats retained CPP.		Inhibiting ERK activity can block retrieval of cocaine-associated memories for 24 hours.
	<b>Group 2</b> Rats were tested for CPP and immediately infused with either U0126 or the control vehicle.	Rats given U0126 showed no CPP.  Control rats showed CPP.		Inhibiting ERK activity immediately after cocaine-associated memories are retrieved can make the memories unavailable for subsequent retrieval at 24 hours and for at least 2 weeks.
	<b>Group 3</b> Rats were tested for CPP and immediately infused with either U0126 or the control vehicle.		Rats given U0126 showed no CPP.  Control rats showed CPP.	
	<b>Group 4</b> Rats received an infusion of U0126 and remained in their home cage with no testing and therefore no opportunity for memory retrieval.		Rats showed a strong CPP for the cocaine-associated environment.	

group exposed to cocaine but not trained to exhibit CPP.

- *Inhibiting ERK activity can block retrieval of cocaine-associated memories for 24 hours:* The investigators infused a compound called U0126, which reduces ERK activity, directly into the NAc cores of some of the CPP-trained rats. When placed in the test cage 30 minutes later, these rats gravitated to the cocaine-associated area much less consistently than did a group of CPP-trained rats that were injected with saline rather than U0126. Tested again 24 hours later, they still exhibited little or no preference for the area.
- *Inhibiting ERK activity at the time cocaine-associated memories are retrieved can make them unavailable for subsequent retrieval for at least 2 weeks:* Rats were placed in the test cage and given U0126 immediately after exhibiting CPP. When retested the following day, they showed no partiality to the drug-associated cage area, nor did a similarly treated group of animals tested 2 weeks later. “These animals had effectively recollected their cocaine experience on day 1, but on day 2 and even 14 days later, there was no evidence that the memory was active,” Dr. Miller notes.

“This last observation provides powerful evidence that disruption of ERK activity blocks memory reconsolidation,” Dr. Miller says. “Memories are unstable during the interval between being recalled and being refiled, and, if the reconsolidation process is disrupted, the memory can be lost. The animals behave as though it had never been formed to begin with. The fact that powerful memories associated with drugs may become pliant and susceptible to disruption by ERK inhibition during reconsolidation suggests opportunities for new therapies.” For example, pending much further research, it is conceivable that an approach combining exposure to a cue with administration of an ERK inhibitor might prevent a patient from reconsolidating—and thus erase—the memory chain linking the cue to craving.

## New Findings on Memory Have Implications For Treatment

Groundbreaking research on the molecular basis of long-term memory could open a new path to the treatment of drug addiction, post-traumatic stress disorder (PTSD), and other conditions in which memories exert a powerful influence on behavior, according to neuroscientists who presented research at a NIDA conference, “Frontiers in Addiction Research.” Their findings suggest that when long-term memories are recalled, they return to a state in which they can be altered or erased before undergoing “reconsolidation” for future potential use. This discovery could lead to the development of medications that disrupt the reconsolidation process and thereby prevent memories associated with drug abuse or trauma from being reestablished.

Dr. Karim Nader of McGill University in Montreal, Canada, explained the process of reconsolidation and how interventions based on that process might work. The goal, he said, is not to simply erase memory, but rather to modulate the memory so that its effects are more manageable in conditions such as PTSD or addiction. “Our research shows that when a consolidated long-term memory is reactivated, it returns to a labile state similar to short-term memory. Neurons must synthesize new proteins in order for the memory to persist. If protein synthesis is inhibited after reactivation, reconsolidation can’t occur,” he said.

Although he cautioned that there is an enormous amount of work to be done before testing the effect in human patients, Dr. Nader said his animal studies have significant clinical implications. “In the case of drug addiction, if drug-related memories could be reactivated and prevented from being restored, drug-seeking behavior could in principle be greatly reduced in one session,” he said. “It sounds like science fiction, but it is not.”

Dr. Susan Volman of NIDA’s Division of Basic Neuroscience and Behavioral Research and Dr. Barbara Sorg from Washington State University cochaired the session on “Reconsolidation of Memory: A New Approach to Treat Drug Addiction?” at the conference, which was held in Washington, D.C., November 11, 2005, in conjunction with the annual meeting of the Society for Neuroscience.

“This research provides important new understanding of the processes that take place when the brain is manipulating memories, and it identifies specific molecules that help shape those processes,” comments Dr. Jerry Frankenheim of NIDA’s Division of Basic Neuroscience and Behavioral Research. “The fact that the intervention with U0126 came after the animals had already learned the cocaine-place association may be important for translating this

research to possible clinical application. There are many ways to block the initial consolidation of memory, but the approach used in this research—interrupting reconsolidation—is much more relevant to intervening in cocaine abuse,” he adds.

#### Source

- Miller, C.A., and Marshall, J.F. Molecular substrates for retrieval and reconsolidation of cocaine-associated contextual memory. *Neuron* 47(6):873-884, 2005. **NN**

## Blocking Protein Also Stops Drug-Linked Memory

NIDA-sponsored researchers at Mount Sinai School of Medicine, New York, have found another way to break the chain of molecular events that binds drug-taking to a familiar environment: inhibiting protein synthesis. Earlier research established that gene-directed protein manufacture is necessary to stabilize a new memory and that blocking this molecular process can keep lasting memories from being formed and even disrupt an established memory.

The Mount Sinai researchers, led by Dr. Cristina Alberini, performed experiments similar to those done by Drs. Miller and Marshall, but exposed the rats to morphine rather than cocaine and used chemicals that blocked protein synthesis rather than ERK. Like ERK inhibition, the protein blocker weakened conditioned place preference, but it did so only when given in close conjunction with an actual morphine administration.

Unlike the ERK inhibition technique used by the UC researchers, “blocking protein synthesis only worked after a repeat of the full experience,” says Dr. Susan Volman of NIDA’s Division of Basic Neuroscience and Behavioral Research. But the take-home message is the same: “It is possible to disrupt the strong association between a drug and place cues.”

The chemicals used in this experiment inhibit protein synthesis in general, and it will take a lot more research to develop pharmacotherapy that goes after specific proteins and molecular pathways involved in CPP, Dr. Volman says. But potential applications, she suggests, might go beyond the addiction-environment link: “If we can use protein synthesis inhibition to uncouple place from relapse, perhaps we’ll ultimately be able to uncouple cues like paraphernalia, or even the memory of the drug experience.”

#### Source

Milekic, M.H., et al. Persistent disruption of an established morphine conditioned place preference. *Journal of Neuroscience* 26(11):3010-3020, 2006.

## Nicotine and Cocaine Vaccines Move Forward

**NICOTINE:** A vaccine to prevent nicotine addiction demonstrated a good safety profile in a recent clinical trial with 68 healthy smokers. Dr. Dorothy Hatsukami of the University of Minnesota and colleagues found NicVAX to be safe and well tolerated, with side effects comparable to those of placebo. Overall, the reported side effects—most commonly general discomfort, headache, and muscle pain—were mild to moderate in severity. The vaccine triggers the production of antibodies that bind nicotine in the blood and keep it from reaching the brain. Nevertheless, healthy smokers who received the vaccine did not experience craving or withdrawal symptoms, nor did they increase the number of cigarettes smoked during a 38-week study and followup.

### Source

- *Pharmacodynamics and Drug Action* 78(5):456-467, 2005.

**COCAINE:** An investigational medication designed to induce the body's natural defenses to inactivate cocaine before it reaches the brain has cleared an important human trials hurdle. Dr. Bridget Martell, Dr. Thomas Kosten, and their colleagues at Yale University tested the compound, now designated TA-CD, in an open-label study involving 18 cocaine-addicted participants who took it for either 8 or 12 weeks. No participant reported adverse effects, and all still had cocaine-specific antibodies in their bloodstream 6 months after their first injection. At the 6-month followup, participants reported exposure to the drug produced only mild euphoric effects, even though blood tests showed waning concentrations of the antibodies.

### Source

- *Biological Psychiatry* 58(2):158-164, 2005. 

## Cocaine Abuse and HIV Are Linked With Coronary Calcification

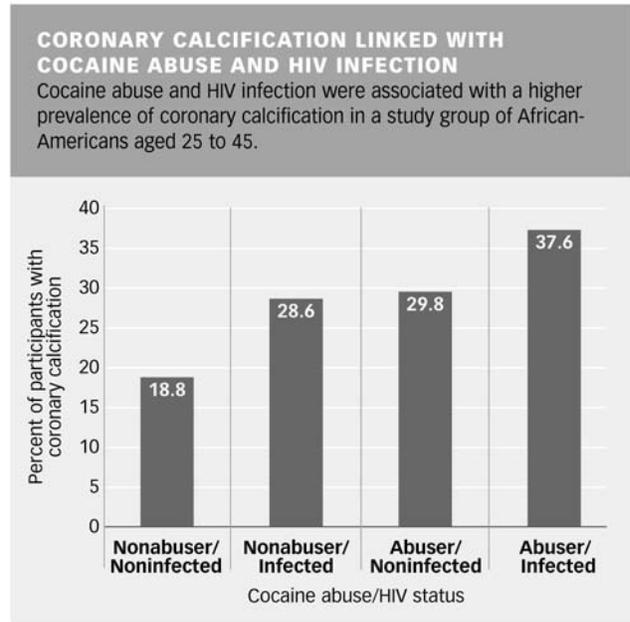
Cardiovascular changes that are potential risk factors for serious heart disease are detected in relatively young people with HIV infection or a history of cocaine abuse.

By Lori Whitten, NIDA NOTES Staff Writer

Cocaine abuse and HIV infection each raise the likelihood that calcium deposits will form in coronary arteries, according to a NIDA-supported study. The findings, by Dr. Shenghan Lai and colleagues at The Johns Hopkins University, suggest that individuals with either problem may develop elevated risks for serious, potentially fatal heart disease. The gradual buildup of calcium deposits and fat along the inner walls of blood vessels produces atherosclerosis, the narrowing and obstruction of the vessels that is a major cause of strokes and heart attacks. Although none of the participants in the study had a clinical heart problem, all were relatively young to have coronary calcification.

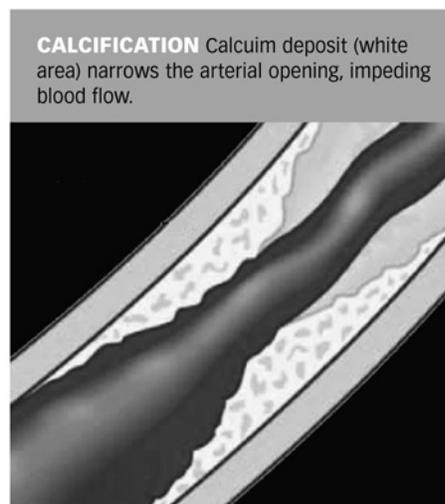
Dr. Lai and his colleagues used cardiac computed tomography (CT) scanning to detect the presence of coronary calcification and the number, size, and volume of calcium deposits in 192 African-American men and women aged 25 to 45. Thirty-two of the participants did not have HIV infection and had never abused cocaine (HIV-/cocaine-), 28 had the infection and were nonabusers (HIV+/cocaine-), 47 did not have the infection and had abused cocaine (HIV-/cocaine+), and 85 had both conditions (HIV+/cocaine+). About two-thirds were men.

The results revealed coronary calcification in almost one-third (31 percent) of the participants. The prevalence was twice as high in the HIV+/cocaine+ group (38 percent) as in the HIV-/cocaine- group (19 percent). In the other two groups, the proportion of participants with the condition fell in between, with 29 percent of the HIV+/cocaine- and 30 percent of the HIV-/cocaine+ groups showing coro-



nary calcification (see chart). In the U.S. population as a whole, the prevalence of coronary calcification among 25- to 45-year-olds is about 18 percent.

Participants with HIV infection and/or a history of cocaine abuse had more calcium deposits and a greater volume of calcification than nonabusers without the infection. Compared with the HIV-/cocaine- group, the total volume of coronary calcium



was 2.9 times as high in the HIV+/cocaine- group, 2.6 times as high in the HIV-/cocaine+ group, and 3.5 times as high in the HIV+/cocaine+ group. The associations held when the researchers took into account cardiovascular disease risk factors, includ-

***“Coronary calcification among people at such a young age is a striking observation and suggests that clinicians should monitor heart disease in these populations, advise patients to make lifestyle changes, and perhaps treat conditions that affect heart health, such as high blood pressure.”***

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ing age, body mass index, lipid levels, blood pressure, and whether patients were taking HIV medication. The study was too small to determine whether HIV and cocaine contribute independently to calcification when both are present, or whether they interact physiologically to promote it even more.

Cardiovascular complications have been well documented in patients who abuse cocaine and also have HIV infection, but this study is the first to show arterial changes prior to the development of cardiovascular symptoms and to link them with cocaine abuse alone and HIV infection alone. Larger, longer studies are needed to confirm Dr. Lai's associations and to determine whether or how cocaine- and HIV-associated calcification progresses to clinical atherosclerosis and heart disease.

Dr. Jag Khalsa of NIDA's Division of Pharmacotherapies and Medical Consequences of Drug Abuse says early

signs of cardiovascular disease should be taken very seriously because they are strongly connected to two major causes of death—stroke and heart attacks. "Coronary calcification among people at such a young age is a striking observation and suggests that clinicians should monitor heart disease in these populations, advise patients to make lifestyle changes, and perhaps treat conditions that affect heart health, such as high blood pressure," says Dr. Khalsa.

#### Source

- Lai, S., et al. Human immunodeficiency virus 1 infection, cocaine, and coronary calcification. *Archives of Internal Medicine* 165(6):690-695, 2005. **NN**

## Modafinil Improves Behavioral Therapy Results In Cocaine Addiction

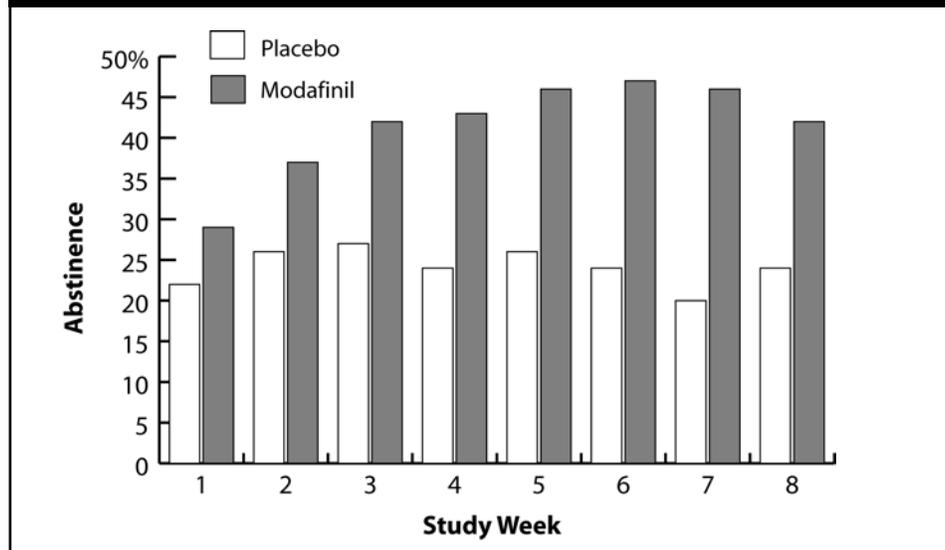
By Patrick Zickler, *NIDA NOTES* Staff Writer

NIDA-supported researchers evaluating modafinil’s potential to enhance behavioral treatment for cocaine addiction have reported a second successful clinical efficacy trial. The new results affirm and extend the promising findings of the earlier, smaller, and less stringent “open label” trial, and they set the stage for large-scale multisite trials that could definitively establish the medication’s usefulness.

Dr. Charles Dackis and colleagues at the University of Pennsylvania Treatment Research Center recruited 62 individuals (44 male, 18 female; mean age, 44.5 years) for their double-blind study. All had come to the Center seeking treatment for cocaine addiction, had ingested at least \$200 worth of cocaine in the 30 days prior to presenting for treatment, and met the cocaine-dependence criteria of the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV). The patients agreed to visit the clinic twice a week for individual sessions of cognitive-behavioral therapy (CBT) and provide urine samples 3 times a week for the 8-week course of the study. Once each week, the clinic staff dispensed a week’s supply of pills, either modafinil in daily doses of four 100 mg pills (30 patients) or an equal number of identical-looking placebo pills (32 patients).

Throughout the study, modafinil-treated patients gave fewer cocaine-positive urine samples than the placebo group. “More impressive, though, is the fact that more than twice as many modafinil patients as placebo patients (33 percent compared with 13 percent) were able to attain abstinence for 3 weeks or more,” Dr. Dackis says. “Maintaining abstinence for a prolonged period during treatment is an important clinical threshold. Cocaine is a binge drug, and it is common in outpatient treatment for a patient to go 4 or 5 days without using, relapse, then

### Combining Modafinil with Behavioral Therapy in Cocaine Addiction Treatment Increases Likelihood of Abstinence



*Abstinence rates among patients who received modafinil plus behavioral therapy during 8-week cocaine addiction treatment were consistently higher than rates among patients who received placebo.*

have another clean week. The long continuous abstinence we saw with modafinil is a strong and encouraging signal that this medication can help patients avoid relapse during the critical first weeks of treatment.” Both groups of patients attended the same average number of CBT sessions, he adds, further supporting the likelihood that modafinil was the factor accounting for reduced cocaine abuse in those who received it.

Modafinil, a medication currently used to treat narcolepsy, enhances levels of glutamate, a chemical that influences the activity of cells throughout the brain. Animal research has shown that repeated exposure to cocaine depletes glutamate levels in brain regions associated with development of dependence and addiction, and that increasing glutamate concentrations will block reinstatement of cocaine self-administration in rats—a model of relapse to drug abuse in humans (see “Brain Glutamate Concentrations Affect Cocaine Seeking,” *NIDA NOTES*, Vol. 19, No. 3, p. 1).

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Modafinil's modulation of glutamate transmission may account for a striking effect reported by patients: "The mechanism for this isn't clear, but some patients receiving modafinil told us that if they did use cocaine it did not produce the irresistible urge to use more, which they had always felt before," Dr. Dackis says. "Some of the patients told me they had flushed cocaine away. In 25 years of treating addiction, no one ever told me they threw away cocaine."

"The body of research suggesting that modafinil is effective in treating cocaine addiction is growing," says Dr. Ivan Montoya of NIDA's Division of Pharmacotherapies and Medical Consequences of Drug Abuse. "Animal research supports the assumption that modafinil reverses the cocaine-induced neurochemical disruptions of glutamate and of dopamine-containing neurons in the brain's reward centers. Clinically, modafinil has effects that are

opposite to the symptoms of cocaine withdrawal, which usually include oversleeping, depression, poor concentration, and craving."

Dr. Dackis and his colleagues are now planning the next test for modafinil: a multisite clinical trial that will include more than 650 participants. The study will evaluate modafinil's efficacy in doses of 200 mg and 400 mg per day in combination with CBT, and results may be available by mid-2006, Dr. Montoya says.

#### Source

- Dackis, C.A., et al. A double-blind, placebo-controlled trial of modafinil for cocaine dependence. *Neuropsychopharmacology* 30(1):205–211, 2005. **NN**

## Disulfiram Reduces Cocaine Abuse

By Lori Whitten, NIDA NOTES Staff Writer

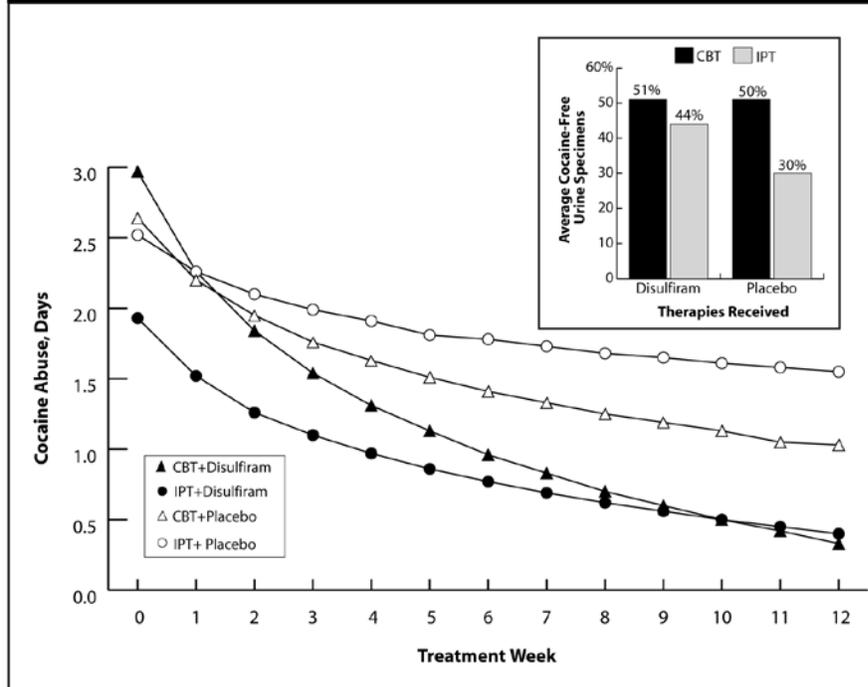
Disulfiram, a well-established medication for the treatment of alcoholism, has helped people addicted to cocaine reduce abuse of the drug from 2.5 days a week to 0.5 days a week on average. The finding builds on previous studies in which NIDA-funded researchers demonstrated the medication's promise in two subgroups of cocaine abusers—alcoholics and those with co-occurring opioid addiction. Their current results suggest that disulfiram is effective in treating the general population of cocaine-addicted patients, including those who are nonalcoholic. The medication's effectiveness in nonalcoholic patients adds to evidence that disulfiram works directly to reduce cocaine abuse rather than indirectly by reducing concurrent alcohol abuse. The investigators also found that, like disulfiram, cognitive-behavioral therapy (CBT) reduced cocaine abuse by 2 days.

Dr. Kathleen Carroll and her colleagues at Yale University School of Medicine in New Haven, Connecticut, treated 121 outpatients for 12 weeks. The 32 women and 89 men met the criteria for cocaine dependence specified in the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*

(DSM-IV) and reported abusing cocaine 13 days on average during the month and 2.5 days during the week before treatment. During the study, each patient received either 250 mg/day of disulfiram or placebo and participated in weekly individual sessions of behavioral therapy, either CBT or IPT (interpersonal psychotherapy). CBT coaches patients to recognize and cope with situations that tend to induce drug craving and abuse. In IPT, patients clarify and address key personal problems related to the substance abuse. On average, patients attended eight behavioral therapy sessions. The type of therapy did not affect rates of treatment completion.

All patients abused cocaine on fewer days during treatment than they had in the weeks before. The extent of recovery depended on the therapy. By the end of treatment, patients taking disulfiram reduced weekly cocaine abuse by 2 days on average, compared with 1 day for

### Both Disulfiram and CBT Reduce Cocaine Abuse in Patients



Over the 12-week study, patients taking disulfiram or participating in cognitive-behavioral therapy (CBT) demonstrated greater reductions in cocaine abuse than those taking placebo or receiving interpersonal psychotherapy (IPT).

those taking the placebo, no matter which psychotherapy group they participated in. Similarly, patients who participated in CBT reduced weekly cocaine abuse by 2 days on average, compared with 1 day for IPT participants regardless of which medication they received. The data were based on self-reported cocaine abuse, but weekly urine tests generally corroborated (84 percent) patient information. More urine samples from participants receiving disulfiram and CBT (51 percent), placebo and CBT (50 percent), and disulfiram and IPT (44 percent) were cocaine negative during the study than those from participants taking the placebo and IPT combination (30 percent); the latter demonstrated the least favorable treatment outcomes.

Dr. Carroll and her colleagues verified compliance with the daily medication regimen by testing urine samples for tracers that were added to the medication and the placebo. Taking the capsules every day was associated with better outcomes among patients who received either disulfiram

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or placebo, although disulfiram's effectiveness remained superior to placebo's when the researchers took medication compliance into account. Dr. Carroll emphasizes that "not taking medication can undercut the benefits of all pharmacotherapies, and an important goal of behavioral therapy is improvement of medication compliance." Dr. Dorynne Czechowicz of NIDA's Division of Clinical Neuroscience, Development and Behavioral Treatment says the findings highlight the importance of integrating addiction medication and behavioral treatment. "All patients in the study participated in some form of behavioral therapy, which facilitated recovery from substance abuse and helped patients stick to the medication regimen," she says.

Disulfiram had a more pronounced benefit for patients who were not alcohol-dependent at the outset of the study and for those who abstained from alcohol during the study. Patients who drank while taking disulfiram tended to take less of the medication than those who did not drink. Instead of deterring drinking and thereby reducing cocaine abuse, the unpleasant physical consequences of mixing alcohol with the medication led patients to stop taking disulfiram when they wanted to drink or abuse cocaine. "These findings seem to validate the clinical observation that patients have to stop drinking before they can kick cocaine abuse," says Dr. Carroll. Patients participating in CBT showed better outcomes than those in IPT, regardless of concurrent drinking. CBT, a well-established behavioral treatment, might be the best option for some patients, including those facing co-occurring

alcohol and cocaine addiction, she says. Patients without concurrent alcoholism may be candidates for disulfiram, CBT, or a combination.

Disulfiram interacts with cocaine to produce an unpleasant sense of hyperstimulation. In laboratory studies, people experiencing a disulfiram-cocaine interaction demonstrated increased heart rate and blood pressure and reported anxiety, paranoia, and restlessness. Animal studies suggest that disulfiram, like cocaine, enhances the activity of the neurotransmitter dopamine. Possibly, when someone has taken disulfiram, subsequent administration of cocaine elevates dopamine to excessive levels that produce discomfort and aversion.

Animal research suggests that disulfiram increases levels of dopamine by blocking an enzyme that breaks dopamine down. People with low levels of the enzyme, dopamine- $\beta$ -hydroxylase (DBH), have increased dopamine activity. Hormones, as well as genes, may influence DBH levels. Researchers suspect that estrogen hormones increase DBH, attenuating the effect of disulfiram, which could explain why women seem to benefit less than men.

#### Source

- Carroll, K.M., et al. Efficacy of disulfiram and cognitive behavior therapy in cocaine-dependent outpatients: A randomized placebo-controlled trial. *Archives of General Psychiatry* 61(3):264-272, 2004. **NN**

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## Disulfiram May Work for Men, but Not Women

Researchers studying disulfiram, an “old” medication for alcoholism that has emerged as a potential “new” treatment for cocaine abuse, have found a possible sex difference in treatment response: Cocaine-addicted men who were treated with the medication had better outcomes than those who were not, whereas women showed no significant difference in outcome.

Dr. Kathleen Carroll of Yale University School of Medicine and her colleagues have conducted several studies on the medication’s effects on cocaine abuse and have moved on to the next step—determining which types of patients benefit from the treatment. There were not enough women in their recent study (see “Disulfiram Reduces Cocaine Abuse”) to analyze sex differences, so the investigators combined data from two of their other treatment studies to compare men’s and women’s responses to disulfiram. “We know that men and women react to cocaine differently. For example, women progress more quickly to cocaine addiction than men. Sex differences in treatment response seemed likely,” says Ms. Charla Nich, lead investigator of the study.

In one study, the investigators treated alcohol- and cocaine-addicted patients with disulfiram and various behavioral therapies; in the second, they tested disulfiram in opioid- and cocaine-addicted patients under treatment with methadone. Altogether, 191 patients participated in the studies, which, when combined, had enough women (36 percent) to permit a valid comparison.

Both studies found that patient groups taking disulfiram reduced cocaine abuse compared with groups receiving placebo. But when the investigators combined and reanalyzed the data, they found that only the men in the groups responded to the medication. The reanalysis indicated that men treated with disulfiram produced a higher percentage of drug-free urine specimens than men in the placebo groups (49 versus 30 percent). Among women, however, the percentage of drug-free specimens was not significantly different with disulfiram or placebo (38 versus 39 percent).

“Our data don’t conclusively prove a sex difference in the response to disulfiram,” says Ms. Nich. “For that, we need studies that directly compare men and women taking the medication.” NIDA’s Dr. Dorynne Czechowicz agrees that researchers should follow up on these intriguing preliminary findings, which “highlight the importance of paying attention to sex differences in medication development and other drug abuse research.”

**Source:** Nich, C., et al. Sex differences in cocaine-dependent individuals’ response to disulfiram treatment. *Addictive Behaviors* 29(6):1123-1128, 2004. 

## Genetic Engineering Reveals Proteins' Key Role in Sensitivity to Cocaine

Genetic engineering strategies like those used at the California Institute of Technology to study nicotine addiction have helped other investigators identify a pair of proteins that seem to influence cocaine addiction.

Dr. Peter Kalivas and his colleagues at the Medical University of South Carolina in Charleston developed a strain of mice lacking two genes, called *Homer1* and *Homer2*, that direct production of proteins linked to cocaine's effects in the brain. The researchers found that the *Homer* "knock-out" mice were more sensitive than unmodified mice to the behavioral effects of cocaine.

Compared with unmodified mice, animals missing either *Homer1* or *Homer2* developed stronger place conditioning—when allowed to move freely, they would spend more time in a compartment where they had received cocaine than in a compartment with no drug association. The knock-out mice also were more sensitive to cocaine's stimulatory effect; when placed in a chamber equipped with photoelectric beams that could measure activity, the knock-outs were approximately 50 percent more active than unmodified mice following cocaine injections. To verify the role of the *Homer* genes in increased sensitivity to cocaine, the researchers restored *Homer* genes in the brains of the knock-outs, eliminating the previously seen differences in stimulation and place conditioning.

"The fact that *Homer* deletions result in these augmented responses to cocaine suggests that disruption of *Homer* protein-regulated signaling in the brain is a central step in development of cocaine addiction," Dr. Kalivas says. Additional evidence of this role is seen in changes that *Homer* deletion causes in levels of the brain messenger chemical glutamate, he adds. *Homer* knock-out mice that had never been exposed to cocaine had nucleus accumbens (NAc) glutamate concentrations about 50 percent lower than mice with the genes—an effect similar to that seen in mice after cocaine withdrawal. This effect, too, was reversed when the scientists injected *Homer* genes into the NAc.

The association between *Homer* activity and the conditions of cocaine withdrawal is particularly intriguing, according to Dr. Kalivas, because other researchers have shown that *Homer* protein levels rise and fall in response to environmental cues and changing levels of stress. "*Homer* may be a window to study the molecular basis of the important link between environmental stress and cocaine addiction."

### Source

- Szumlinski, K.K., et al. Homer proteins regulate sensitivity to cocaine. *Neuron* 43(3):401-413, 2004. **NN**

## Researchers Investigate Cocaine “Abstinence Syndrome”

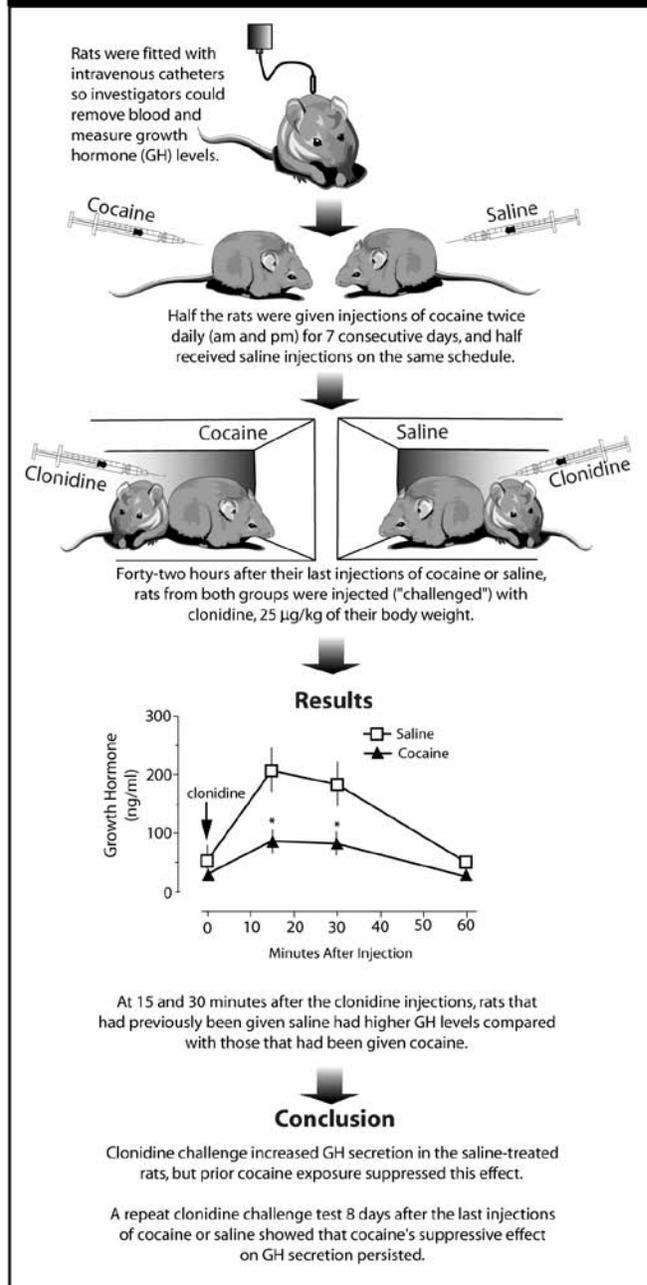
By Lori Whitten, NIDA NOTES Staff Writer

Researchers have long focused on motivation as the centerpiece of the addiction puzzle, based on the observation that in many addicted individuals, compulsive drug-seeking behavior overtakes the most fundamental motivators, including food and sex. Now, however, researchers are beginning to examine another aspect of addictive drugs—their powerful and long-lasting effects on mood. People who have recently stopped abusing stimulant drugs commonly experience “abstinence syndrome”: low energy, irritability, restlessness, an inability to feel pleasure, and problems with concentration. Anxiety and panic attacks also are sometimes associated with cocaine abstinence. Addiction researchers are examining the neurobiology underlying abstinence syndrome with an eye toward improving current therapies’ ability to alleviate these symptoms and prevent relapse.

NIDA investigators concentrated recently on the impact of cocaine on the neurotransmitter norepinephrine (NE), one of the two neurochemicals most responsible for mood. Stimulation of brain cells by serotonin and NE is central to positive mood, feeling energetic, and maintaining focus as well as sleep, appetite, and coping with stress. Two recent animal studies, one conducted by investigators at NIDA’s Intramural Research Program (IRP) in Baltimore and another by NIDA-funded researchers at Harvard Medical School’s New England Primate Research Center in Southborough, Massachusetts, suggest that cocaine may compromise NE’s ability to stimulate brain cells by altering a communication protein, called the  $\alpha_2$ -adrenergic receptor, on the surfaces of the cells.

In the Baltimore study, Dr. Michael Baumann and colleagues hypothesized that by giving rats cocaine regularly—twice-daily injections at 15 mg/kg of the animals’ body weight for 7 days—and then abruptly stopping it, they would reduce the  $\alpha_2$ -adrenergic receptors’ responsiveness. To assess the adrenergic system in the cocaine-exposed, now “abstinent” rats, the researchers used the clonidine challenge procedure, which indirectly indicates  $\alpha_2$ -adrenergic receptor activity by measuring how much plasma levels of growth hormone (GH) increase following exposure to the drug clonidine (see “Clonidine Challenge Test Results Suggests That Cocaine Abuse Desensitizes Adrenergic System”). Confirming the researchers’ hypothesis, the cocaine-exposed animals showed a blunted GH response—less than half that of saline-exposed animals—15 and 30 minutes after the clonidine challenge. The rats’ response was still low, but returning toward

### Clonidine Challenge Suggests That Cocaine Abuse Desensitizes Adrenergic System



*Clonidine elevates growth hormone (GH) secretion in rats, a response mediated through the  $\alpha_2$ -adrenoreceptors in the brain. When rats are exposed to repeated cocaine injections, GH secretion in response to clonidine is lowered. The clonidine challenge test is used to measure  $\alpha_2$ -adrenoreceptor sensitivity in humans as well as animals.*

normal, when the researchers repeated the challenge procedure 8 days after daily injections stopped.

The findings suggest that cocaine consumption and cessation may lower recovering individuals' moods by desensitizing the  $\alpha_2$ -adrenoreceptors, but the results are preliminary. "The adrenergic system is complex, with multiple pathways in the brain and body," says Dr. Baumann. "We still have much to learn about how drug exposure affects all these pathways, how it affects serotonin, and how they both influence growth hormone."

People with depression secrete less GH in response to the clonidine challenge than do those without the condition, a clinical finding that suggests possible links between NE receptor function, mood disorders, and cocaine withdrawal. "Although investigators are only beginning to characterize norepinephrine's role in addiction, a growing body of animal and clinical research suggests important connections between the adrenergic system, mood and anxiety disorders, and the depression-like symptoms experienced by people trying to overcome cocaine addiction," Dr. Baumann says.

### A Role in Relapse?

In a study that explored the chemical basis of mood and cocaine relapse, Dr. Roger Spealman and colleagues hypothesized that blocking  $\alpha_2$ -adrenergic receptors in monkeys would generate anxiety and induce a resumption of previously extinguished cocaine-seeking behavior.

The researchers trained monkeys to seek cocaine by pressing a lever. When the monkeys reached a high rate of lever pressing, the researchers disconnected it from the injection device. The monkeys kept trying the lever for a while, but with no more cocaine forthcoming, gradually left off. The investigators hypothesized that giving monkeys a drug to reduce NE activity would make the animals anxious, and the anxiety would intensify their urge for cocaine to the point where they would resume pressing the lever despite recent experience of its futility.

Dr. Spealman and colleagues gave the now "abstinent" animals various doses of two  $\alpha_2$ -adrenergic blocking agents, yohimbine and RS-79948, in separate test sessions. Both  $\alpha_2$ -adrenergic receptor blockers set the animals to pressing the lever again. The increase ranged from 1.5 to 4 times the response to injections of sterile water, depending on the dose and drug. The yohimbine injections also increased physiological and behavioral signs of anxiety: salivary cortisol levels and self-grooming and scratching.

To confirm that yohimbine's behavioral effects were due to its inhibition of the  $\alpha_2$ -adrenergic system, rather than any of the other neurotransmitter systems this agent

affects, the researchers conducted further experiments. First, they gave the monkeys yohimbine plus clonidine, a drug that selectively blocks yohimbine's effects on the  $\alpha_2$ -adrenergic receptors. With this regimen, the animals resumed lever pressing hardly or not at all. Next, the researchers gave the monkeys yohimbine plus flupenthixol, a drug that reduces dopamine activity and has no effect on yohimbine's inhibition of  $\alpha_2$ -adrenergic activity. Under this regimen, the animals did resume lever pressing. Both of these findings pointed to  $\alpha_2$ -adrenergic suppression as the key to yohimbine's effects in the first experiment. Yohimbine did not stimulate movement or make the

animals restless, which indicates that it worked by blocking receptors, not simply by mimicking the stimulant effects of cocaine.

"It makes sense physiologically that the adrenergic system might play a role in addiction; cocaine activates norepinephrine as much as it stimulates dopamine," says Dr. Spealman. Work by others suggests that cocaine abuse leads to long-term desensitization of the NE system in areas of the brain involved in reward and stress-induced reinstatement of drug-

seeking. "This has led some researchers to speculate that the desensitized adrenergic system increases vulnerability to further norepinephrine disturbances—for example, those caused by stress or drug re-exposure—which may increase relapse risk," explains Dr. Spealman.

Researchers continue to seek to unravel the complexities underlying withdrawal and relapse to drug-taking. If, as scientists now think, these phenomena arise from sequential alterations in both the reward and mood pathways, "addiction medications may have to target different neurotransmitters at various stages of abstinence," says Dr. Minda Lynch of NIDA's Division of Basic Neurosciences and Behavior Research.

