

A Collection of

**NIDA
NOTES**

**NATIONAL INSTITUTE
ON DRUG ABUSE**

30 Years
1974-2004

Articles That Address



**RESEARCH
ON COCAINE**

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

NN0066

Introduction

The National Institute on Drug Abuse (NIDA) supports more than 85 percent 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:

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- 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.

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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”

Two-Object Recognition Test Mimics Test Used with Infants



Photo credit: Dorothy Cameron, the Johns Hopkins University Bloomberg School of Public Health.

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 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.

Sources

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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

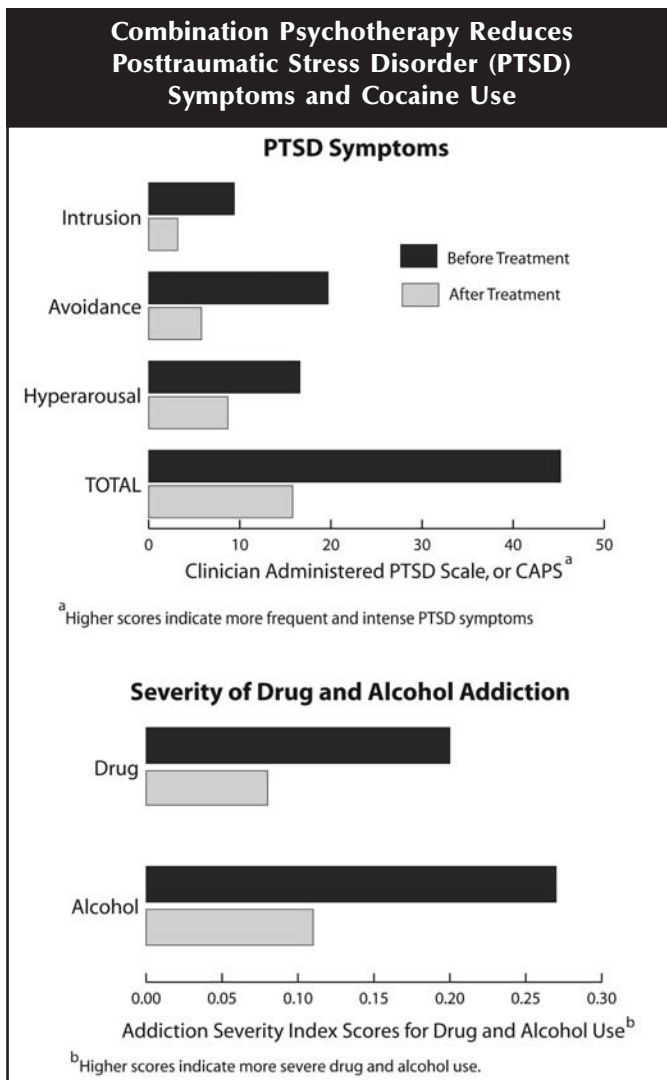
worse. Thus, integrated treatment is recommended as the way to treat patients with both disorders. Yet until recently, the most effective nonpharmacological treatment for PTSD, known as exposure therapy, was considered too risky to use with cocaine-dependent patients. The therapy seeks to desensitize 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.

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

- Brady, K.T., et al. Exposure therapy in the treatment of PTSD among cocaine-dependent individuals: Preliminary findings. *Journal of Substance Abuse Treatment* 21(1):47–54, 2001. **NN**

Researchers Probe for Clues to ADHD Medications' Protective Effects

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

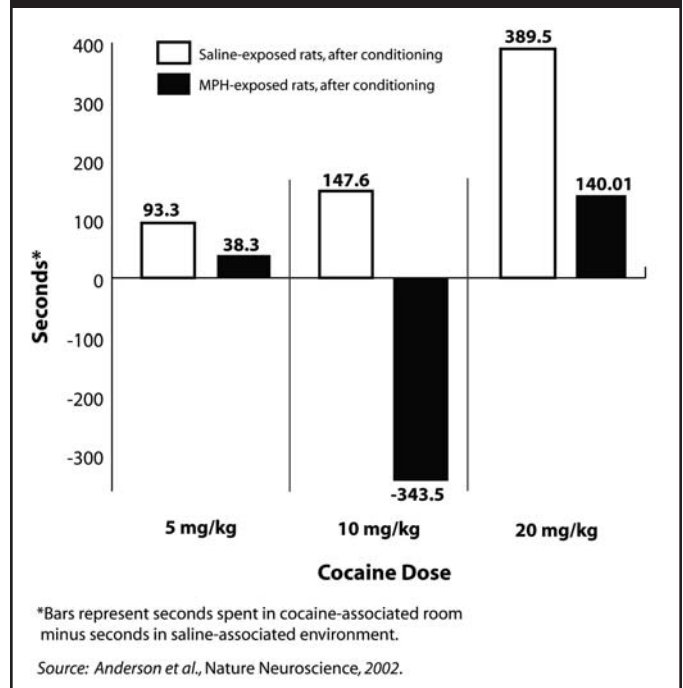
More than 2 million American children—an estimated 5 to 10 percent of preteens—have been diagnosed with attention-deficit/hyperactivity disorder (ADHD). For many of these children, treatment with psychostimulant medications such as Ritalin (methylphenidate, or MPH) suppresses the impulsivity, fidgeting, 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 7).

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.