### Sources

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- Lee, B.; Tiefenbacher, S.; Platt, D.M.; and Spealman, R.D. Pharmacological blockade of  $\alpha_2$ -adrenoreceptors induces reinstatement of cocaine-seeking behavior in squirrel monkeys. *Neuropsychopharmacology* 29(4):686-693, 2004. **NN**

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***"It makes sense physiologically that the adrenergic system might play a role in addiction; cocaine activates norepinephrine as much as it stimulates dopamine."***

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## Cocaine-Related Environmental Cues Elicit Physiological Stress Responses

By Lori Whitten, *NIDA NOTES* Staff Writer

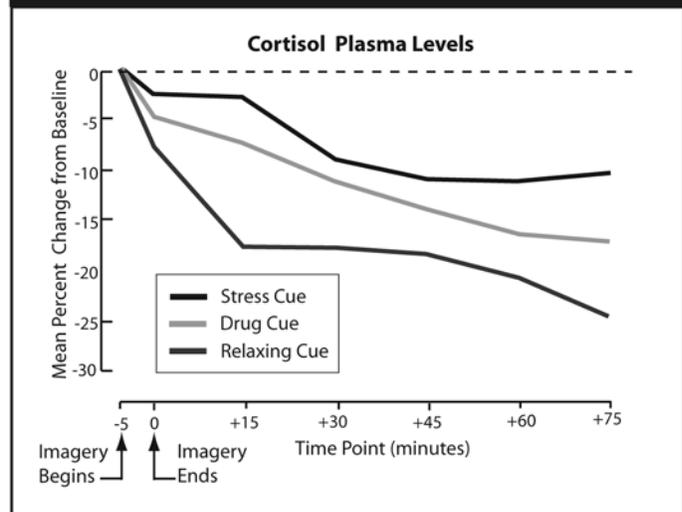
Overcoming addiction is in part a learning process, and people in recovery work to make and maintain healthy changes. In behavioral therapy, clinicians help patients learn techniques to avoid or navigate safely through experiences that evoke powerful urges to consume drugs: stressful situations and the people, places, and things the patient associates with past drug-taking experiences. Recent NIDA-funded research has demonstrated that cocaine-addicted patients respond to these drug-associated features in the environment as if they were stressful situations, with the release of adrenaline and other hormones that increase pulse rate and blood pressure, among other effects. The investigators also found that these responses of cocaine abusers take a long time to normalize, perhaps indicating that the drug heightens sensitivity to stress.

Dr. Rajita Sinha and colleagues at the Yale University School of Medicine in New Haven, Connecticut, conducted their study with 54 cocaine-addicted men and women, aged 21 to 50, at an inpatient research facility. Before entering treatment, the patients had abused cocaine for an average of 9 years; immediately prior to treatment, they had, on average, consumed the drug 3 or more times per week and spent \$224 weekly to buy the drug. Almost all (94 percent) consumed cocaine in its smoked form (crack). Each patient had been abstinent for 2 weeks prior to the laboratory sessions.

To study physiological and emotional responses to stress and cocaine-related cues in the laboratory, the investigators drew on the patients' individual experiences. They elicited from each patient detailed accounts of three past personal experiences: one very stressful, one relaxing, and one specifically related to taking cocaine. From each patient's stories, the researchers created three tape recordings that would, when played back, rekindle his or her feelings of stress, relaxation, and cue-induced craving (see "Reliving A Stressful Situation: Excerpt From a Guided Imagery Tape"). To enhance the strength of the responses, the researchers trained the patients in guided imagery—how to relive a scene mentally while listening to a tape, as if it were happening at that moment.

Each patient participated in three 3-hour testing sessions. Throughout each session, the patient sat on a hospital bed wearing headphones, an intravenous catheter in one arm for drawing blood, a blood pressure monitor on the other arm, and a pulse sensor on one finger. For the first hour,

### Drug Cues Induce Physiological Stress Responses in Cocaine-Addicted Patients



*Cortisol levels, which normally decline in the morning, remain relatively high in cocaine-addicted patients after they listen to a five-minute tape of a stressful or drug-related experience, but not after they listen to a relaxing tape. Cue-induced elevations in cortisol and other stress hormones persisted for up to 30 minutes.*

an adaptation period, the patient practiced tape-guided progressive relaxation while periodically reporting anxiety and craving levels. Next, the patient heard one of the 5-minute tapes based on his or her own experiences, introduced with a message to "Close your eyes and imagine yourself in the following situation." Over the three testing sessions, conducted on different days, the patient relived all three of his or her stressful, drug-related, and relaxing experiences. When the tape finished, the patient rated the vividness of the scenes and his or her cocaine craving and anxiety. A nurse monitored the patient's pulse and blood pressure and drew blood samples periodically during the testing and for 75 minutes after the tape ended.

The researchers found similar responses to the stressful and drug-related tapes. Patients' pulses increased and their blood pressure rose while they listened to both. Blood levels of biochemicals involved in the stress response—including noradrenaline, cortisol, prolactin, adrenocorticotrophic hormone, and adrenaline—were elevated when

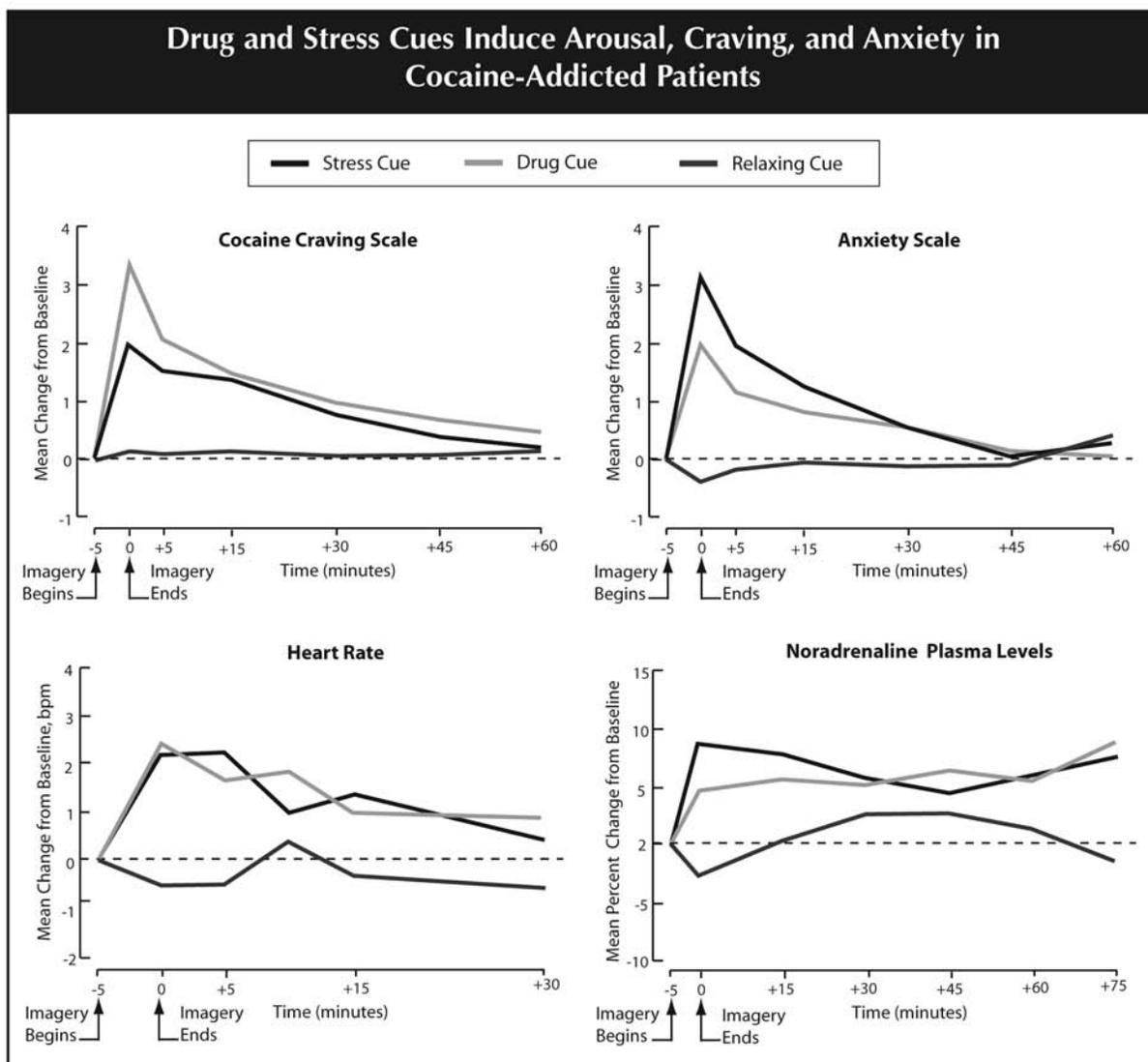
participants listened to stressful and drug-related tapes compared with when they listened to the relaxing tapes. Stressful and drug-related tapes also increased participants' subjective responses—craving and anxiety—compared with the relaxing tapes.

The stress responses generated in the study were in keeping with previous laboratory studies with cocaine abusers, says Dr. Sinha. “Stress reactions after both the stressful and drug-related tapes in this study were similar to or higher than those observed when researchers have used other techniques to induce stress—for example, requiring participants to prepare and give a speech in 5 minutes.”

### Stress Response Persists

Normally the stress response, including the adrenaline rush and increased heart rate, breathing, and blood pressure, returns quickly to normal once a threat has passed. “What was different and striking in our patients was that they continued to show stress after the tape was over—up to 30 minutes longer than would be expected,” says Dr. Sinha. The results suggest that cocaine abusers' stress responses may take longer to normalize, perhaps indicating a heightened reactivity to stress.

Dr. Sinha and her colleagues are following up with patients in this study to determine whether those with more intense biological reactions and craving in response



*Cocaine-addicted patients showed greater arousal and increased pulse and biochemical stress response, as well as increased craving and anxiety, when they mentally relived a 5-minute stressful or drug-related personal experience than when they listened to relaxation tapes. Arousal persisted for up to 30 minutes after the imagery stopped.*

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to the tapes are more likely to relapse. Similarly, they are using brain-imaging technology to determine whether neural activation after patients listen to stressful and cocaine-related tapes predicts relapse. In addition, to determine whether drug abuse is related to a heightened stress response, Dr. Sinha is planning studies that compare the stress reactivity of addicted and nonaddicted people.

“Understanding the effects of chronic drug use on how people handle stress—particularly the craving and biological responses that occur after stressful situations—will allow us to develop medications that are effective against craving induced by drug and stressful environmental cues,” says Dr. Harold Gordon of NIDA’s Division of Clinical Neuroscience, Development and Behavioral Treatment.

#### Source

- Sinha, R., et al. Hypothalamic-pituitary-adrenal axis and sympatho-adreno-medullary responses during stress-induced and drug cue-induced cocaine craving states. *Psychopharmacology* 170(1):62-72, 2003. **NN**

### Reliving a Stressful Situation: Excerpt From a Guided Imagery Tape

There is a knock on the door. You feel tense all over your arms, legs, back, and forehead. “You are going to get evicted,” he says. Your heart beats faster. You had been paying rent to your boyfriend, but he never gave it to them. You feel the butterflies in your stomach. You have no place to go. “The second notice will be here in a couple of days,” he is saying, but your mind is racing. You feel shaky all over. “What am I going to do? Where will I go?” you say. You have cramps in your stomach. You grit your teeth and call your mother. She has no money to help you. You’ve run out of options. There is a deep intense pain inside you and tears come to your eyes.

## A Single Cocaine “Binge” Can Establish Long-Term Cue-Induced Drug-Seeking in Rats

By Lori Whitten, *NIDA NOTES* Staff Writer

When people abuse a drug, they learn to associate its pleasurable effects with the surroundings in which they experience them. This learning plays a major role in addiction. Former drug abusers find that even after years of successful abstinence, they may experience intense cravings upon encountering people, places, and things that were present during their drug-taking.

Researchers have been trying to understand how the brain forms such associations and how cues motivate drug-seeking. Until now, scientists have generally assumed that many pairings of drug use and environment are needed to establish drug-cue learning, but Dr. Friedbert Weiss and his colleagues at The Scripps Research Institute in La Jolla, California, recently showed otherwise. In a NIDA-funded animal study, they demonstrated that rats can acquire such long-term learning in the space of a single 2-hour session of access to cocaine. The rapid formation of drug-cue associations seems exceptional; the investigators also demonstrated that in contrast to cocaine, sweetened condensed milk—a food rats find highly palatable—does not produce persistent effects after a one-time exposure.

The investigators chose white noise as the cue they would pair with cocaine and then test. To begin, they placed rats in a special learning chamber where white noise signaled cocaine availability and pressing a lever produced an intravenous infusion of the drug. During a 2-hour session, the rats could press the lever freely; the only restriction on their cocaine intake was a 20-second time-out after each infusion to prevent overdose. On average, each rat pressed the lever 43 times.

The researchers hypothesized that during this initial session, the rats learned to seek out the cocaine experience and the rats’ brains established a link between white noise and the drug experience similar to the environmental cues learned by people addicted to cocaine. Their next experimental step would put the rats into a state corresponding to abstinence in a former cocaine abuser. To accomplish this, they returned the animals to the test cage, now with the white noise turned off and the lever disconnected from

the infusion device. The rats obtained nothing when they pressed the lever that previously had delivered cocaine, and they gradually gave up. When a rat had pressed the lever five or fewer times in three consecutive 1-hour sessions, the researchers concluded that its drug-seeking behavior was “extinguished.” The animal’s motivation was not strong enough for it to keep pressing a lever that had not delivered an infusion in many tries.

In the first two stages of their experiment, Dr. Weiss and colleagues had established white noise as the sole environmental feature in the rats’ experience reliably associated with cocaine availability, and the rats had ceased drug-seeking (lever-pressing) behavior. The investigators were now ready to test whether the now “abstinent” rats would respond to white noise by reinstating drug-seeking. Immediately after the rats abandoned lever-pressing, and at 3-month intervals, the researchers returned rats to the test chamber and turned on the white noise. The rats indeed responded by pressing the lever. Moreover, the white noise cue motivated the rats to seek cocaine session after session, even though they never received any, for up to an entire year. In comparison, a different environmental cue associated with saline infusions motivated only a few lever presses throughout the experiment.

“Drug-cue learning has a well-known role in craving and relapse in addicted individuals,” says Dr. Weiss. “Our observations demonstrate that it takes very little experience with cocaine to establish environmental associations that become powerful cues for cocaine relapse—and contribute to progression from initial sporadic drug use to addiction.”

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### Food Doesn’t Elicit the Same Cue Response

In a second experiment that demonstrated the unique reinforcing power of drugs, Dr. Weiss and colleagues showed that a highly palatable food did not produce persistent motivating effects. Following the same procedures they used in the cocaine experiment, the investigators trained a different group of rats to associate white noise with access to sweetened condensed milk (SCM). During

**“...it takes very little experience with cocaine to establish environmental associations that become powerful cues for cocaine relapse...”**

access to SCM, rats pressed the lever 80 times on average. Subsequent sessions in the test cage extinguished the rats' SCM-seeking. The investigators then tested white noise's ability to induce the now "abstinent" rats to resume pressing the lever. It did not, either immediately or 3 months after extinction. The results indicate that a "natural" reinforcer does not have cocaine's ability to produce a long-lasting motivational association in a single session of exposure.

"Clearly, an exceptionally strong association is established when cocaine is paired with a cue," says Dr. Susan Volman of NIDA's Division of Basic Neurosciences and Behavior Research. "This finding is consistent with other evidence that drugs produce especially rapid and long-lasting learning."

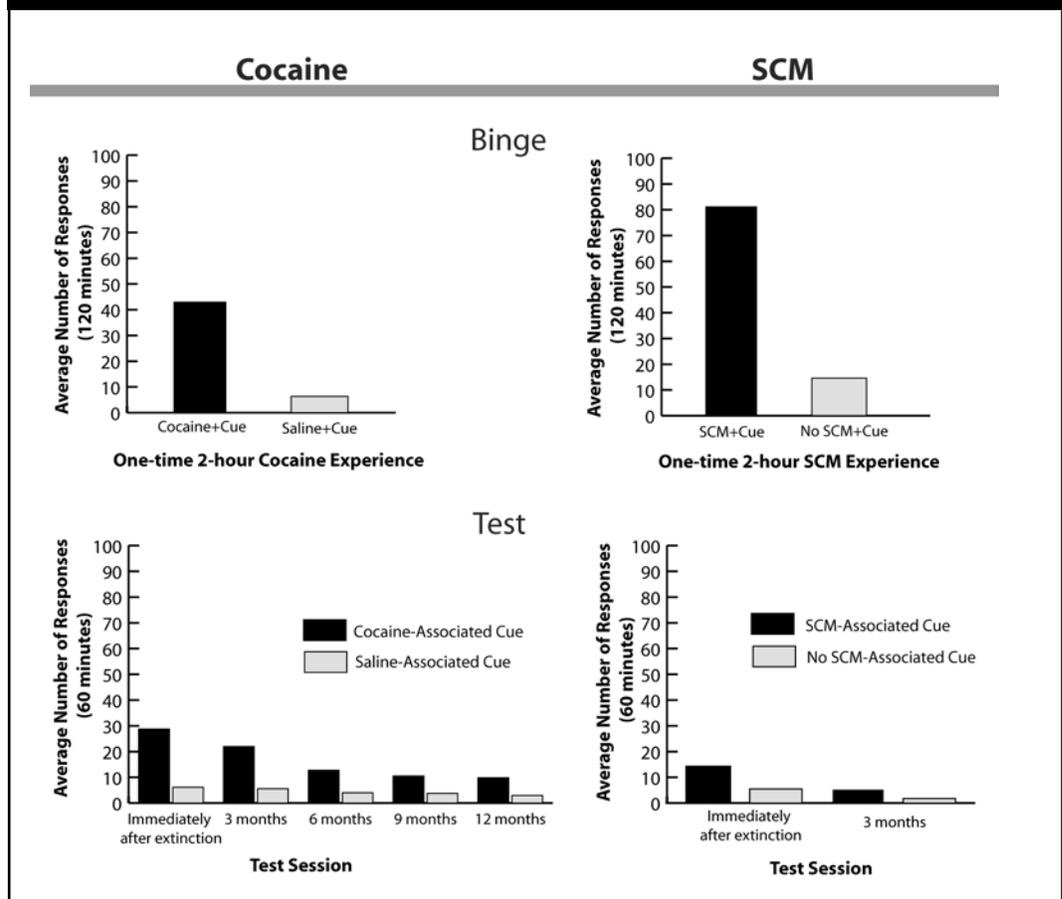
Scientists don't yet know the exact neurobiological mechanisms that form learned associations from drug experiences.

However, researchers have observed that drugs induce changes in brain cells, or neural adaptations, similar to those underlying normal learning. These adaptations result in a modification of the brain's neural circuitry—the interconnected networks of neurons responsible for behavioral, cognitive, and emotional and motivational processes.

Dr. Volman explains, "Drugs may produce such rapid and long-lasting learning because

they have a double effect: They produce intense pleasure that reinforces behavior and they enhance neural adapta-

## Study Underscores Power of Cocaine Cues to Re-Induce Drug-Seeking In Rats



Up to a year after a 2-hour session of free access to cocaine, rats responded more strongly to a cue paired with cocaine versus the control, a saline-associated cue. In a second experiment, a 2-hour session of free access to a desired food—sweetened condensed milk (SCM)—produced no such long-lasting cue responsiveness.

tions at the same time. These brain changes might underlie sustained drug-directed behavior and the ability of cues to prompt drug-seeking." In future studies, Dr. Weiss and his colleagues intend to address the physiological mechanisms underlying the different behavioral responses to drugs and to natural reinforcers.

### Source

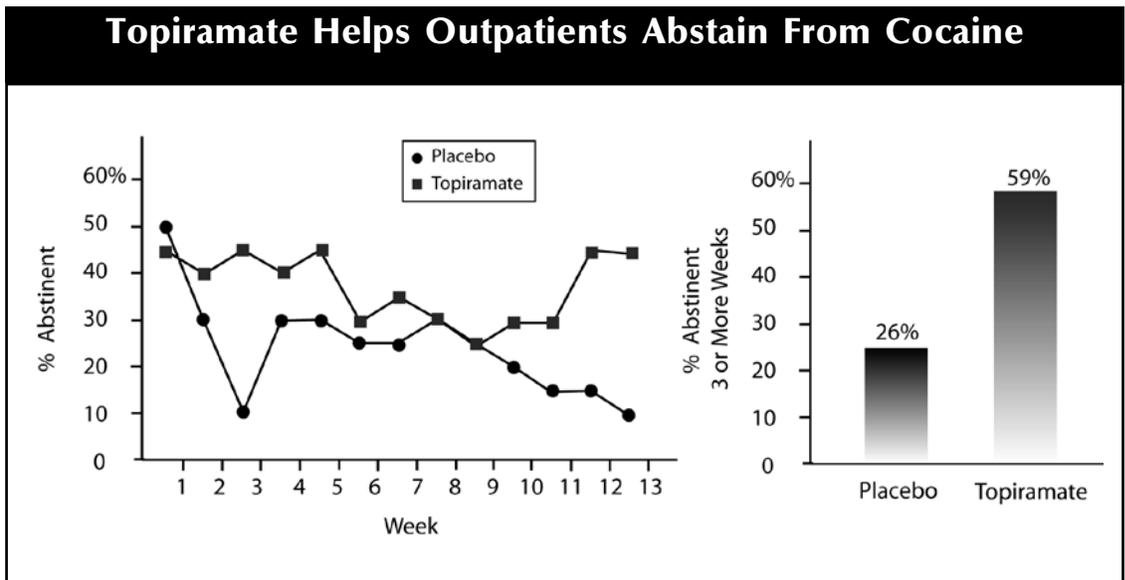
- Ciccocioppo, R.; Martin-Fardon, R.; and Weiss, F. Stimuli associated with a single cocaine experience elicit long-lasting cocaine seeking. *Nature Neuroscience* 7(5):1-2, 2004. **NN**

## Topiramate Shows Promise in Cocaine Addiction

By Lori Whitten, NIDA NOTES Staff Writer

In a small pilot study, topiramate—a medication currently used to treat seizure disorders—has helped cocaine-addicted outpatients stay off the drug continuously for 3 weeks or more. That may not seem like a long time, but previous research has shown that outpatients who avoid relapse for 3 to 4 weeks during treatment with behavioral therapy and medication have a good chance of achieving long-term cessation. In other clinical trials topiramate has helped prevent relapse to alcohol and opiate addiction; these new results with cocaine add to hopes that it may prove a versatile treatment medication for several drugs of abuse.

Dr. Kyle M. Kampman and colleagues at the University of Pennsylvania School of Medicine and the Veteran Affairs Medical Center in Philadelphia treated 40 crack-cocaine-smoking outpatients, mostly African American males, for 13 weeks at the University of Pennsylvania Treatment Research Center (TRC). All participants met the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)* criteria for cocaine dependence. They were typical of the chronic, relapsing abusers who seek treatment at the TRC: They abused cocaine an average of 10 years, preferring crack to the powder form, and demonstrated the average level of drug-related problems. However, participants' abuse was atypical in one way; they were on the "milder end of the addiction severity spectrum measured by cocaine withdrawal symptom severity and days of abuse and money spent on cocaine," says Dr. Kampman. On average, participants abused cocaine 6 to 8 days and spent \$300 to \$500 on the drug in the month before treatment compared with the 10 to 13 days and \$400 to \$600 reported by most patients at the facility.



In almost every week of the study, more patients were abstinent in the topiramate group than in the placebo group. Of the 40 participants in the study, more patients taking topiramate achieved 3 or more continuous weeks of abstinence from cocaine.

Because topiramate exacerbates cocaine withdrawal symptoms, the investigators selected patients who were able to attain at least 3 days of self-reported abstinence immediately before starting the trial and who, based on their level of addiction, were not likely to enter severe withdrawal. Dr. Kampman says that about 40 percent of patients treated at the TRC experience relatively mild withdrawal symptom severity.

After a 1-week baseline period, Dr. Kampman's team gave topiramate to 20 study participants, and placebo to the other 20. To avoid potential topiramate side effects, including sedation and slurred speech, they initiated treatment with 25 mg/d and increased it by 25 mg/d every week to 200 mg/d. They maintained this maximum dose during weeks 8 through 12, then tapered to zero during week 13. The patients also received cognitive behavioral coping skills therapy twice weekly throughout the study. The researchers verified cocaine abstinence two times a week with urine tests.

By the end of the 13th week, almost 60 percent of patients taking topiramate attained 3 or more weeks of continuous abstinence from cocaine compared with 26 percent of those taking placebo. All 40 patients showed improvement from week 1 to week 13, as reflected by

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lower Addiction Severity Index (ASI) scores. Patients taking the medication improved more, with average scores in the topiramate group falling by 69 percent, from 0.210 to 0.066, compared with 50 percent, from 0.162 to 0.081, in the placebo group. Dr. Kampman says the improvement in ASI scores reflects fewer days of cocaine abuse and patients' perceptions of reduced cocaine-related problems.

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***“Patients saw the improvement in their condition, which is an important part of recovery.”***

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“Patients saw the improvement in their condition, which is an important part of recovery,” he says.

#### **Possible Mechanisms**

“Based on our findings and other work showing this medication's effectiveness as a treatment for alcohol and opiate addiction, topiramate appears to have great potential as a relapse prevention medication for people who have achieved initial abstinence from cocaine,” says Dr. Kampman.

All addictive drugs deliver pleasurable effects by enhancing the neurotransmitter dopamine in the mesocorticolimbic pathway—areas of the brain involved in reward and motivation. Topiramate seems to change the brain's response to cocaine by indirectly influencing dopamine through two other neurotransmitter systems—gamma aminobutyric acid (GABA) and glutamate. Animal studies have suggested to scientists that either activating GABA-producing neurons or blocking glutamate receptors would lessen craving in cocaine-addicted human subjects. “Topiramate does both simultaneously, a unique dual action that appears to underlie its promise as a relapse prevention medication,” says Dr. Kampman.

“These are preliminary results, but researchers are very excited about the potential topiramate has shown as a treatment for a range of problems, including addiction to several drugs and some impulse control disorders,” says Dr. Frank Vocci, director of NIDA's Division of Pharmacotherapies and Medical Consequences of Drug Abuse. In addition to its initial successes in preventing relapse in patients with alcohol, opiate, and now cocaine addiction, animal studies have suggested it may attenuate nicotine addiction. “Topiramate may prove an effective treatment for patients who are addicted to multiple drugs,” Dr. Vocci adds.

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***“Topiramate may prove an effective treatment for patients who are addicted to multiple drugs.”***

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Dr. Kampman plans additional studies to further evaluate topiramate as a treatment for cocaine addiction. In addition to confirming the present results, obtained with African American male crack smokers, the medication must be tried in other racial groups, women, and powder-cocaine abusers. Dr. Kampman and his colleagues also plan to study topiramate therapy for patients with coexisting cocaine and alcohol addiction—a group that comprises half of people treated for cocaine abuse.

#### **Source**

- Kampman, K.M., et al. A pilot trial of topiramate for the treatment of cocaine dependence. *Drug and Alcohol Dependence* 75(3):233-240, 2004. **NN**

## Men and Women May Process Cocaine Cues Differently

By Lori Whitten, NIDA NOTES Staff Writer

Some aspects of cocaine addiction and recovery are different for men and women—including the reasons for seeking drug rehabilitation, response to treatment, and vulnerability to relapse. Women are more likely to seek cocaine abuse treatment in response to co-occurring depression, remain abstinent after treatment, and relapse in response to interpersonal problems and negative feelings. Cocaine-addicted women also demonstrate greater craving than men in response to drug cues. In the first brain imaging study of cocaine craving by cocaine-addicted women, NIDA-funded researchers have made observations that, if borne out in larger studies, may point to neurological sources of these differences.

Dr. Clinton Kilts and colleagues at the Emory School of Medicine in Atlanta used positron emission tomography (PET) to measure drug-craving-related changes in regional cerebral blood flow—a correlate of neural activity—in eight cocaine-addicted African-American women aged 35 to 46. The women had abstained from cocaine use for 1 to 14 days and reported frequent periods of cocaine craving in the 30 days preceding the study. While lying in the PET scanner, each woman listened to a 1-minute recording of a script describing her personal experiences of acquiring the drug and anticipating sensations associated with taking cocaine. Each patient's script was derived from her own answers to an autobiographical questionnaire and narrated in the first person: "...I start thinking about how good it's going to feel to take that first hit...with my eyes wide open I take my lighter out of my pocket, put it to the stem, and get ready to take that first, good blast...."

The researchers injected each woman with a radiotracer and took pictures of the blood flow in her brain as she listened to the script and relived the scene in her mind. After each brain scan, the women rated the urge to use

cocaine, vividness of the mental image, and their emotions. They repeated this process twice.

The women also underwent imaging in three control situations: resting, listening to a script of a personal experience in nature, and listening to a script designed to provoke anger. The researchers verified that the mental imagery of the cocaine-related script induced a greater urge to use cocaine than the nature or anger script. By comparing the brain scans produced in response to the different scripts, the researchers were able to evaluate cerebral blood flow while the women were craving cocaine versus when they were relaxed and not thinking of the drug. The procedure also distinguished changes related to

**Selected Key Brain Regions Affected by Cue-Induced Cocaine Craving in Cocaine-Addicted People**  
(Cocaine-use imagery compared with neutral imagery)

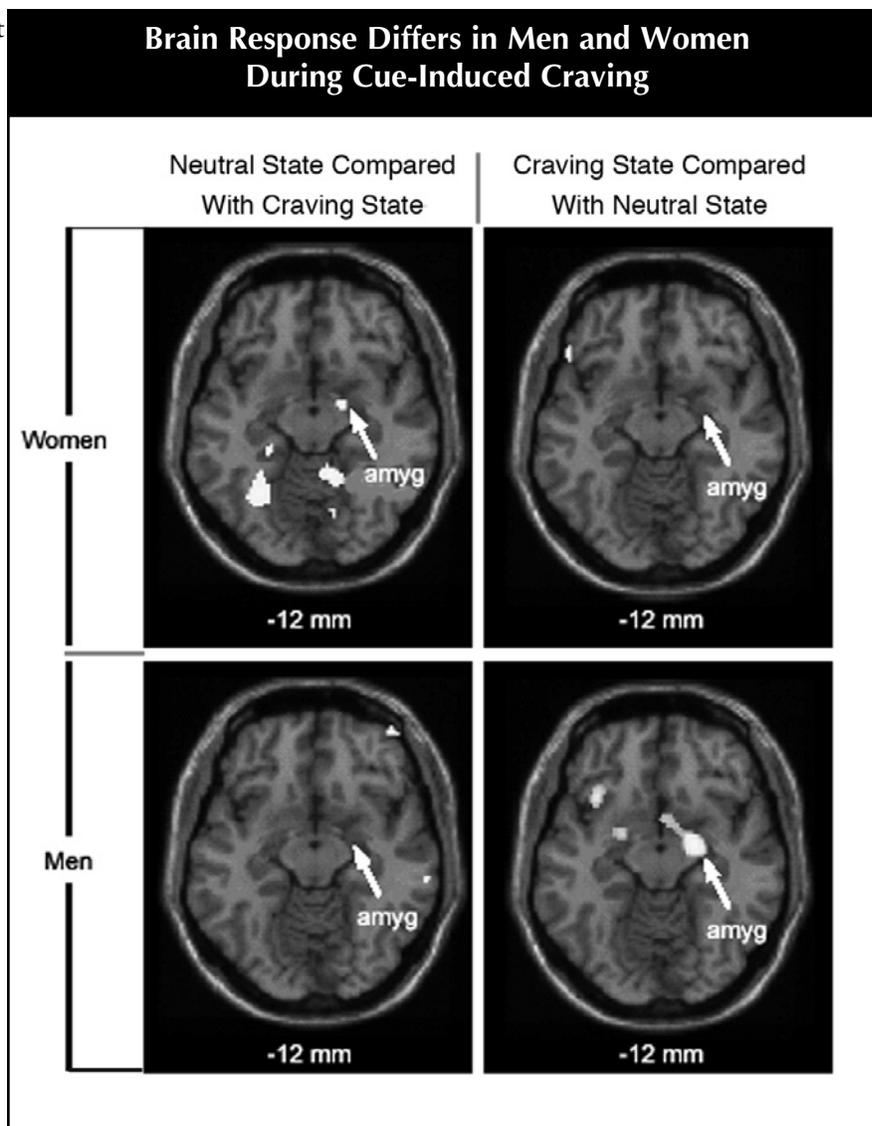
Brain Region	Putative Role in Behavior	Activity Changes During Cocaine Craving	
		Men	Women
Right nucleus accumbens	Processes anticipated and attained rewards—probably contributes to the expectation of pleasure during craving	Increased activity	Increased activity
Amygdala	Generates and regulates emotional responses; assesses the positive or negative value of experiences and forms associations between experiences and emotional consequences	Increased activity	Decreased activity
Dorsal anterior cingulate cortex	Monitors competing options, inhibits goal-inappropriate behavior, and plans movements related to obtaining rewards; activity influenced by past experiences—possibly provides cognitive control of drug-seeking behavior	Increased activity	Increased activity, greater than that of men
Ventral anterior cingulate cortex	Regulates emotional response to cocaine cues; activation may precede craving onset	Increased activity	Increased activity, less than that of men
Frontal cortex	Monitors relationship of drug cue to drug availability; provides inhibition or control over actions; activity influenced by past experiences—possibly counter-regulates emotional input	Increased activity	Increased activity, greater than that of men

craving from those that might simply reflect strong general emotional reactions (as in the anger-inducing script). To examine possible sex differences in the neural representation of cocaine craving, the investigators compared the findings in women with results from eight cocaine-addicted men of similar ages and backgrounds who experienced the same process.

In both men and women, cue-induced cocaine craving activated several brain areas involved in determining a cue's reward value and controlling reward-related behaviors, including the right nucleus accumbens—a structure that seems to produce the expectation of pleasure during drug craving (see table, "Selected Key Brain Regions Affected by Cue-Induced Cocaine Craving in Cocaine-Addicted People"). "These common activations suggest that both sexes may process cocaine-use memories—mental images that are associated with strong emotions—as cues that guide reward-based decisionmaking," says Dr. Kilts. However, men and women also showed some dissimilar neural responses to cocaine cues. Most notably, activity of the amygdala—a structure that assesses whether an experience is pleasurable or aversive and connects the experience with its consequences—fell in women during cocaine craving. "This finding is notable because our study and others have shown cue-induced amygdala activation in men," says Dr. Kilts. "Reduced neural responses in the amygdala may result from greater activation of the frontal cortex in women. The frontal cortex inhibits the activity of structures involved in emotional responding to drug cues, and our observations were consistent with previously reported sex differences in frontal cortical areas."

"As a field, we need more and better controlled studies of sex differences in factors that cause relapse," says Dr. Kilts. Combining imaging technologies in the same study—for example, PET with magnetoencephalography—would improve the localization of neural activity. "We could better define the neural responses that occur before, during, and after drug cues—illuminating the temporal sequence of the craving experience in men and women," he says.

"This research reveals that men and women differ in a critical brain area in their responses to cocaine craving," says Dr. Steven Grant of NIDA's Division of Clinical



*These PET scans show differences in blood flow between a neutral state and a cocaine-craving state. White areas indicate an increase in blood flow. Most notable is the decrease in blood flow in the women's amygdala (top right panel) during craving; men show an increase in blood flow during craving (bottom right panel).*

Neuroscience, Development, and Behavioral Treatments. "Differences in the amygdala may indicate that male and female abusers crave the drug for different reasons or hope to achieve different results from taking the drug. Imaging studies that examine gender differences in specific behavioral aspects of drug craving will provide insight on how to tailor treatment programs to meet the needs of men and women."

#### Source

- Kilts, C.D.; Gross, R.E.; Ely, T.D.; and Drexler, K.P.G. The neural correlates of cue-induced craving in cocaine-dependent women. *American Journal of Psychiatry* 161(2):223-241, 2004. **NN**

## Sigma Antagonists: Potential Cocaine Medications With Novel Activity

By Patrick Zickler, *NIDA NOTES* Staff Writer

Investigators in NIDA's Intramural Research Program (IRP) have confirmed and extended previous findings that rimcazole, a medication developed in the 1980s to treat schizophrenia, weakens some of cocaine's effects in rodents. The new findings strengthen speculation that drugs like rimcazole that act at sigma receptors might help recovering individuals avoid temptations to relapse to cocaine. Rimcazole and related compounds share a novel mechanism of action, a sigma receptor blockade, that appears to have significant potential for loosening cocaine's hold on addicted individuals.

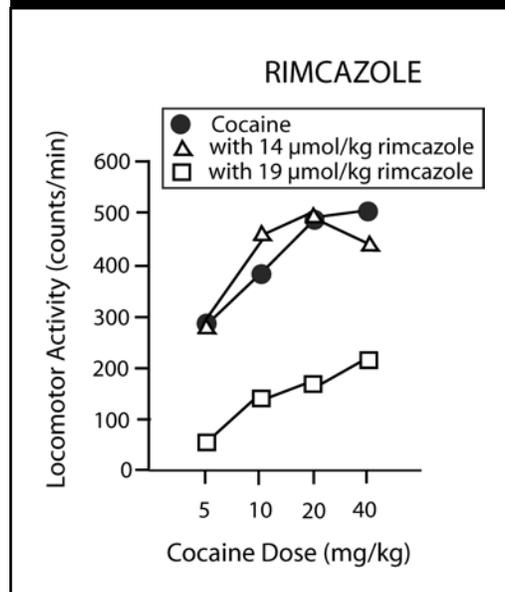
Drs. Jonathan Katz and Amy Newman and IRP colleagues showed that pretreating mice with rimcazole reduced one of cocaine's signature effects on rodent behavior: increases in locomotor activity—more running around. The impact on movement varied with the dosages of rimcazole and

cocaine: At the maximum, a 73  $\mu\text{mol/kg}$  dose of rimcazole reduced by 57% the amount of locomotor activity rats exhibited following administration of cocaine (40 mg/kg). Other rimcazole-like compounds reduced locomotor activity following cocaine exposure by up to 47%, also depending on dosages.

The demonstration that rimcazole attenuates locomotor stimulation by cocaine confirms previous similar findings by other researchers. The IRP team established for the first time an additional potentially important effect of rimcazole-like compounds: In rats, a closely related compound called SH3-28 weakens the subjective sensations that distinguish the cocaine experience. Rats pretreated with SH3-28 lost some of their ability to tell the difference between injections of cocaine and injections of saline—plain salt water.

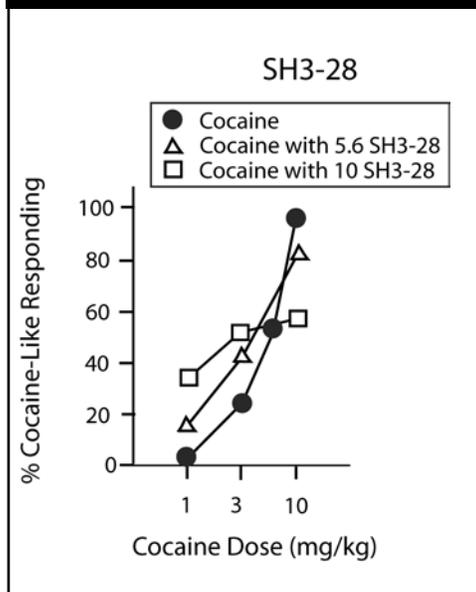
In this experiment, the researchers first taught rats they could obtain food by choosing the correct lever between two options: To be rewarded, the animals needed to push one lever after receiving a cocaine injection and the other lever after receiving a saline injection. Once trained, rats pressed the cocaine-associated lever nearly 100% of the time after an injection of cocaine; however, when pretreated with 19  $\mu\text{mol/kg}$  of SH3-28 prior to receiving cocaine, they pushed the correct lever only about 60% of the time. Should these results carry over to people, rimcazole or a rimcazole-like medication might be used in treatment of cocaine abuse. Recovering individuals who abused cocaine while taking the medication would learn that the drug did not produce the

### Coadministration of Rimcazole With Cocaine Blocks Locomotor Stimulation in Mice



*When administered with cocaine, rimcazole blocked the stimulant effects of cocaine on locomotor activity.*

### Pretreatment With Rimcazole Analog SH3-28 Decreases Subjective Effects of Cocaine in Rats



*In rats conditioned to press a lever in response to cocaine injection, SH3-28 pretreatment reduced the accuracy of the animals' responses to cocaine.*

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desired stimulant sensations, reducing their motivation for future use.

“This area of research is still in the early stages of effectiveness testing, but if the present results prove reliable and can be extended to humans, it would appear that rimcazole and its analogs may have promise in further drug discovery efforts toward the treatment of cocaine abuse,” says Dr. Frank Vocci, director of NIDA’s Division of Pharmacotherapies and Medical Consequences of Drug Abuse.

### **The Mechanisms of Action**

Rimcazole achieves its cocaine-suppressing effects at least in part by binding to and blocking the sigma receptor. This is a protein on the surface of some brain cells that receives chemical messages and relays them to the interior of the cells, stimulating or inhibiting some cellular activities. Compounds that block the sigma receptor inhibit cells from responding to dopamine, a chemical messenger that contributes to many of the addictive effects of cocaine as well as of other addictive drugs.

Rimcazole also binds to another protein on the cell surface, called the dopamine transporter. Most chemicals that attach here mimic the effects of cocaine, which itself is a potent dopamine transporter blocker. The IRP researchers are currently investigating whether rimcazole and rimcazole-like compounds produce an effect opposite to cocaine’s because their sigma blockade overrides their dop-

amine transporter effect, or whether some more complicated interaction between the two comes into play. So far, the evidence seems to point to the latter possibility.

“Our findings suggest that the interaction of sigma receptor ligands and cocaine is complex and appreciably different from competitive antagonism—that is, rimcazole and its analogs do not appear to physically block cocaine from its binding site,” says Dr. Katz. “It is possible that the effects of these compounds are due to the particular balance of dopamine transporter and sigma receptor actions they produce.”

The IRP team’s research constitutes the initial studies in a program of drug discovery. Future investigations will examine whether rimcazole and related compounds block other stimulant-induced effects of cocaine, attempt to isolate the exact nature of their effects at the sigma receptor and dopamine transporter, and—if the compounds continue to show promise—evaluate their safety and efficacy in animals and people.

### **Source**

- Katz, J.L., et al. Behavioral effects of rimcazole analogs alone and in combination with cocaine. *European Journal of Pharmacology* 468(2):109-119, 2003. **NN**

## Behavioral Modification Changes the Brain's Biochemical Response to Cocaine, Curbs Relapse Caused by Stress

By Tom Hollon, *NIDA NOTES* Contributing Writer

The scientific view of drug addiction as a chronic brain disease rests on many studies showing that addictive drugs change the brain in ways that cause compulsive drug seeking and drug taking. NIDA research recently demonstrated that the converse can also sometimes be true: In rats, behavioral modification changed the biochemistry of the brain and thereby reduced the motivation to self-administer cocaine.

Dr. David W. Self of the University of Texas Southwestern Medical Center in Dallas and colleagues at the Yale University School of Medicine and Harvard Medical School induced cocaine dependency in a set of experimental animals and then examined the impact of the behavioral technique called "extinction training" on the rats' behavior and glutamate receptors in one of the brain's major communications systems. Their finding that the training increased quantities of the glutamate receptors underscores the potential effectiveness of behavioral treatments for addiction and relapse prevention.

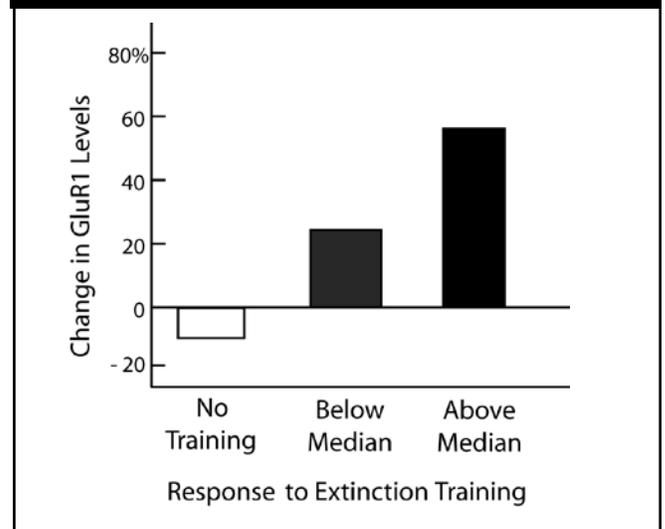
### Extinction Training and Glutamate

The researchers began their experiments by training rats to self-administer cocaine at will by pressing a lever. Animals trained in this way become "cocaine dependent"—that is, they develop behavioral and neurobiological changes that simulate the effects of addiction in people. The rats then underwent extinction training. In this technique, the researchers put animals into cages where they have self-administered a drug, but with a difference: Now, when the animals press the lever, no drug is dispensed. After a number of tries—more for some, less for others—the animals lose interest in the lever. Basically, extinction training reeducates animals, teaching them that the association between pressing the lever and getting a drug no longer holds.

In their first experiment, the researchers measured how extinction training affected the frequency of the cocaine-dependent rats' lever pressing and the supply of two glutamate receptors in the part of the brain known as the shell of the nucleus accumbens (NAc). The receptors, GluR1 and GluR2, act as relays in the brain's glutamate system, which uses the neurotransmitter glutamate to send messages from cell to cell.

As expected, extinction training changed the rats' behavior: Among the rats that received it, the frequency of

### Stronger Training Response Correlates With Higher Receptor Levels



*Rats that responded more strongly to extinction training showed greater increases in glutamate receptor levels. Rats that did not receive training demonstrated a decrease in glutamate receptors. Percent changes shown are relative to control rats not exposed to cocaine.*

lever pressing declined from a range of 39-44 presses in a 4-hour interval to a rate equivalent to 22-34 presses. These rats were also found to have 39% more GluR1 and 31% more GluR2 than matched cocaine-dependent rats not subjected to extinction training. Strengthening the conclusion that extinction training was responsible for these increases, the sizes of the declines in lever pressing correlated with the amount of increase in GluR1. Rats whose declines exceeded the median averaged a 58% increase in GluR1, while those whose declines were less than the median averaged a 24% increase.

"We discovered something profound—that simply allowing an animal to press a lever and not get any drug completely changed the brain's response to cocaine," Dr. Self says.

A second experiment confirmed the relationship between the glutamate receptors and successful extinction training. It also showed that the relationship goes the other way, too: Having more receptors at the time of extinction training increases the response to the training. In prepara-

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tion for this experiment, the researchers used genetic engineering to artificially increase GluR1 and GluR2 in some cocaine-dependent rats' NAc. In the first hour of training, these animals pressed levers for cocaine roughly 20 times, while animals whose receptors were not enhanced performed about 40 lever presses. The animals with the extra glutamate receptors also achieved the milestone of fewer than 20 lever presses after only 2 to 2.5 days of training, compared with more than 4 days for the other animals.

Summarizing the results of the two experiments, Dr. Self says, "There is a reciprocal relationship between extinction training and the level of glutamate receptors. Extinction training causes transient increases in glutamate receptors, while higher quantities of glutamate receptors facilitate extinction of drug-seeking behavior."

To explain why rats with enhanced glutamate receptors are more likely to pass up cocaine, Dr. Self points to one of the key functions of the glutamate system: It helps enable an animal or a person forego short-term pleasures for the sake of safety or longer-term goals. In this situation, the prefrontal cortex, the brain's seat of foresight and planning, releases glutamate molecules into the NAc, the brain's pleasure center, that override the motivation for the short-term pleasure. Previous research has shown that chronic cocaine exposure reduces the cortex's glutamate production, weakening its influence over the pleasure center. Dr. Self suggests that increasing the number of glutamate receptors in the NAc may partially compensate for the glutamate shortage by relaying more signals from the glutamate that still remains.

A more difficult question—one the researchers are pursuing now—is why extinction training increased glutamate receptors in the NAc. Although cocaine also caused glutamate shortages in rats that were taken off it without extinction training, those animals did not respond with compensatory increases in receptors.

### Stress and Relapse

In a subsequent experiment, Dr. Self and his colleagues demonstrated that raising GluR1 levels in the NAc reduced formerly dependent rats' tendency to respond to stress by reverting to cocaine self-administration. Most surprising, the reduction in response was documented 3 weeks after the elevated GluR1 levels returned to normal.

After inducing cocaine dependency, genetically increasing the supply of glutamate receptors in the NAc, and a single session of extinction training, the researchers gave their experimental rats a 3-week timeout. Then, they returned the rats to their training cages and administered three types of stimulus: a "priming" dose of cocaine, a light

that flashes when the lever in the cage is ready to dispense cocaine, and a series of mild electrical shocks to the paw. These stimuli correspond to triggers that commonly cause addicted people to relapse—drug exposure, environmental cues associated with previous drug use, and stress. Each usually causes rats to revert to drug self-administration. Dr. Self and his colleagues found, however, that when their extinction-trained rats received foot shocks, those whose GluR1 levels were higher resumed lever pressing about 87% less frequently than those with less GluR1.

"This was really surprising," says Dr. Self. "It suggested that glutamate receptor increases during extinction training have long-term effects on stress-induced relapse, even after receptor quantities return to normal."

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***"Perhaps extinction training teaches the animal to cope with stress by inhibiting craving, which stress normally would increase."***

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To account for this finding, Dr. Self suggests that "there is a similarity between stress and extinction training. Foot shock is mild and basically irritates the animal, the rat equivalent of a bad day at work. Extinction is stressful too—the frustration of looking for a drug you anticipate but don't get. Perhaps extinction training teaches the animal to cope with stress by inhibiting craving, which stress normally would increase."

Dr. Nancy S. Pilotte of NIDA's Division of Neuroscience and Behavioral Research agrees that behavioral changes sustained beyond the transient period of glutamate receptor elevation are an important finding. "This tells you it is extremely important to follow animals after drugs are withdrawn, a stage of addiction we know fairly little about," she says. "We know a lot about acute affects, but very little about what happens to animals when they are no longer receiving drugs."

Currently, no equivalent to extinction training exists for treating people. However, Dr. Self believes that in the future, virtual reality technology may make such an approach possible. "A very realistic video game might make it possible to recreate many of the anticipatory and emotional responses involved in preparing for the drug experience without ever actually receiving the drug," he explains. "Repeated 'virtual drug taking' could extinguish these emotional responses by strengthening the brain pathways that exert inhibitory behavioral control over drug craving."

### Source

- Sutton, M.A.; Schmidt, E.F.; Choi, K-H.; Schad, C.A.; Whisler, K.; Simmons, D.; Karanian, D.A.; Monteggia, L.M.; Neve, R.L.; and Self, D.W. Extinction-induced upregulation in AMPA receptors reduces cocaine-seeking behaviour. *Nature* 421(6918):70-75, 2003. 

## Brain Glutamate Concentrations Affect Cocaine Seeking

By Tom Hollon, *NIDA NOTES* Contributing Writer

NIDA-supported research has produced evidence that a medication that supplements recovering cocaine addicts' brain concentrations of the neurotransmitter glutamate may reduce their vulnerability to relapse. Although the research was done with laboratory rats, the substance used to bolster glutamate levels was acetylcysteine, a medication that is safe for humans and used routinely in emergency rooms to treat overdoses of the analgesic acetaminophen.

Dr. Peter Kalivas and colleagues at the Medical University of South Carolina in Charleston measured the glutamate concentrations in the fluid surrounding the cells in rats' nucleus accumbens (NAc) in the absence of cocaine exposure; after training the animals to voluntarily self-administer the drug by pressing a lever in their cage; and 3 weeks after removing the animals' access to cocaine. Compared with the concentrations in nonexposed animals, those during cocaine self-administration were markedly higher, and those after forced abstinence markedly lower. The investigators concluded that rats repeatedly exposed to cocaine develop glutamate concentration deficits in the NAc that persist for a considerable time after access to the drug is removed.

Dr. Kalivas and colleagues next investigated whether cocaine or acetylcysteine would restore the rats' glutamate levels and the effect on the animals' motivation to self-administer cocaine. As in their first trials, the researchers began by training rats to press a lever to obtain cocaine, then removed the cocaine from the solution the rats received when they pressed the lever. As before, these procedures left the rats with reduced NAc glutamate concentrations; the rats also lost interest in pressing the lever because it no longer delivered cocaine. At this point the researchers injected some of the animals with a single dose of cocaine and others with a dose of acetylcysteine followed by a dose of cocaine. The initial cocaine and acetylcysteine doses both increased glutamate to the elevated levels that followed cocaine self-administration. However, the rats given only cocaine resumed drug-seeking behavior—they began pressing the lever to try to self-administer cocaine—while those given acetylcysteine prior to cocaine did not.

"Restoration of glutamate by acetylcysteine blocked reinstatement of drug seeking in rats trained to self-administer cocaine," Dr. Kalivas says. "This strongly indicates that susceptibility to relapse is due in part to diminished levels of extracellular glutamate associated with drug withdrawal.

### A Possible Addiction Therapy, Built From the Ground Up



*Training chambers like this one are used to study animals' responses to drugs. By pressing the lever, the rat obtains an infusion of a drug, a medication, or saline through the tube. Using such apparatus, NIDA scientists showed that cocaine abuse reduces brain glutamate levels, and treating animals with acetylcysteine reduces subsequent cocaine seeking.*

Our finding could well apply to people, too, since self-administration and reinstatement in animals are reliable models of addiction and relapse in humans."

Dr. Kalivas' findings add to a growing body of information describing glutamate's important role in the neurobiological processes underlying drug abuse and addiction. Glutamate is a neurotransmitter, a chemical that acts as a messenger between brain cells. NIDA investigators have lately focused attention on glutamate in part because it influences levels of another neurotransmitter, dopamine, in the brain's pleasure center, the NAc. Fluctuations in NAc dopamine levels underlie the euphoria of initial drug use and contribute to other aspects of cocaine and other drug abuse and addiction. Glutamate signals also amplify the addictive effects of nicotine (see "Nicotine's Multiple Effects on the Brain's Reward System Drive Addiction," *NIDA NOTES*, Vol. 17, No. 6, p. 1), and contribute to a condition called "long-term potentiation," which causes brain cells that have been exposed to addictive drugs to release dopamine more abundantly in response to subsequent exposure (see "Addictive Drugs and Stress Trigger Similar Change in Brain Cells, Animal Study Finds," *NIDA NOTES*, Vol. 18, No. 5, p. 1).

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The scientists' successful use of acetylcysteine to restore normal glutamate levels supports their hypothesis that cocaine reduces glutamate concentrations in the fluid surrounding cells in the NAc. They suspect that repeated drug exposure followed by drug withdrawal disrupts a process known as cystine-glutamate exchange: molecules of cystine enter NAc nerve cells, which pump molecules of glutamate out in exchange. The exchange normally maintains appropriate concentrations of both chemicals inside and outside the cells, but disruption by drugs may result in a shortage of extracellular glutamate. The researchers speculate that acetylcysteine rectifies this shortage because it forms cystine molecules when it is metabolized. These molecules then enter the cells and prompt them to pump out additional glutamate.

Dr. Nancy S. Pilotte of NIDA's Division of Neuroscience and Behavioral Research says Dr. Kalivas's glutamate research demonstrates the value of moving beyond studies that focus on the dopamine-triggered pleasure associated with abuse and addiction. "We need to move on from

thinking of dopamine as the center of the universe," she says, adding that the payoff for broader research perspectives may be "more molecular targets for development of medications."

Following up on the results of his animal studies, Dr. Kalivas has begun a clinical trial to determine whether acetylcysteine can control substance abuse patients' craving for cocaine once they have achieved abstinence. He and his colleagues are also conducting further laboratory studies to evaluate whether the compound may prevent animals from seeking opioids or alcohol as effectively as it prevents them from seeking cocaine.

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## Cocaine Abusers' Cognitive Deficits Compromise Treatment Outcomes

By Arnold Mann, NIDA NOTES Contributing Writer

Cognitive impairment may be an important factor in explaining treatment failure among cocaine abusers, according to results from a new NIDA-funded study by Dr. Efrat Aharonovich and colleagues at New York's Columbia University. These findings are already leading researchers to modify current treatments for cognitively impaired cocaine abusers, with hopes of improving success rates.

Cognitive-behavioral therapy (CBT) is an effective treatment for cocaine addiction, but dropout rates range from 33 to 64 percent. This study is the first to examine the role of impaired cognition as a contributor to this statistic. The researchers found that patients with impaired attention, learning, memory, reaction time, and cognitive flexibility—all documented consequences of chronic cocaine abuse—were much more likely to drop out of the 12-week CBT program than those not cognitively impaired. In addition, the dropout rate was related to the degree of cognitive impairment, with the more impaired patients more likely to stop treatment.

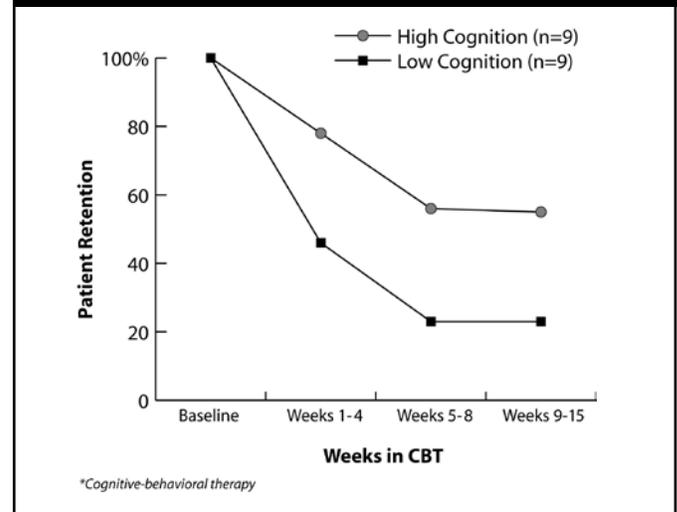
"These data show very clearly that cocaine abusers with cognitive deficits are most likely to drop out of [CBT] treatment," says Dr. Aharonovich. This is particularly true during the first 4 weeks of treatment, when the dropout rate is highest. Further, she adds, cognitively impaired patients who manage to stick it out beyond the first 4-week course are "most likely not going to do as well" as patients without cognitive deficits.

The impetus for the study, Dr. Aharonovich notes, was realizing that "some patients were coming to sessions and just not 'getting it.' We were losing a lot of patients. I thought maybe we were delivering a treatment that they were receiving but not understanding."

In CBT's one-on-one therapy sessions, the therapist teaches the patient to recognize the connections between the thoughts, feelings, and actions that undermine his or her attempts to become abstinent. Patients are taught to avoid specific situations associated with their drug abuse, to use techniques like "thought stopping" to cope with cravings, and to focus on emotions that may trigger drug use.

"You have to be pretty intact cognitively to really stick with CBT," says Dr. Edward Nunes, a researcher in the study. "This is a therapy that involves a lot of analyzing, thinking ahead, planning, and controlling impulses. If the cognitive functioning is a little off, it's going to make it hard for those patients to thrive in treatment."

### Cognitive Status a Factor in Cocaine Abusers' Time in CBT\*



Cognitively impaired cocaine abusers are more likely than abusers with higher cognition to drop out of outpatient CBT, particularly in the first 4 to 6 weeks.

Cocaine abusers' cognitive deficits have been well documented. The drug constricts cerebral blood vessels, resulting in decreased blood flow to the brain. Magnetic resonance imaging (MRI) studies also reveal an increased presence of microvascular lesions and clots in cerebral blood vessels, which can also restrict blood flow. Chronic cocaine use can also deplete the neurotransmitter dopamine, which contributes to impaired cognition.

Eighteen cocaine-addicted patients participated in the study. All tested positive for cocaine use in the previous 72 hours and reported using cocaine at least four times in the month before admission and for at least 12 months before study enrollment. Patients were excluded from the study if they were HIV-positive or had conditions known to cause cognitive impairment independently of cocaine abuse, including mood disorders, psychosis, attention-deficit/hyperactivity disorder, seizure disorders, or a previously diagnosed learning disability.

Each patient was scheduled for 15 once-a-week, 1-hour CBT sessions. Eleven patients received gabapentin, a medication used to quell cravings; the remaining seven received a placebo. Urine specimens were collected three times a week and analyzed for cocaine and six other commonly abused drugs. Patients who attended at least 12 CBT sessions were

considered completers, based on the standard 12-week CBT treatment.

When the researchers analyzed the data, there were no significant differences in age, sex, ethnicity, employment, or education between treatment dropouts and completers. Prior duration of cocaine use was similar for both quitters and completers. Of the 11 patients on medication, 7 dropped out; 5 of the 7 patients on placebo dropped out. Thus, the overall completion rate for all patients in the study was 33 percent. Medication had no effect on the study results, the researchers concluded.

Big differences emerged, however, in the cognitive abilities of dropouts and completers. The researchers used MicroCog computerized testing to determine each patient's level of cognitive performance at admission. Treatment completers performed at higher cognitive levels than dropouts across all the measured cognitive domains—attention, abstract reasoning, memory, spatial processing, and reaction time. Completers also performed significantly faster and with greater accuracy on proficiency testing than did dropouts, and they required significantly less time to complete cognitive tasks than the dropouts.

Patients in the low-cognition group were more likely to drop out early, during the first 4 weeks of treatment, than those in the high cognition group—55 percent versus 22 percent. And the average proportion of drug-free urine specimens among patients in the high-cognition group was significantly higher than in the low-cognition group.

“The dropout rate was higher for patients with more impairment and lower for the patients with less impairment,” says Dr. Nunes.

“We finally have empirical data to very clearly show that patients with cognitive impairments at treatment entry are more likely to drop out of CBT,” says Dr. Aharonovich. “If you are able to process what the therapist is telling you, you are more likely to stay in treatment. But if you can't, you're more likely to drop out.”

One potential response, Dr. Aharonovich suggests, is to prescreen patients and provide modified treatment for the cognitively impaired—a smaller curriculum, or “CBT Lite,” as she puts it. The goal would be to simplify tasks and pare down the number of topics and skills covered, much as a teacher would do with learning-disabled children. “In the fragile first 4 to 6 weeks of treatment,” she says, “I would, for example, propose increasing session frequency from 60 minutes once a week to 30 minutes twice a week. This would decrease session lengths and reduce the demands on memory and attention.”

To augment this strategy, greater use of visual techniques, like node-link mapping, is recommended. “This is a modi-

fication of CBT,” says Dr. Nunes. “Instead of just talking about the sequence of events that leads up to use—the places, people, thoughts, cravings—the therapist diagrams it all out.”

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***“If you are able to process what the therapist is telling you, you are more likely to stay in treatment. But if you can't, you're more likely to drop out.”***

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Cognitive remediation techniques, or “brain exercises,” which recently showed positive results in a study by Dr. William Fals-Stewart, may help the cognitively impaired patient, observes Dr. Nunes, as may drug therapies designed to improve cognitive ability. At Yale University in New Haven, Connecticut, for example, Dr. Thomas Kosten has begun trials using amiloride to improve cerebral blood flow in patients addicted to cocaine. Drs. Aharonovich and Nunes and Dr. Adam Bisaga, also at Columbia,

are now testing memantine, which has been used in Europe to prevent brain cell damage in Alzheimer's patients and patients suffering from other forms of dementia.

The problem with medications, Dr. Aharonovich says, is getting enough cognition restored quickly to combat the high dropout rate in the first 4 weeks of therapy. “Usually, these medications require more than 4 weeks to take effect,” she says, “so we need to do something to modify the therapy at the very beginning to be able to capture patients and hold them in treatment.”

“Dr. Aharonovich's research supports the notion that a substantial number of drug abusers have some degree of cognitive impairment that could impede their ability to get the most benefit from treatment,” says Debbie Grossman, M.A., of NIDA's Division of Treatment Research and Development. “This study highlights the importance of considering the cognitive functioning of drug abuse patients so that cognitive remediation can be incorporated into treatment, and/or treatments can be adapted and matched to the cognitive ability of the patient. Further research is critically needed to develop, modify, and test ‘cognitive-friendly’ drug dependence treatments that could lead to improved treatment response and outcome.”

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## The Long Road to Medication Development: Cocaine Treatment Moves to Clinical Trials

By Neil Swan, *NIDA NOTES* Contributing Writer

At the culmination of a research journey that began more than 20 years ago, GVG (vigabatrin)—a medication widely used to treat epilepsy outside the United States—is about to be tested in large-scale clinical trials that will determine whether its promising pharmacological properties can translate into effective treatment medication for cocaine abuse. Winning FDA approval of any pharmaceutical therapy for use in the United States is an exacting, costly, time-consuming process. It involves lengthy research, testing in animals and, finally, testing in increasingly larger groups of selected, medically suitable humans to show that the drug is not only therapeutically effective, but safe to use. Testing medications to treat drug addiction is especially challenging, as it involves recruiting—and gaining the support and cooperation of—drug-addicted people.

After more than 20 years, it appears that GVG is nearing the final hurdles to winning FDA approval for use in treating cocaine addiction. Detailed below is this long journey, not untypical of the process many medications go through before providing relief to their intended recipients.

### Identifying GVG's Promise

In the 1980s, Dr. Stephen L. Dewey of Brookhaven National Laboratory in Upton, New York, and a colleague, Dr. Jonathan D. Brodie of the New York University School of Medicine in New York City, were seeking new treatments for schizophrenia. “Very few people in the mid-1980s looked at interactions between neurotransmitter systems, but rather examined transmitter systems independent-

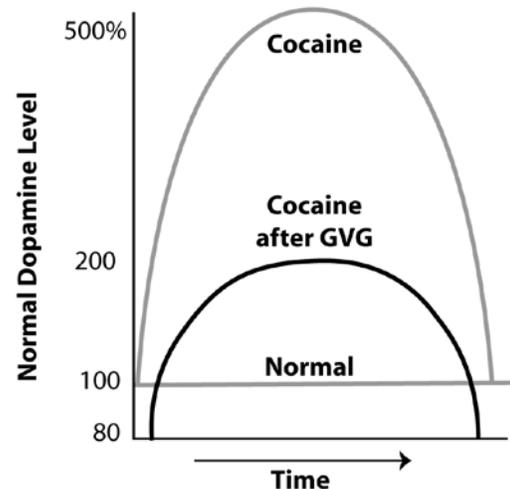
*Developing a medication to treat cocaine addiction has long been a research priority of NIDA's Medications Development Program. According to the National Survey on Drug Use and Health, an estimated 2 million people were current cocaine users in 2002. The available treatment offerings for these individuals as well as people addicted to methamphetamine and other stimulant drugs are exclusively behavioral, as no treatment medications have yet proven effective.*

**Dr. Frank Vocci, Director**  
Division of Treatment Research and Development

ly,” explains Dr. Dewey. As studies continued over years and preliminary research showed that GVG modulates GABA, which in turn reduces dopamine levels, the scientists launched a long series of preclinical experiments testing GVG's potential as a treatment medication for addiction.

“Two decades and 15 publications later, we knew that GVG can safely block the biochemical effects of addictive drugs—nicotine, morphine, methamphetamine, amphetamine, ecstasy, and alcohol—including the increased brain dopamine levels they trigger,” Dr. Dewey says. “This medication can also block the behavioral fallout from dopamine surges: drug self-administration, changes in brain-stimulation reward threshold, relapse resulting from addiction-induced cues, and drug sensitization—the

### GVG Blocks Cocaine-Triggered Dopamine Increases in Animals



**Brain Dopamine Levels Under Various Conditions**

*Cocaine increases dopamine levels in animals to as much as 500 percent of normal levels in critical brain areas. However, when animals are given GVG before being given cocaine, their dopamine levels increase to no more than twice normal levels, indicating the reward-reinforcement response has been blocked or greatly reduced.*

need to consume more and more of a drug to achieve dopamine-based feelings of pleasure.”

With evidence of GVG’s ability to block the addictive effects of all psychostimulants, the researchers focused their research on its potential as a pharmaceutical therapy for cocaine addiction. Throughout this research, Dr. Dewey charted how dramatically GVG therapy inhibits cocaine-induced increases in brain dopamine levels in animals. However, plans to test GVG as a treatment for cocaine abuse in humans were sidetracked in 1998, when research showed that 10 to 30 percent of epilepsy patients taking the drug lost some portion of their normal field of vision.

### Meeting a Safety Challenge

Not willing to give up on GVG’s potential, Dr. Dewey and his Brookhaven colleagues set out to find a low-dosage course of GVG that could effectively block the addictive responses of cocaine in rats without impairing their vision. The researchers’ strategy: compare the effects of a single large dose of 150-450 mg/kg GVG with those of the same total dose administered over 3 days, at 50-150 mg/kg per day. The scientists found that the anti-addictive effect of GVG persists when it is administered gradually. The drug inhibited the effect of cocaine after a 3-day “washout” period when GVG administration stopped. Further, the inhibitory effect of gradual administration actually exceeded in magnitude and duration the effect of the identical total one-shot dose, the researchers found.

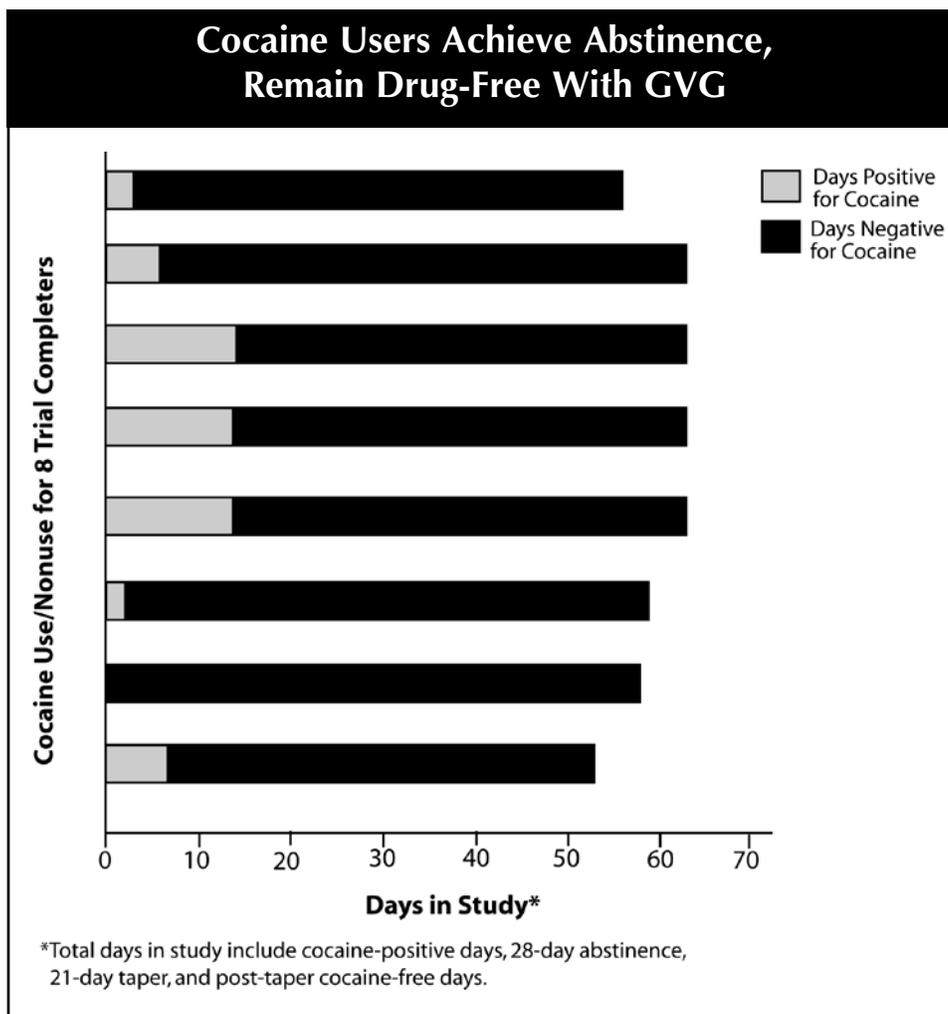
The researchers concluded that people can probably sustain GVG maintenance therapy, possibly for years, with little or no increased risk of developing medication-induced vision defects.

### Launching Clinical Trials

Using human dosages based on the GVG dosages that safely countered cocaine’s effect in rats and primates, Drs. Dewey and Brodie launched a clinical trial with 20 cocaine abusers in a drug treatment center directed

by Dr. Emilia Figueroa in Mexicali, Mexico. Following the dosing strategy devised for animals, the researchers introduced GVG therapy with a strategy of “ramping the patients’ doses up, and then tapering them off,” explains Dr. Dewey.

Of the 20 patients enrolled in the study, 8 remained in the program and were drug-free for periods of 46 to 58 days. Twelve enrollees failed to complete the clinical trial; of these, 8 dropped out within the first 10 days, having decided they were not ready to stop abusing cocaine. Four enrollees participated in the study for 25 to 43 days while continuing to abuse cocaine, albeit in greatly reduced amounts. Most patients who completed the trial reported losing their craving for cocaine after 2 to 3 weeks of GVG. Once they stopped cocaine abuse, 6 of the 8 completers



*Of 20 cocaine abusers enrolled in a GVG clinical trial, 8 completed the trial (28-day abstinence plus 21-day taper) and were drug-free for 46 to 58 days total. Once cocaine use ceased, 6 of the 8 completers were entirely drug-free for the duration of the study. Most patients who completed the trial reported that their craving for cocaine stopped 2 to 3 weeks after receiving GVG.*

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were drug-free for the duration of the study. No vision problems were reported.

Encouraged by the Mexico results, the researchers look forward to the next step—a larger, double-blind, placebo-controlled trial that they hope to initiate soon in Toronto, Canada. Catalyst Pharmaceutical Partners, which holds the license from Brookhaven to develop GVG as a treatment for drug addiction, has helped move this trial forward.

Another smaller trial is also being projected for the United States. Dr. Frank Vocci, Director of NIDA's Division of Treatment Research and Development, says that NIDA is ready to cooperate once FDA gives its approval to go ahead.

“We are still early in the clinical trial process,” notes Dr. Vocci. “However, if additional trials safely and successfully replicate early treatment results, GVG has the potential to provide us with an effective medication for preventing relapse in cocaine-dependent patients.”

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***If additional trials safely and successfully replicate early treatment results, GVG has the potential to provide us with an effective medication for preventing relapse in cocaine-dependent patients.***

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Commenting on the impressive GVG research record, Dr. Vocci concludes, “The data these researchers have compiled is the most comprehensive on a potential medication for addiction therapy that we’ve seen,” he says. “It’s a very interesting medication that involves a very interesting mechanism.”

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## Cocaine May Compromise Immune System, Increase Risk of Infection

By Patrick Zickler, NIDA NOTES Staff Writer

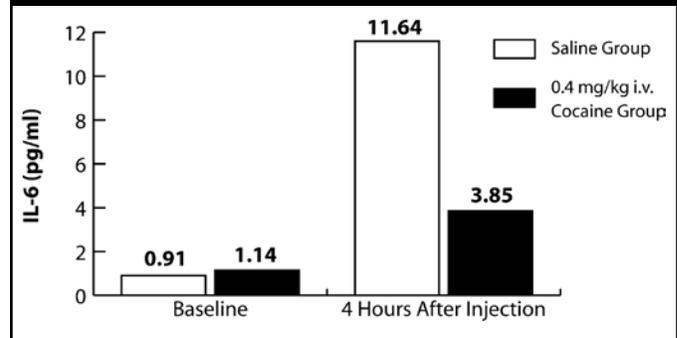
Cocaine abusers are more likely than nonusers to suffer from HIV, hepatitis, sexually transmitted diseases, and other infections. Most of this increased incidence is the result of conditions and behaviors—for example, injecting drugs, poor nutrition, and unsafe sex—that often are associated with drug abuse. Now, NIDA-supported investigators at the McLean Hospital Alcohol and Drug Abuse Research Center in Belmont, Massachusetts, have found that cocaine itself has a direct biological effect that may decrease an abuser's ability to fight off infections.

Dr. John H. Halpern, along with colleagues at McLean Hospital and Harvard Medical School, found that a key immune system component, a protein called interleukin-6 (IL-6), responded less robustly to an immunological challenge in male and female abusers injected with cocaine than in those who received placebo. "When your body detects a foreign object, IL-6 helps trigger the release of a cascade of other immune system components that isolate and neutralize the threat," explains Dr. Halpern. "If the balance of this response is disrupted, your body cannot fight infection as effectively as it should."

The study involved 30 participants (16 women, 14 men, ages 21-35) with a history of cocaine abuse, including at least one drug administration within the past month. The investigators placed an intravenous catheter in one arm of each participant and measured IL-6 levels. The catheter is detected as foreign by the body's immune system and triggers an immune response. After 30 minutes, the researchers injected cocaine or saline solution (0.4 mg/kg) into each participant's other arm; 4 hours later, they measured IL-6 levels again. In participants given saline, IL-6 levels had more than quintupled in response to the presence of the catheter, increasing from an average of less than 2 trillionths of a gram (picograms, or pg) per milliliter of blood to an average of more than 11 pg/ml. In men and women who received cocaine, however, IL-6 levels barely doubled—from less than 2 pg/ml to an average of 3.8 pg/ml.

"The findings in this study show that in people with a history of cocaine abuse, exposure to the drug establishes conditions that can lead to immediate harm," Dr. Halpern says. "In such subjects, we found that cocaine impairs the body's defense system for at least 4 hours. We can't rule out the possibility that IL-6 response returns to normal shortly after that time. But even if the blunted immune

### Cocaine Use May Increase Infection Risk



*Elevations in the protein interleukin-6 (IL-6) play a key role in resisting infections when viruses, bacteria, or foreign objects, such as a catheter, enter the body. IL-6 elevations following insertion of a catheter were smaller in volunteers given cocaine than in volunteers given saline, suggesting that the drug may impair cocaine users' ability to fight off infectious diseases.*

response lasts only a few hours, it makes it more likely that an infection like HIV or just a common cold can take hold," Dr. Halpern says.

"This research suggests a link between cocaine use and compromised immune response and could help explain the high incidence of infectious disease among drug abusers," observes Dr. Steven Grant of NIDA's Division of Treatment Research and Development. "It reminds us that the health consequences of drug abuse reach far beyond disruption of the brain systems involved in abuse and addiction."

The findings also have significance in another context, Dr. Grant adds. "The IL-6 findings are a small but possibly significant part of a much larger study designed to gather a wide range of information on the acute and chronic effects of abused drugs on the brain, endocrine system, and immune function. This kind of discovery-based research can yield unexpected, sometimes important, insights."

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## New Animal Model Simulates Human Exposure, Confirms Harm From Prenatal Cocaine

By Kimberly Martin, *NIDA NOTES* Contributing Writer

Research has shown that some children exposed in the womb to cocaine may have memory and attention deficits that hinder their ability to learn. These children also may have difficulties completing complex tasks or tests that involve distractions, and they tend to perform poorly on visual recognition memory and attention tasks.

Now, Dr. Bret Morrow and his colleagues at Yale University have demonstrated in rats that prenatal exposure to cocaine may cause long-term changes in an area of the brain responsible for short-term memory. Previous animal studies have reported negative effects of cocaine on cognitive performance, but doubts persisted about the applicability of study results to humans. The new findings help allay those doubts, which are based partly on differences in how people use cocaine and in how cocaine was administered to rats in earlier experiments. By designing an experiment that closely simulates the way humans use cocaine, the Yale team has enhanced the applicability of cognitive impairment in rats prenatally exposed to cocaine to that observed in children.

“To more closely replicate the way human fetuses are exposed to cocaine, we administered the drug to the pregnant rats intravenously. This enabled us to use dosages similar to those taken by people. Also, the way cocaine is absorbed and metabolized when it is administered intravenously is much closer to what we see in humans,” says Dr. Morrow. “Additionally, tests commonly used in rat studies to assess cognitive deficits—maze and swimming tests—rely on artificial manipulation of the animal’s environment, such as food restriction, reward, or stress. Our test, a two-object recognition task that relied on the rat’s own motivation to complete the task, is comparable to one used with human infants to assess short-term memory.”

Cocaine was administered to pregnant rats twice a day for 11 days before they gave birth. At ages equivalent to human adolescence and adulthood, the male offspring were placed in a cage with two identical objects, allowed to explore the objects, then removed from the cage. After delays of 20 minutes, 1 hour, and 24 hours, the rats were returned to the cage with one of the former objects and a new object. The time a rat spent actively exploring the new and former objects was recorded. If he spent more time exploring the new object, the rat was considered to remember the former object. To count as “exploring”



*This rat is exploring an object during the two-object recognition task. He was previously exposed to one object, whereas the other is new. The rat was considered to remember the former object if he spent more time exploring the new one. Rats exposed to cocaine before birth did not demonstrate a preference for the new object, indicating no memory of the familiar object.*

time, the rat had to be actively exploring the object, with his nose within about 2 cm of the object.