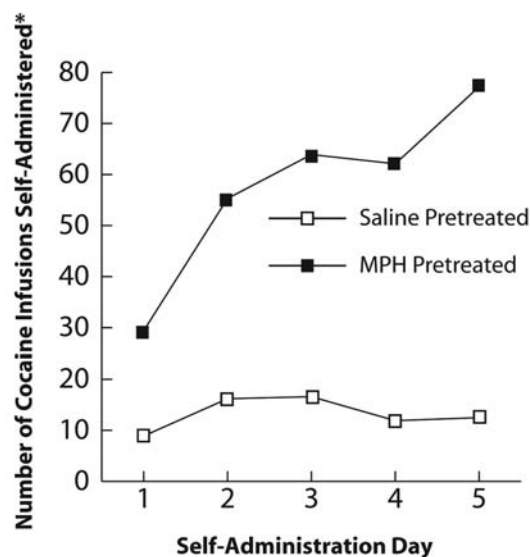
Despite these findings, Dr. Andersen cautions, it is still too early to make assumptions about any neurobiological effect of MPH on vulnerability to cocaine abuse.

"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 mg/kg). Poking through the other

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 mg/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.

hole triggered an infusion of saline solution. The scientists 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.”

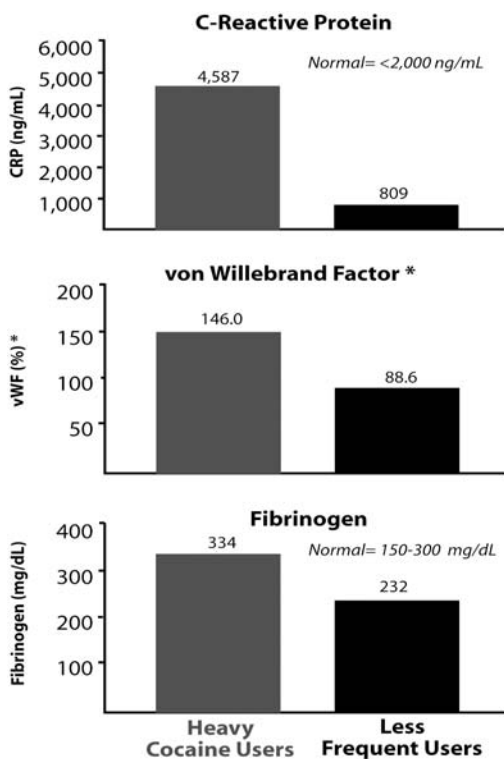
Participants in the study were 20 individuals (10 women and 10 men, average age 26 years) who used cocaine 2 to 6 times per month but were drug free at the time of the study. They received injections of low (0.2 mg/kg) or moderate (0.4 mg/kg) doses of cocaine or of saline solution, and their clotting-related 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).

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."

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

By Robert Mathias, NIDA NOTES Staff Writer

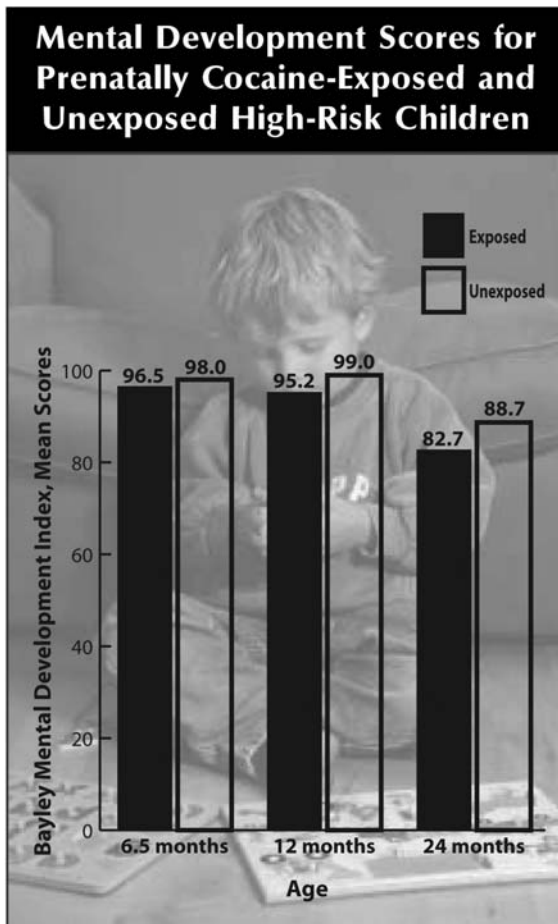
Since the mid-1980s, up to 1 million children born in the United States are estimated to have been exposed to cocaine in the womb. Determining cocaine's impact on these children's development has been difficult because there often are other possible explanations for physical and mental problems the children 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.



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.

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

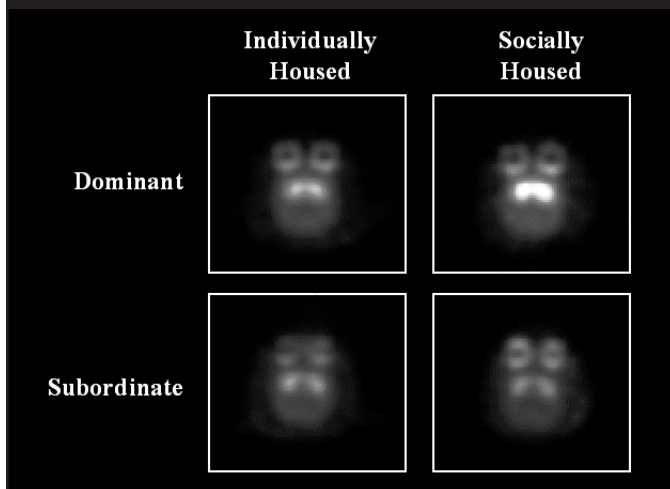
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Social Environment Appears Linked to Biological Changes in Dopamine System, May Influence Vulnerability to Cocaine Addiction

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.