“The rats that were not exposed to cocaine spent more time exploring the novel object than the familiar object after 20-minute and 1-hour delays, but not after 24 hours,” says Dr. Morrow. “We interpreted this behavior as memory of the familiar object from the previous exposure. The rats that were prenatally exposed to cocaine did not demonstrate a preference for the novel object over the familiar object at any time. This behavior was interpreted as their having no memory of the familiar object. These findings indicate that in the rat model, prenatal exposure to cocaine may result in long-lasting deficits in short-term memory.”

In a separate study, the researchers found that adolescent rats prenatally exposed to cocaine as described above had long-term changes in the frontal cortex. They showed excess activation of neurons in the prefrontal cortex, the brain area governing short-term memory. Activation was measured by the concentration of Fos, a protein produced by excited neurons. “Fos activation during development can change the way a neuron responds in the future; in other words, it undergoes a long-term adaptation,” says

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Dr. Morrow. “In some cases, this may indicate important adaptations that help the animal meet new challenges. However, in cocaine-exposed animals, we believe that the excessive Fos activation may lead to deficits in attention and memory.”

“This type of animal model is valuable in guiding research into the possible mechanisms and consequences of exposure to drugs of abuse during human development,” says Dr. Laurence Stanford of NIDA’s Division of Treatment Research and Development. “Animal models allow us to reduce the number of variables and confounding factors that are present when pregnant women abuse drugs. Research with children strongly suggests a significant dose effect, with the severity and presence of deficits linked to the extent of exposure. Maternal health may also play a role in the effects of prenatal drug exposure. For example, the appetite-suppressing effects of cocaine and resulting nutritional deficits can contribute to growth retardation in the womb. For the purposes of reducing the

number of variables, and thus attempting to isolate the effects of prenatal cocaine exposure, this research is a valuable experiment.”

“This animal model may prove valuable not only for probing neurological and cognitive deficits caused by prenatal cocaine exposure, but also for testing potential therapies,” says Dr. Susan Volman of NIDA’s Division of Neuroscience and Behavioral Research.

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## Joint Treatment of PTSD and Cocaine Abuse May Reduce Severity of Both Disorders

By Robert Mathias, NIDA NOTES Staff Writer

Many individuals who abuse cocaine, alcohol, and other substances also suffer from posttraumatic stress disorder (PTSD) related to life-threatening or other traumatic events they have experienced or witnessed. Individuals with PTSD suffer recurring flashbacks, anxiety, and other symptoms that can impede substance abuse treatment. Similarly, substance abuse can make PTSD symptoms

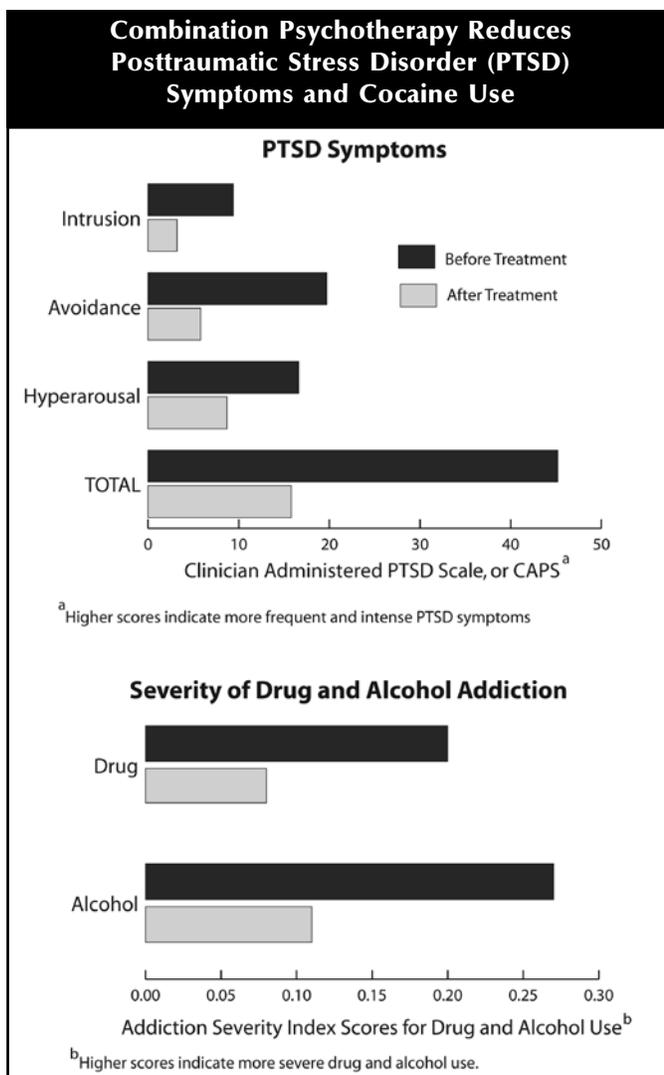
worse. Thus, integrated treatment is recommended as the way to treat patients with both disorders. Yet until recently, the most effective nonpharmacological treatment for PTSD, known as exposure therapy, was considered too risky to use with cocaine-dependent patients. The therapy seeks to desensitize patients to the distressing emotional effects of the trauma that triggered their PTSD by requiring them to repeatedly and graphically describe it.

“Researchers and clinicians have been reluctant to use exposure therapy with cocaine-dependent patients,” says Dr. Kathleen Brady of the Medical University of South Carolina in Charleston. “Drug abuse patients were thought to be likely to turn to alcohol and drugs to cope with the emotional demands placed on them by recounting the fear-inducing experience.”

A preliminary study led by Dr. Brady suggests that the belief that exposure therapy would do these patients more harm than good may not be merited. In the study, instead of triggering emotional distress and relapse to substance abuse, treatment that combined exposure therapy for PTSD with substance abuse counseling produced substantial improvement in both disorders.

Thirty-nine cocaine-dependent individuals with PTSD, 32 of them women, participated in the outpatient study. The majority of participants had developed PTSD following such severe traumatic experiences as rape (74 percent), aggravated assault (89 percent), and other physical assault (95 percent). Individuals who feel intense fear and helplessness or horror during such terrifying events can later develop distressing symptoms that can impair their ability to live and work normally.

PTSD symptoms fall into three general categories: “intrusions,” such as flashbacks or nightmares in which the person reexperiences the traumatic event; “hyperarousal” or anxiety, which can be marked by extreme vigilance and jumpiness, difficulty sleeping or concentrating, and irritability; and “avoidance” of people, activities, and situations that might trigger memories of the incident. When symptoms persist for more than 3 months, PTSD is considered chronic. Chronic sufferers often have additional psychiatric disorders. An estimated 30 to 60 percent of individuals with substance abuse disorders have PTSD, according to studies cited by Dr. Brady.



*Fifteen cocaine-dependent patients with PTSD who completed a psychotherapy that addressed both disorders significantly reduced cocaine use and had fewer and less intense PTSD symptoms, as assessed by physicians.*

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The study used a psychotherapy developed by Dr. Brady and her colleagues that combines counseling for drug abuse with exposure therapy for PTSD. “We wanted to evaluate whether cocaine-dependent PTSD patients could safely tolerate the therapy and whether it would be effective in reducing the severity of their PTSD symptoms and cocaine use,” Dr. Brady says. The combined therapy consists of 16 90-minute individual sessions. In the first 3 weeks, patients participate in two counseling sessions a week that concentrate solely on their drug abuse problems and developing relapse prevention skills. “The therapy in those first sessions gives people a chance to experience some sobriety and provides them the coping techniques and strategies they will need to deal with high-risk situations and the urges to use drugs they may experience when they get into the exposure therapy,” Dr. Brady says.

Once patients start to feel comfortable sharing their feelings with the therapist and are willing to engage in exposure therapy, a technique called imaginal exposure is used to address their PTSD symptoms. In imaginal sessions, patients describe in detail the circumstances and feelings they experienced during the traumatic event that triggered their disorder. They also develop a list of situations or places they have been avoiding because they associate them with the event. Between sessions, patients carry out assignments in which they gradually expose themselves to similar situations that are safe but fear-inducing. If, for example, they were abducted from a parking lot and assaulted, they may have become fearful of any parking lot or areas with cars in them. Assignments could involve going to such areas, first with a friend, then by themselves in the middle of the day.

“We are trying to get at the irrational fears and inappropriate avoidance of situations that are interfering with their lives,” Dr. Brady says. “By talking about their experience over and over in the imaginal sessions, they are basically reliving it. The point of the exposure is to desensitize them to the trauma, thereby reducing the fear, anxiety, and emotion from the memory itself. By the end of successful therapy, patients are able to go through their entire traumatic scenario and feel much less distressed because they are able to separate irrational fears from simply thinking about the event.”

The goal of the therapy is that the intrusion, arousal, and avoidance symptoms all recede. The exposure has done its job when someone can go through his or her detailed recalling of the event and score no higher than 5 on a 20-point scale that measures how much distress they are feeling, says Dr. Brady.

Fifteen of the 39 study participants completed the combined therapy, attending at least 10 of the 16 sessions, including a minimum of 3 exposure therapy sessions. Assessments by both patients and clinicians indicated that those who completed treatment experienced significant reductions in all three PTSD symptom categories and in cocaine use from study entry to treatment completion.

Using a self-administered Impact of Events Scale, patients reported a 53-percent reduction in “intrusion” symptoms and a 27-percent reduction in inappropriate avoidance behaviors. Over the same period, clinicians using a 30-item structured clinical interview tallied a 66-percent reduction in “intrusions,” a 70-percent reduction in “avoidances,” and a 47-percent reduction in hyperarousal symptoms. By the end of treatment, completers also had reduced cocaine use by 60 percent and reported experiencing significantly fewer substance-related problems. Followup assessments indicated that treatment completers had maintained these improvements in both PTSD symptoms and cocaine use 6 months after treatment ended. In contrast, no differences emerged in any PTSD or substance-abuse-related scores at treatment completion or 6 months later among noncompleters.

“This study provides promising preliminary evidence that exposure therapy can be used safely and effectively in treating PTSD in some cocaine-dependent individuals without increasing the risk of relapse,” says Dr. Brady. The improvements in PTSD symptoms were comparable to those reported by other studies that used exposure therapies to treat patients with no substance abuse disorder. Dropout rates, though high, also were similar to those in previous studies that used other psychotherapies to treat cocaine-dependent patients.

Nevertheless, the small number of patients in the study and the high dropout rates underscore the need for randomized controlled studies to replicate these results, Dr. Brady cautions. Such studies also could provide information that would help to identify patients who are likely to benefit from this treatment, as well as those who might need different approaches.

#### Source

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## Researchers Probe for Clues to ADHD Medications' Protective Effects

By Jill Schlabig Williams, *NIDA NOTES* Contributing Writer, and Patrick Zickler, *NIDA NOTES* Staff Writer

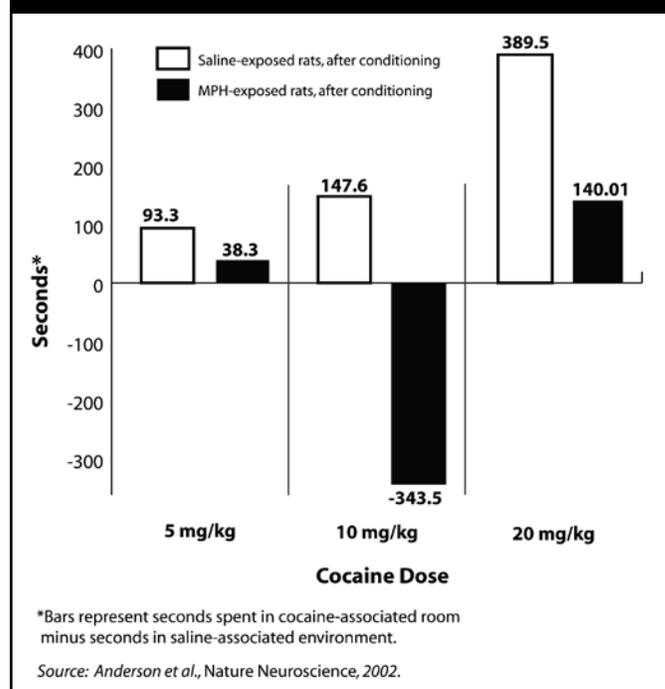
More than 2 million American children—an estimated 5 to 10 percent of preteens—have been diagnosed with attention-deficit/hyperactivity disorder (ADHD). For many of these children, treatment with psychostimulant medications such as Ritalin (methylphenidate, or MPH) suppresses the impulsivity, fidgeting, and inability to concentrate that characterize the disorder. Appropriate use of psychostimulants in children with ADHD also has been shown to reduce the likelihood that these children will develop drug or alcohol use disorders when they reach adolescence and adulthood. (see “Studies Link Stimulant Treatment of ADHD in Childhood to Lower Risk of Later Substance Abuse” on page 43).

While the benefits of psychostimulant treatment for ADHD are clear, scientists are only beginning to explore how these medications help protect children with ADHD against later drug abuse. Two possible explanations have been proposed—one neurobiological and the other psychosocial. Stimulant medications might make drugs less desirable through direct neurobiological effects in the brain that reduce the pleasurable effect that drugs elicit. A second explanation is that the medications may reduce children's vulnerability by helping them act less impulsively, perform better in school, and relate better to others, thereby reducing negative feelings and the likelihood of joining socially deviant peer groups—psychosocial characteristics known to be risks for drug-taking. Possibly, both mechanisms contribute to reduced risk.

Two recent NIDA-supported studies have begun to investigate the neurobiological effect of stimulant medications by studying rats exposed to MPH. Researchers at the McLean Hospital in Belmont, Massachusetts, and the Chicago Medical School exposed rats to MPH during periods when the animal brain is in developmental stages that correspond to human childhood and adolescence.

Scientists stipulate that while responses observed in laboratory animals are suggestive, they do not necessarily indicate that humans will be affected in the same way. Moreover, because researchers have yet to identify the specific brain features that give rise to ADHD, it is even less possible to say whether the current results with MPH have relevance for young people who receive MPH for that disorder. With those caveats, however, the results of these preliminary studies suggest that MPH does have a neurobiological effect that lasts into adulthood.

### Adult Rats Exposed to MPH (Ritalin) During “Childhood” Spent Less Time in Cocaine-Associated Environment



Before place conditioning, rats spent equal time in the saline- and cocaine-associated rooms. After place conditioning, rats exposed to saline in childhood showed a dose-related preference for the cocaine-associated room. However, MPH-exposed rats actively avoided the room they had been conditioned to associate with cocaine at a 10 mg/kg dose. Although these rats spent slightly more time in the room they associated with cocaine at a 20 mg/kg dose, this difference did not reach the level of statistical significance and thus did not show that they were attracted to this room more than the saline-associated room.

### Exposure During Childhood

At McLean Hospital, Dr. Susan Andersen and her colleagues injected groups of eight male rats with either MPH (2 mg/kg) or saline twice daily. The animals were exposed to the medication during a period when the rat brain is in a developmental stage equivalent to human childhood—on days 20 through 35 following birth. At adulthood (day 60), the rats were tested with a method called place conditioning, in which they learn to associate drug effects with a particular environment. On two consecutive days, the rats received

two conditioning trials in which both saline-exposed and MPH-exposed rats were given saline and confined for 1 hour to a side room of a three-room cage before being returned to the central room. Three hours later, the rats received cocaine in a 5, 10, or 20 mg/kg dose and were confined to the other side room for 1 hour before being returned to the central room. On the third day of the study, the rats were allowed to freely explore the entire cage for 30 minutes, while researchers measured the time they spent in the room associated with saline and in the room associated with cocaine.

Adult rats that initially received placebo in childhood showed a dose-related preference for the room associated with cocaine. The higher the dose of cocaine they received, the more time they spent in the room they had learned to associate with cocaine. However, the MPH-exposed rats did not follow this pattern. After receiving either moderate or high cocaine doses, they did not establish place preference for the cocaine-associated room. MPH-exposed rats that received a moderate cocaine dose tended to avoid the cocaine-associated room, spending less time there than in the saline-associated room. MPH rats that received a high dose of cocaine spent slightly more time in the cocaine-associated room, but only about one-third as much time as the unexposed rats. "Their response was definitely blunted," Dr. Andersen says.

The findings reported by Dr. Andersen's research group suggest that, in rats, MPH exposure has a neurobiological effect that is protective later in life. "Rats exposed to MPH during the period equivalent to human childhood experience behavioral changes that endure into adulthood and are more sensitive to cocaine's unpleasant effects," Dr. Andersen observes.

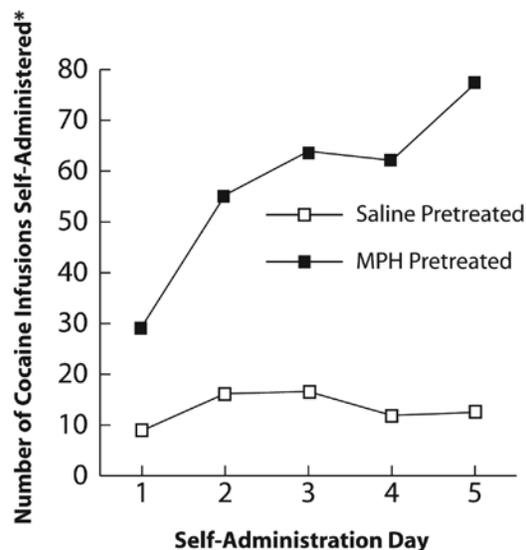
Despite these findings, Dr. Andersen cautions, it is still too early to make assumptions about any neurobiological effect of MPH on vulnerability to cocaine abuse.

"There is still a great deal of research to be done in this area. We need to investigate the role of dose, gender, age of exposure, and treatment duration and to examine how MPH affects other reward systems, such as responses to sex or food," concludes Dr. Andersen.

### Exposure During Adolescence

At the Chicago Medical School, Dr. Cindy Brandon, Dr. Frank White, and colleagues exposed male rats to daily doses of MPH (2 mg/kg) or saline from days 35 to 42 after birth, when the rats are going through a period of brain development corresponding to human adolescence. When the rats reached adulthood (56 days of age), they were put into boxes with two holes into which they could poke their noses. Poking through one hole triggered an infusion of cocaine (75 µg/kg). Poking through the other hole triggered an infusion of saline solution. The scientists

### Adult Rats Exposed to MPH (Ritalin) During "Adolescence" Self-Administered More Cocaine



\*Cocaine dosage was 75 µg/kg per infusion.

Source: Brandon et al., *Neuropsychopharmacology*, 2001.

*Adult rats exposed to MPH during the period corresponding to human adolescence self-administered significantly more cocaine than did rats exposed to placebo in adolescence. Rats self-administered 75 µg/kg of cocaine by poking their noses into a hole in their treatment chamber. This action switched on an infusion pump for 3 seconds, delivering cocaine via a jugular catheter.*

recorded the number of pokes in both holes over 5 days.

Rats that had not been exposed to MPH during adolescence triggered few infusions, and the rate did not increase over the course of the experiment. Rats that had been exposed to MPH in adolescence, however, began self-administering cocaine on the first day and triggered increasingly more infusions on each successive day. By day 5, they were self-administering cocaine at a rate more than seven times that of the rats not exposed to MPH. "Adult animals exposed to MPH during adolescence were considerably more vulnerable to the reinforcing effects of cocaine," Dr. White explains. "From these results, it is reasonable to suspect that in humans, adolescent exposure to MPH may increase future vulnerability to low doses of cocaine."

### Implications for Future Research

This study, like the work done by Dr. Andersen's group, suggests that exposure to MPH has a neurobiological effect that persists into adult life. However, in this study, the effect is to increase risk rather than to confer protection. "It's important to keep in mind that my study and Dr.

Andersen's study measured two different behaviors. Place preference studies can be seen as a model of the animals 'wanting' the drug, while self-administration studies involve actually taking the drug. These methods are not measuring the same processes in the brain," Dr. Brandon says.

"What these animal studies suggest is that, on a neurobiological level, early exposure to MPH has effects that persist into later life," says Dr. Susan Volman of NIDA's Division of Neuroscience and Behavioral Research. "They also indicate that the timing of exposure—whether the animals are exposed during childhood or adolescence—plays a role in later behavior in the animals."

Only continued investigation will clarify the extent to which the neurobiological results seen in rats, which do not have ADHD, might also be relevant to humans with or without ADHD. "There's still a great deal we need to learn about exposing a developing brain to MPH," Dr.

Volman says. "We just don't know enough yet about the enduring changes that may result."

#### Sources

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- Brandon, C.L.; Marinelli, M.; Baker, L.; and White, F.J. Enhanced reactivity and vulnerability to cocaine following methylphenidate treatment in adolescent rats. *Neuropsychopharmacology* 25(5):651–661, 2001. **NN**

## Studies Link Stimulant Treatment of ADHD in Childhood to Lower Risk of Later Substance Abuse

Children treated for attention-deficit/hyperactivity disorder (ADHD) with stimulant medications are less likely to develop substance abuse disorders later in life than are children with ADHD who are not given stimulants, according to NIDA-supported researchers. Dr. Timothy Wilens and his colleagues at the Massachusetts General Hospital and Harvard Medical School in Boston reviewed long-term studies in which stimulant-treated and untreated children with ADHD were evaluated later in life and concluded that stimulant therapy cuts in half the likelihood of subsequent substance abuse disorders.

The researchers examined six studies with a combined total of 647 children with ADHD who had been treated with stimulants and 360 who had not. On average, the studies followed up on the participants for 6 years (range 4 to 15 years) after treatment ended and they were more than 20 years old (range 15 to 22 years of age). Four of the six studies included treated and untreated participants with similar severity in their initial diagnoses. The studies found less incidence of any substance abuse disorder in participants treated with stimulants. One study in which the severity of initial diagnosis was not similar for treated and untreated groups found

that participants who received stimulants were more likely to smoke and to abuse cocaine, but not more likely to abuse alcohol or marijuana. The other study in which diagnostic severity was not matched found that stimulant-treated participants were more likely to abuse alcohol or marijuana.

"Considering all six studies, there was an almost twofold decrease in the likelihood of substance abuse disorders risk for youths treated previously with stimulant medication," Dr. Wilens says.

The Harvard group's findings counter concerns voiced by some practitioners that exposure to stimulants might increase children's disposition to subsequently abuse drugs. "These findings should reassure clinicians and families by providing compelling evidence that pharmacotherapy with stimulants for ADHD does not lead to substance abuse disorders, but instead seems to have protective effects," says Dr. Wilens.

#### Source

- Wilens, T.E., et al. Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. *Pediatrics* 111(1):179–185, 2003. **NN**

## Cocaine's Effect on Blood Components May Be Linked to Heart Attack and Stroke

By Patrick Zickler, NIDA NOTES Staff Writer

Cocaine use increases the risk of sudden heart attack and may also trigger stroke, even in users who otherwise are not at high risk for these sometimes fatal cardiovascular events. The risk is related to narrowing of blood vessels and increases in blood pressure and heart rate. Recently, NIDA-supported researchers at the Alcohol and Drug Abuse Research Center at McLean Hospital in Belmont, Massachusetts, have identified changes in blood components that may also play a role in cocaine-related heart attack and stroke.

Dr. Arthur Siegel and his colleagues studied the effect of cocaine on blood factors that respond to inflammation by promoting clotting to initiate repair. They found that a component that promotes clotting—von Willebrand factor (vWF)—increases and remains elevated for hours after a single exposure to cocaine. They also found that, compared with less frequent users, heavy users of cocaine have elevated levels of vWF, fibrinogen (a clotting factor), and C-reactive protein (CRP), a blood protein that increases in concentration in response to inflammation and is a reliable indicator of risk for heart attack.

“These findings suggest that cocaine creates a temporary risk for heart attack or stroke by increasing clotting factors,” Dr. Siegel explains. “Elevated CRP levels could indicate that long-term use of the drug is triggering inflammation in the cardiovascular system.”

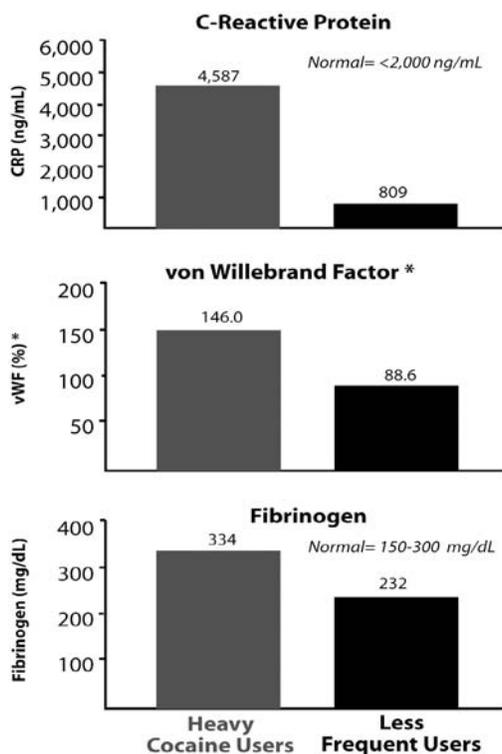
Participants in the study were 20 individuals (10 women and 10 men, average age 26 years) who used cocaine 2 to 6 times per month but were drug free at the time of the study. They received injections of low (0.2 mg/kg) or moderate (0.4 mg/kg) doses of cocaine or of saline solution, and their clotting-related blood components were measured every 30 minutes for 4 hours. In participants who received moderate doses of cocaine, but not those receiving low-dose cocaine or saline, levels of vWF increased by roughly 40 percent and remained elevated for 4 hours.

“With healthy subjects, it’s not unusual to see a temporary increase in vWF after normal activity such as exercise,” Dr. Siegel says. “But the increase is balanced by higher levels of factors that control clotting. The increases that followed cocaine administration were not accompanied by compensatory increases in protective factors.”

The researchers also compared the blood factor levels of the original study participants to those of 10 other individuals (6 women, 4 men, average age 41 years) who used the drug far more heavily—6 to 20 times per week, on average—when both groups were drug free. The heavy cocaine users had higher levels of vWF, fibrinogen, and CRP.

“Elevated levels of CRP and clotting factors that we see in the heavy users suggest that repeated use of cocaine poses an exposure-related and cumulative risk for heart attack or stroke,” Dr. Siegel says. “The fact that neither group showed any compensatory increase in anticlotting mechanisms

### Key Blood Component Levels Are Higher in Heavy Cocaine Users



\*vWF is measured by immunoassay. Percentages indicate binding activity in sample compared with activity in a reference standard. Fifty to 150 percent is considered normal.

Cocaine users who reported heavy use (6 to 20 times per week) show higher levels of C-reactive protein, von Willebrand factor, and fibrinogen—blood components that contribute to clotting—than do less frequent users (2 to 6 times per month).

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suggests that cocaine use upsets the body's ability to maintain a balance between risk and protective factors and tips the scale toward increased risk for heart attack or stroke."

The findings are preliminary, Dr. Siegel cautions, and based on a relatively small sample of cocaine users. "Other factors certainly play a role in CRP levels, and cocaine alone is probably not responsible for the elevated levels we found. For example, age is a factor but does not account for all of the difference. Smoking also may be a factor. In our study, cocaine users who smoked had higher CRP levels than those who did not. On the whole, these findings suggest that cocaine compounds the effects of other risk factors."

If larger studies confirm the relationship between elevated CRP levels and cumulative cocaine exposure, the blood component may serve as a marker for damage, Dr. Siegel says. Moreover, he adds, "measuring CRP is simple and inexpensive, and could be used as a test for the effects of cocaine in much the same way as blood composition

is used to test for diabetes. It could serve as an objective measure of risk for heart attack and stroke and provide a way for patients and treatment providers to assess progress during drug treatment."

#### Sources

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- Siegel, A.J., et al. Effect of cocaine usage on C-reactive protein, von Willebrand factor, and fibrinogen. *American Journal of Cardiology* 89:1133–1135, 2002. **NN**

## Study Finds Significant Mental Deficits in Toddlers Exposed to Cocaine Before Birth

By Robert Mathias, NIDA NOTES Staff Writer

Since the mid-1980s, up to 1 million children born in the United States are estimated to have been exposed to cocaine

in the womb. Determining cocaine's impact on these children's development has been difficult because there often are other possible explanations for physical and mental problems the children may have, such as the mother's use of other substances during pregnancy and poor prenatal care. Now, a NIDA-supported study that was able to separate the effects of cocaine from those of many other such factors has found that children born to poor, urban women who used cocaine throughout pregnancy were

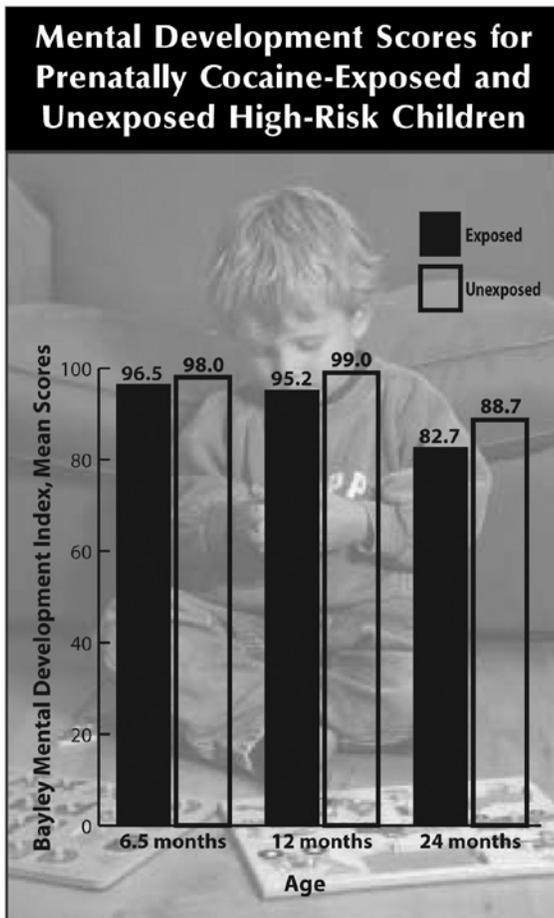
nearly twice as likely as children with similar backgrounds but no prenatal cocaine exposure to have significant cognitive deficits during their first 2 years of life.

The study, led by Dr. Lynn Singer of Case Western Reserve University in Cleveland, Ohio, is the first to show a clear association between prenatal cocaine exposure and cognitive impairment in 2-year-olds. "Since cognitive performance at this age is indicative of later performance, these children may continue to have learning difficulties that need to be addressed when they reach school age," Dr. Singer says.

"The findings of this well-controlled study make an important contribution to a growing body of knowledge about the effects of prenatal cocaine exposure that may help us to identify those exposed children who are at increased risk of developmental harm," says Dr. Vince Smeriglio of NIDA's Center on AIDS and Other Medical Consequences of Drug Abuse. Previous findings from other NIDA-supported studies that have been following cocaine-exposed children from birth have produced conflicting results about cocaine's impact on developmental outcomes at this age, he notes. "Comparing and contrasting the circumstances in this study with those found in other studies of cocaine-exposed children may enable us to identify specific biological and environmental factors that increase or reduce the developmental risk from cocaine exposure," Dr. Smeriglio says.

The study followed a group of 415 infants born at a large urban teaching hospital from 1994 through 1996 to mothers from low socio-economic backgrounds who had been identified by the hospital staff as being at high risk of drug abuse. Women who participated in the study were given urine tests for drug use immediately before or after delivery and interviewed shortly after they gave birth to produce estimates of the type, frequency, and amounts of drugs they had used during pregnancy. Each baby's first stool, known as meconium, also was analyzed for the presence of cocaine and its metabolites to help establish the level of drug exposure. Of the 415 babies in the study, 218 had been exposed to cocaine and 197 had not. Both groups of infants also had been exposed to tobacco, alcohol, and marijuana during pregnancy.

Researchers measured the children's developmental progress at 6.5, 12, and 24 months of age with the Bayley



Tests of mental development at 6.5, 12, and 24 months showed average scores of cocaine-exposed and unexposed children from comparable backgrounds were below the normative score of 100 for children in the general population. At age 2, cocaine-exposed children did significantly poorer in mental development than children in the comparison group.

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Scales of Infant Mental and Motor Development. Motor tests assessed the infants' ability to control and coordinate their movements. Mental tests assessed language, memory, and ability to solve problems at 12 and 24 months. For example, children were asked to describe objects in pictures, remember where an object had been hidden, and put shaped objects into the correct spaces cut out on form boards.

To isolate cocaine's effect, researchers adjusted test results for the effect of other risk factors, such as other drugs used during pregnancy; characteristics of biological mothers and alternative caregivers; the infants' head size, weight, length, and gestational age at birth; and the quality of their postnatal home environments. The analysis showed that while prenatal cocaine exposure had not affected the infants' motor development, it was clearly linked to significant deficits in their cognitive performance at age 2. Cocaine-exposed children scored 6 points lower on the Mental Development Index (MDI), averaging 82.7 percent compared to 88.7 percent for unexposed children and an average general population score of 100. Other findings include the following:

- From 6.5 to 24 months, MDI scores declined for both groups, but cocaine-exposed children had a greater decline—14 points compared to a 9-point decline for unexposed children.
- Almost 14 percent (13.7 percent) of cocaine-exposed children had scores in the mental retardation range, below 70 on the MDI, nearly twice the 7.1-percent rate found in the unexposed children and almost five times the rate (about 2.8 percent) expected in the general population.
- Nearly 38 percent (37.8 percent) of cocaine-exposed children had developmental delays requiring remedial intervention, nearly double the 20.9 percent rate for unexposed children.

The study found that other influences, including the mother's intelligence scores and educational level, exposure to other substances, and the quality of the postnatal home environment, also played significant roles in poor outcomes for cocaine-exposed children. "However, after controlling for these factors in our analysis, we found that cocaine still has a harmful effect on cognitive performance," Dr. Singer says. Additional support for this conclusion

comes from mothers' self-reports and biological data from mothers and infants that established a direct link between cocaine dose and toddlers' cognitive performance. These data showed that children of mothers who used more cocaine and used it more frequently during pregnancy performed worse on the MDI than children of mothers who used less of the drug.

"The only risk factor we couldn't completely control for is the effect of other drugs used during pregnancy," Dr. Singer says, "because it is nearly impossible to find children who have been exposed only to cocaine." The study partially adjusted for this influence by including children who had been heavily exposed to alcohol, tobacco, and marijuana in both groups. "Animal studies suggest there are possible synergistic effects of these drugs in combination, and the study may not have been large enough to control for these effects," she notes.

"We believe that cocaine exposure is a neurologic risk factor that may take a poor child who has a lower IQ potential because of maternal and other risk factors and push him or her over the edge to mental retardation," Dr. Singer says. For example, average IQ scores for both cocaine-exposed and unexposed toddlers in the study were well below the average score for the general population. "In effect, cocaine lowered the range of IQ scores and that means more children may require early stimulation and educational programs," she says.

"While many children in this study may require special educational services when they enter school, it is important not to assume that the findings from a single study, with its unique characteristics, necessarily apply to all cocaine-exposed children," cautions NIDA's Dr. Smeriglio. Ultimately, NIDA's extensive portfolio of research on groups of cocaine-exposed children being raised in a variety of settings should provide detailed information about mother, child, environment, and drug-use characteristics that can be used to develop interventions that reduce risk of harm and guide clinical care for cocaine-exposed children.

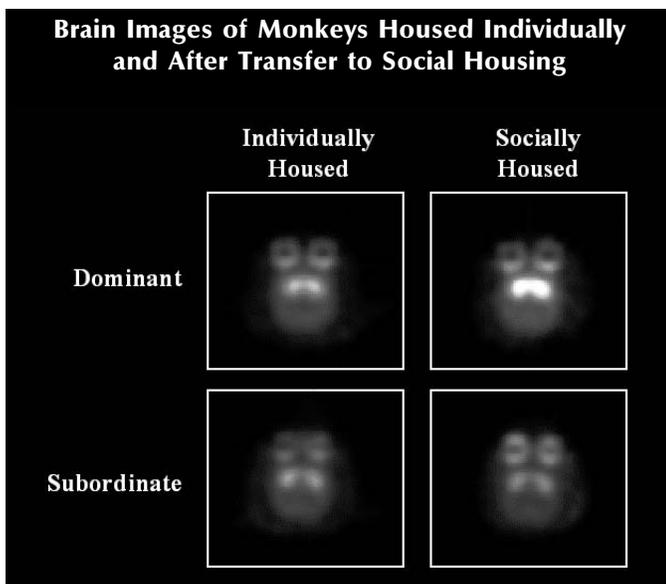
#### Source

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## Social Environment Appears Linked to Biological Changes in Dopamine System, May Influence Vulnerability to Cocaine Addiction

By Kimberly R. Martin, NIDA NOTES Contributing Writer

Cocaine is known to be a highly addictive drug; however, little is known about the factors that make some individuals more vulnerable to it than others. Recently, NIDA-supported researchers at Wake Forest School of Medicine in Winston-Salem, North Carolina, have provided potential insight as to why some drug abusers have an increased susceptibility to cocaine addiction. They have found a link in monkeys between environmental conditions, the brain chemical dopamine, and the addictive qualities of cocaine. In the study, transferring the animals from individual to social housing produced biological changes in some animals that decreased their response to cocaine.



*In these PET scans, lighter colors represent increases in markers of dopamine D<sub>2</sub> function. Greater levels of D<sub>2</sub> markers in socially housed, dominant monkeys—attributed to their living in an enriched environment—suggest that positive changes in one’s environment can result in a biological protection from cocaine addiction.*

Previous studies have indicated that certain environmental conditions—such as living in an enriched environment with access to more resources or reduced stress—may reduce animals’ self-administration of drugs, particularly cocaine. Animal studies also have suggested that environmental conditions may affect the activity of dopamine. Specifically, these studies have indicated that animals’

housing conditions and social rank can affect dopamine’s ability to bind to dopamine D<sub>2</sub> receptors and thereby initiate the cellular processes that produce feelings of pleasure and reward. Taken together, these findings inspired the Wake Forest researchers to look for a three-way link between environment, dopamine D<sub>2</sub> receptor function, and drug self-administration.

The researchers studied 20 macaque monkeys that were first housed individually and then assigned to social groups of 4 monkeys per housing group. Social hierarchies were allowed to develop in each group, and social rank was determined by observations of aggressive and submissive behavior. “Placement of the monkeys in social groups is modeling two extremes—socially derived stress for the most subordinate monkeys and environmental enrichment for the dominant monkeys,” said Dr. Michael Nader, who led the study. “Although these variables have been studied in other animal models, in our model the stressors and environmental variables were not artificially produced in the lab. The model also allows us to study issues related to cocaine-induced changes in social behavior and the interactions of those changes with the reinforcing effects of cocaine.”

Positron emission tomography (PET) was used to measure the amount and availability of dopamine D<sub>2</sub> receptors while the monkeys were individually housed and 3 months after their placement into social groups. After the second PET scan, monkeys were trained to self-administer cocaine by pressing a lever. They were allowed access to cocaine during daily sessions; the rate of cocaine self-administration was determined by the number of times the lever was pressed.

The second PET scan revealed that the monkeys that had become dominant now had 20 percent more dopamine receptor function compared to when they were housed alone. In the subordinate monkeys, dopamine receptor function was unchanged. Although dominant monkeys did not avoid cocaine completely, they had significantly lower intakes of cocaine than subordinate monkeys.

“The increase in markers of dopamine D<sub>2</sub> receptor function among dominant monkeys may be the result of an increase in the number of dopamine D<sub>2</sub> receptors, a decrease in the amount of circulating dopamine competing for the receptors, or both as a consequence

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of becoming dominant,” says Dr. Nader. “This suggests that, regardless of an individual’s past, positive changes in the environment may result in a biological protection from the effects of cocaine. In other words, living in an enriched environment may enhance dopamine function and thus cause the pleasurable effects associated with cocaine use to be diminished.”