Brain Images of Monkeys Housed Individually and After Transfer to Social Housing



In these PET scans, lighter colors represent increases in markers of dopamine D₂ function. Greater levels of D₂ 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 D₂ 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 D₂ 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 D₂ 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 D₂ receptor function among dominant monkeys may be the result of an increase in the number of dopamine D₂ receptors, a decrease in the amount of circulating dopamine competing for the receptors, or both as a consequence 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 D₂ 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 D₂ receptor function and thereby lower their risk for drug abuse.

“Dr. Nader’s research shows that environmental experiences can increase dopamine D₂ 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 D₂ receptors in drug abuse, points to the need for additional research to identify both environmental factors that promote low dopamine D₂ receptor levels and the associated vulnerability to cocaine’s reinforcing effects as well as environmental factors that give rise to high levels of dopamine D₂ 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.”

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

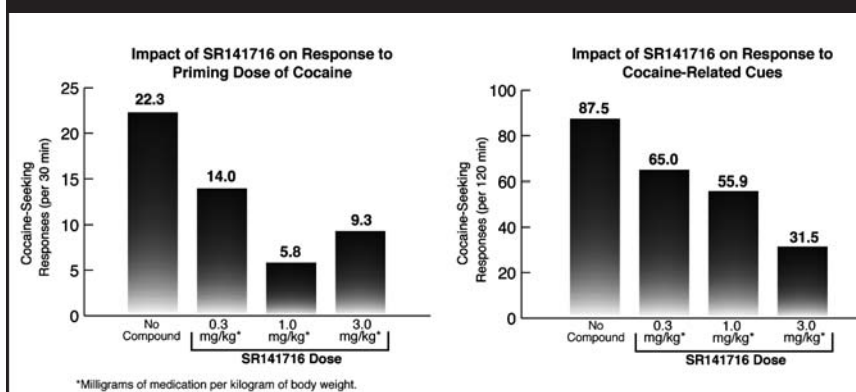
By Robert Mathias, *NIDA NOTES* Staff Writer

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

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.

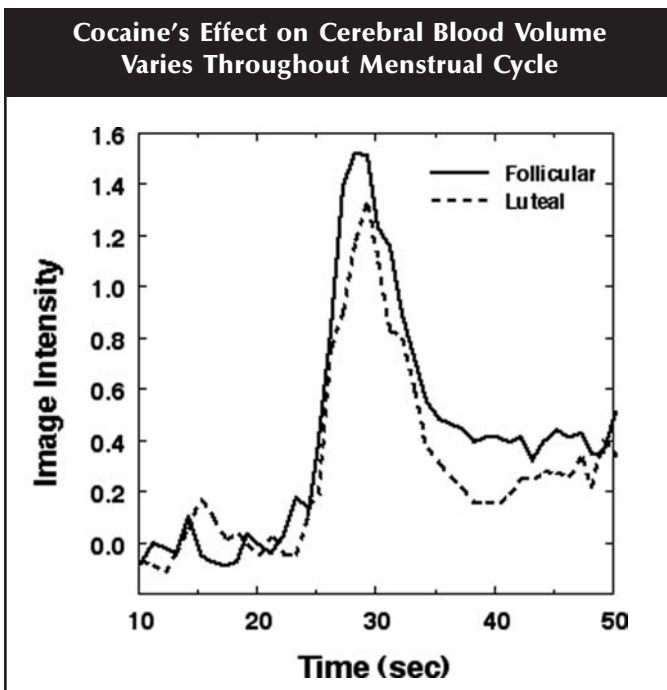
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Cocaine's Effects on Cerebral Blood Flow Differ Between Men and Women

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.



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).

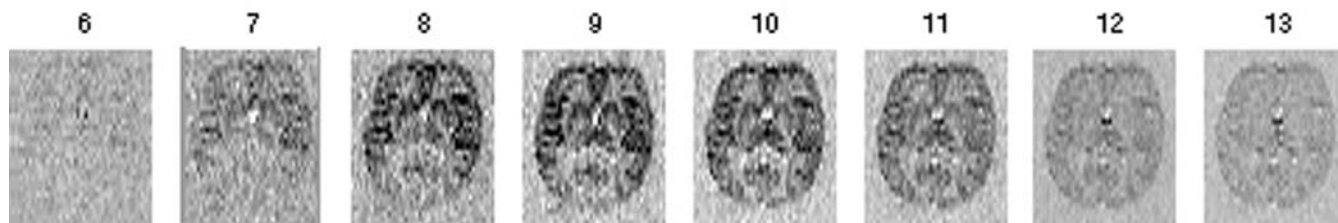
Each woman was given a dose of cocaine and underwent a DSC MRI scan of cerebral blood volume during both phases of her menstrual cycle. During the first part of the menstrual cycle, estrogen levels are high and progesterone levels are low; during the second part, progesterone levels rise. In each imaging 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 hormone-like 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