The Wake Forest team’s findings in monkeys have implications for understanding and possibly reducing drug abuse vulnerability in people. In people as in monkeys, drugs’ effects on dopamine levels and function are a key to the motivation for abuse. There is evidence that individuals with low levels of dopamine D<sub>1</sub> receptors have higher risk for abusing drugs. In these individuals, reduced dopamine function may produce less bountiful feelings of pleasure and reward from natural activities, making drug-induced euphoria more compelling. The new results suggest that it may be possible to identify environmental improvements that enhance individuals’ dopamine D<sub>1</sub> receptor function and thereby lower their risk for drug abuse.

“Dr. Nader’s research shows that environmental experiences can increase dopamine D<sub>1</sub> receptor levels, which in turn are associated with a decreased vulnerability to cocaine self-administration,” says Dr. Cora Lee Wetherington of NIDA’s Division of Neuroscience and Behavioral Research. “This work, along with previous research regarding the role of dopamine D<sub>1</sub> receptors in drug abuse, points to the need for additional research to identify both environmental factors that promote low dopamine D<sub>1</sub> receptor levels and the associated vulnerability to cocaine’s reinforcing effects as well as environmental factors that give rise to high levels of dopamine D<sub>1</sub> receptors that confer resistance to cocaine’s reinforcing effects. Such research could point to risk and protective factors that could be translated into better prevention and treatment interventions.”

#### Source

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## Study Opens Promising New Approach to Developing Medications To Prevent Relapse to Cocaine Use

By Robert Mathias, *NIDA NOTES* Staff Writer

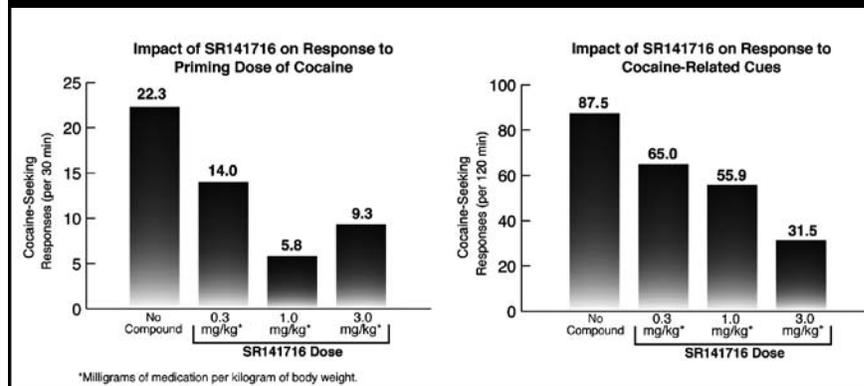
Cocaine treatment patients who encounter people, situations, or settings they associate with past drug abuse often experi-

ence strong urges to use cocaine and slip back into addictive use. Such cue-induced relapse can occur long after patients have stopped using the drug. Now, research teams from Vrije Universiteit (VU) Medical Center in The Netherlands and NIDA's Intramural Research Program (IRP) in Baltimore have shown that they can dramatically reduce cue-induced relapse to cocaine-seeking in rats by blocking a specific type of brain receptor that is activated by cannabinoids, a class of chemicals that includes the active ingredient in marijuana. The study opens a promising new approach to developing medications that may help to prevent cue-induced relapse to cocaine abuse by humans.

"We found that blocking cannabinoid (CB-1) receptors in the brain reduces the relapse-provoking effects of stimuli associated with past cocaine use without interfering with the brain's primary reward pathways," says Dr. Taco De Vries, who led the experiments in Amsterdam. This finding suggests that medications similar to the compound (SR141716) the researchers used to block this receptor may be able to help cocaine treatment patients remain abstinent without diminishing their capacity to experience pleasure from normally rewarding activities, he notes.

In the experiment, Dr. De Vries and Dr. Yavin Shaham of NIDA's IRP first trained rats to self-administer cocaine by poking their noses into a specific hole in their chambers. During daily training sessions, a light was turned on to indicate when cocaine was available and an electrical switch was clicked while cocaine was being administered. Once rats responded regularly for cocaine, researchers turned off the cocaine supply for 2 weeks. As a result, when the rats poked their noses into the active hole during their daily drug-taking sessions, they got no cocaine and their drug-seeking behavior was gradually extinguished. The light and the clicking (light/click) cues that previously had accompanied cocaine administration were not turned on during these extinction sessions.

### Compound Blocks Major Triggers of Drug Relapse



*SR141716, a compound that blocks rats' CB-1 receptors, dramatically reduced resumption of cocaine-seeking responses triggered by two of the three most common triggers of relapse in humans: a priming dose of cocaine and environmental cues associated with cocaine reward. The compound did not reduce cocaine-seeking triggered by stress.*

The researchers then established that the rats would resume nose-poking at the cocaine-paired hole when they were exposed to any of three major stimuli known to provoke relapse to cocaine abuse by humans after periods of abstinence:

- the drug itself—a computer-controlled injection of a priming dose of cocaine;
- drug-related environmental cues—the light/click stimuli previously linked to cocaine reward; and
- stress—precipitated by intermittent electrical foot shocks.

Administering a compound that blocked the rats' CB-1 receptors before exposure to these stimuli significantly reduced cocaine-seeking triggered either by the priming dose of cocaine or by reexposure to the light/click cues. The CB-1 antagonist did not affect resumption of cocaine-seeking triggered by the footshock stressor. These results show that pharmacologically blocking the CB-1 receptor can selectively reduce the drug-stimulus effects of two of the three most common triggers of relapse to drug use.

Significantly, the researchers found that the CB-1 antagonist did not reduce cocaine self-administration in another

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group of rats that had not had the drug withdrawn to extinguish their cocaine-seeking behavior. This result shows the compound did not alter the rats' ability to experience cocaine's primary rewarding effects, Dr. De Vries says. The CB-1 antagonist also did not deter rats from continuing to self-administer sucrose, another rewarding substance. Together, these experiments indicate that primary brain reward pathways are not blocked by the cannabinoid antagonist and suggest that a CB-1 antagonist may be able to selectively block relapse provoked by cocaine cues or the drug itself without producing unpleasant effects such as a general loss of ability to feel pleasure.

The CB-1 antagonist's failure to block relapse triggered by the footshock stressor suggests that the neurobiological mechanisms of stress-induced reinstatement of cocaine-seeking are different from those of drug- and cue-induced reinstatement, says Dr. Shaham, who led this portion of the study. Studies by Dr. Shaham, Dr. Jane Stewart of Concordia University in Montreal, and Dr. Lin Lu of Shanghai Medical University indicate that stress-induced relapse is precipitated through activation of specific neurotransmitters in the brain that regulate the body's

response to stressful situations. Compounds that block the release of these brain neurotransmitters or their action on their receptors have been shown to block stress-induced but not cue- or drug-induced reinstatement of cocaine-seeking.

With this new study, researchers have now identified underlying biological mechanisms involved in three of the most common precipitators of relapse to drug use, as well as compounds that effectively deactivate those mechanisms. "The next step would be to evaluate whether a CB-1 antagonist could be used in combination with agents that block the release of stress neurotransmitters as relapse-prevention medications," Dr. De Vries says.

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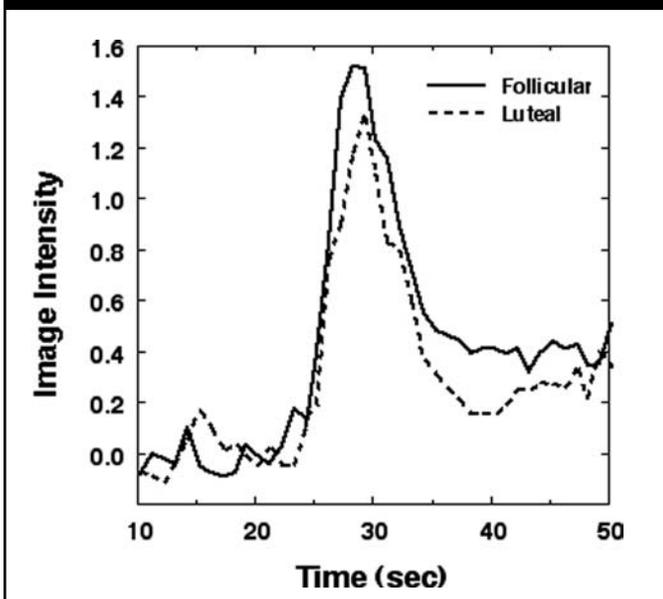
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## Cocaine's Effects on Cerebral Blood Flow Differ Between Men and Women

By Jill S. Williams, NIDA NOTES Contributing Writer

Researchers studying the effects of cocaine on the brain have found that men and women with comparable drug use histories do not exhibit comparable damage. One study showed that women suffered less neuronal injury than men; another, that cocaine-dependent women have fewer abnormalities in blood flow to the brain than do cocaine-dependent men. Now, a recent NIDA-funded study has taken an important step toward explaining these differences between the sexes.

**Cocaine's Effect on Cerebral Blood Volume Varies Throughout Menstrual Cycle**



Magnetic resonance (MR) image intensity was measured to compare the hemodynamic effects of cocaine during two phases of a woman's menstrual cycle. Following cocaine administration during the follicular phase, image intensity was relatively high, reflecting cerebral blood flow at 97 percent of its pre-cocaine baseline. When the drug was given during the luteal phase, lower image intensity reflected a fall in blood flow to 82 percent of baseline.

Cocaine constricts blood vessels, temporarily narrowing arteries and reducing blood flow to the brain, heart, and other areas of the body. Repeated exposure to cocaine can lead to blood-flow deficits in the brain that persist long after cocaine use has ended, causing permanent damage.

Dr. Marc J. Kaufman and colleagues at McLean Hospital, Harvard Medical School, in Belmont, Massachusetts, found that cerebral blood flow during the follicular phase of women's menstrual cycles (days 1 through 14, prior to ovulation) is not affected by exposure to cocaine. In women during their luteal phase (after ovulation, typically days 15 through 28) and in men, cocaine restricts cerebral blood flow.

"We hypothesized that the differences in blood flow might be caused by sex hormones," says Dr. Kaufman. "We decided to investigate whether women with high levels of estrogen, which improves blood-vessel elasticity, are more resistant to the vasoconstrictive effects of cocaine."

Dr. Kaufman and his colleagues used dynamic susceptibility contrast magnetic resonance imaging (DSC MRI) to study cocaine-induced changes in cerebral blood volume in 13 healthy young women (average age 28) with histories of occasional cocaine use. The women's self-reported lifetime cocaine use averaged 13 exposures (ranging from 1 to 40).

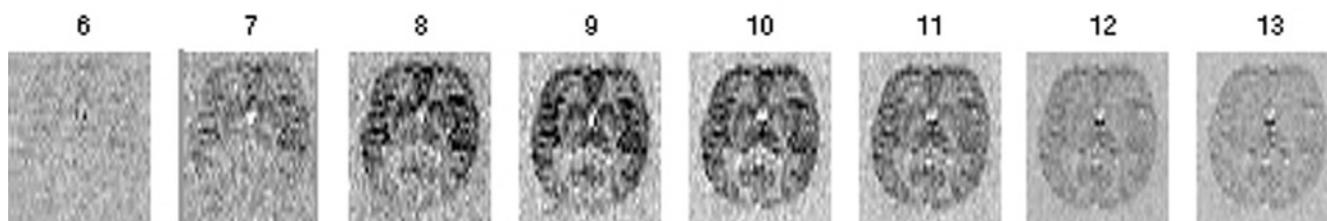
Each woman was given a dose of cocaine and underwent a DSC MRI scan of cerebral blood volume during both phases of her menstrual cycle. During the first part of the menstrual cycle, estrogen levels are high and progesterone levels are low; during the second part, progesterone levels rise. In each imaging session, two brain images were collected: one as a baseline measure of cerebral blood volume and the second 10 minutes after cocaine administration.

The study found no significant changes in cerebral blood volume after cocaine administration during the women's follicular phase. During the luteal phase, when progesterone levels are highest, the women's cerebral blood flow fell approximately 10 percent after cocaine administration. These data compare to Dr. Kaufman's findings in a similar 1998 study, that men experience, on average, a 20-percent reduction in cerebral blood volume after cocaine administration.

"We found what we were expecting," says Dr. Kaufman. "There was a minimal change in follicular cerebral blood volume, attributable, we believe, to the protective effects of estrogen. The greater vasoconstrictive effect of cocaine in luteal-phase women may be attributable to the progesterone, which has been shown to increase cocaine's vascular toxicity."

## Using Magnetic Resonance Imaging (MRI) To Track Cerebral Blood Volume

### Seconds After Contrast Injection



A sequence of magnetic resonance images taken at 1-second intervals after a woman received an intravenous blood marker progresses from light to dark to light as her cerebral blood flow carries the marker into her brain and washes it back out again. The total marker present in all the images, measured as their intensity (darkness), reflects total cerebral blood volume. To study the hemodynamic effects of cocaine, investigators compared two such sequences, obtained before and after administration of the drug, during each menstrual period.

Dr. Kaufman's next step will be to administer estrogen or progesterone to men and luteal-phase women and measure the effects on cerebral blood volume after cocaine administration. The ultimate goal will be to develop a hormonelike medication to counteract the vascular effects of cocaine.

"Beyond confirming that cocaine does have a damaging effect on the brain and is not safe to use, this research contributes to our understanding of the drug's deleterious effects," says Dr. Steven Grant, of NIDA's Division of Treatment Research and Development. "Additionally, the research points out that we've got to stop thinking of both

sexes as the same when it comes to the effects of drugs. Dr. Kaufman has shown that cocaine affects men and women differently."

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## Blood Pressure Medication May Improve Cocaine Treatment Results in Patients With Severe Withdrawal Symptoms

By Robert Mathias, NIDA NOTES Staff Writer

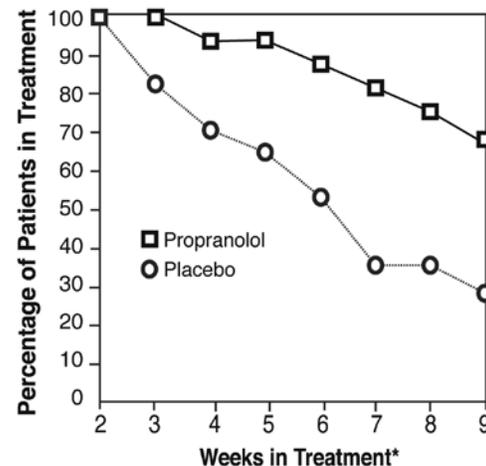
A medication used to treat high blood pressure may be an effective add-on therapy for cocaine-dependent patients who suffer severe withdrawal symptoms when they stop using the drug, a NIDA-funded study indicates. Patients who experienced severe anxiety and other symptoms and were treated with the medication—propranolol—stayed in treatment longer and used less cocaine than a comparable group of patients who were treated with a placebo, the study shows.

Cocaine-dependent patients who experience severe withdrawal symptoms generally use cocaine heavily and are more dependent on the drug than patients who have less severe withdrawal symptoms. “These patients are unable to stop using the drug for significant periods and are more likely to drop out of treatment programs,” says Dr. Kyle Kampman of the University of Pennsylvania School of Medicine in Philadelphia, who conducted the study. “This is not a tiny subgroup. We’ve found that about 40 percent of the cocaine abusers who come into the Day Treatment Program of the Philadelphia Veterans Affairs Hospital have withdrawal severity scores that are high enough to put them at risk for doing poorly in treatment.”

Dr. Kampman and his colleagues theorized that propranolol might lessen the severity of symptoms such as anxiety and craving experienced by newly abstinent cocaine treatment patients. Propranolol belongs to a class of medications called beta-adrenergic blockers that inhibit the effects of adrenaline in the central and peripheral nervous systems, where it works to arouse the body’s “fight or flight” response to dangerous or stressful situations. Beta-adrenergic blockers have been used clinically to treat general anxiety and anxiety associated with alcohol withdrawal. The researchers thought propranolol’s tempering of symptoms such as palpitations and sweating might also reduce cocaine craving associated with such symptoms.

In the study, the researchers used an interviewer-administered questionnaire, the cocaine selective severity assessment (CSSA), to measure cocaine withdrawal symptoms among 108 treatment-seeking cocaine-dependent men and women. The CSSA assesses the intensity of 18 symptoms including anxiety, cocaine craving, depressed mood, appetite changes, sleep disturbances, and altered heart rates that patients may experience when they stop using cocaine. In a previous study, the researchers found that

**Effect of Propranolol on Cocaine Treatment Retention In Patients With Severe Withdrawal Symptoms**



\* Administration of propranolol or placebo began after a 1-week baseline period.

*Nearly 69 percent of cocaine treatment patients experiencing severe withdrawal symptoms who received propranolol completed the treatment program, compared to 29 percent of patients with similar symptoms who were treated with a placebo.*

patients who had high CSSA scores when they entered treatment were likely to drop out of treatment.

Following a 1-week lead-in period in which all subjects were given a placebo, researchers randomly assigned patients to receive either propranolol or a placebo daily for 8 weeks. All subjects also received cognitive-behavioral counseling twice a week. Urine tests for cocaine were conducted three times a week throughout the trial to assess cocaine use. Treatment retention, cocaine withdrawal symptoms, craving, mood, and anxiety symptoms were evaluated weekly.

When the researchers analyzed results for all study subjects, they found that propranolol-treated subjects had less severe cocaine withdrawal symptoms during the trial, but they did not do significantly better on any other outcome measure than those treated with the placebo. However,

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when the researchers looked at outcomes in conjunction with the severity of cocaine withdrawal symptoms, they found that propranolol-treated individuals who had CSSA scores in the upper third of all subjects at baseline were much more likely to complete the treatment program than subjects with similar baseline CSSA scores who were treated with placebo. Among subjects with high CSSA scores, 69 percent of those who received propranolol completed treatment, compared to 29 percent of those treated with a placebo. Propranolol-treated high-CSSA subjects also had significantly lower urine levels of benzoylecognine, a cocaine metabolite, than did placebo-treated subjects, indicating they used less cocaine throughout the trial. There were no significant gender differences in any outcome measures.

### Treatment and Research Implications

Although the study's findings are preliminary, they suggest that propranolol may be a useful add-on treatment for the substantial subset of cocaine-dependent patients who have severe withdrawal symptoms. However, treatment outcomes in propranolol-treated subjects were still far from optimal. Additional medication or more intense counseling may be needed to treat such patients effectively, the researchers indicate. "Clinicians can use the CSSA score to predict treatment outcomes and try to match people to appropriate levels of treatment," says Dr. Kampman. "If you put someone with a high score in once- or even twice-a-week individual counseling, they just aren't going to do well. They need more intensive treatment."

The study also has implications for researchers testing cocaine treatment medications, Dr. Kampman says. "Until now, clinical trials haven't separated out those patients who need to be detoxified," he says. "They come in with 'hot' urines [indicative of heavy, current cocaine use], have a lot of withdrawal symptoms, and have trouble getting abstinent. They are so different from people who enter treatment with cocaine-free urines and low withdrawal symptoms, that if you put the two groups together when you test a medication, you are going to miss significant treatment effects. In our studies, we are now dividing patients into two distinct populations based on initial assessment of the severity of their withdrawal symptoms. For patients who have a lot of withdrawal symptoms, we test medications that have the potential to reduce severity of these symptoms to see if it will help them get clean and stay in treatment. For patients who have few withdrawal symptoms and less difficulty achieving initial

abstinence, we select a medication that might work better to prevent relapse."

### Additional Medications Research

In addition to propranolol, Dr. Kampman has been testing the potential of other medications to improve treatment outcomes for cocaine-dependent patients with severe withdrawal symptoms. Results of a preliminary trial of amantadine, which may alleviate cocaine's disruption of the brain's dopamine system, were promising. Patients with severe cocaine withdrawal symptoms at the start of treatment used less cocaine during the trial than those who received a placebo.

Following up on these results, Dr. Kampman and his colleagues now are conducting a large, double-blind prospective study of the effectiveness of amantadine and propranolol individually and in combination. The study is targeted specifically at cocaine-dependent patients who score in the upper one-third of patients on the CSSA.

"We know that amantadine slightly increases the release of dopamine, which in turn might reduce the dysphoria—the pervasive unhappiness and restlessness—that also is associated with cocaine withdrawal," says Dr. Maria Majewska of NIDA's Division of Treatment Research and Development. "If amantadine can reduce dysphoria and propranolol can reduce the anxiety and the arousal associated with craving, maybe this will be a winning combination with this population. We are cautiously optimistic as we await the results of the trial."

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## Methamphetamine, Cocaine Abusers Have Different Patterns of Drug Use, Suffer Different Cognitive Impairments

By Patrick Zickler, *NIDA NOTES* Staff Writer

NIDA-supported research has found that methamphetamine abusers typically use the drug throughout the day in a pattern that resembles taking medication, while cocaine abusers often exhibit a binge pattern, using the drug continuously over a period of several evening and nighttime hours. And, according to the researchers at the University of California, Los Angeles (UCLA), the drugs appear to cause different types of deficits in reasoning and concentration.

### Patterns of Use

Dr. Sara Simon and her UCLA colleagues interviewed 120 methamphetamine abusers and 63 cocaine abusers to determine patterns of drug use. Ninety-seven of the methamphetamine abusers and 56 cocaine abusers were recruited from treatment programs; the others were currently using the drug and not seeking treatment.

Continuous use—more than 20 times per month—was more common for both cocaine abusers (52 percent) and methamphetamine abusers (70 percent) than was any other pattern of drug use. Among those who used either drug fewer than 20 times per month, methamphetamine abusers were 4 times as likely as cocaine abusers (48 percent compared with 12 percent) to use the drug at least once per week in a regular cycle.

“The typical methamphetamine abuser reported using the drug when he or she first got up in the morning,

to remove 50 percent of the drug) of methamphetamine is 12 hours. Cocaine’s half-life is roughly 1 hour, and the drug’s high lasts about 20 to 30 minutes.

Understanding the patterns of use for methamphetamine and cocaine will help treatment providers and drug users identify circumstances that may lead to relapse to drug use. “Differences in use patterns indicate different triggers and different times and places when the recovering abuser is particularly vulnerable,” says Dr. Simon.

### Effects on Reasoning and Memory

In another study, Dr. Simon and her colleagues evaluated the effects of methamphetamine and cocaine on learning and memory in 40 methamphetamine abusers and 40 cocaine abusers who were not in treatment and 80 individuals who had never used either stimulant drug. The researchers administered tests to evaluate memory, perceptual speed and ability to manipulate information, ability to ignore irrelevant information, general intelligence, verbal fluency, and executive function (abstract reasoning, reactive flexibility, and ability to use feedback).

Methamphetamine abusers performed more poorly than nonusers of stimulants in tests of word recall, perceptual speed, ability to manipulate information, and abstract thinking. Cocaine abusers scored more poorly than nonusers of stimulants in tests measuring ability to recall words and pictures and working memory.

“Methamphetamine abusers displayed impairments on the tests of perceptual speed and manipulation of information that were not seen in the cocaine group. Moreover, in tests that require both speed and manipulation, there was even more difference between the groups than on tests of either skill separately,” Dr. Simon says.

“Overall, both drugs are associated with similar cognitive deficits,” Dr. Simon says. “The most striking difference is that methamphetamine abusers have more trouble than cocaine abusers at tasks requiring attention and the ability to organize information.”

**Methamphetamine** abusers typically take the drug early in the morning, and take it at 2- to 4-hour intervals throughout the day.

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**Cocaine** abusers usually take the drug in the evening rather than the daytime, and take it continuously over a period of several hours.

The infographic features chemical structures for both drugs. Methamphetamine is shown as a benzene ring attached to a propyl chain with an amino group. Cocaine is shown as a tropane alkaloid with a tropane ring system, a methyl ester group, and a tropane ring.

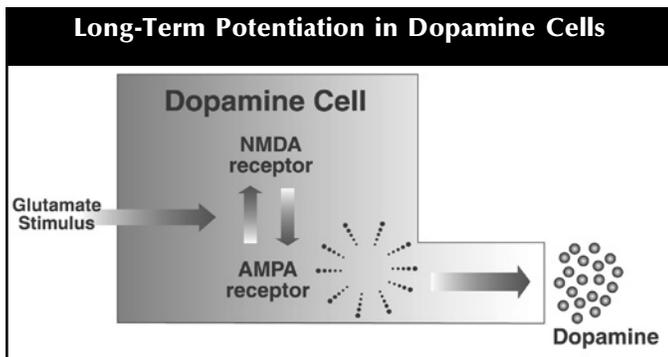
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## Altered Cellular Activity May Be First Step in Progression to Cocaine Addiction

By Patrick Zickler, NIDA NOTES Staff Writer

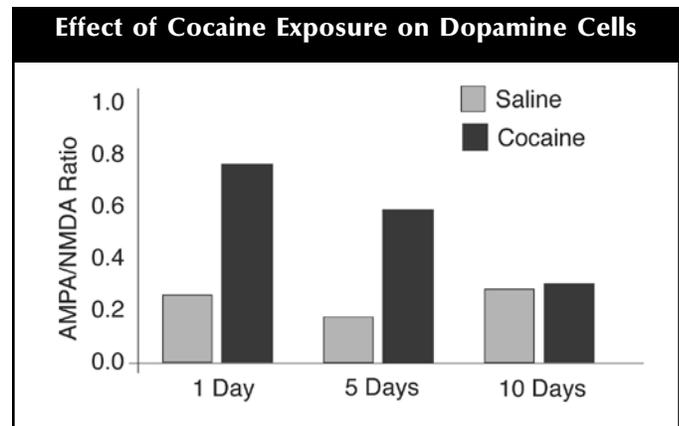


When the brain chemical glutamate reaches dopamine cells in the ventral tegmental area, it activates specific sites called NMDA receptors and AMPA receptors. Electrical current generated by the AMPA receptors triggers the release of dopamine, a chemical associated with the pleasurable effects of addictive drugs. Release of dopamine is enhanced by a condition called long-term potentiation (LTP), which is thought to play a role in associative learning and memory formation. When LTP has been established a glutamate stimulus results in higher AMPA currents; therefore, the cell is likely to release dopamine more abundantly than it would have previously. NIDA-supported researchers have found that a single exposure to cocaine can establish LTP in mice, and that the enhanced activity lasts for more than 5 days.

NIDA-supported research has identified a neurobiological mechanism that could be involved in initiating the compulsive drug-seeking behavior that is the behavioral hallmark of cocaine addiction. Scientists have shown that, in mice, a single exposure to cocaine induces changes in brain cells that are very similar to long-term potentiation, a process that plays an important role in associating experiences with feelings and motivation.

When a stimulus induces long-term potentiation in a cell, the cell will respond more strongly to future exposures to the same stimulus. Using mice, Dr. Robert Malenka of Stanford University in Palo Alto, California, along with Dr. Antonello Bonci and his colleagues at the University of California, San Francisco, showed that cocaine induces this effect on dopamine (DA) cells in the brain's ventral tegmental area (VTA). When stimulated by cocaine, these mouse cells release the neurotransmitter DA, a brain chemical that leads to feelings of pleasure. By increasing the responsiveness of the VTA DA cells, cocaine-induced potentiation could create powerful associations between drug taking, the situations in which drugs are taken, and feelings of pleasure.

To assess the effect of cocaine, Drs. Malenka and Bonci measured the electrical currents generated in VTA DA cells by activation of structures known as AMPA receptors—sites that, along with NMDA receptors respond to another neurotransmitter, glutamate. In general, the more current that flows through a cell's AMPA receptors, the more DA the cell will release. The researchers showed that exposure to a dose of cocaine (15 mg/kg of body weight) comparable to doses used by humans caused a higher current to flow through AMPA receptors; consequently the VTA neurons would be expected to release DA more abundantly.



Mice injected with a single dose of cocaine exhibited a higher ratio of AMPA to NMDA currents—an indication of long-term potentiation—in dopamine cells in the ventral tegmental region 1 day and 5 days after the drug exposure. Mice injected with saline showed no long-term potentiation.

“A single injection of cocaine more than doubles the activation of the dopamine cells. The changes were still present 5 days later, but not 10 days after injection,” Dr. Malenka says. “This finding alone does not explain cocaine’s ability to produce compulsive drug-seeking behavior. But for the first time it describes how cocaine can trigger a mechanism that contributes a small but important part of the complex cascade of events that leads to addiction.”

“Two aspects of this study have particular significance,” says Dr. Susan Volman of NIDA’s Division of Neuroscience and Behavioral Research. “First, the effect was obtained with a single dose of cocaine. Second, the effects of

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cocaine were indistinguishable from long-term potentiation, which suggests that, for nearly a week after it is administered, cocaine utilizes the cellular mechanism involved in normal adaptive learning.” By forging associations between experiences and positive or negative feelings, long-term potentiation of DA and other types of brain cells is a key mechanism in learning and memory and, in this way, has an impact on future behavior.

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## Biochemical Brain Abnormality Found in School-Age Children Prenatally Exposed to Cocaine

By Robert Mathias, NIDA NOTES Staff Writer

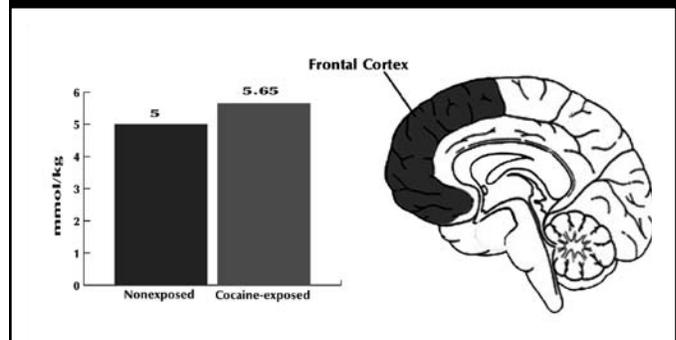
Exposure to cocaine before birth may affect the way a child's brain functions many years later, according to a recent NIDA-funded study. The brain-imaging study found a chemical abnormality in the brains of 8-year-old children that may reflect alterations in metabolic processes that enable brain cells to use energy and function properly, the researchers say.

"These children were exposed to cocaine only during gestation and their brains have had 8 years to recover from that exposure," says Dr. Joseph Frascella of NIDA's Division of Treatment Research and Development. "It is surprising that they are still showing these deficits so many years later." The new finding suggests that early exposure to drugs has more long-lasting effects on the brain than previously thought, he notes.

The nature and extent of possible developmental damage to infants and children from prenatal exposure to cocaine has been the subject of much apprehension and scientific study. In the 1980s, anecdotal reports of abnormalities among cocaine-exposed children contributed to fears that these children were irreparably damaged and would never be able to function in society. Subsequent scientific research has dispelled such exaggerated concerns for the vast majority of prenatally exposed children. NIDA-funded studies that have been tracking the development of groups of cocaine-exposed babies through adolescence now indicate that most seem to function normally, but some may have subtle impairments in their ability to control emotions and focus attention that could put them at risk of behavioral and learning difficulties.

Previous brain-imaging studies of children prenatally exposed to cocaine have yielded conflicting information about the drug's effects on the developing central nervous system. Some studies have found abnormalities in brain structure, while others have not. Studies in abstinent adult cocaine abusers, using an imaging technique called magnetic resonance spectroscopy (MRS), have suggested that chronic cocaine use may cause persistent damage to neurons in the frontal lobes of males and that brain metabolic abnormalities also could exist despite a normal-appearing brain structure. Dr. Lynne Smith of the Harbor-UCLA Medical Center in Torrance, California, and Dr. Linda Chang of Brookhaven National Laboratory, in Upton, New York, used this MRS technique to see if similar biochemical abnormalities might be present in the brains of

### Creatine Level Alterations in Frontal White Matter of Cocaine-Exposed Children



*MRS scans suggest cocaine-exposed children did not have significant nerve damage or loss in the brain regions that were examined. However, cocaine-exposed children had significantly higher levels of the brain metabolite creatine than nonexposed children in a frontal area of the brain made up of "white matter," which consists mainly of nerve fibers and specialized support cells. The abnormality may reflect alterations in metabolic processes that enable brain cells to use energy and function properly.*

children who had been prenatally exposed to cocaine, even if they appeared to have no structural damage.

The researchers used magnetic resonance imaging (MRI) to assess brain structure and MRS to examine brain biochemistry in 14 8-year-old children who had been exposed to cocaine in the womb. They administered the same brain scans to a control group of 12 age-matched, nonexposed children. The MRS scans measured levels of various chemicals in different brain regions. Increased or reduced concentrations of these chemicals can indicate either damage to nerve cells or alterations in brain cell function in these regions. The researchers assessed a frontal area of the brain, made up of "white matter," which consists mainly of nerve fibers and specialized support cells. They also looked at an area deep in the brain called the basal ganglia, which contains clusters of nerve cell bodies, or "gray matter."

The study found no difference between the exposed and nonexposed children in concentrations of N-acetyl-aspartate (NAA), a nerve cell metabolite, in either the frontal area or the basal ganglia. Because NAA levels are markers for the density and integrity of nerve cells, the

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normal NAA found in children prenatally exposed to cocaine suggests they did not have significant nerve damage or loss in the two brain regions that were examined. The MRI evaluations also showed no brain structure abnormalities in children in either group. However, cocaine-exposed children had significantly higher levels of creatine in the white matter of the frontal lobes than nonexposed children. Elevated creatine levels indicate that the brain cells of cocaine-exposed children use energy differently in this region.

“All brain cells require creatine for all functions,” says Dr. Chang. “The altered creatine levels we found could affect how both nerve cells and support cells are functioning in the brain. We also have found the same abnormal creatine levels in frontal white matter in adult cocaine abusers more than a year after they have stopped using cocaine. The drug seems to have a particularly long-lasting effect on energy metabolism in this brain area that merits further investigation.”

“The frontal area of the brain is involved in our ability to control impulses and sustain attention on a task,” notes

Dr. Frascella. Thus, it is possible that the altered brain function found in this area could be a biological basis for findings from other research that some cocaine-exposed children are more impulsive and easily distracted than their peers. However, additional research is needed to make this determination, he says.

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## Even Modest Cocaine Use May Cause Brain Changes That Could Contribute to Addiction

By Robert Mathias, NIDA NOTES Staff Writer

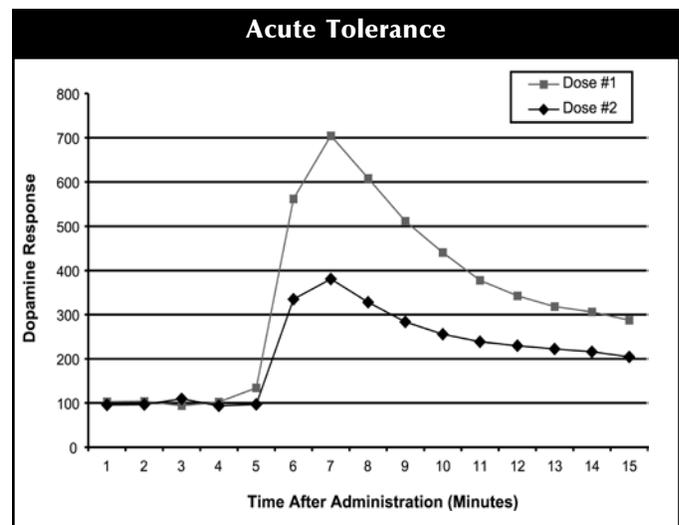
A major goal of drug abuse research is to determine how voluntary drug use turns into compulsive drug use and addiction. A recent NIDA-supported study sheds light on drug-induced brain changes that may play an important role in this process. The study, conducted in rhesus monkeys, found that even a single low dose of cocaine reduced the brain's response to an identical dose of the drug taken later in the same day. Conversely, weekly exposure to low doses of cocaine made the monkeys' brains progressively more sensitive to the drug. These findings suggest that even occasional cocaine use can alter brain function in ways that may put voluntary users at increased risk of addiction.

***“This rapid development of tolerance to cocaine’s effects could underlie the repeated consumption of escalating doses of the drug that is typical of human cocaine binge sessions.”***

“Perhaps the most striking aspect of this study is the relatively low drug exposure—in each session and cumulatively over the course of the study—that resulted in progressive changes in brain response,” says Dr. Charles Bradberry of Yale University School of Medicine in West Haven, Connecticut, who conducted the study. “Previous research in rats indicates that these changes in brain function are essentially permanent and may contribute to cocaine use becoming compulsive,” he says. Characteristic patterns of human cocaine consumption in which cocaine is taken repeatedly can result in much higher levels of exposure and could lead to more pronounced changes in brain function, Dr. Bradberry adds.

The study assessed changes in brain function in four rhesus monkeys that were permitted to take a maximum of two doses of 0.5 mg of cocaine per kilogram of their body weight once a week for 6 months. A previous study conducted by Dr. Bradberry indicated that the 0.5 mg/kg

dose produces blood levels of cocaine in the monkeys that are equivalent to those found in humans who experience euphoria when given cocaine in laboratory settings. The monkeys self-administered each dose by pressing a lever when a light indicated that cocaine was available. The weekly self-administration of low doses of cocaine was designed to simulate human patterns of weekend cocaine use.



*Acute Tolerance—Exposure to a single low dose of cocaine made the monkeys’ brains less responsive to a subsequent dose of the drug taken shortly thereafter, a phenomenon called acute tolerance. This illustration shows extracellular dopamine levels in a monkey’s brain after it has self-administered two identical doses of cocaine. The second dose, taken after the effects of the first dose wore off, produced lower levels of dopamine.*

Each week, the researchers measured extracellular levels of dopamine in a region of the monkeys’ brains that corresponds to the limbic system in human brains. Cocaine-induced dopamine increases in this region are thought to trigger euphoria and play a significant role in cocaine abuse and addiction.

### Short-Term Brain Changes

Within each weekly session, the researchers measured the monkeys’ extracellular dopamine levels after the initial dose of cocaine. When the monkeys’ extracellular dopamine returned to pre-cocaine levels, the researchers

allowed the monkeys to administer the second dose of the drug. The dopamine level did not rise as much following the second dose. This phenomenon, where exposure to a drug makes the brain less responsive to a subsequent exposure shortly thereafter, is called acute tolerance.

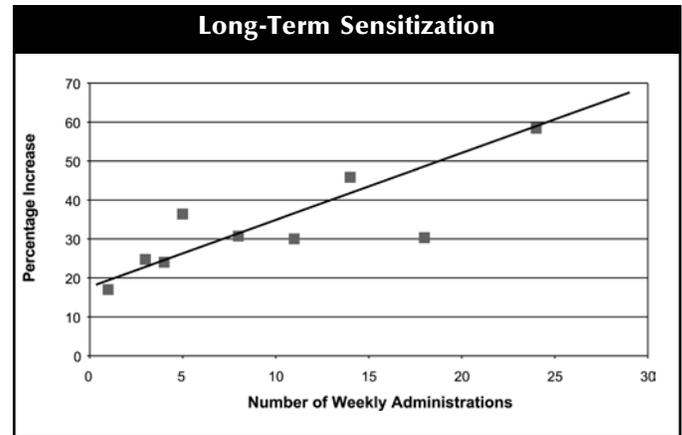
“This rapid development of tolerance to cocaine’s effects could underlie the repeated consumption of escalating doses of the drug that is typical of human cocaine binge sessions,” Dr. Bradberry says. “Research we are conducting now suggests that this acute tolerance may be important in regulating how much cocaine someone takes in a given session.” Instead of limiting the monkeys’ cocaine intake, the new research permits the animals to continue to infuse cocaine after the first two doses. “Animals that show the most tolerance will take as much cocaine as they can as soon as it is available,” Dr. Bradberry says. “Animals that do not show as much tolerance don’t take as much.”

### Long-Term Brain Changes

The modest doses of cocaine once a week also caused long-lasting changes in the way the monkeys’ brains responded to the drug over time. As the study progressed, the same 0.5 mg/kg dose of cocaine that began each weekly session produced increasingly greater changes in the levels of extracellular dopamine in the monkeys’ brains than it did at the beginning of the study.

“This finding demonstrates for the first time that when primates are exposed to a pattern of occasional cocaine use, they develop neurochemical sensitization, a phenomenon marked by an increase in brain response following repeated administration of a drug,” says Dr. Jane Acri of NIDA’s Division of Treatment Research and Development.

“Our knowledge of exactly how people become addicted to drugs is in its early stages,” Dr. Acri says. “Now, we are



*Long-Term Sensitization—Modest weekly exposure to cocaine gradually made the monkeys’ brains more responsive to the drug, a phenomenon called neurochemical sensitization. This illustration shows weekly changes in extracellular dopamine levels in a monkey’s brain after it has taken the first dose of cocaine in each session. In later weeks, the same dose of cocaine produces progressively higher levels of dopamine than it did in earlier weeks.*

trying to elucidate the factors involved in the transition from drug use to addiction. While it is still unclear how sensitization affects this transition, we think it may play a role. Demonstrating these initial changes in animals is a very big step in understanding this process from a biological point of view.”

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## Cues for Cocaine and Normal Pleasures Activate Common Brain Sites

By Patrick Zickler, NIDA NOTES Staff Writer

Cocaine abusers may experience a powerful urge to take the drug when they encounter environmental cues such as people, places, or paraphernalia that they associate with drug use. This cue-induced craving may be accompanied by physical sensations—light-headedness, increased heart rate, or a mild drug-like “high”—like those produced by cocaine.

The similarity of cue-induced sensations to those of actual cocaine use suggests that some of the brain structures affected by cocaine are also affected by cocaine-related cues. Now, NIDA-supported research using two brain imaging techniques has shown that limbic regions of the brain, where cocaine is thought to produce its pleasurable effects by disrupting normal action of the brain chemical dopamine, also are activated by viewing videos containing cocaine-related scenes. Moreover, one study indicates that cues related to normal pleasures, such as sex, also activate the same sites.

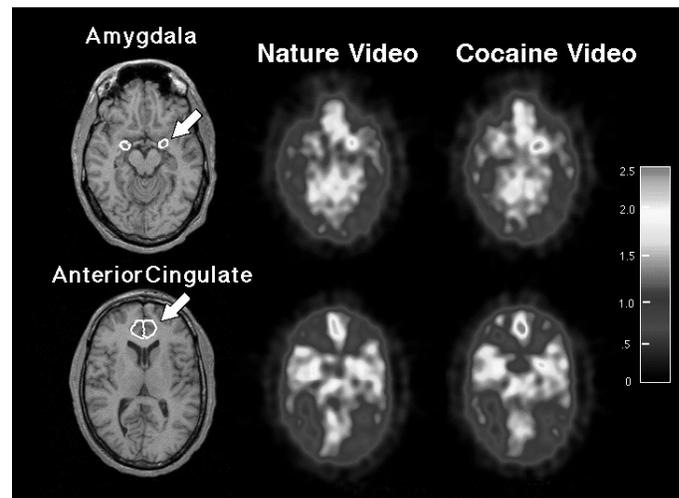
### Cocaine Cues Activate Sites in Limbic Region

At the University of Pennsylvania in Philadelphia, Dr. Anna Rose Childress and her colleagues used positron emission tomography (PET), which measures cerebral blood flow, to detect activation of nerve cells in the brain, to monitor the effect of cocaine-related cues on activity in limbic regions of the brain.

Participants in the study—14 adult male in-treatment cocaine users and 6 adult males who had never used cocaine—underwent PET imaging while watching a 25-minute video that contained images and sounds of simulated purchase, preparation, and smoking of crack cocaine. During the same imaging session, the participants watched a 25-minute nature travelog. Before and after watching each video, the men rated their feelings of drug-like high, craving for drugs, relaxation or tension, and general sense of well-being. The cocaine group, but not the non-cocaine group, reported craving and a drug-like high during the drug-related video. The nature video produced no subjective drug-like sensations in either group.

“The cocaine video that induced drug craving was associated with increased activation of two of the brain’s limbic regions, the amygdala and the anterior cingulate, in the cocaine patients,” Dr. Childress says.

Cocaine abusers showed increased limbic activation when watching the video containing cocaine-related scenes, but



*Positron emission tomography shows that limbic regions in the brains of in-treatment cocaine users are activated by watching cocaine-related videos. Watching videos of nature scenes does not result in activation of these regions. This suggests that cue-induced craving for cocaine reflects activity in specific regions of the brain. (Greater activation is denoted by shades at the top end of the scale to right.)*

not when watching the nature video. The participants who had never used cocaine showed no limbic activation when viewing either the cocaine-related or nature video.

“Activation of these two limbic regions during cue-induced craving is consistent with the role they play in mood, emotional response, and reward learning,” Dr. Childress says. The regions also play a part in establishing associations between environmental signals and biologically significant stimuli such as food, sexual partners, and pain, Dr. Childress says, and are linked to the nucleus accumbens, a brain structure involved in associating behaviors and pleasurable rewards. “The interconnectedness of these regions makes it possible to experience the pleasures of rewards and to recognize opportunities to obtain them,” she says. If common sites are involved in both normal and drug-related stimulus and response, this could pose problems for some potential pharmacological approaches to treating cocaine addiction, according to Dr. Childress. “Medications designed to block the limbic activation might reduce cocaine craving, but patients might be less likely to take the medication if it also blunts mood and motivation,” she says.

### Cues for Cocaine and Sex Act On Same Sites

At the Medical College of Wisconsin in Milwaukee, Dr. Elliot Stein and his colleagues used functional magnetic resonance imaging (fMRI), which measures blood oxygen levels, to show that the same limbic regions activated by cocaine and cocaine-related videos also are activated by videos containing scenes of normal nondrug stimulus. In this study, 31 adult males—17 cocaine users and 14 nonusers—watched 4-minute films depicting either drug use, nature scenes, or explicit sexual activity. Participants completed brief questionnaires describing their reactions to each film.

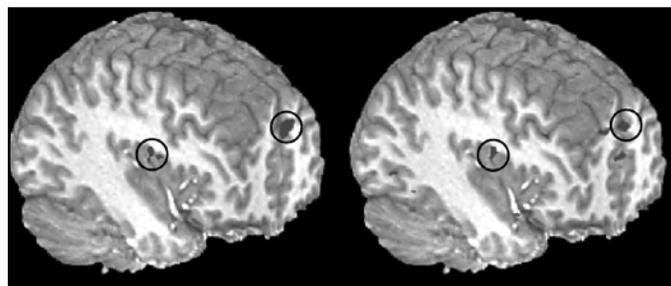
Cocaine users reported craving while viewing the film depicting drug use, and fMRI data revealed increased activation of sites in the limbic and other regions of their brains. These regions showed far less activation in nonusers viewing the same film. Both groups reported excitement while watching the sex film, although the levels of excitement were lower for drug users. Imaging revealed similar patterns of brain activation in both groups while watching the sex video, with less intense activation among drug users. There were no differences between users and nonusers when viewing the nature film.

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***“Cocaine craving does not merely act on the brain’s reward circuits, but also takes over these sites and in essence rewrites normal emotionally driven preferences.”***

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“Most of the brain regions identified through fMRI as cocaine craving sites were similarly activated by the sexual stimulus. This suggests that common brain circuits are involved in response to drug and nondrug arousing stimuli,” Dr. Stein says. “The fact that cocaine users’ brains exhibited



*Functional magnetic resonance imaging shows activation of the same brain sites in cocaine addicts watching a cocaine-craving-inducing film (left) and non-drug-using subjects watching a film depicting explicit sexual scenes (right). This suggests that cue-induced cocaine craving and sexual excitement are associated with the same brain sites.*

relatively weak activation in response to the sex film suggests that cocaine craving does not merely act on the brain’s reward circuits, but also takes over these sites and in essence rewrites normal emotionally driven preferences,” Dr. Stein says.

The fact that cocaine cues seem to act on brain sites associated with emotional response, information processing, and working memory may be relevant to development of treatment approaches. “On an optimistic note, it suggests that what we know about normal learning, memory, and emotions could be usefully applied to cue-induced craving and the development of appropriate pharmacological, behavioral, and cognitive therapies,” Dr. Stein says.

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## Alcohol-Treatment Medication May Help Reduce Cocaine Abuse Among Heroin Treatment Patients

By Robert Mathias, NIDA NOTES Staff Writer

A NIDA-supported study has found evidence that combining disulfiram, a medication long used to treat alcohol addiction, with buprenorphine, a new opiate-addiction treatment medication awaiting approval by the Food and Drug Administration (FDA), can reduce cocaine abuse among the more than 50 percent of heroin-addicted individuals who also abuse cocaine. In the study, patients addicted to both opiates and cocaine who were treated with a combination of disulfiram and buprenorphine achieved 3 weeks of continuous abstinence from cocaine faster and stayed abstinent longer than those who received only buprenorphine.

“This study provides evidence that this well-established treatment for alcoholism, disulfiram, works with the newest opiate treatment medication, buprenorphine, to reduce cocaine abuse in opiate addicts,” says Dr. Tony George of Yale University Medical School in New Haven, Connecticut, one of the study’s investigators. “Buprenorphine is expected to be used widely to treat heroin addiction once it is approved by FDA. If additional research confirms our results, disulfiram may be a useful adjunct to buprenorphine for physicians to use with patients who also abuse cocaine,” he says.

In the study, which was led by Dr. Richard Schottenfeld, also of Yale, 20 patients addicted to heroin and cocaine were treated with buprenorphine for their opiate addiction. Eleven of these patients were randomly assigned to receive disulfiram also, and nine to get placebo pills. Of the 15 patients who completed the 12-week study, the 8 disulfiram-treated patients were abstinent from cocaine for 7.8 weeks compared to 3.3 weeks of abstinence for the 7 placebo-treated patients. Nearly half of the patients in both groups achieved 3 weeks of continuous abstinence, but disulfiram-treated patients achieved that measure after 24.6 days, less than half the 57.8 days it took placebo-treated patients. Opiate use declined in both groups with no significant differences between disulfiram and placebo-treated groups over the course of the study.

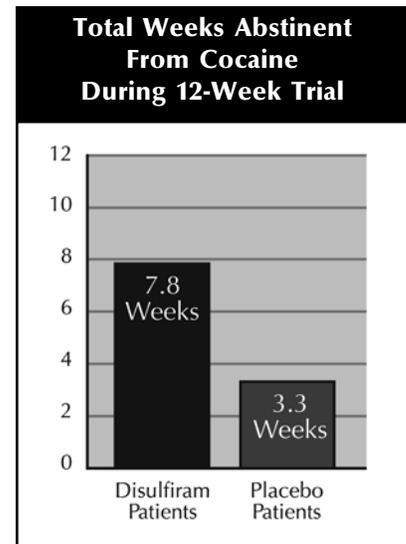
### Disulfiram and Cocaine, Alcohol, and Heroin Addiction

The findings from this study join a growing body of evidence from other Yale studies in recent years that disulfiram may reduce cocaine abuse among patients who also

are addicted to alcohol or heroin, says Dr. Schottenfeld. Initially, scientists began to look at whether disulfiram would reduce cocaine use because of the medication’s known aversive effects on alcohol, he explains. Marketed as Antabuse, disulfiram has been used by physicians for more than 40 years to treat alcoholism. Patients who drink alcohol while on this medication can experience unpleasant reactions such as nausea, vomiting, and flushing.

Initial studies at Yale indicated that disulfiram decreases abuse of both cocaine and alcohol in patients who abuse both substances. Those findings are being tested now in a NIDA-funded study at the University of Pennsylvania in Philadelphia. Results from the Philadelphia study could provide independent confirmation of the Yale findings and yield additional information about the strong link between alcohol and cocaine use, says Dr. Maria Majewska of NIDA’s Division of Treatment Research and Development. “Some 70 to 80 percent of cocaine-dependent individuals also abuse alcohol,” she notes.

Last year, Yale researchers found that disulfiram also reduces cocaine use among opiate-dependent methadone treatment patients who use very little alcohol. “Since the opiate addicts in our new study also used little alcohol, these two studies suggest that disulfiram may be reducing cocaine use directly and not as a result of its effects on alcohol use,” Dr. George says.



*Disulfiram-treated patients averaged more than twice as many weeks of abstinence from cocaine as placebo-treated patients during the course of the 12-week trial.*

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## Exploring How Disulfiram Works

While the main goal of disulfiram research now under way is to confirm disulfiram's efficacy in treating cocaine abuse, researchers also are seeking to increase understanding about how disulfiram works to inhibit this abuse.

Understanding this process could lead to development of a new class of cocaine treatment medications that would better target this mechanism with increased efficacy and reduced adverse effects.

Disulfiram may exert its anticocaine effects by increasing levels of the brain chemical dopamine through blocking the activity of an enzyme called dopamine- $\beta$ -hydroxylase (DBH) that metabolizes the brain chemical dopamine. Since cocaine also boosts dopamine activity in the brain, the combination of disulfiram and cocaine may raise dopamine to excessive levels, producing a reaction that increases unpleasant effects associated with cocaine, such as anxiety and paranoia, Dr. Schottenfeld hypothesizes. This hypothesis is supported by laboratory studies at Yale in which disulfiram-treated patients had a more sustained physiological response to cocaine and reported that they experienced unpleasant, often anxiety-related, effects from it, he says.

Additional evidence that DBH may play a role in producing aversive reactions to cocaine comes from recent genetic studies at Yale led by Dr. Joseph Cubells. Dr. Cubells found that cocaine-abusing patients whose genetic makeup predicts low levels of DBH were much more paranoid than those with genes predicting high DBH activity. "The more frequent occurrence of this paranoia in low-DBH individuals may result from cocaine interacting with their genetic makeup to produce some form of functional hyperstimulation of their dopamine systems," Dr. Schottenfeld says.

Disulfiram may curb cocaine use through a DBH-mediated increase in dopamine levels in two slightly different but related ways, says Dr. Schottenfeld. When people stop using cocaine they may experience a decline in dopamine function and crave the drug to compensate for this reduction, he says. "In the absence of cocaine, disulfiram may increase dopamine levels sufficiently to reduce the drive to use cocaine," he says. "However, if a patient on disulfiram slips and uses cocaine, the medication may make cocaine's effects so unpleasant they deter further use."

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## Nicotine Craving and Heavy Smoking May Contribute to Increased Use of Cocaine and Heroin

By Patrick Zickler, NIDA NOTES Staff Writer

People who abuse drugs are also likely to be cigarette smokers. More than two-thirds of drug abusers are regular tobacco smokers, a rate more than double that of the rest of the population. NIDA researchers have found that craving for nicotine appears to increase craving for illicit drugs among drug abusers who also smoke tobacco, and this relationship suggests that smokers in drug treatment programs may be less successful than nonsmokers in staying off drugs.

At NIDA's Intramural Research Program in Baltimore, Dr. Stephen Heishman and his colleagues examined the interaction of craving for nicotine and craving for other drugs and found that situations that increased desire to smoke also increased desire to use drugs. The study involved male and female adult smokers who were not trying to stop smoking and had histories of abusing alcohol, cocaine, heroin, marijuana, and/or other substances.

The researchers asked participants to listen to recorded scripts describing scenes and then to rate their urge to smoke and their desire to use other drugs. In the first part of the study, which involved 18 participants, the scripts had content that was generally pleasant (watching children on a sunny beach), unpleasant (a friend asking to borrow money), or neutral (doing household chores). Some scripts also included people expressing a desire to smoke, while others did not mention smoking at all (see "Cues Trigger Craving"). Both the scripts including a mention of smoking and those containing negative emotional content increased the participants' craving for drugs, as well as for smoking.

In the second part of the study, 24 participants heard scripts with only pleasant content (enjoying the beach, talking on the phone with an old acquaintance, or visiting friends). These scripts also contained descriptions of tobacco craving that increased in intensity from no mention of smoking to asking the question, "How could you really enjoy yourself fully unless you were smoking?" Participants reported that craving for both drugs and tobacco increased as the intensity of the tobacco craving messages in the scripts increased.

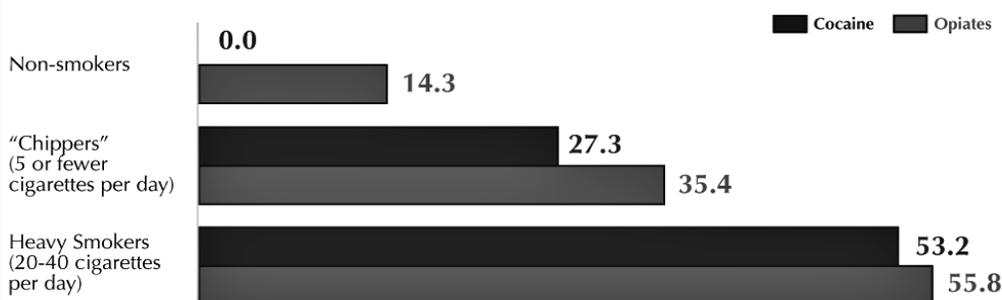
"One of our more interesting findings was that scripts that elicited craving for tobacco also elicited craving for the subject's drug of choice. This suggests that real-world situations that produce tobacco craving also may result in craving for drugs of abuse," Dr. Heishman says. The findings also suggest that treatment for heroin, cocaine, or alcohol addiction might be more effective if it included concurrent treatment of tobacco addiction, he says.

In a NIDA-supported study at the University of California, San Diego, doctoral candidate Dominick Frosch and his colleagues at the Integrated Substance Abuse Program at the University of California, Los Angeles, investigated the relationship between levels of cigarette smoking and levels of cocaine and heroin use among 32 individuals who had been in a methadone treatment program for at least 4 months. The participants included 10 nonsmokers (6 female, 4 male) and 22 smokers (16 female, 6 male). The smokers were equally divided among heavy smokers (20 to 40 cigarettes per day) and "chippers" who smoked 5 or fewer cigarettes per day.

"Compared with heavy smokers, chippers have less intense

### Cigarette Smoking Associated With Use of Cocaine and Opiates

Percentage of Urine Samples Testing Positive for Cocaine or Opiates



*Among patients in a methadone treatment program for opiate addiction, levels of cocaine or opiate use were directly related to levels of cigarette smoking.*

craving for their first cigarette of the day and can more comfortably avoid smoking in situations where it is not permitted,” Mr. Frosch explains.

The researchers evaluated the connection between tobacco smoking and illicit drug use among the smokers and nonsmokers by using breath and urine samples from the participants over a 7-day period. They found that the amount of cocaine and heroin use was closely related to the level of tobacco use. “The more cigarettes smoked, the more likely the person was to use illegal drugs,” Mr. Frosch says. “These findings provide compelling reasons for implementing smoking cessation programs for patients in methadone treatment, as the benefits of smoking cessation may extend to opiate addiction as well.”

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## Cues Trigger Craving

To evaluate the impact of the urge to smoke on craving for other drugs, Dr. Stephen Heishman and his colleagues asked participants to rate their desires for tobacco and other drugs after listening to recorded “scripts” of scenes involving pleasant, unpleasant, or neutral situations and containing “urge” or “no-urge” smoking cues. The scripts were originally developed by Dr. Stephen Tiffany and colleagues at Purdue University.

*Pleasant, no-urge script:* You’re at the beach, lying on a blanket. The warm sun penetrates your skin and relaxes you thoroughly. A fresh breeze blows over your body as you run your hands through the clean white sand and let the grains fall through your fingers. You’re feeling refreshed and at ease, and pleasant thoughts run through your mind. You can hear the sound of waves splashing rhythmically against the shore. Nearby there are some children playing a game. A bright red beach ball lands near your blanket. You look up and see two of the children running toward you to get their ball. You stand up, pick up the ball, and toss it to them. They laugh and giggle and run back to their game. You go to the blanket and lie down. You’re enjoying this day completely.

*Pleasant, urge script:* You’re at a friend’s house sitting in a big comfortable chair. You’re with people you’ve known a long time, and you’re enjoying yourself very much. You’re sipping a drink, and you’re feeling totally at ease.

Many of your friends are smoking cigarettes, just as you used to do. You’ve gone an entire week without smoking. As you sit there listening to the conversation and laughter, you begin to wonder what a cigarette would taste like. The more you think about smoking, the stronger your desire becomes. Maybe just tonight when you’re with your friends and having a good time, it would be okay to smoke. How could you really enjoy yourself fully unless you were smoking? Your desire to smoke becomes intense, and you know that there’s no good reason not to ask one of your friends for a cigarette

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## Potential Cocaine Medications Show Effectiveness Against Psychosis, Seizures

By Steven Stocker, *NIDA NOTES* Contributing Writer

Synthetic compounds that have shown promise for treating cocaine addiction also may be useful for treating phencyclidine (PCP)-induced psychotic reactions, schizophrenia, and cocaine-induced seizures and death, researchers have found. The compounds are called dopamine D<sub>3</sub> receptor agonists, or D<sub>3</sub> agonists for short.

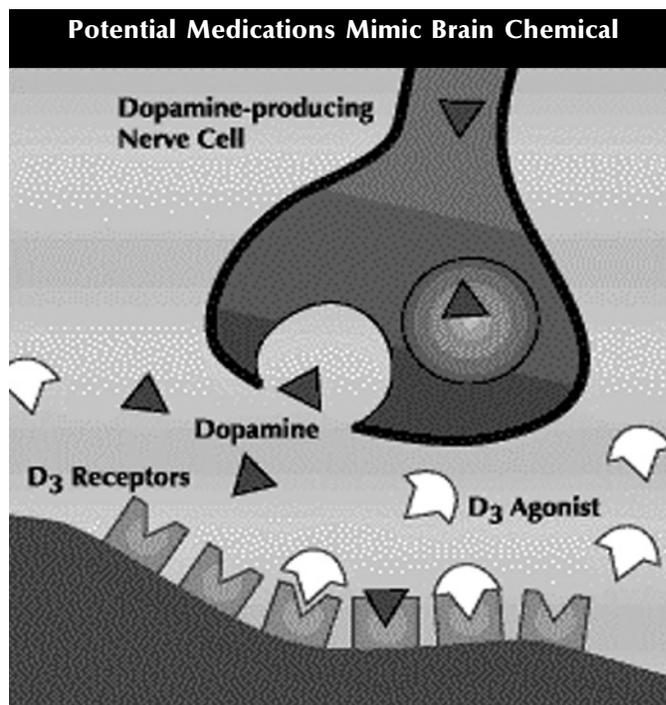
Dopamine is one of several chemicals called neurotransmitters that carry messages between the brain's nerve cells, or neurons. After being released by a transmitting neuron, neurotransmitters interact with molecules called receptors on the surface of a receiving neuron, affecting the neuron's activity. The combined activity of the brain's neurons is responsible for all of the brain's functions—such as feeling, thinking, and controlling movements—just as the combined electrical activity in a computer is responsible for all of the computer's functions. At present, five types of dopamine receptors, designated D<sub>1</sub> through D<sub>5</sub>, have been identified.

Agonists are compounds not normally found in the body that stimulate receptors in the same way that neurotransmitters do. Consequently, D<sub>3</sub> agonists are compounds that stimulate D<sub>3</sub> receptors.

### The PCP-Schizophrenia Connection

Dr. Jeffrey Witkin, Dr. Maciej Gasiór, and their colleagues at NIDA's Intramural Research Program in Baltimore, Neurogen Corporation in Branford, Connecticut, and the University of Groningen in the Netherlands have found that, in mice, a D<sub>3</sub> agonist called (+)-PD 128,907 can block psychotic-like behavior induced by a PCP derivative. Because research suggests that compounds that can reduce this type of psychotic behavior also will reduce symptoms of schizophrenia, Dr. Witkin's team believes the agonist has potential to treat schizophrenia as well.

Developed as a general anesthetic in the late 1950s, PCP became widely abused as a hallucinogen starting in the late 1960s. PCP abusers began appearing at hospital emergency rooms exhibiting symptoms that were nearly indistinguishable from those of schizophrenia, including hallucinations, paranoia, emotional withdrawal, and loss of speech. This commonality of symptoms led researchers to suspect that whatever PCP was doing in the brain might also be happening in the brains of schizophrenics.



*Compounds that show promise for treating psychosis and cocaine-induced seizures mimic the action of the messenger chemical dopamine on certain nerve cells in the brain. The compounds—called D<sub>3</sub> agonists—stimulate molecules on nerve cells that receive dopamine messages—called dopamine D<sub>3</sub> receptors. Scientists have yet to learn how this action reduces psychotic symptoms and seizures.*

The Witkin group's discovery of the potential of D<sub>3</sub> agonists for treating PCP psychosis and schizophrenia sprang from their exploration into another property of D<sub>3</sub> agonists that previous research had unveiled—their potential for reducing cocaine self-administration in rats, a finding that suggests they may reduce cocaine craving in humans. In the course of the researchers' exploration of that property, they noticed that (+)-PD 128,907 produced an unusual sedative effect on the animals that was similar to that of clozapine, a medication commonly used for treating schizophrenia.

"Clozapine produces a very striking depressant action that can be distinguished from that of other types of depressant drugs," explains Dr. Witkin. "Animals on clozapine are reactive to stimuli in the environment, and yet they

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are sedate. Also, their movements are normal. In contrast, other sedative-like compounds tend to make animals uncoordinated.”

Because the D<sub>1</sub> agonist acted like a medication for schizophrenia and because of the similarities between PCP psychosis and schizophrenia, the researchers decided to try the agonist in mice exhibiting psychotic-like symptoms as a result of being given a PCP derivative. Among those symptoms are headweaving, a popcorn-like jumping, and repetitive treading with a forepaw. The forepaw treading is easiest to measure.

Dr. Witkin and his colleagues found that (+)-PD 128,907 reduced this forepaw treading as effectively as clozapine and more effectively than haloperidol, the most commonly used antipsychotic medication. The compound also caused no movement disorders. “This is good news because haloperidol treats only some schizophrenic symptoms and also causes severe movement disorders,” says Dr. Witkin. “Clozapine, on the other hand, is effective against all symptoms and generally does not cause movement disorders but can cause a life-threatening blood disorder. Altogether, these findings indicate that (+)-PD 128,907 might be an effective alternative to clozapine and haloperidol for treating schizophrenia,” he says.

### **Blocking Cocaine-Induced Seizures and Deaths**

Dr. Witkin and Dr. Gasior next tested the effectiveness of D<sub>1</sub> agonists against cocaine-induced seizures and deaths in mice. They pursued their new line of research on the basis of a NIDA-funded study at the University of Miami showing that the brain’s D<sub>1</sub> receptors might be involved in seizures and deaths among cocaine abusers.

Again, (+)-PD 128,907 proved effective, and so did the other D<sub>1</sub> agonists. Whether given before or after a cocaine overdose was administered, the compounds completely blocked the convulsant and lethal effects of the cocaine. “This is a dramatic finding because current medications do not work very well against the seizures and other consequences of cocaine overdoses,” says Dr. Witkin.

Why D<sub>1</sub> agonists should reduce cocaine self-administration, psychotic-like behavior, and cocaine-induced seizures and death is not yet clear, says Dr. Witkin. “More often than not in medications development, researchers find an interesting effect of a compound through trial and error, and then they try to figure out why the compound has that effect,” he says. “That’s where we are now with the D<sub>1</sub> agonists.”

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## Combining Drug Counseling Methods Proves Effective in Treating Cocaine Addiction

By Patrick Zickler, NIDA NOTES Staff Writer

NIDA's research into treatments for cocaine abuse has identified a variety of effective treatments ranging from group drug counseling to individualized psychotherapies. In a NIDA-funded clinical trial investigating the efficacy of four types of treatment, patients who received group drug counseling combined with individual drug counseling were more likely to reduce their drug use than were patients who received group drug counseling alone or in combination with psychotherapies that are used to treat addictions.

The NIDA Collaborative Cocaine Treatment Study involved 487 patients with relatively low levels of psychiatric severity whose principal diagnosis was cocaine dependence as defined by the Diagnostic and Statistical Manual of Mental Disorders. The drug counseling therapies evaluated in the multisite study are specifically designed to treat drug use; the psychotherapies—supportive-expressive therapy and cognitive therapy—are less focused on drug use.

The study involved patients recruited at five sites—the University of Pennsylvania in Philadelphia; the Western Psychiatric Institute and Clinic at the University of Pittsburgh; Massachusetts General Hospital in Boston; McLean Hospital in Belmont, Massachusetts; and Brookside Hospital in Nashua, New Hampshire. Each research center provided four treatments: group drug counseling alone, group drug counseling combined with individual drug counseling, group drug counseling combined with cognitive therapy, or group drug counseling combined with supportive-expressive therapy. Each of the 487 patients was randomly assigned to one of the therapies. Treatment results were evaluated through patient self-reporting, weekly observed urine testing, and the Addiction Severity Index—an interview-based assessment used to measure treatment outcome.

During each of the 6 months of treatment, and at 3 months and 6 months after treatment ended, patients who received combined individual and group drug counseling

used less cocaine and drugs overall than did patients who received other forms of treatment. A higher percentage of combined drug counseling patients were able to achieve abstinences of 1, 2, and 3 months than were patients in the other study groups. During the 6 months after treatment ended, 38 percent of patients who completed combined counseling treatment maintained drug-free periods of 3 consecutive months compared with 27 percent of patients treated with group counseling alone, 23 percent of patients treated with cognitive therapy plus group counseling, and 18 percent of patients receiving supportive-expressive therapy plus group counseling. In addition, patients who received combined drug counseling showed more improvement in Addiction Severity Index ratings than did patients receiving other treatments. "These results underline the valuable role of well-designed drug counseling in treating drug abuse. More specifically, this study demonstrates the

effectiveness that combined counseling therapies can have in treating cocaine addiction," notes Dr. Jack Blaine of NIDA's Division of Treatment Research and Development.

"The success of combined drug counseling treatment compared with the psychotherapies may be due to the fact that drug counseling delivers a message that is simple and strong—stay away from the situations where you use drugs and the people you use drugs with. The counselors at all sites

involved in our study were able to deliver that message effectively," says Dr. Paul Crits-Christoph of the University of Pennsylvania, who coordinated the multicenter study.

### Criteria for Success

"The success of combined drug counseling compared with other treatments is the result of the nature, intensity, and quality of counseling," Dr. Crits-Christoph says. "We paid a great deal of attention to selecting and training counselors, all of whom had extensive previous experience treating patients with substance abuse disorders." The counselors and psychotherapists received more than a year of training in standardized therapy using published manu-

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***Patients who received combined individual and group drug counseling used less cocaine than did patients who received other forms of treatment.***

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als, and were evaluated during training and certified prior to participation in the collaborative treatment study.

Group drug counseling, given to all study participants, consisted of weekly sessions for the full 6 months of the study and individual meetings with the group counselor once per month during a 3-month “booster” phase following the 6 months of active treatment. Patients in individual drug counseling and psychotherapy treatments participated in twice-weekly sessions during the first 3 months, weekly sessions during the second 3 months, and monthly meetings during the booster phase.

Group drug counseling treatment involved an initial 3-month phase during which patients were educated about the concepts in recovery from addiction, and a second 3-month phase that involved open group discussions focusing on patients helping each other solve problems encountered in recovery. Individual drug counseling focused on helping patients achieve and maintain abstinence through behavioral changes such as avoiding situations that trigger drug use. Group drug counseling and individual drug counseling encouraged patient involvement in self-help and support groups such as Cocaine Anonymous outside of scheduled treatment sessions.

Cognitive therapy involved identifying the underlying beliefs related to a patient’s drug use. Therapists worked with patients to evaluate the advantages and disadvantages of their beliefs. They also employed role-playing, behav-

ioral experiments, and scheduling and monitoring activities. Supportive-expressive therapy involved identifying interpersonal conflicts that relate to a patient’s drug use. Therapists helped patients interpret the role that these conflicts play in drug use and problems encountered in stopping drug use.

Because treatment and training were based on published manuals, it may be possible for other treatment programs to achieve similar results, Dr. Crits-Christoph notes. “If other programs can apply these tools with the intensity that characterized this study, their outcomes should be similarly successful.”

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## Research Shows Effects of Prenatal Cocaine Exposure Are Subtle But Significant

By NIDA Director Dr. Alan I. Leshner

There is a traditional belief in the Aymara community of Peru and Bolivia that if a woman sees a corpse during pregnancy, her baby is likely to be sickly. The scientific understanding of prenatal exposures to toxic substances is more complicated. Depending on the specific substance and dose and the particular organ systems that are developing at the time of the exposure, impacts may vary greatly in type and severity. While exposure to alcohol has a devastating impact on some children, exposures to cocaine and other illicit drugs seem to produce much more subtle effects.

In the 1980s, observers reported a variety of possible abnormalities among some infants of mothers who used crack cocaine during pregnancy. Among them were lethargy and nonresponsiveness, frenetic movements, low pain thresholds, problems relating to caregivers, and absence of normal playfulness. These anecdotal reports amplified the existing alarm over an epidemic of drug use that had already produced extraordinary accounts of violence and familial dysfunction. Scientific research was needed to determine which of the suspected abnormalities were real, which were actually due to cocaine exposure, and what was portended for these children's future.

Since the beginning of the crack epidemic, NIDA-supported researchers have been following two important lines of investigation into the effects of prenatal exposure to cocaine. Basic researchers have been looking at cocaine's impact on fetal development in laboratory animals. At the same time, clinical researchers have been conducting longitudinal studies to track groups of cocaine-exposed babies in order to determine how prenatal exposure would influence their development from birth through adolescence.

To date, NIDA's longitudinal studies have confirmed that some children with prenatal cocaine exposure have problems with aspects of motor skills, IQ, fussiness and



***The ultimate objective of NIDA's research program is to be able to design and provide effective assistance to children who need to overcome difficulties resulting from fetal cocaine exposure.***

consolability, and attention span. Executive function—the ability to gather and use information in pursuit of one's own aims—also may be compromised. In general, these findings are consistent with results from studies with laboratory animals, which have shown that cocaine alters the development of neural systems that are crucial to behavior and response to stimuli.

There are three important points to make about what we have learned so far. First, worries that “crack babies” would never be able to function in society have turned out to be unfounded for the great majority of these children. Despite the documented deficits of some of the children in our longitudinal studies, most have passed one developmental milestone after another, albeit some more slowly than their unexposed peers. Researchers have had the gratifying experience of watching many of these children grow, walk, talk, interact with their families and social environments, and progress from grade to grade in school.

Second, even though our worst fears about prenatal cocaine exposure have not been realized, we should not be complacent. While studies have clearly established that such exposure damages few children beyond any hope of help, they have also shown that some children are affected in ways that put them in need of special help. Even when deficits are relatively slight, their potential negative consequences can be important over the long term. A child with slightly more

difficulty in settling down to tasks, for example, may do poorly in school. A child who has minor difficulties in controlling emotions may develop significant family and social problems over time, especially in environments that feature drug abuse and its associated ills.

Brain function deficits that are slight on an individual basis also can have sizable impacts on society. For example, a recent analysis by researchers at Brown University in Providence, Rhode Island, of data from several studies

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concluded that children with fetal cocaine exposure have IQs that average 3.3 points lower than those of unexposed children from the same socioeconomic environments. For most children, a difference of such magnitude would not matter much in terms of school performance or life prospects. For some children, however, 3.3 IQ points can spell the difference between functioning in the regular classroom and needing specialized help. The Brown researchers estimated that lower IQs associated with fetal cocaine exposure increase the number of children in the Nation who need special educational services by as many as 80,550 per year. The cost of providing these services could be as high as \$352 million each year.

Finally, some children who have avoided major problems so far may still hit snags in the future. The oldest children in the longitudinal studies are approaching adolescence. Will fetal cocaine exposure produce heightened vulnerability to subsequent drug abuse and addiction during this often-difficult developmental stage? Some evidence from animal studies suggests that it may. Given an unrestricted supply of cocaine, the offspring of mice injected with cocaine during pregnancy self-administer more of the drug than do other mice. Also suggestive is a recent finding by NIDA-funded researchers that the fetal mouse brain has active dopamine receptors. The researchers speculate that cocaine stimulation during gestation could enhance the proliferation of these receptors during human fetal development. If so, the resulting extra abundance of receptors might predispose the individual to react strongly to addictive drugs.

We still have much to learn about cocaine's impact on the developing human brain. Not only are the brain alterations associated with fetal cocaine exposure various and

often subtle, they also may manifest themselves in different ways as children grow. Moreover, the environments associated with prenatal cocaine exposure almost always contain other potential stumbling blocks for child development. These can range from poor maternal nutrition during pregnancy and prenatal or postnatal exposures to other drugs to parental neglect or abuse and elevated risks for a variety of other illnesses.

To isolate the specific effects of cocaine exposure from all of these confounding factors is a daunting challenge, but NIDA-supported researchers have made impressive strides in developing research protocols, interview techniques, and evaluation tools that help discriminate cocaine's effects. NIDA continues to strongly encourage researchers to explore ways to further develop these resources. As this research bears fruit, and even better tools—such as improved brain imaging, reliable biologic measures of cocaine exposure, and innovative instruments for cognitive assessment—become available, our understanding of the impact of prenatal cocaine exposure will grow.

The *NIDA NOTES* article “NIDA Studies Clarify Developmental Effects of Prenatal Cocaine Exposure” reports on some of the latest studies that are isolating the impacts of prenatal cocaine exposure from those of the environment.

The ultimate objective of NIDA's research program, of course, is to be able to design and provide effective assistance to children who need to overcome difficulties resulting from fetal cocaine exposure. In fact, there is good reason to hope that the insights into human development gained from these studies also will benefit children who were never exposed to drugs. **NN**

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***Even though our worst fears about prenatal cocaine exposure have not been realized, we should not be complacent.***

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## NIDA Studies Clarify Developmental Effects of Prenatal Cocaine Exposure

By Patrick Zickler, *NIDA NOTES* Staff Writer

NIDA-funded studies have demonstrated that cocaine can reach into the womb and disrupt the embryonic development of crucial neurological systems in animals, but the effects of prenatal cocaine exposure on human development are far more difficult to assess. Mothers who use cocaine may use other drugs, and factors such as prenatal care, nutrition, and home environment contribute to a child's development before and after birth. Thus, isolating the impact of prenatal cocaine exposure is difficult, but NIDA-supported research has begun to provide a clearer picture of the damage prenatal cocaine exposure causes.

"We now have data from longitudinal studies that have followed mothers from early in their pregnancies and their children from birth into early childhood," says Dr. Vincent Smeriglio of NIDA's Center on AIDS and Other Medical Consequences of Drug Abuse. "These studies take into account many confounding factors that are associated with cocaine use. What we see in some of these children is a pattern of subtle neurobehavioral effects associated with prenatal cocaine exposure. These include effects on a child's attention and alertness, IQ, and motor skills. The effects are not as profound as some early reports suggested, but they are very real," he says.

### Effects on Attention, Alertness, and Intelligence

Studies with laboratory animals have revealed cocaine-related effects on development within regions of the brain that regulate attention, arousal, and reaction to stresses. Research involving children born to mothers who used cocaine during pregnancy has found a profile of effects related to these same brain regions. The effects are not dramatic—cocaine-exposed children were more likely than unexposed children to have scores at the low end of the normal ranges on tests that measure alertness, attention, and intelligence. However, the effects persist from birth through early childhood and suggest that cocaine-exposed children may have to work harder—or will need more help—focusing their attention, remaining alert, and processing information than do unexposed children.

NIDA-supported research conducted by Dr. Linda Mayes at the Yale University School of Medicine in New Haven, Connecticut, suggests that cocaine has an effect on regions of the brain that regulate a child's ability to pay attention, which has important implications for learning and memory.



*Dr. Marylou Behnke (left) and Dr. Fonda Davis Eyler have found that babies exposed prenatally to cocaine are less alert and attentive than are unexposed infants.*

Dr. Mayes and her colleagues studied more than 600 children—either not exposed to any drug or exposed prenatally to cocaine; to cocaine and marijuana, tobacco, or alcohol; or to marijuana, tobacco, or alcohol but not to cocaine. The children were examined at ages 3, 12, 18, and 24 months. "In a variety of settings, cocaine-exposed children appear to require more stimulation to increase arousal and attention but are less able to control higher states of arousal than are unexposed children," Dr. Mayes says.

NIDA-funded research conducted at the University of Florida in Gainesville has demonstrated an association between the amount of cocaine used by a pregnant mother and her child's performance on tests used to measure alertness and attention. Dr. Fonda Davis Eyler and Dr. Marylou Behnke studied more than 300 infants, half whose mothers used cocaine during pregnancy and half whose mothers did not. "The amount of cocaine used during pregnancy was negatively related to the baby's

scores on tests of orientation, attention, and alert responsiveness,” says Dr. Eyler.