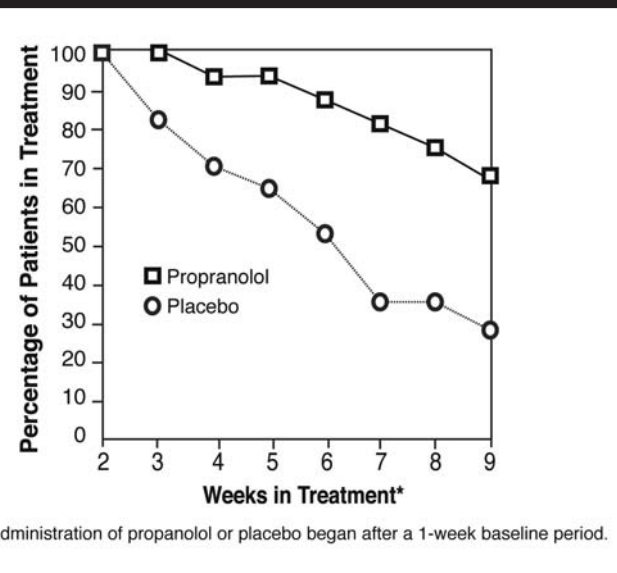
A medication used to treat high blood pressure may be an effective add-on therapy for cocaine-dependent patients who suffer severe withdrawal symptoms when they stop using the drug, a NIDA-funded study indicates. Patients who experienced severe anxiety and other symptoms and were treated with the medication—propranolol—stayed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



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,

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 with-

drawal 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, then using approximately every 2 to 4 hours during their waking day. Most of the descriptions of use more closely resembled taking a medication than using a drug for pleasure,” Dr. Simon says. “Cocaine abusers reported patterns that fit a picture of recreational use: They began in the evening and continued until all the cocaine on hand had been used.”

The different patterns of use may in part be a result of the drugs’ different effects in the body, the researchers say: Methamphetamine triggers the release of large amounts of the neurotransmitter dopamine into areas of the brain that regulate feelings of pleasure, whereas cocaine blocks the removal of dopamine, resulting in an accumulation that causes continuous pleasurable stimulation of brain cells. The effects of methamphetamine typically last more than 10 hours, and the half-life (the time it takes for the body 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

Methamphetamine abusers typically take the drug early in the morning, and take it at 2- to 4-hour intervals throughout the day.

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 two chemical structures: methamphetamine at the top and cocaine at the bottom, each associated with its respective text description.

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

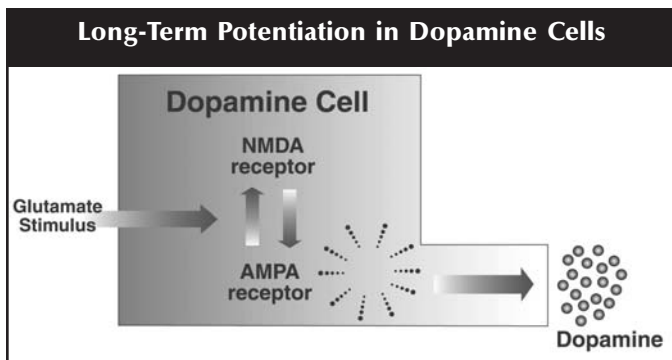
that methamphetamine abusers have more trouble than cocaine abusers at tasks requiring attention and the ability to organize information.”

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Altered Cellular Activity May Be First Step in Progression to Cocaine Addiction

By Patrick Zickler, NIDA NOTES Staff Writer

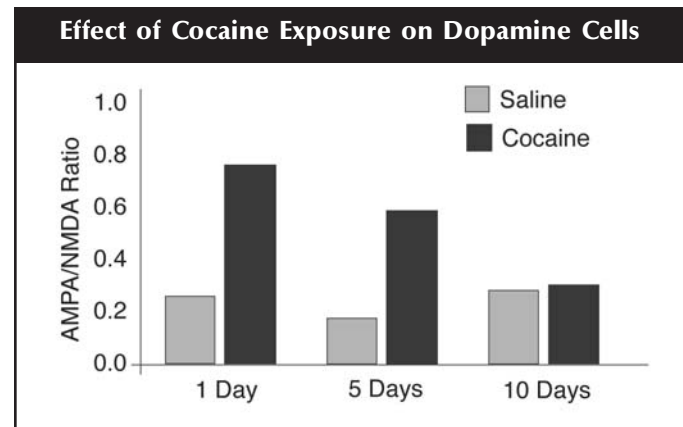


When the brain chemical glutamate reaches dopamine cells in the ventral tegmental area, it activates specific sites called NMDA receptors and AMPA receptors. Electrical current generated by the AMPA receptors triggers the release of dopamine, a chemical associated with the pleasurable effects of addictive 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 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

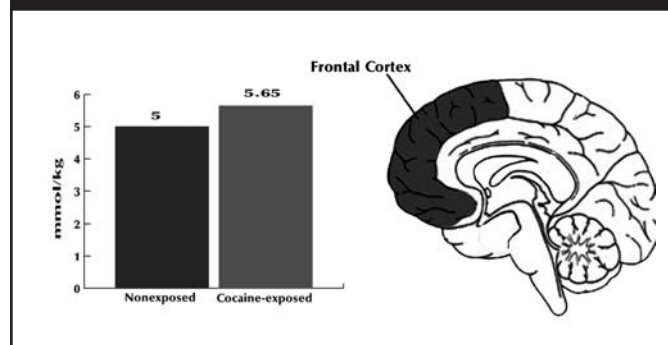
Exposure to cocaine before birth may affect the way a child's brain functions many years later, according to a recent NIDA-funded study. The brain-imaging study found a chemical abnormality in the brains of 8-year-old children that may reflect alterations in metabolic processes that enable brain cells 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 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