Unlike many other studies that have examined the effects of prenatal cocaine exposure, the research conducted by Dr. Eyler and Dr. Behnke involved women from poor rural populations rather than women from urban areas where cocaine abuse often is accompanied by abuse of a variety of other drugs. “Cocaine is pervasive in this community, but other illicit drugs—except marijuana—are not. This makes it easier for us to isolate the effects of cocaine,” Dr. Behnke notes.

Although the researchers caution that it is impossible to attribute the observed effects solely to cocaine use, they note that the number of significant correlations with cocaine are far greater than would be expected by chance. “The results seem to fit into an overall pattern of effects. Twice as many cocaine-exposed infants as controls—a fourth of the sample—were unable to achieve and maintain the quiet alert state that examiners need to administer some parts of the test,” observes Dr. Eyler. “In simple comparisons as well as in more complex correlations with amount of usage, it was the cocaine-exposed infants who demonstrated significant detriments, and it was always in the areas of responsiveness and regulation of attention,” she says.

At the Western Psychiatric Institute and Clinic in Pittsburgh, NIDA-funded researcher Dr. Gale Richardson and her colleagues also have found an association between prenatal cocaine exposure and central nervous system deficits. “Cocaine has effects that are independent of other prenatal and postnatal factors. This has been true at each of the three age phases in our study—at birth, at age 1, and at age 3, the neurobehavioral effects are there,” Dr. Richardson says.

At birth, the children exposed prenatally to cocaine showed more abnormal reflexes, less motor maturity, and poorer ability to regulate their state of attentiveness than did unexposed children. At 1 year and at 3 years, those children were less adaptable and more likely to be fussy and overly persistent than were unexposed children.

At 3 years, the exposed children scored lower on an intelligence test than did unexposed children, were more restless, had shorter attention spans and less focused attention, and made more attempts to distract the examiner than did children who were not exposed to cocaine before birth, Dr. Richardson notes.

The study will follow children through 10 years of age and will allow researchers to control for many of the circumstances, such as multiple drug exposure and pre- and postnatal environment, that might mask or confound cocaine-related effects. “We have a large sample of women who were enrolled early in their pregnancies from a prenatal care clinic, not a drug treatment program. We have

continued to interview the mothers extensively to collect as much information as possible about the postnatal environment,” Dr. Richardson says.

### Effects on Motor Development

NIDA-funded research conducted by Dr. Robert Arendt and Dr. Lynn Singer at Case Western Reserve University in Cleveland has shown an association between prenatal cocaine exposure and decreased motor development in children at age 2. Their study involved nearly 200 cocaine-exposed and unexposed infants recruited from an urban hospital newborn nursery and pediatric clinic.

“The cocaine-exposed children performed significantly less well on both the fine and the gross motor development indices. These findings indicate that the lag in development extends beyond the neonatal period in exposed children,” Dr. Arendt says.

“Motor functions are more ‘hard-wired’ than behavior, and are less likely to be influenced by environment as a child grows up. The effects of cocaine exposure on motor development that show up early should still be there as the child grows older,” Dr. Singer says. “We previously found motor development effects in the cocaine-exposed group when we looked at them at 4 months and again at 12 months. Now we know that these effects persist through age 2,” she adds.

Preliminary data from examination of the same children at age 4 suggest that cocaine-related deficits in fine motor development last into early childhood, although the motor skill problems associated with prenatal cocaine exposure are not more severe than those seen in some unexposed children in the course of normal clinical practice, Dr. Arendt notes. “These kids can be helped with physical



*During their first few years of life, children develop the fine motor skills that help them learn to write and draw. NIDA-supported research suggests that prenatal exposure to cocaine has a damaging effect on the development of these skills and on a child's ability to remain alert and attentive.*

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therapy and other interventions just as successfully as any other child with similar motor problems. It's important to know that they will need some help, and it's important to see to it that they get this help. Without properly developed motor skills, it is difficult for a child to control a pencil to draw a picture or write their ABCs," Dr. Arendt says.

"No study involving mothers and children in an environment of drug abuse can perfectly isolate the effects of cocaine or any other drug from the combined effects of that environment, but we can use statistical methods and study design to control for many of the confounding variables. What we see is that cocaine does have an effect that is independent of other variables," Dr. Arendt says.

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## Cocaine's Pleasurable Effects May Involve Multiple Chemical Sites In the Brain

By Steven Stocker, NIDA NOTES Contributing Writer

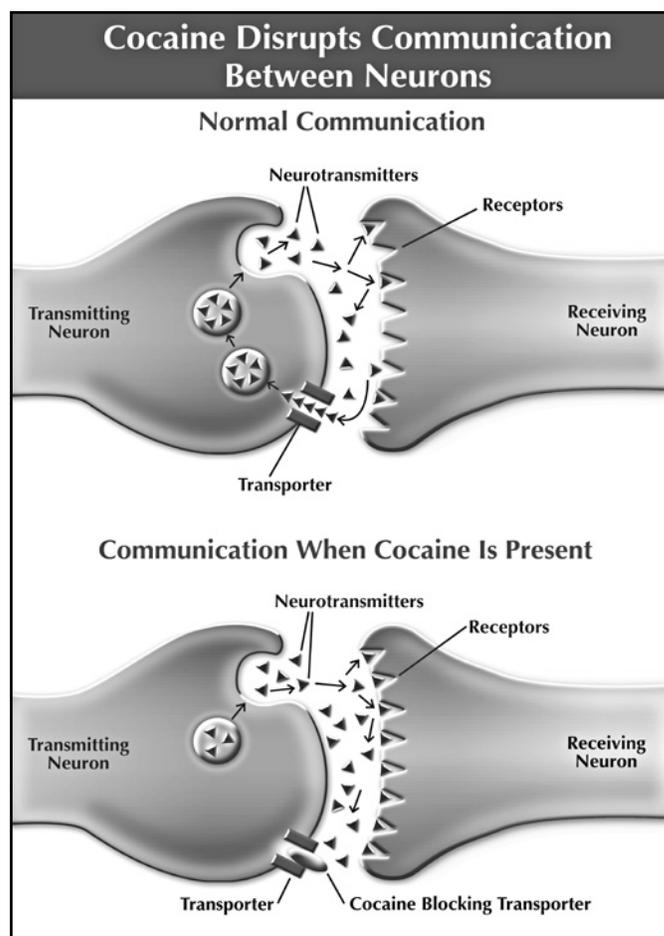
Recent studies with genetically altered mice have suggested that cocaine's euphoric effects may involve not just one, but several, chemical sites in the brain. These studies indicate that medications for treating cocaine addiction may need to target these multiple sites just as cocaine does.

Scientists have known for many years that cocaine blocks the reuptake of certain chemicals by nerve cells, or neurons, in the brain. Neurons release these chemicals, called neurotransmitters, to send messages to other neurons in the vicinity. Once communication has taken place, the neurons that sent the neurotransmitters recycle them for further use. Proteins called transporters, located on the surface of the sending neurons, latch onto the neurotransmitters outside the neurons in the extracellular space and transport them back inside for re-release at a later time.

Early studies showed that cocaine blocks the transporters for three different neurotransmitters: dopamine, serotonin, and norepinephrine. Later, one vein of research suggested that cocaine's blockade of the dopamine transporter was most important for producing the drug's euphoric effects. By blocking the dopamine transporter, some scientists theorized, cocaine might raise the level of extracellular dopamine in brain regions involved in the feeling of pleasure. This excess dopamine could continue to affect neurons in these regions, giving rise to euphoria.

If this hypothesis is true, then eliminating the dopamine transporter in the brain should eliminate cocaine's euphoric effects. To test the hypothesis, scientists produced mice lacking dopamine transporters by inactivating or "knocking out" the gene for the transporter in mouse embryos. When these dopamine transporter "knockout" mice matured, the researchers studied whether they found cocaine to be rewarding. Researchers used two techniques to study whether elimination of the dopamine transporter nullified cocaine's rewarding effects.

Dr. Beatriz Rocha, then at the University of North Texas Health Science Center in Fort Worth and now in NIDA's Intramural Research Program (IRP) in Baltimore, and Dr. Marc Caron's group at Duke University in Durham, North Carolina, used a procedure in which the mice pressed a lever to receive a cocaine injection. If the mice continually pressed the lever at a high rate, this would indicate that they found cocaine rewarding.



*During normal communication between nerve cells, or neurons, the transmitting neuron releases neurotransmitter molecules that stimulate the receiving neuron by binding to receptor molecules on its surface. After this communication has occurred, transporter molecules collect the released neurotransmitters and transport them back into the transmitting neuron for later release. When cocaine is present, the drug blocks the transporter, preventing neurotransmitter reuptake so that the neurotransmitters continue to stimulate the receiving neuron.*

Dr. Ichiro Sora, Dr. George Uhl, and their colleagues in NIDA's IRP, the IRP of the National Institute of Mental Health in Bethesda, Maryland, and the University of Wÿrzburg in Germany used a different procedure called conditioned place preference. In this procedure, mice were given cocaine injections when they were in one com-

partment of a two-compartment chamber and were given nothing when they were in the other compartment. Later, the researchers would observe which compartment the mice moved to when they were given a choice. If the mice found cocaine rewarding, they would spend more time in the compartment where they had received the cocaine injections.

Using the different procedures, both groups found that their knockout mice found cocaine rewarding despite not having the dopamine transporter. The mice either self-administered cocaine or chose the side of the cage where they had received cocaine.

“This finding surprised us at first,” says Dr. Uhl. “It shows that the dopamine transporter is not necessary for cocaine reward.” Dr. Rocha says that she, too, was surprised by her findings, but the fact that she and her colleagues and Dr. Uhl’s group had complementary results adds weight to the findings.

If the dopamine transporter is not the crucial site for producing cocaine reward, then what is? Apparently not the serotonin transporter, because Dr. Uhl’s group also studied serotonin transporter knockout mice and found that these mice also found cocaine rewarding.

Dr. Uhl and Dr. Rocha speculate that perhaps cocaine produces its rewarding effects by blocking the dopamine transporter and the serotonin transporter at the same time. Thus, the elevation in the levels of both dopamine and serotonin might produce the feelings of pleasure.

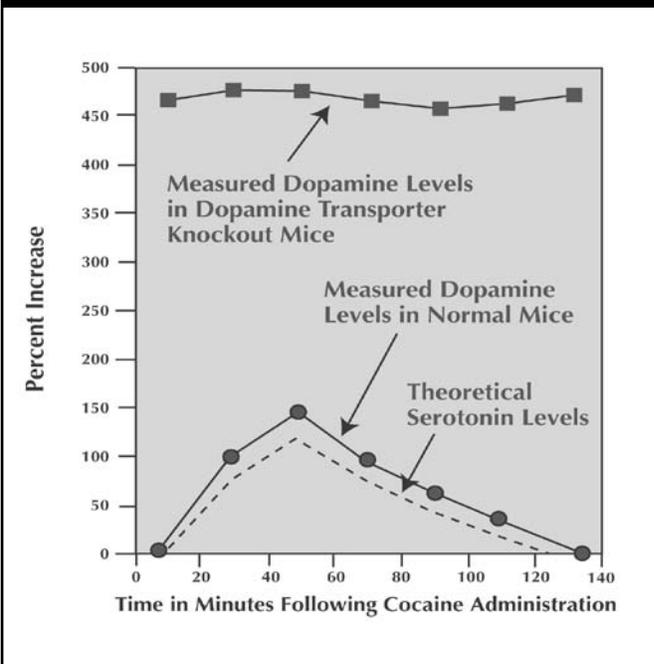
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***The explanation for cocaine’s powerful attraction may be that it affects several neurotransmitters, all of which are involved in mediating pleasure.***

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In Dr. Rocha’s study, the researchers found that the extracellular dopamine level in a key brain region in the dopamine transporter knockout mice was nearly five times higher than normal because the transporters were no longer there to shuttle the dopamine molecules back inside the neurons. When the knockout mice were given cocaine, the extracellular dopamine level did not go any higher because the animals had no dopamine transporters for cocaine to block. Although the researchers have yet to measure the extracellular serotonin levels in these knockouts, Dr. Rocha figures that the levels increased and then decreased as other studies have shown they do in normal mice because knocking out the dopamine transporter

**Effects of Cocaine on Neurotransmitter Levels**



*In normal mice, researchers have found that cocaine raises the levels of dopamine and serotonin outside neurons about 150 percent, but the levels return to normal after about 2 hours. In Dr. Rocha’s study, the researchers found that the dopamine levels in dopamine transporter knockout mice were about 500 percent higher than normal because no transporters were available to shuttle the dopamine molecules back inside the neurons.*

*Although the researchers have yet to measure the extracellular serotonin levels in these knockouts, Dr. Rocha theorizes that the levels increase then decrease as in normal mice because knocking out the dopamine transporter probably would not affect cocaine’s blockade of the serotonin transporter.*

probably would not affect cocaine’s blockade of the serotonin transporter.

The increase in serotonin, combined with the already high level of dopamine, may be why cocaine is rewarding for the dopamine transporter knockout mice, according to Dr. Rocha.

Dr. Uhl also believes that more than one neurotransmitter in the brain probably mediates cocaine reward, if only because more than one neurotransmitter probably mediates pleasure in general. “If a species is not rewarded by activities such as eating or sexual interactions, that species is not going to survive,” he says. “So it makes sense that the brain would have redundant systems so that if a mutation or some other factor disrupts one system, the other systems can still operate normally to produce reward.” Different neurotransmitters might mediate different aspects of reward, he says. The explanation for

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cocaine's powerful attraction may be that it affects several neurotransmitters, all of which are involved in mediating pleasure.

### **Selective or Nonselective?**

Both Dr. Uhl and Dr. Rocha think that the results of their dopamine transporter knockout studies support the idea that medications for treating cocaine addiction should target other neurotransmitters in addition to dopamine. Dr. David McCann, chief of NIDA's Pharmacology and Toxicology Branch, notes that starting in the early 1990s NIDA, in collaboration with pharmaceutical firms, began developing a number of potential cocaine treatment medications that prevent cocaine from acting at neurotransmitter transporters. Some of these compounds are selective for the dopamine transporter, while others act more or less equally at dopamine, serotonin, and norepinephrine transporters.

A compound that is selective for the dopamine transporter is GBR12909. A compound that blocks all three trans-

porters about equally is NS2359, which was developed by NIDA and NeuroSearch, a Danish pharmaceutical firm. Animal studies with these compounds have indicated that they are safe and potentially effective in humans, and they are now in the early phases of human clinical trials.

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## Blood-borne Medications Could Intercept Drugs Before They Reach the Brain

By Patrick Zickler, *NIDA NOTES* Staff Writer

The damage done by cocaine and other drugs of abuse takes place among neurons deep in the brain, but the drugs are transported to these nerve cells by the blood. A number of researchers are investigating possible medications that could intercept and neutralize cocaine and other drugs in the bloodstream, preventing them from initiating the neurochemical reactions that lead to abuse and addiction.

"This represents a different approach to therapeutic research, which has most often focused on interfering with a drug's activity in the brain. This strategy is aimed at preventing the drug from reaching the brain," says Dr. Steven Sparenborg of NIDA's Medications Development Division.

Blood-borne medications, referred to as peripheral blockers, would offer several advantages over other pharmacological approaches to addictions, notes Dr. David Gorelick of NIDA's Intramural Research Program. They do not require knowledge of how or where the abused drug acts in the brain, they would be effective against drugs with multiple sites of action in the brain, and they could protect against a drug's actions—such as cardiovascular toxicity—at sites outside the central nervous system.

Peripheral blockers are modeled after the enzymes and antibodies of the body's natural defense system, according to Dr. Sparenborg. One peripheral blocker approach would bind drugs like cocaine, phencyclidine (PCP), or nicotine to antibodies, creating a drug-antibody complex that is too large to move through blood vessel walls into the brain. This would trap the drug within the bloodstream until it could be eliminated from the body through normal kidney activity. Another approach would enhance the rate at which naturally occurring enzymes break down drug molecules into inactive byproducts. A third method under investigation employs an engineered antibody that both binds to and breaks down drugs. Although individuals might overcome the action of these peripheral blockades by taking more of the drug and overwhelming the antibody or enzyme, effective blood-borne medications would serve as valuable components of treatment programs that protect against relapse or counteract acute toxic effects from drugs of abuse.

"There is still a long way to go with this research, but the validity of the approach has been demonstrated in animal

tests. First-phase clinical trials of an active cocaine vaccine are under way now, and we're encouraged by the progress," says Dr. Sparenborg.

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***These results suggest that catalytic antibodies have the unique potential both to treat the acute effects of cocaine overdose and to block some of the chronic reinforcing effects of abuse.***

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### Immunization

Molecules as small as cocaine typically do not trigger the body's immune system to create antibodies. However, Dr. Barbara Fox and her colleagues at ImmuLogic Pharmaceutical Corporation in Waltham, Massachusetts, have developed a technique that links cocaine derivatives to a larger protein molecule, or carrier, to stimulate an immune reaction. Animals vaccinated with the cocaine-carrier combination develop cocaine-specific antibodies that bind with cocaine in the blood, preventing most of the drug from reaching the brain.

"In mice, the vaccine induced an antibody response that kept cocaine from reaching its targets in the central nervous system," says Dr. Fox, now with Addiction Therapies, Inc., in Wayland, Massachusetts. "And it appears to be long-lasting. Periodic boosters maintained the response for more than a year, which is a significant portion of a mouse's life."

The vaccine, which is currently being studied in first-phase human trials by researchers with Cantab Pharmaceuticals, uses a protein that generates a strong antibody response as a carrier. More than two dozen fragments of the cocaine molecule are bound to the carrier. When injected into animals, the large protein molecules stimulate the production of antibodies that recognize the cocaine fragments. Moreover, the antibodies also bind to norcocaine, one of cocaine's minor but pharmacologically active metabolites, or byproducts, but do not bind to the

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more abundant but inactive ones. “This means that the antibodies don’t become saturated with inactive metabolites and lose the capacity to bind with cocaine,” Dr. Fox says.

Dr. Fox and her colleagues found that injecting cocaine into rats immunized with the compound resulted in significantly higher levels of cocaine in the blood, and correspondingly lower levels in the brain, than did injecting the same amount of cocaine into nonimmunized animals. As much as 63 percent of administered cocaine was bound in the blood as soon as 30 seconds after administration. In addition, immunized rats were much less likely to self-administer cocaine than were nonimmunized rats. This finding, Dr. Fox notes, suggests that the vaccine could help prevent relapse in patients in drug treatment programs. “This is not a ‘magic bullet’ treatment. Patients could overcome it by taking more drug. But for motivated patients it could be a very valuable part of a comprehensive treatment program,” Dr. Fox says.

### Enzymes

Naturally occurring enzymes can break down cocaine and other drugs before they reach the brain, but they cannot rapidly neutralize the amounts of drugs that are typically ingested by drug abuse patients. Studies involving cocaine abusers suffering acute toxic reactions show a significant relationship between activity levels in the blood of butyrylcholinesterase (BChE), an enzyme produced in the liver, and the severity of cocaine toxicity. Patients with severe reactions to cocaine tend to have lower levels of BChE. NIDA-supported research has demonstrated that enhancing BChE activity can lead to improved treatment of cocaine overdose.

Gilberto Carmona, a doctoral student in NIDA’s Intramural Research Program, has shown that the metabolism of cocaine in the blood can be dramatically increased and the drug’s effects decreased by raising BChE activity. Mr. Carmona and his colleagues demonstrated that cocaine half-life—the time needed for half the drug to be cleared from the blood—dropped from more than 5 hours to less than 5 minutes in rats pretreated with purified BChE that raised the enzyme’s blood activity 400-fold. The increase in BChE activity significantly decreased the increased motor activity caused by a cocaine injection and changed the pattern of cocaine metabolism, resulting in production of predominantly nontoxic byproducts rather than pharmacologically active ones.

NIDA-supported researcher Dr. Oksana Lockridge at the University of Nebraska in Omaha has found that naturally-occurring variations in human BChE have different capacities for cocaine metabolism. “People who don’t have the typical variant may react to a ‘standard’ dose of cocaine as though it were an overdose,” Dr. Lockridge says. “Other variants exist at levels as low as one-third of

normal levels, and people with these variants are probably at very high risk for cocaine toxicity.”

Building on this knowledge of BChE variants, Dr. Lockridge and her colleagues engineered a mutant form of BChE—designated A328Y—that demonstrated four times the catalytic activity of normal BChE when tested in the laboratory. Dr. Kenneth Dretchen at Georgetown University in Washington, D.C., is conducting animal trials of A328Y to determine if the more active variant can be used as a treatment for cocaine overdose. “We know that the butyrylcholinesterase can reduce cocaine-induced convulsions, hyperactivity, and hypertension, and we know that A328Y will act much more aggressively to break cocaine down into inactive metabolites. A328Y could prove to be a valuable ‘crash cart’ tool for treating acute cocaine toxicity in emergency room situations,” he says.

### Catalytic Antibodies

Dr. Donald Landry, a researcher at Columbia University College of Physicians and Surgeons in New York City, has developed a cocaine-specific catalytic antibody—a compound that combines features of antibodies that bind to cocaine molecules with features of enzymes that break the drug down into inactive fragments.

The catalytic antibody developed by Dr. Landry and his colleagues uses a molecule that mimics the structure of a cocaine molecule in its transition state—the shape of a cocaine molecule undergoing a chemical reaction. When the catalytic antibody binds to cocaine, the drug molecule takes on the configuration of the transition state. “This accelerates the rate of cocaine hydrolysis to inactive fragments. The antibody then releases the fragments and is free to bind to another cocaine molecule and initiate another cycle,” Dr. Landry explains.

“Each molecule of the most potent antibody we have developed breaks down more than 2 cocaine molecules per minute and retains more than 95 percent of its activity through at least 200 turnovers,” Dr. Landry says.

Animal tests of the antibody—designated mAB 15A10—demonstrate that it can reduce the toxic effects of cocaine overdose. Other tests show that pretreatment with the compound will prevent rats from self-administering cocaine.

“These results suggest that catalytic antibodies have the unique potential both to treat the acute effects of cocaine overdose and to block some of the chronic reinforcing effects of abuse,” Dr. Landry says. “A humanized version of the antibody mAB 15A10 could be useful either as an emergency treatment for overdose or as part of a broader treatment program for addiction.”

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## Coping Skills Help Patients Recognize and Resist the Urge to Use Cocaine

By Patrick Zickler, *NIDA NOTES* Staff Writer

For some cocaine abusers, urges to use cocaine come out of the blue. But more often the urge is associated with an identifiable situation that triggers drug use. A behavioral science research study supported by NIDA has led to the development of a treatment technique that helps cocaine users control their drug use by recognizing and coping with these high-risk situations.

Dr. Damaris Rohsenow, Dr. Peter Monti, and their colleagues at Brown University's Center for Alcohol and Addiction Studies in Providence, Rhode Island, have developed a cocaine-specific coping skills training (CST) technique that can be used as part of a treatment program to help cocaine abuse patients identify situations that trigger their urges to use cocaine and modify their behavior to avoid drug use.

In the study, patients who received CST as part of treatment "had significantly shorter and less severe relapses during the 3-month followup period than did patients who received standard treatment," Dr. Rohsenow says.

Patients who received CST were taught to identify high-risk situations, called triggers, associated with drug use. These triggers were broadly categorized into topic areas such as anger, money, frustration, or depression. Patients then focused on specific personal examples of triggers and analyzed the sequence of actions, called a "behavioral chain," that led to drug use in those situations.

Patients learned how to avoid or modify the trigger situation when possible. "For example, if a money trigger is associated with getting a paycheck, they might arrange for their paycheck to be directly deposited in their bank. Or if drug use is associated with their lunch break, patients could eat with a group of coworkers rather than going out alone," Dr. Rohsenow explains.

For situations in which the trigger could not be avoided, patients developed a repertoire of cognitive and behavioral skills to modify the behavioral chain and reduce their personal risk of drug use. "A phone call from an ex-spouse might be an 'anger' trigger that can't be avoided. But patients can use coping skills training to change how they behave in response to the call. They can 'talk out' their anger with friends or do something physical like go out and play basketball," Dr. Rohsenow says.

The study involved 128 male and female patients selected from 2 drug abuse treatment facilities. Standard treatment

at these facilities is an abstinence-based program that combines the principles of the Alcoholics Anonymous 12-step program with educational information presented in group formats, individual counseling sessions, and family or marital therapy. Roughly half the patients received standard treatment plus eight 1-hour sessions of CST. The other half received standard treatment plus eight 1-hour sessions of meditation-relaxation training (MRT), a procedure that often is used as part of treatment programs but has no significant effect on substance use. The MRT procedure assured that all patients in the study spent the same amount of time in contact with therapists.

The patients were evaluated at 1 and 3 months follow-

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***Coping skills training can help patients identify situations that trigger their urges to use cocaine and modify their behavior to avoid drug use.***

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ing treatment. Roughly 45 percent of patients from each group suffered relapses following treatment, but relapsing CST patients averaged only 6.2 days of drug use compared with more than 13 days of cocaine use for patients who received MRT.

The improvement in outcome for most CST patients was far better than these average figures suggest, Dr. Rohsenow points out, because one relapsed CST patient used cocaine for 49 out of 90 days in the followup period. The other CST patients averaged only 3.8 days of drug use.

Among CST patients, the longest binges averaged 2.8 days—less than half as long as the binges for the other patients, which lasted an average of 6 days.

"Patients with CST training were able to change the way they thought and then change the way they behaved in situations that posed a risk of relapse," Dr. Rohsenow says.

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## Cocaine Activates Different Brain Regions for Rush Versus Craving

By Steven Stocker, *NIDA NOTES* Contributing Writer

Using a brain imaging technology called functional magnetic resonance imaging (fMRI), NIDA-funded scientists have shown that different parts of the human brain are activated during cocaine "rush" versus cocaine craving. This technology is also being used to identify the parts of the brain that become active when a cocaine addict sees or hears environmental stimuli that trigger a craving for cocaine. These studies may be useful in the development of medications for treating cocaine addiction, because they help scientists pinpoint specific brain regions that need to be targeted by medications for countering cocaine's multiple effects.

Developed in the early 1990s, fMRI can visualize areas of the brain that many researchers believe are regions with increased nerve cell activity. Images can be produced quickly, enabling volunteers to describe their sensations at the same time that the images are being produced. As a result, fMRI allows researchers to closely associate regions of brain activity with specific emotions.

Using fMRI, Dr. Hans Breiter and his colleagues at the Massachusetts General Hospital in Boston administered cocaine to cocaine-addicted volunteers whom they had trained to continuously rate their feelings of rush, high, low, and craving. The rush experience involved elevated heart rate and sweating, along with feelings of "speeding" or "being out of control." The high experience was generally associated with feelings of euphoria, self-confidence, well-being, and sociability. The low experience involved negative emotions, such as anxiety, paranoia, and the loss of any feelings of pleasure. Craving was defined as the desire to use more cocaine.

Rush and high both peaked within 3 minutes after the volunteers received cocaine. While the rush dissipated quickly, the high decreased more gradually. The low slowly increased, peaking 11 minutes after receiving cocaine, and craving peaked 12 minutes after receiving cocaine.

The researchers determined that certain areas of brain activity were associated more with feelings of rush, and other areas were associated more with feelings of craving. "We only looked at brain regions associated with rush and craving because these were the two ratings that were the most distinct from each other," says Dr. Breiter. "The rush scores were coming down at the same time that the craving scores were going up."



*Dr. Hans Breiter, left, Dr. David Kennedy, center, and Dr. Randy Gollub will use images produced by this magnetic resonance imaging scanner to identify areas of the brains of cocaine-addicted volunteers that become activated during cocaine rush and craving.*

Rush was associated with activity in many areas of the brain, including the ventral tegmentum in the midbrain and the basal forebrain, or base of the forebrain. This activity peaked shortly before the volunteers reported that they had reached peak rush, and then the activity began to dissipate, much like the reported rush.

No areas of brain activity directly paralleled the ratings for craving. What did seem to be associated with craving was the fact that activity in a few regions continued after all others had stopped. These regions included the nucleus accumbens and the right parahippocampal gyrus, both in the forebrain.

"Craving may not be mediated by one or two distinct brain regions," says Dr. Breiter. "Rather, the craving that occurs shortly after taking cocaine may be due to a change in the pattern of brain activity over time. Many brain regions are active when the volunteers report feelings of rush. Over time, however, only a few brain regions remain activated. This change in activation pattern may be what causes the subjective experience of craving."

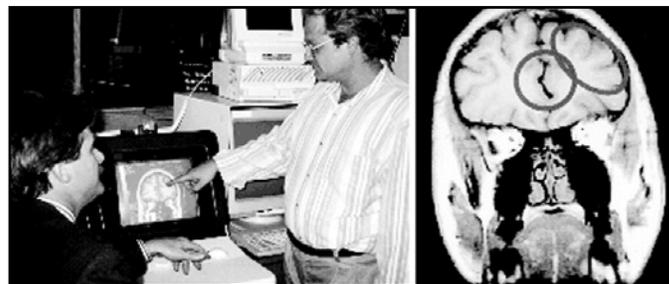
These results bear out similar findings in animals. Some of the regions of activity that were associated with rush or craving have been implicated in animal studies as being important in producing the pleasurable feelings associated with cocaine use. The regions include the ventral tegmentum, nucleus accumbens, and basal forebrain. "This study provides a bridge between the animal studies and the human studies," says Dr. Breiter.

Instead of investigating the craving that occurs after cocaine is injected, Luis Maas, Dr. Scott Lukas, Dr. Perry Renshaw, and their colleagues at McLean Hospital in Belmont, Massachusetts, used fMRI to investigate brain activation during what is known as cue-induced craving. In this type of craving, cocaine-related stimuli or cues from the environment, such as seeing someone cook crack cocaine or smoke a crack pipe, trigger memories of the drug-taking experience, which elicit craving. “What we think is happening is not unlike what happened in the Pavlov’s dog experiment,” says Dr. Lukas. In this experiment, Russian physiologist Dr. Ivan Pavlov rang a bell shortly before he presented food to hungry dogs. After many pairings of the bell with food, Dr. Pavlov found that merely ringing the bell caused the dogs to salivate.

In the McLean Hospital experiment, the researchers showed crack cocaine abusers a 10-minute videotape that consisted of segments with crack cocaine-related images and sounds alternating with segments that involved neutral stimuli, such as images of butterflies. When the volunteers saw the cocaine-related segments, two brain regions in particular became activated—the anterior cingulate and the left dorsolateral prefrontal cortex, both in the fore-brain. However, when the volunteers saw the neutral segments, these regions remained inactive. “The brain regions that became active during the cocaine-related portions of the videotape are associated with changes in mood state and with positive reinforcement. They are also in an area of the brain where memories are stored,” says Dr. Lukas. “Consequently, we think that we are seeing the ‘turning on’ of cocaine-related memories.”

These results are consistent with a previous study conducted by Dr. Steven Grant, Dr. Edythe London, and their colleagues in NIDA’s Division of Intramural Research. This study utilized a different imaging technology called positron emission tomography (PET) that, like fMRI, produces images of brain regions with increased nerve cell activity but takes longer to produce these images.

In that study, as in the McLean Hospital study, the researchers exposed cocaine abusers to cocaine-related stimuli, such as equipment used for snorting cocaine powder, plus a videotape showing people snorting cocaine and smoking crack. After the volunteers reported that they felt cocaine craving, the PET images showed increased nerve cell activity in certain brain regions, including the two identified in the McLean Hospital study.



Dr. Scott Lukas, left, and Dr. Perry Renshaw discuss the brain scan of a cocaine-addicted volunteer that shows which brain regions were activated when the volunteer watched a videotape of cocaine-related images. Two regions that became activated are circled on the brain scan shown at right.

The fact that brain imaging techniques can visualize brain regions associated with the subjective effects of cocaine could be particularly useful to scientists developing medications for treating cocaine addiction, according to Dr. Joseph Frascella, chief of NIDA’s Etiology and Clinical Neurobiology Branch. Earlier studies with animals have provided good indication of which regions are affected by cocaine, he says. “However, it is difficult to assess craving or the subjective feelings of rush or euphoria in animals,” he says. “You can’t exactly ask an animal, ‘How much are you craving at this point?’” The value of fMRI in particular is that human volunteers can tell researchers what they are feeling and at the same instant the researchers can see increased activity in brain regions that are associated with that subjective state, says Dr. Frascella. “This type of work is helping scientists identify the brain systems that need to be targeted by medications that counter cocaine’s subjective effects,” he says.

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## Cocaine Abuse May Lead To Strokes and Mental Deficits

By Steven Stocker, *NIDA NOTES* Contributing Writer

In 1977, a 43-year-old man came to an emergency room in New York City after having injected cocaine into a muscle in his left arm. Between 1 and 2 hours after the injection, he had begun having trouble speaking and was weak in his right arm and leg. After performing a brain scan, doctors at the hospital determined that the man had had a stroke on the left side of the brain. Although the man also abused other drugs, the fact that the stroke had occurred shortly after he had injected cocaine suggested that cocaine had contributed to the stroke. This case was one of the earliest verified reports of a stroke associated with cocaine use. In their report, the doctors concluded, "If, in fact, cocaine played a causal role [in the stroke], we anticipate that more strokes will be seen among the many abusers of this agent in American cities."

Their prediction turned out to be correct. In subsequent years, cocaine-related strokes became more frequent, particularly in the mid-1980s after the advent of crack cocaine. These strokes involved sudden dramatic reductions in blood flow to areas of the brain, resulting in neurological symptoms, such as paralysis, loss of speech, and dementia.

In the late 1980s, researchers began noticing another type of blood flow disturbance associated with cocaine use. This second type involved less dramatic but more persistent reductions in cerebral blood flow that could lead to difficulties concentrating, slowed thought processes, and memory deficits.

Until recently, scientists could only theorize about how cocaine was causing these cerebral blood flow disturbances. Now NIDA-supported scientists have learned more about how cocaine causes strokes and produces the persistent blood flow deficits. Other NIDA-funded researchers have observed that the brain damage caused by these deficits interferes with drug treatment, and they are studying how to modify treatment to accommodate patients with this type of brain damage.

### Short-term Reductions in Blood Flow

Using magnetic resonance angiography (MRA), an imaging technique that shows blood flow in large- and medium-sized arteries in the brain, NIDA-funded researchers Dr. Marc Kaufman and Dr. Jonathan Levin and their colleagues at McLean Hospital in Belmont, Massachusetts,



*Dr. Marc Kaufman (left) and Dr. Jonathan Levin of McLean Hospital will review images from this brain scanner for signs of cocaine-related narrowing of the volunteer's arteries.*

have demonstrated that cocaine use temporarily narrows arteries in the brain, thereby reducing the blood supply to various brain regions. Researchers had suspected this for many years because they knew that cocaine could cause vasoconstriction, or narrowing of blood vessels, in the heart and other regions of the body. This study conclusively demonstrated this effect in the human brain.

The researchers administered either cocaine or a placebo solution to 24 men, ages 24 to 34. The volunteers had used cocaine occasionally but were not dependent on the drug. The cocaine doses administered were relatively low, resulting in cocaine blood levels that were at the low end of the range typically experienced during cocaine abuse.

Images of the brain were obtained before and 20 minutes after the cocaine was administered. By comparing before and after images, the researchers could see where blood vessels were narrowed. Among the 7 men who received the placebo, only 1 showed blood vessel narrowing, but among the 9 men who received the lowest dose of cocaine, 3 had vasoconstriction in several brain arteries. Among the 8 men who received a higher dose, 5 showed this effect. The vasoconstrictions ranged from small reductions in

blood vessel diameter to more significant obstructions of blood flow.

The more often the men had used cocaine in the past, the more likely the drug was to narrow blood vessels, which suggests that cocaine has a cumulative effect on brain arteries. "This cumulative effect may start with as few as 5 to 10 exposures to cocaine," says Dr. Kaufman. "As a result, people who use cocaine many times probably have a high incidence of vasoconstriction in their brains."

One possible outcome of cocaine's cumulative effect may be a stroke. As a result of many cocaine exposures, brain arteries may be more reactive to the chemical stimuli that normally cause them to constrict, Dr. Kaufman says. This constriction could substantially reduce the blood supply to a region for several minutes, thereby damaging nerve cells and possibly causing stroke-like symptoms. A more likely outcome of the cumulative effect would be persistent blood flow reductions to large areas of the brain. These reductions are less substantial than those that occur in a stroke and may not kill nerve cells, but they could cause thinking and memory deficits, says Dr. Kaufman.

### **Long-term Reductions in Blood Flow**

Scientists began to observe that cocaine could cause persistent blood flow deficits in the brain in the mid-1980s. NIDA-funded scientist Dr. Nora Volkow and her colleagues at the Brookhaven National Laboratory in Upton, New York, and at the University of Texas Health Science Center in Houston used another imaging technique called positron emission tomography (PET), which can show the flow of blood in the brain tissue rather than in the brain arteries, as MRA does. When the researchers compared PET scans of young adult cocaine-abusing men with scans of normal volunteers, they found that most of the abusers had less blood flow in some areas of the brain. When the researchers performed PET scans again 10 days later, the blood flow deficits were still there, even though the abusers had stopped using cocaine. Many of the volunteers had difficulties concentrating and performing simple calculations, which the researchers concluded were associated with the blood flow deficits.

Subsequently, other scientists verified that cocaine abusers had blood flow deficits in the brain and that these deficits persisted long after the individuals stopped abusing cocaine. Using a technique similar to PET called single photon emission computed tomography (SPECT), Dr. Tony Strickland of Charles R. Drew University of Medicine and Science in Los Angeles and the University of California, Los Angeles, School of Medicine and his colleagues took brain images of cocaine abusers who had abstained from cocaine for at least 6 months before evaluation. Even after this long period of abstinence, the images showed that the abusers still had blood flow deficits compared to control subjects, suggesting that the deficits



*Dr. Tony Strickland of Charles R. Drew University of Medicine and Science tests a volunteer for cocaine-related mental deficits.*

may be long-term or perhaps even permanent.

In addition to taking brain images with SPECT, Dr. Strickland's group also administered neuropsychological tests to the cocaine abusers. These tests detected many abnormalities that seemed to be associated with reduced activity in the parts of the brain affected by the reduced blood flow. These abnormalities included deficits in attention, memory, concept formation, and mental flexibility. The tests also showed that long-term cocaine abusers had trouble inhibiting inappropriate behaviors, a condition psychologists call disinhibition.

Dr. Levin, who worked on the MRA study with Dr. Kaufman, thinks that chronic cocaine abuse may lead to strokes and long-term blood flow deficits by accelerating atherosclerosis in brain arteries. Atherosclerosis is a thickening on the inside of blood vessels that some researchers believe makes the vessels more likely to go into vasospasm, which is a vasoconstriction that lasts for minutes rather than seconds. "Let's say a blood vessel in a person's brain has atherosclerosis as a result of some injury to the blood vessel. If the person takes a compound such as cocaine that causes vasoconstriction, the part of the blood vessel that is likely to go into spasm is the part with the atherosclerosis," explains Dr. Levin. This vasospasm may then damage the inner lining of the blood vessel, which would further promote the development of atherosclerosis. If the person continues to take cocaine, more vasospasms would occur and hence more atherosclerosis. "It becomes a vicious cycle," he says.

This would explain how cocaine could cause strokes. Eventually, the vasospasms induced by cocaine last so long that nerve cells die from a lack of blood. The explanation for the persistent blood flow deficits might be that the atherosclerosis is slowly clogging the inside of the blood vessels, thereby reducing blood flow. One piece of evidence in favor of this theory is that aspirin has been shown to reverse temporarily the cerebral blood flow deficits caused

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by cocaine. Aspirin inhibits the formation of blood clots that are part of the atherosclerotic process.

Using a technology called transcranial Doppler sonography (TCD), Dr. Ronald Herning, Dr. Jean Lud Cadet, and colleagues in NIDA's Division of Intramural Research in Baltimore have found evidence that cocaine abusers do indeed have significant atherosclerosis in their brain arteries. In TCD, very high frequency sound waves are bounced off the blood flowing in large arteries in the brain, and the characteristics of the reflected sound waves can be used to estimate the constriction of the arteries. "Our data suggest that cocaine abusers in their thirties have arteries that are as constricted as those of normal subjects in their sixties," says Dr. Herning.