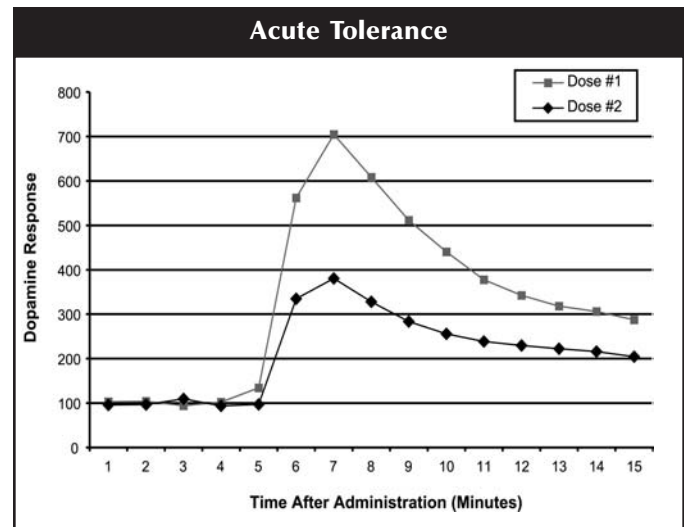
A major goal of drug abuse research is to determine how voluntary drug use turns into compulsive drug use and addiction. A recent NIDA-supported study sheds light on drug-induced brain changes that may play an important role in this process. The study, conducted in rhesus monkeys, found that even a single 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

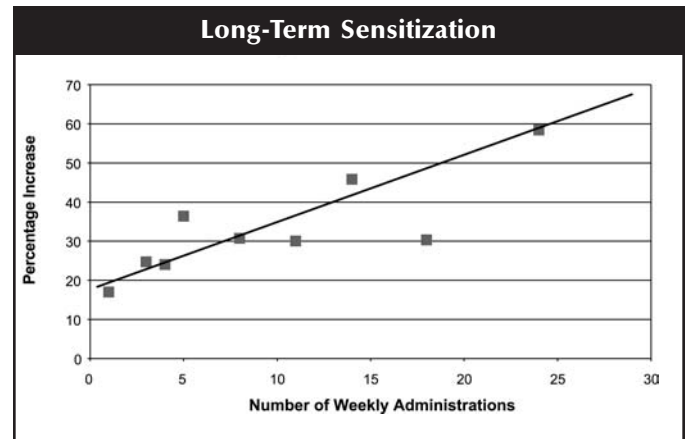
dopamine returned to pre-cocaine levels, the researchers allowed the monkeys to administer the second dose of the drug. The dopamine level did not rise as much following the second dose. This phenomenon, where exposure to a drug makes the brain less responsive to a subsequent exposure shortly thereafter, 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.



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.

“Our knowledge of exactly how people become addicted to drugs is in its early stages,” Dr. Acri says. “Now, we are 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.

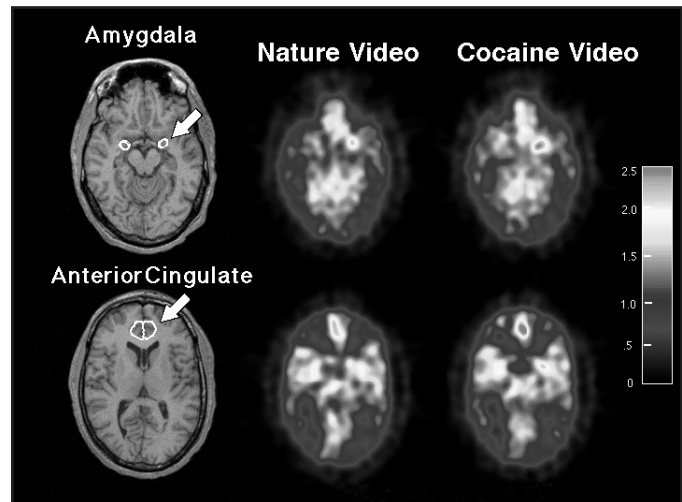
Cocaine Cues Activate Sites in Limbic Region

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.

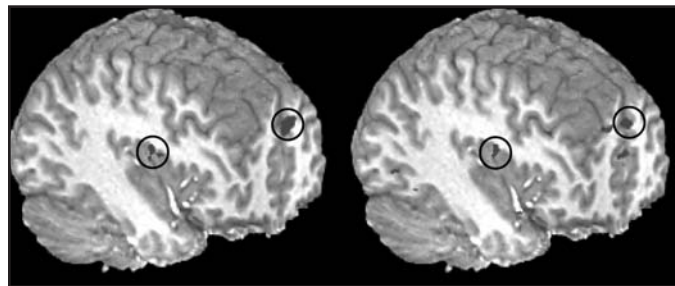
Cues for Cocaine and Sex Act On Same Sites

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.

“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.”

“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 relatively weak activation in response to the sex film suggests



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.

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.

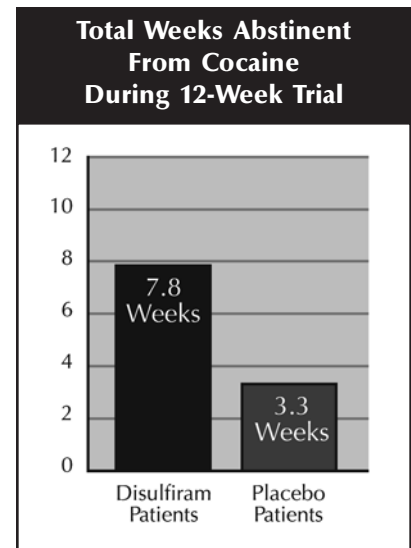
Disulfiram and Cocaine, Alcohol, and Heroin Addiction

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.

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- β -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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Large Study Expands Probe of Disulfiram's Effects on Cocaine Use

Dr. Richard Schottenfeld of Yale University School of Medicine in New Haven, Connecticut, has begun enrolling patients in a clinical trial that is large enough to establish more definitively than previous studies whether disulfiram reduces cocaine abuse in opiate-addicted patients being treated with buprenorphine. About 180 patients are expected to participate in the trial.

"We want to get more people abstinent from cocaine and see them stay that way while they are on the medication," Dr. Schottenfeld says. "We're also doing some genetic subtyping to see if we can get more data on whether disulfiram reduces cocaine use by blocking the enzyme called dopamine- β -hydroxylase (DBH) that metabolizes dopamine," he says. "If disulfiram is working this way, it should work best in the people who already have low

DBH activity because of their genetic makeup. If such a gene-medication interaction occurs, it will give us important information about who is going to respond better to the medication or even what the proper dose should be."

Getting this additional genetic information won't prove that disulfiram is working to reduce cocaine use through DBH, Dr. Schottenfeld emphasizes. "It will help us to better understand the mechanism through which this medication works," he says. "While disulfiram is great in a lot of ways, it affects many systems and we may run into unwanted side effects with it. So, if we find more evidence that it works through this DBH mechanism, maybe ultimately we can find a medication to target that mechanism more directly." **NN**

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.

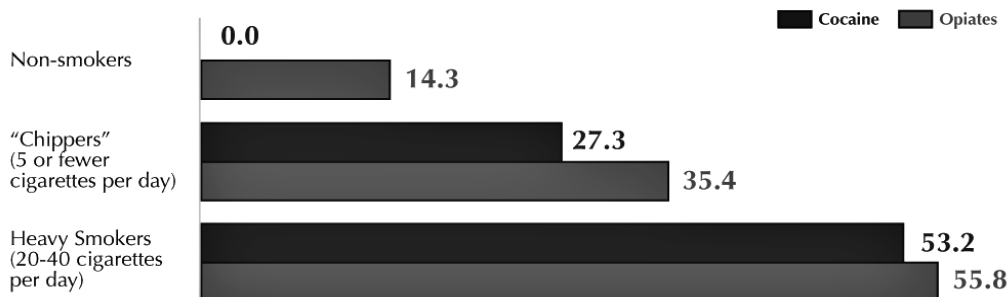
In the second part of the study, 24 participants heard scripts with only pleasant content (enjoying the beach, talking on the phone with an old acquaintance, or visiting friends). These scripts also contained descriptions of tobacco craving that increased in intensity from no mention of smoking to asking 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 non-smokers 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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Cocaine, Marijuana, and Heroin Abuse Up, Methamphetamine Abuse Down

By Robert Mathias, NIDA NOTES Staff Writer

Cocaine abuse indicators increased in many U.S. metropolitan areas during 1998 and the first half of 1999, according to a NIDA-supported network of drug abuse researchers who regularly report data on drug abuse in the United States. The rise follows several years of stable or declining use, the researchers reported at the December 1999 meeting of the Community Epidemiology Work Group (CEWG).

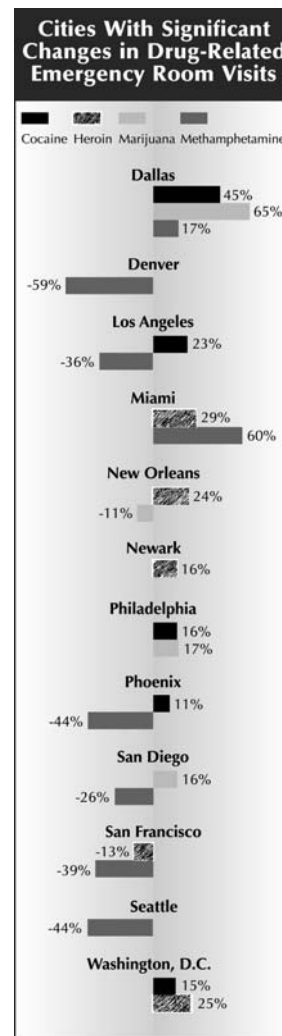
CEWG researchers meet twice a year to report on such drug abuse indicators as drug-related deaths, hospital emergency department (ED) visits, and treatment admissions. Data from 20 cities presented at the December meeting indicate that marijuana and heroin abuse also continued to increase in most areas of the country. However, methamphetamine abuse declined in most cities, including some areas that have been hardest hit by the problem. Highlights from the meeting's advance report are:

Cocaine. Indicators of cocaine abuse increased in half of the 20 CEWG cities, remained stable or mixed in 8, and decreased in 2. Five cities reported significant increases in cocaine-related ED incidents and 9 cities reported large increases in the number of cocaine-related deaths.

Heroin. Heroin abuse indicators increased in 10 CEWG cities, were stable or mixed in 9, and decreased in 1. Heroin abuse and snorting of the drug continued to increase among younger populations, such as college students. These trends were particularly apparent in East Coast cities where pure forms of white powder heroin, which can be snorted, are most available. Heroin-related deaths also increased in many areas of the country.

Marijuana. Seventeen CEWG cities reported increases in problems associated with marijuana abuse. The percentage of drug abusers whose primary drug of abuse was marijuana continued to increase in many cities. Rates of marijuana-related ED visits also continued the consistent, often dramatic, increases shown over the last 6 years. Increases in marijuana-related problems may be tied to increased availability, higher potency, and lower prices for the drug along with perceptions that marijuana abuse is less risky than abuse of other drugs, the report indicates.