### Mental Deficits

Drug treatment providers should be aware that mental deficits that develop in cocaine abusers as a result of reduced blood flow may hamper the ability of these patients to benefit from treatment, says Dr. Strickland. Some patients have trouble paying attention or remembering conversations; others disrupt the therapy by being disinhibited. They constantly interrupt the therapist, they begin tasks without waiting for all the instructions, and they may become aggressive.

Dr. Strickland recommends giving new drug abuse patients neuropsychological screening tests to identify their deficits. Once these deficits are identified, the therapist can modify the drug treatment to accommodate the deficits, he suggests. For example, if the patient has trouble paying attention and remembering, the therapist could present information in small segments and repeat each segment until the patient learns it.

A major component of therapy is simply informing these patients that their long-term drug abuse has changed the way their brains function, Dr. Strickland says. "Some of these patients know that something is wrong but don't know what it is," he says. "They are relieved to learn that they're not 'crazy' and that the source of their problems is that drugs have altered the way their brains process information. They also are relieved to learn that they can take steps to enhance their performance."

"Compared to patients who have brain injury from motorcycle accidents, gunshot wounds, or other causes, drug abuse patients have considerably less impairment," notes Dr. Strickland. "We're successful in helping traumatic brain injury patients, and so the chances of helping patients with drug-induced brain injury are comparatively good."

In addition to modifying drug abuse treatment to accommodate the mental deficits of cocaine abusers, NIDA scientists are also investigating the possibility of treating their blood flow and mental deficits with medications. TCD will be particularly useful for monitoring the blood flow effects of medications, says Dr. Herning. "TCD is a quick, easy, relatively inexpensive measure that can be used repeatedly, so you can give your subjects medications and monitor them weekly, which you cannot do with PET or SPECT."

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## Brain Scans Open Window To View Cocaine's Effects on the Brain

By Neil Swan, NIDA NOTES Staff Writer

New NIDA-funded research supports a widely held theory that cocaine-induced euphoria is precipitated by blocking the normal flow of the chemical messenger dopamine in the brain. The findings also help clarify why cocaine addicts "binge" on the drug. A related study by the same research team challenges another theory about where in the brain this dopamine action occurs.

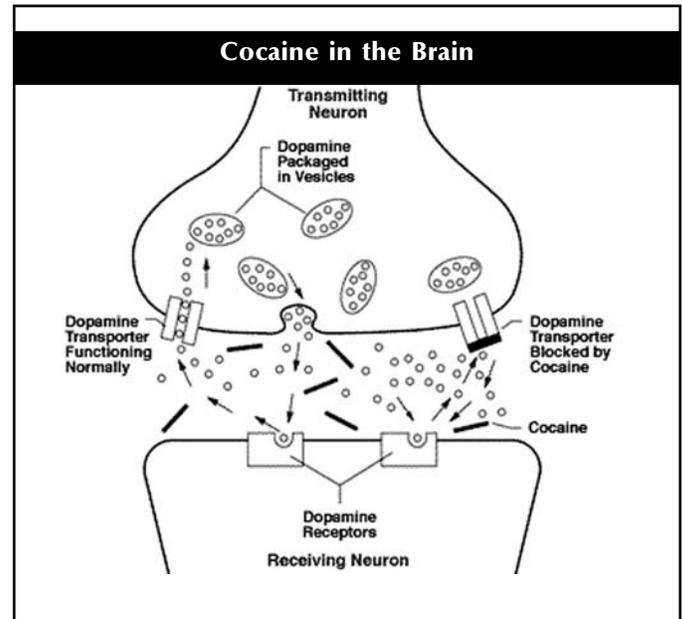
Dopamine is a neurotransmitter, a chemical that carries messages from one nerve cell, or neuron, to another or from one functional section of the brain to another. This neurotransmitter is associated with body movement, awareness, judgment, motivation, and pleasure. Researchers believe it is responsible for the addictive effects of drugs such as cocaine.

Dopamine flows from neurons into the synapses, or spaces between neurons, to form a temporary link that serves to transmit signals between neurons. Then, normally, after it has transmitted its signal to the neighboring neuron, it vacates these spaces, returning to the same neuron that released it in a recycling process called reuptake. Dopamine moves from the synaptic gap back inside the neuron by attaching to "transporter" molecules on the neuron's surface.

Cocaine, however, attaches to the same transporter binding sites as dopamine. This means that, when cocaine is introduced, dopamine cannot bind to the dopamine transporter and is stranded in the synapses. Thus, cocaine's blocking action leads to an increase of dopamine levels in the synapses that, scientists believe, normally produce feelings of pleasure. Cocaine's action intensifies these feelings into euphoria, studies show.

Now, Dr. Nora Volkow of NIDA's Regional Neuroimaging Center at Brookhaven National Laboratory in Upton, New York, has provided visual evidence to confirm this theory of how cocaine blocks the reuptake of dopamine. Dr. Volkow used brain images to show that, in cocaine addicts, dopamine is directly involved in the euphoria that reinforces the drug abuser's desire to take drugs.

"The results affirm the theory that dopamine transporter blockade plays a crucial role in the rewarding and reinforcing properties of cocaine in humans," she says, adding that this role may explain why cocaine addicts sometimes binge uncontrollably.



*The neurotransmitter dopamine transmits brain signals by flowing from one neuron into the spaces between neurons and attaching to a receptor on another neuron. Normally, dopamine then is recycled back into the transmitting neuron by a transporter molecule on the surface of the neuron. But if cocaine is present, the drug attaches to the transporter and blocks the normal recycling of dopamine, causing an increase of dopamine levels in the spaces between neurons that leads to euphoria.*

Dr. Volkow theorizes that cocaine bingeing may result from the corruption of primeval survival-of-the-species urges that are controlled by dopamine. Dopamine activity is known to control urges to begin—and to repeat—acts that are necessary for survival such as eating, drinking, and engaging in sex. Satisfying these urges results in pleasure or gratification. "Pleasure is a natural reinforcer to increase the probability that a species will engage in a given behavior and continue that behavior," she says. Once these urges have been satisfied, the body's normal response is satiety or "that's enough." Repeated cocaine use, however, turns off this normal satiety response so that users continue craving and drug seeking behavior, she suggests. This short-circuiting of the satiety response could explain why cocaine abusers binge even in the face of powerful negative side effects, she adds.

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“When satiety is suppressed, the pleasurable properties of cocaine serve as a trigger for activating brain pathways that will then maintain the drug-consuming behavior,” she concludes.

Dr. Volkow used a brain imaging technology called positron emission tomography (PET) to study 17 long-term users of cocaine. She found that the intensity of the cocaine-induced high or euphoria that the volunteers reported was related directly to cocaine’s ability to block the dopamine transporter system.

Using intravenous injections of cocaine at doses comparable to those typically used by abusers, Dr. Volkow found that cocaine blocked between 60 percent and 77 percent of the dopamine transporter binding sites in the brains of the addicts. She found that at least 47 percent of the binding sites had to be blocked by cocaine before the volunteers said they felt a drug-induced high.

A related study by Dr. Volkow measured drug responses of cocaine addicts and of nonaddicted volunteers who had not developed craving for the drug. In that study, she used PET imaging to compare responses to intravenous administration of methylphenidate, a stimulant drug that, like cocaine, increases synaptic levels of dopamine.

Many researchers have theorized that elevated dopamine levels associated with the reinforcing effects of cocaine

occur in the brain region called the nucleus accumbens. However, Dr. Volkow found that cocaine-dependent volunteers experienced decreased, not increased, levels of dopamine release, compared to nonaddicted volunteers, in the striatum, where the nucleus accumbens is located. Instead, addicts’ response to methylphenidate was greater than that of nonaddicts in the thalamus, a brain region that carries sensory signals to the cerebral cortex. This thalamic response in the cocaine addicts was associated with cocaine craving and was not seen in nonaddicted volunteers. “Thus, our findings challenge the notion that addiction involves an enhanced dopamine response to cocaine in the striatum,” Dr. Volkow reports. The data suggest that the brain’s thalamus region may have an addiction-related role in dopamine levels and functions, she says.

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## NIDA Brain Imaging Research Links Cue-Induced Craving to Structures Involved in Memory

By Neil Swan, *NIDA NOTES* Staff Writer

For years, drug abuse researchers have known that when addicts are exposed to drug-related cues, such as the sight of drug

paraphernalia or even a drug-using companion, these stimuli can spark powerful drug craving. Using brain-imaging techniques, scientists are literally seeing the changes that these environmental cues trigger in the brain as they are taking place.

Researchers in NIDA's Division of Intramural Research (DIR) have recently published brain imaging findings that show that cue-induced drug craving is linked to distinct brain systems that are involved in memory.

"Drug craving is a central aspect of addiction and poses an obstacle to treatment success for many individuals," says NIDA Director Dr. Alan I. Leshner. "Twenty years of neuroscience research have brought us to where we can actually see increases in specific brain activity that are linked to the experience of craving. If we can understand the mechanisms that cause craving in people addicted to cocaine or other drugs, more effective treatment strategies can be developed that counteract craving."

Using positron emission tomography (PET), Dr. Edythe D. London and her colleagues at DIR's Addiction Research Center (ARC) in Baltimore produced brain images showing that, in people who have used cocaine, cocaine-use cues spark increased glucose metabolism in brain regions that are associated with memory. Increased glucose metabolism indicates enhanced neural activity. By questioning the volunteers whose brains were scanned, researchers correlated computer-screen images with the cocaine users' responses about intensity of craving sensations. To make the correlation, the brain images were examined for color changes that are calibrated to show areas of increased glucose metabolism.

In the study, DIR researchers compared metabolic activity in the brains of 13 volunteers who had used cocaine with activity in the brains of a control group of 5 volunteers



*Dr. Steven Grant is lead investigator on the craving study. The study continues with the latest PET imaging scanner at the Center, probing how drug-related cues may disrupt normal memory functions.*

who had never used cocaine. The scans were taken after the groups were exposed to both cocaine-related cues and neutral cues. The cocaine-related stimuli consisted of observing drug paraphernalia and viewing a videotape of cocaine users.

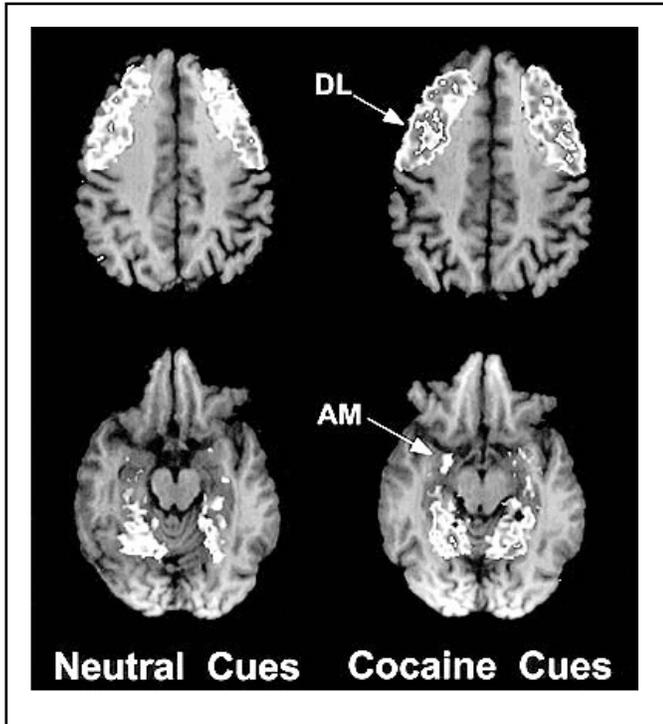
The cocaine-user group responded to the cocaine-related cues, but not to the neutral cues, with increased glucose metabolism, which was visible in the PET images and with their own reports that they were experiencing craving. The greater the reports of craving, the greater the metabolic activity in three key areas of the brain, the researchers found. The volunteers who had never used cocaine reported no cocaine cue-induced craving and showed no visual signs of cue-induced brain activity.

Among the brain regions activated by the cocaine cues were the dorsolateral prefrontal cortex, amygdala, and cerebellum, which are all involved in aspects of memory and learning. The amygdala has been linked to emotional aspects of memory. The findings suggest that a neural network involving these brain regions integrates the emotional and cognitive aspects of memory and reacts to environmental cues and memories by triggering cocaine craving.

"These three areas show cue-induced activity changes that are highly correlated with the behavioral measure, which is craving," says Dr. London, director of the NIDA Brain Imaging Center and initiator of the study. "Thus, we have identified brain circuits that may be targets for pharmacotherapy or other treatments. We now have a practical system for testing potential interventions. This system overcomes the limitations of an addict's own subjective evaluations of craving sensations by using the PET scan-



*Dr. Edythe D. London, director of NIDA's new Brain Imaging Center, initiated the craving study that has found links between cue-induced craving and the brain structures involved in memory. A pharmacologist, she began brain imaging research in 1979 and came to DIR in 1981.*



PET scans conducted at NIDA's Brain Imaging Center reveal selective activation of brain circuits during cocaine craving. Scans from volunteers who experienced a high level of cue-induced cocaine craving show activation of brain regions implicated in several forms of memory. The scans at right show activation of the dorsolateral prefrontal cortex (DL), which is important in short-term memory, and the amygdala (AM), which is implicated in emotional influences on memory. When these volunteers were exposed to neutral (non-drug-related) cues, this activation was not seen (scans at left).

ner to see, objectively, actual responses within the brain that correlate to craving.”

Until now, the three brain regions identified by the researchers have been associated with memory functions, but not with drug craving, says Dr. Steven Grant, the

study's lead investigator. These new findings support the hypothesis that memory may be more critical to drug craving than is the traditional concept of reinforcement. “The amygdala, which is involved in giving memories emotional color, puts an emotional aspect on the cue-induced craving sensations,” he adds.

The current research into cue-induced craving continues with new PET scanning equipment recently installed at the ARC.

Dr. London and her colleagues are using the new scanner to test whether cue-induced craving impairs an addict's ability to perform simple daily tasks. Preliminary findings confirm the hypothesis that cues can intrude into working memory functions, producing distracting daydreams or cocaine-oriented thoughts, says Dr. Grant. “Activation, by drug-related cues, of brain regions that integrate the emotional and cognitive parts of memory could contribute to one of the hallmarks of addiction—the excessive focus on activities that lead to further drug use,” Dr. London says.

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## Anxiety and Stress Found to Promote Cocaine Use in Rats

By John A. Bowersox, NIDA NOTES Contributing Writer

Although cocaine users typically report that the drug enhances their feelings of well-being and reduces anxiety, cocaine also is known to bring on panic attacks in some individuals. What's more, studies have shown that long-term cocaine use leads to increased anxiety. Severe anxiety, along with restlessness and agitation, is also among the major symptoms of cocaine withdrawal.

Recent NIDA-funded research now suggests that there could be a different aspect to the relationship between cocaine use and anxiety: anxiety and stress may be among the factors that lead to cocaine abuse.

In separate studies that may prove useful for understanding the behavioral and biological mechanisms involved in the initiation of cocaine use and dependence, Dr. Nick E. Goeders of Louisiana State University in Shreveport and Dr. Klaus Miczek of Tufts University in Boston have reported that rats under stress learn to give themselves cocaine more quickly than do nonstressed rats.

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***The stressed rats in the experiment learned to self-administer cocaine twice as fast as did animals that were not exposed to the stressor.***

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Both studies involved exposing rats to stressful situations and then assessing how quickly the animals learn to self-administer cocaine by pressing a bar in the testing chamber. Cocaine doses were at first very low but were increased gradually to determine the minimum dose at which the rat would learn the cocaine self-administering task.

In Dr. Goeders' experiment, the level of stress the rats were under was determined by measuring levels of the stress hormone corticosterone in their blood. "It looks like corticosterone may make them more sensitive to cocaine," says Dr. Goeders, who found that rats with the highest levels of corticosterone learned the cocaine self-administration task at doses far lower than did rats with low levels of the stress hormone.

Initially, three groups of rats learned that if they pressed a bar in the testing chamber they would be rewarded with

food pellets. Environmental stress was then introduced by periodically delivering very brief (one thousandth of a second) electric shocks to the animals' feet.

One group received random footshocks that were delivered noncontingently—that is, whether or not the animals pressed the food bar. Another group also received random shocks but only after the food bar was pressed. The third group served as the control and received no footshocks. As measured by levels of corticosterone in their blood, the group that received random, noncontingent footshocks experienced a significantly higher level of stress than did either of the other two groups.

Each group of animals was then given the opportunity to self-administer a cocaine solution by pressing a second bar in the testing chamber. Rats in the noncontingent shock group required only half as much cocaine as animals in the other two groups did to learn to press the bar for the drug.

Instead of footshocks, Dr. Miczek's experiment employed a "social stress" design in which a rat is exposed to, but shielded from, a more aggressive rat. "Although the first animal is protected from the aggressive rat by a screen and cannot be injured, it still is threatened," explains Dr. Miczek.

A variety of physiological indicators of stress, including increased blood pressure, heart rate, and plasma corticosterone levels, confirmed that animals presented with this situation experienced stress. Dr. Miczek reports that the stressed rats in his experiment learned to self-administer cocaine twice as fast as did animals that were not exposed to the stressor.

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***Research also is important for understanding how external factors may make some individuals more vulnerable to cocaine abuse.***

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As strong as his and Dr. Goeders' findings appear to be, however, he cautions that further studies are needed before broad conclusions about the association between stress and vulnerability to cocaine abuse can be made.

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“Support for the notion that stressors sensitize animals to self-administration of drugs remains controversial,” says Dr. Miczek. He adds that certain important stressors, such as being threatened, have been shown to activate the same dopaminergic brain region that cocaine self-administration is known to activate. Although the recent studies report strong correlations between stress and how quickly rats learn to self-administer cocaine, they do not provide direct evidence of a biological mechanism through which this occurs, he notes.

Dr. Goeders says that his laboratory is trying to provide such evidence by blocking corticosterone receptors in the rat brain and then performing the same studies of stress and cocaine self-administration described above. If the stress hormone is responsible for increasing the rate at which stressed rats learn to self-administer cocaine, he explains, blocking the hormone’s brain receptors should block the effect of the hormone.

“We’re trying to determine if a specific type of corticosterone receptor mediates the effect of stress on cocaine self-administration.” These studies could help scientists gain a better understanding of the biology of initiation of cocaine use and abuse, he says.

Dr. Roger Brown, who heads NIDA’s Behavioral Neurobiology Research Branch, adds that this kind of

research also is important for understanding how external factors may make some individuals more vulnerable to cocaine abuse. These studies shed light on “the situations or conditions that contribute to drug abuse,” he says. “In humans, we know that there are factors beyond drug/brain receptor interactions that affect drug-taking behavior.” In these studies, he adds, scientists have begun to address how one of these possible factors, stress, interacts with the biochemical pathways known to be involved in cocaine abuse.

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## Cocaine Affects Men and Women Differently, NIDA Study Shows

By John A. Bowersox, *NIDA NOTES* Contributing Writer

A recent NIDA-funded study suggests that gender differences will become an increasingly important consideration in drug abuse treatment strategies. The study by researchers affiliated with Harvard Medical School found that cocaine affects men and women differently and that hormonal fluctuations play an important role in women's responses to the drug.

In the study, Dr. Scott E. Lukas and his colleagues at the Alcohol and Drug Abuse Research Center in Belmont, Massachusetts, measured a variety of responses to cocaine in six male and six female volunteers. On separate days, the volunteers snorted single doses of cocaine and placebo powder in equal amounts relative to their body weights. The men were tested once, but the women were tested at two different times during their menstrual cycle: once during their follicular phase and again during their luteal phase. The follicular and luteal phases, respectively, correspond to the times before and after ovulation. The researchers calculated the phases of each woman's cycle from the onset of menstruation:

- Dose 1 (midfollicular phase) was given 5 to 9 days after the onset of menstruation;
- Dose 2 (midluteal phase) was given 18 to 22 days after the onset of menstruation.

The researchers found that at both points in the menstrual cycle the women were much less sensitive to the drug than the men were. The men in the study had significantly more episodes of euphoria, or good feelings, and dysphoria, or bad feelings. When asked to rate the severity of their dysphoria, the men judged the bad feelings to be more unpleasant than the women did. The men also experienced greater heart rate and blood pressure increases and detected cocaine's effects sooner than the women did. Although the men and women received equivalent doses of cocaine, women had lower levels of the drug in their blood than the men; their cocaine blood levels were even lower when they took the drug during the luteal phase of their menstrual cycle.

Dr. Lukas says that differences in the speed with which cocaine is metabolized may account for the drug's different effects in men and women. In the body, cocaine is broken down into inactive metabolites by enzymes known as cholinesterases. Although men have higher levels of

these enzymes in their blood plasma, women have higher levels of a type of cholinesterase enzyme found in red blood cells, Dr. Lukas explains. The red blood cell enzyme metabolizes cocaine much more actively than the plasma enzyme does.

Physical changes that occur during the menstrual cycle also may contribute to women's decreased sensitivity to intranasal cocaine, says Dr. Lukas. The increase in certain hormone levels during the luteal phase causes women's mucous membranes, including those that line the nasal passages, to secrete more mucus. Dr. Lukas says that the increased mucus may act as a barrier to the absorption of cocaine when women snort the drug during the luteal phase of their menstrual cycle.

"We believe that the gender differences in cocaine's effects that we observed are due to a combination of metabolic differences and the greater physical barrier to cocaine absorption created by the increase in mucosity," says Dr. Lukas. He adds that other as yet unknown factors could also help produce cocaine's differing effects.

Dr. Lukas says the findings, which he presented at the 1994 meeting of the College on Problems of Drug Dependence, might help explain, at least from a physiological perspective, why the prevalence of cocaine use among women has traditionally been much lower than it has been among men. According to the National Household Survey on Drug Abuse, approximately 3.1 million men and 1.4 million women used cocaine at least once during 1993. Women also appear to take cocaine less frequently than men do. The 1993 survey, which was conducted by the Substance Abuse and Mental Health Services Administration, estimates that about 365,000 men compared with 111,000 women used cocaine at least once a week.

Many women have reported that they did not get high when they first tried cocaine, says Dr. Lukas, adding that women's low sensitivity to the drug combined with its high price create a strong disincentive to its continued use. On the other hand, he says, some women may become heavy users because they need to take more cocaine to get the same effect as men.

If further studies substantiate Dr. Lukas' findings, they could have important implications for the treatment of

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cocaine abusers, says Dr. Elizabeth Rahdert, a research psychologist in NIDA's Division of Clinical and Services Research.

"Therapists would have to realize that for women, the response to cocaine will be different at different times of the month and not a steady state as it is for men," she says.

Presumably, she adds, patterns of craving and response to withdrawal could also fluctuate with a woman's menstrual cycle, and treatment professionals would have to recognize that women could be more vulnerable to relapse at different points in their cycle. Furthermore, treatment strategies designed to address male usage patterns would have to be modified in accordance with women's usage patterns.

Dr. Lukas' work reflects NIDA's increased interest in examining the gender-specific effects of drug abuse. Basic research findings such as the discovery that sex hormones can interact with neurotransmitters during normal brain functioning have fueled this interest.

"Previously, drug abuse research on women focused mainly on issues related to pregnancy and the effects of drug abuse on the developing fetus," says Dr. Cora Lee Wetherington, a psychologist in NIDA's Division of Basic Research.

"More recently, we've seen a shift with the realization that the treatment needs of women may be different from those of men. Although issues related to childbearing and child-rearing are still important areas of drug abuse research, researchers are questioning whether treatment strategies that were developed through research conducted largely on male subjects are appropriate for women," says Dr. Wetherington.

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## Inner-City Cocaine Abusers in Baltimore Respond to Voucher-Based Treatment

By Michael D. Mueller, *NIDA NOTES* Contributing Writer

Although reports on voucher-based treatment of cocaine abuse are encouraging, most of the research to date has been carried out on white males in Vermont, a largely rural State. The question on the minds of drug abuse researchers in metropolitan areas has been, "How well does it work with inner-city cocaine abusers?"

In Baltimore, Dr. Kenneth Silverman of Johns Hopkins University, Dr. Kenzie Preston of NIDA's Division of Intramural Research (DIR), and their colleagues tested the voucher-based treatment of cocaine abuse on an especially challenging population: injecting heroin abusers in methadone treatment with a history of heavy cocaine abuse.

The voucher-based strategy produced impressive results. "The vouchers are powerful reinforcers, even among inner-city patients dependent on more than one drug," says Dr. Silverman. "When the vouchers are tied to cocaine-free urine, they help patients stay off cocaine for many weeks or months at a time."

"Moreover, cocaine abusers often report a loss of control over their ability to not use the drug," explains Dr. Silverman. "The vouchers are a reward for not using cocaine. And rewards—even relatively small ones—can be strong motivators."

The Baltimore study involved 37 patients randomly assigned to two groups. Both groups received standard counseling for methadone treatment, but they differed in how vouchers were made available to patients.

Patients in Group A received a voucher for each cocaine-free urine sample, with samples collected three times a week over 12 weeks. The value of the voucher increased with the number of consecutive cocaine-free urine specimens.

Each patient in Group B was "yoked" to a patient in Group A. That is, Group B patients also received vouchers matched in pattern and value to those earned by their counterparts in Group A. However, Group B vouchers were not tied to the outcome of urine tests. Group B patients were told that they would receive vouchers in an unpredictable manner and that the vouchers could be used to help them stop using cocaine by purchasing goods and services that promote a healthy lifestyle.

Dr. Silverman found that the treatment worked when the voucher was tied to a cocaine-free urine sample. Patients given vouchers for clean urines stayed off cocaine for more

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***Patients given vouchers for clean urines stayed off cocaine for more weeks and for longer stretches of time than patients whose vouchers were not tied to the outcome of urine tests.***

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weeks and for longer stretches of time. Nearly half of the patients in Group A stayed off cocaine for continuous periods ranging from 7 to 12 weeks.

In contrast, only one patient in Group B was able to string together more than 2 cocaine-free weeks. The differences between the two groups were both clinically and statistically significant.

"The study design made it clear that the strength of the voucher is in the link to cocaine-free urine," says Dr. Silverman, "and not in the monetary value of the vouchers or the access they give to community services. They work because they reinforce a particular behavior—not using cocaine."

The drop in cocaine use was not offset by an increase in the use of alcohol or other drugs. Researchers found slight decreases in the use of opiates and alcohol.

"These results are very encouraging," says Dr. Silverman. "We must find more effective ways to treat cocaine abuse. Further, cocaine abuse is often intertwined with other drug addictions. It's a common problem in methadone treatment programs."

However, he is cautiously optimistic. "There's a lot to learn about this voucher-based approach. We need to see how it works over longer periods of time and find out why it doesn't work for some cocaine abusers.

"Still," says Dr. Silverman, "the short-term effectiveness of this approach is good news. We may be able to extend abstinence through continued reinforcement. And, as others have observed, keeping cocaine abusers off cocaine for even short periods of time may provide windows of opportunity for other treatments to take hold and start working."

Dr. Preston, principal investigator for the study, says that researchers also are interested in exploring how well

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contingency management strategies such as the voucher-based approach work when joined with medical treatment. “It’s possible,” says Dr. Preston, “that the most effective treatment for cocaine abuse will be in the combination of contingency management with medication.”

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## Voucher System Is Effective Tool in Treating Cocaine Abuse

By Michael D. Mueller, *NIDA NOTES* Contributing Writer

One of the biggest challenges in treating cocaine abuse is getting cocaine abusers to stay in treatment long enough to take the first difficult steps toward recovery. However, the voucher-based approach developed by Dr. Stephen T. Higgins and colleagues at the University of Vermont may help cocaine abusers take those vital first steps.

"This voucher-based strategy that has come out of Vermont represents important progress," says Dr. John J. Boren, the NIDA program officer overseeing this research. "The vouchers help hold cocaine abusers in treatment."

The Higgins approach allows cocaine abusers to build up points during outpatient treatment. The points, earned with urine specimens that test negative for cocaine, are recorded on vouchers, which can be exchanged for items that promote healthy living. These items include YMCA passes and continuing education materials.

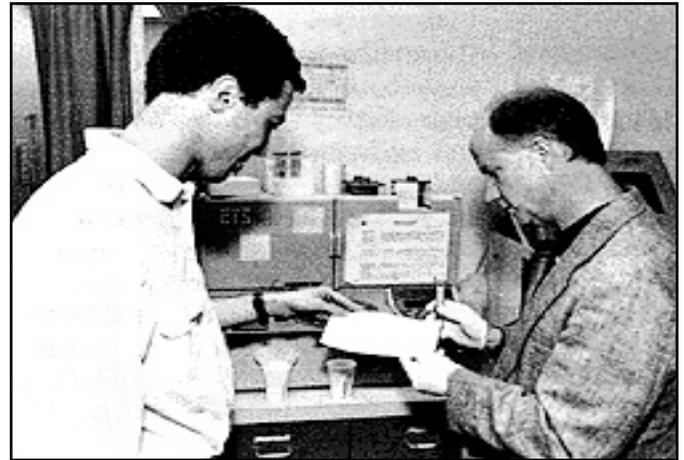
"Cocaine abusers never receive cash-only vouchers," emphasizes Dr. Higgins. "The patients and counselors must agree on the items to be purchased with the vouchers."

Urine specimens are collected three times a week, and the vouchers increase in value the longer the person stays off cocaine. Patients receive bonus vouchers at the end of the week if all three urine specimens have tested negative.

Cocaine is highly addictive; 1 to 2 million Americans are dependent on it. Up to 80 percent of cocaine abusers drop out of treatment programs, according to Dr. Higgins.

Further, Dr. Higgins points out, "The demand for cocaine abuse treatment is so large, and the environmental influence of the addiction process so powerful, that we must find ways to help cocaine abusers on an outpatient basis. Sure, we can treat them in the hospital, but then they return to their home communities, where they face old influences, often without alternatives and skills to withstand the lure of cocaine."

The voucher-based system creates an alternative, builds coping skills, and strengthens social relationships. The approach involves more than regular urine tests and vouchers for points. It also includes intensive counseling directed at employment, recreation, relationships, skills training, and structuring the day. Family and friends are brought into the counseling process. Patients who are alcohol dependent are also given Antabuse therapy to treat their dependence.



*Dr. Stephen Higgins (right) gives a patient a voucher that can be exchanged for items that promote healthy living. The voucher, similar to the one shown on the following page, is earned with urine specimens that test negative for cocaine.*

Thus, the Higgins approach to treating cocaine dependence focuses on behavior, creating paths for behavior change, rewarding positive change, and strengthening social relationships that reinforce healthy choices. The treatment package has several parts, but the voucher piece seems particularly strong, notes Dr. Higgins.

To many, stacking vouchers against cocaine addiction is like pitting David against Goliath. However, like David, the vouchers have proven to be more effective than expected.

"It surprises many people that a stack of paper can outweigh the powerful urge to use cocaine," says Dr. Higgins. "But it makes sense in terms of what we know about why people use drugs. Also, cocaine users reach a point where they want help."

The key to the success of the vouchers is that they have a "reinforcing effect" that competes with the one produced by cocaine use. They are an alternative that is available immediately, but only if cocaine is not used. This is the heart of the theory that drives the treatment strategy.

Cocaine produces powerful reinforcing effects. When cocaine abusers use cocaine, the drug acts directly on particular areas of the central nervous system, which makes the user want to use cocaine again, often producing cycles of intensive, repeated use or "binges."

The voucher, on the other hand, is reinforcement for not taking cocaine. Although the dollar value of the voucher may not be great, the value of this alternative, immediate reinforcer can be quite high.

“Many areas of research support the concept of alternative reinforcement as important to preventing and treating drug abuse,” observes Dr. Higgins. “Quite simply, reinforcement is a basic principle of human behavior. When we’re discussing cocaine use, we’re talking about behavior that is very sensitive to its consequences.”

Cocaine abuse is not guided by a moral compass or free will. The drug acts on “reward centers” in the brain. Further, some researchers believe that the effects of cocaine on these reward centers are just as powerful as the effects of food and sex, notes Dr. Higgins.

Dr. Higgins and his colleagues are searching for ways to apply these principles of behavioral pharmacology to drug abuse treatment.

Dr. Higgins is quick to point out that, “Though cocaine is a powerful reinforcer, its use is context-dependent. Usually, the lifestyles of cocaine abusers are in such a state that their natural reinforcers for healthy behavior are in disarray or not available.

“Cocaine abusers, and especially ‘crack’ abusers, often come from deprived environments,” he says. “Many times, those neighborhoods provide an almost ideal environment for cocaine to exert its powerful reinforcing effects. There are few prosocial alternatives.

“We need to work toward creating environments in which those reinforcing effects are less powerful—in which people have positive, drug-free alternatives.”

Dr. Higgins and his colleagues began researching the voucher-based strategy in 1990. First, they compared the behavior-change package to a more traditional outpatient counseling program in a study of 28 cocaine abusers over a 12-week period. The more traditional program operates on the premise that cocaine abuse is a treatable disease; it includes counseling, lectures, videotape presentations, self-help sessions, and working with a sponsor.

Eleven of the 13 patients assigned to the behavior change program completed 12 weeks of treatment, compared to 5 of the 15 patients in the traditional program. The researchers found that patients in behavioral treatment had significantly longer periods with cocaine-free urine. The findings were much the same for a subsequent study of 38 patients over 24 weeks.

Next, Dr. Higgins narrowed his research to the voucher part of the treatment program. He found that 90 percent in the voucher group completed a 12-week treatment program, compared to 65 percent in the no-voucher group. Over 24 weeks, 75 percent in the voucher group, versus

40 percent in the no-voucher group, completed treatment. When it came to continuous cocaine abstinence, the voucher group averaged 11.7 weeks; the no-voucher group, 6 weeks.

Recently, the researchers reported on a followup of patients who took part in the 24-week study. Cocaine use was evaluated 3 months and 6 months after the completion of the 24-week program. Again, the voucher-based behavioral package produced significantly greater cocaine abstinence than the more traditional approach.

Although the findings are encouraging, Dr. Higgins and others caution that most research to date has been on white males in Vermont, a rural State. Further studies are needed to determine the effectiveness of the vouchers over longer periods of time and among women, urban populations, and other cultural groups.

Dr. Higgins’ research results are supported by those of Dr. Kenzie Preston of NIDA’s Division of Intramural Research, Dr. Kenneth Silverman of Johns Hopkins University, and their colleagues, who found that the voucher system seems effective in treating inner-city cocaine abusers.

“An immediate application of the voucher approach—which has demonstrated its short-term effectiveness—might be to reduce cocaine abuse among pregnant women,” suggests Dr. Higgins. The voucher-based intervention could lead to healthier newborns. It would also be cost-effective, as neonatal intensive care units are extremely expensive, he says.

This voucher certifies that _____ has received _____ points today, to equal a total of _____ points to date.  Date _____ Staff Signature: _____
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Some observers question the acceptability of “paying” cocaine abusers not to use cocaine. In answer, Dr. Higgins says, “We don’t view it as paying them to do the right thing. No cash changes hands. We are finding ways to provide alternative positive reinforcement. We combine the vouchers with behavioral therapy so that when the vouchers are gone, the individual can then find support for a cocaine-free lifestyle among his or her natural resources.”

Dr. Higgins’ academic training dovetails with what he learned about drug abuse during his youth in Philadelphia. “I grew up around a lot of drug abuse. What I saw on the streets agrees with the scientific studies that

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tell us that there are things we should be doing to give young people alternatives to cocaine,” he says.

“We need to look for forms of alternative reinforcement or incentive programs that can be used in community settings,” he continues. “Perhaps local merchants would be willing to contribute goods and services. Access to sports facilities and coaches are examples of healthy alternatives. We need to think creatively.”

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## NIDA-Supported Scientists Identify Receptor Associated with Cocaine Abuse

By John A. Bowersox, *NIDA NOTES* Contributing Writer

Much of NIDA's cocaine treatment medication research is directed toward finding compounds that counteract the specific changes that cocaine causes in the brain. Scientists know that cocaine affects the brain's dopaminergic pathways—areas that use the chemical dopamine to transmit messages between brain cells. They have found that cocaine prevents the reuptake, or retrieval, of dopamine by the brain cells that release it. The resulting flood of dopamine overstimulates the receptor molecules to which dopamine binds, an effect that scientists believe may account, in part, for cocaine's addictive effects.

Over the last few years, researchers have identified several kinds of dopamine receptors, each possessing distinct molecular properties and having different anatomical distributions within the brain. Scientists hope to identify potential targets for new cocaine treatment medications by determining whether some types of dopamine receptors play a larger role than others in producing cocaine's addictive effects.

NIDA-funded researchers at The Scripps Research Institute in La Jolla, California, have reported that one of these receptors, known as D-3, looks particularly promising as a target for cocaine treatment medication development.

"It looks like a pretty good bet," says Scripps researcher Dr. George F. Koob about the D-3 receptor's potential as a target for cocaine therapies. In animal experiments, Dr. Koob and Dr. S. Barak Caine found that the D-3 dopamine receptor appears to be a central factor in cocaine use.

The researchers reported that rats that had access to cocaine on a daily basis took less of the drug when given compounds that selectively bind to D-3 receptors. The rats in the study were trained to self-administer a cocaine solution intravenously. After baseline rates of cocaine use were established, the researchers added various dopamine agonists, compounds that bind to and stimulate dopamine receptors, to the rats' cocaine source.

Drs. Koob and Caine found that agonists with high affinities for D-3 receptors reduced cocaine intake more effectively than did agonists with low affinities for D-3 receptors. In fact, the higher an agonist's affinity for the D-3 receptor, the more effective it was at reducing cocaine self-administration.

The researchers hypothesize that D-3-selective agonists may reduce cocaine intake by enhancing cocaine's reinforcing properties. In this view, the rats took less cocaine because, when combined with the D-3 agonists, a smaller dose of cocaine felt the same as their "regular" dose. They believe, however, that much remains to be learned about the role that the D-3 receptor plays in cocaine reinforcement.

The researchers also examined whether the rats would self-administer the D-3 agonists in the absence of cocaine—a step necessary to determine the agonists' abuse potential. Ideally, therapies for drug abuse should have little or no abuse liability. They found that the rats self-administered only very high doses of the high-affinity D-3 agonists—the doses of these compounds that reduced cocaine intake were not self-administered. This is important, says Dr. Koob, because it suggests that, at therapeutic levels, D-3 agonists would have low potential for abuse.

NIDA officials say that they are encouraged by Dr. Koob's findings. "We're excited about his work, and we're hoping to follow it up in the context of our preclinical cocaine treatment discovery testing program," says Dr. Carol Hubner of NIDA's Medications Development Division (MDD). Dr. Hubner notes that some of the compounds that Dr. Koob studied have entered MDD's preclinical drug discovery program.

Dr. Koob reports that new research from his laboratory, done in collaboration with Drs. Jean-Charles Schwartz and Pierre Sokoloff in Paris, and Dr. Larry Parsons, a NIDA postdoctoral fellow, confirms these earlier findings. "We have tested new agonists that are even more selective for the D-3 receptor and have observed an even greater reduction of cocaine intake in rats," he says. He adds that his new research also has defined more precisely the area of the brain at which the D-3 receptor mediates cocaine abuse.

"We believe that the site of action of the D-3 receptor is localized to the shell of the nucleus accumbens," he says. The D-3 receptor's localization to this structure, which lies on the underside of the midbrain, has important implications for cocaine treatment medication development, he says.

Because D-3 receptors are concentrated in an area of the brain associated with emotional and endocrine functions and not in areas that regulate motor functions, he says, therapies targeted at D-3 receptors specifically may

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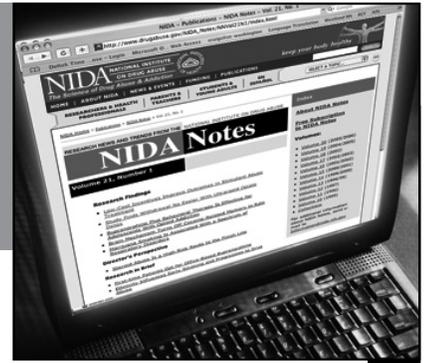
reduce cocaine intake without producing motor side effects. Other medications that target dopamine receptors nonspecifically have been shown to cause side effects that are similar to the movement disorders associated with Parkinson's disease.

"We don't expect that there would be any Parkinsonian side effects with medications that specifically target the D-3 receptor," says Dr. Koob.

#### Sources

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