Methamphetamine. Indicators of methamphetamine abuse decreased in West Coast and Southwest areas where abuse of the drug has been a major problem for years.



Many CEWG cities reported statistically significant increases from 1997 to 1998 in hospital emergency department (ED) visits due to cocaine, heroin, and marijuana use. However, methamphetamine-related ED visits declined sharply in most cities where rates had previously been highest. Source: Substance Abuse and Mental Health Services Administration, Drug Abuse Warning Network, 1998 (July 1999 Update).

Sharp declines in methamphetamine-related ED visits were reported in 1998 in six CEWG areas. Several areas also reported that methamphetamine treatment admissions, hospital mentions, and deaths continued to decline in the first half of 1999. Researchers cited several possible reasons for these decreases, including initiation of national and community methamphetamine abuse prevention programs and enactment of laws that make it more difficult to obtain the chemicals needed to produce the drug.

Club Drugs. Thirteen cities reported problems with MDMA (ecstasy) abuse. The drug is available at raves and nightclubs in most areas. Ecstasy abuse also is increasing in other settings, such as college campuses. Nine areas reported GHB (gamma-hydroxybutyrate) abuse at raves and clubs. Numerous medical emergencies and several deaths were associated with GHB abuse.

For More Information

The CEWG "Advance Report, *Epidemiologic Trends in Drug Abuse*, December 1999," is available from NIDA's Web site, www.drugabuse.gov. **NN**

Some Cocaine Abusers Fare Better With Cognitive-Behavioral Therapy, Others With 12-Step Programs

By Barbara Shine, NIDA NOTES Contributing Writer

New evidence has been found in support of the hypothesis that a cocaine abuser's personal characteristics affect what kind of treatment will work best to reduce his or her drug use. The evidence surfaced in a recent study in a clinic at the San Francisco Veterans Affairs Medical Center (VAMC), in which Dr. Sharon Hall and her coinvestigators at the University of California, San Francisco (UCSF), compared the efficacy of cognitive-behavioral therapy (CBT) with 12-step facilitation (12SF). The study was supported by NIDA and the U.S. Department of Veterans Affairs.

CBT theory holds that our surroundings strongly influence our thinking and behavior, so CB therapists teach their patients new ways of acting and thinking in response to their environment. In the case of CBT for addiction, patients are urged to avoid situations that lead to drug use and to practice drug refusal skills.

The 12-step recovery method—used in Alcoholics Anonymous and Cocaine Anonymous, for example— involves fellowship and mutual support through regular group meetings as a path toward recovery from addiction. While 12-step programs are not affiliated with any religious group, there is a spiritual component—belief in a “higher power” of some kind—that helps members achieve and maintain abstinence.

Dr. Hall and her team recruited 128 crack cocaine smokers from inpatient and outpatient programs at the VAMC.

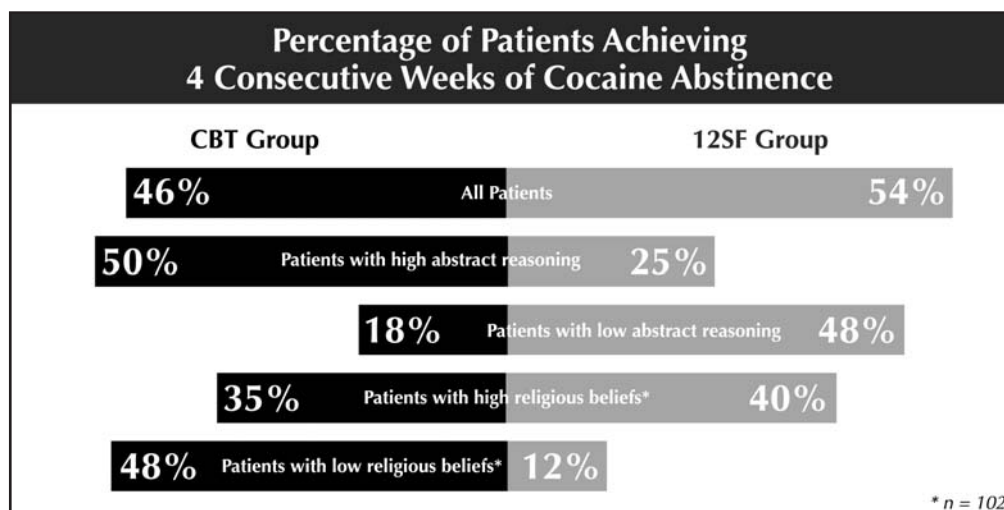
Patients were assigned to either CBT or 12SF. Both groups were expected to attend three group therapy sessions and one individual counseling session each week for 12 weeks.

The CBT approach aimed at helping patients strengthen their commitment to abstinence, deal effectively with urges and risky situations, recognize and change irrational thoughts, manage negative moods, and increase positive moods and social support. Therapists also encouraged participants to attend Rational Recovery, a cognition-based self-help group.

Participants in the 12SF group were introduced to the 12 steps of Cocaine Anonymous and encouraged to work on the first steps of the program. They were urged to attend 12-step meetings in the community in addition to their clinic-based group and individual sessions.

Group therapy was the primary intervention, but individual sessions allowed the therapists to conduct psychosocial histories and develop clinic-mandated treatment plans. In addition, the individual sessions gave participants an opportunity to discuss matters that were not covered adequately in group time.

Content for both CBT and 12SF was organized into manuals. *The Recovery Group Treatment Manual* was based on the work of cognitive theorists A. T. Beck, F. D. Wright, C. F. Newman, and B. S. Liese (*Cognitive Therapy*



Patients who were abstinent in the cognitive-behavioral treatment (CBT) tended to have high abstract reasoning scores and low religious motivation scores, while patients who were abstinent in the 12-step facilitation (12SF) program tended to have low abstract reasoning scores and high religious motivation scores.

of *Substance Abuse*, New York: Guilford Press, 1993). *The Self-Management Group Treatment Manual* was drawn from J. Nowinski and S. Baker's *Twelve-Step Facilitation Handbook: A Systematic Approach to Early Recovery From Alcoholism and Addiction* (New York: Lexington Books, 1992).

Although participants attended, on average, fewer than half the planned group and individual therapy sessions, the great majority completed their followup assessments, in which urine samples were tested to confirm abstinence from cocaine. Eighty-nine percent of all participants were tested at the final, 26-week followup.

Overall, the CBT patients were more likely than 12SF patients to remain abstinent for 4 consecutive weeks. However, when the researchers added the patients' abstract reasoning skills into the analysis, another pattern emerged.

In the CBT group, patients who scored high on a test of abstract reasoning were more likely to achieve a 4-week abstinence than those with low scores. In the 12SF group, the opposite was found: those who scored low on the abstract reasoning test were more likely to achieve sustained abstinence. In addition, in the 12SF group, but not the CBT group, patients with high scores on a scale measuring religious motivation were significantly more likely than their peers with low scores to achieve 4 weeks of continuous abstinence.

The researchers caution that this study population was not typical of cocaine abusers nationwide: all were veterans, all were homeless or marginally housed, and men were over-represented. Nevertheless, "These findings show that treatment for cocaine abuse can work and that effective treatment can be provided in a typical clinic setting," says Dr. Hall. "Our study reinforces the importance of getting patients into treatment that corresponds to their personal characteristics."

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For More Information

Copies of the CBT and 12SF therapy manuals in manuscript form are available from Dr. Hall at UCSF. Send e-mail requests to smh@itsa.ucsf.edu. 

Nicotine Medication Also Reduces Craving in Cocaine Addicts

By Patrick Zickler, NIDA NOTES Staff Writer

Craving, the almost irresistible urge to use drugs, is one of the most vexing problems associated with drug addiction. Craving is the result of changes that drugs cause in the brain and may be triggered by physical discomfort associated with abstinence from the drug. Craving also may be triggered by external, environmental factors, such as the sights, sounds, and social situations associated with drug use. In this “cue-induced” craving, the urge to use drugs often is powerful enough to cause a relapse to drug abuse months or even years after a person has stopped using drugs.

Dr. Malcolm Reid, a NIDA-supported researcher at the New York University School of Medicine and the New York Veterans Affairs Medical Center in New York City, has found that mecamylamine—a medication that blocks the rewarding effects of nicotine—can reduce cue-induced craving in patients addicted to cocaine and may help these patients avoid relapse.

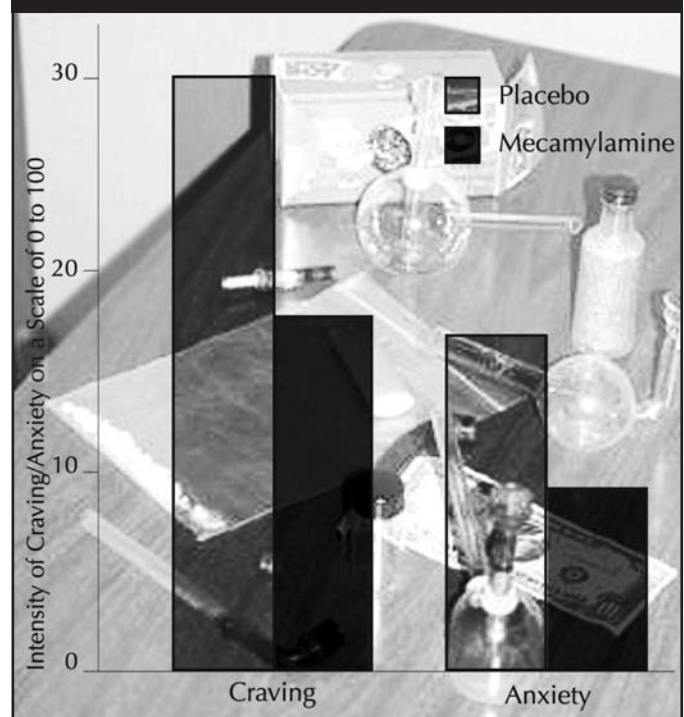
In earlier research, Dr. Reid found that nicotine significantly increased cue-induced craving for cocaine in addicted patients who also smoked tobacco. “This finding suggested that a medication like mecamylamine, which blocks some of nicotine’s effects in the brain, might also reduce the cue-induced craving that nicotine causes,” Dr. Reid says.

Dr. Reid recruited 23 cocaine-addicted patients, 20 men and 3 women with an average age of 40, from outpatient drug addiction treatment programs. All patients were regular cigarette smokers and had used crack cocaine within the last 3 months. Patients were instructed to abstain from tobacco for at least 1 day and from cocaine for 2 days before participating in the craving test sessions. Abstinence was verified by laboratory tests.

The participants were shown a series of neutral cues as well as cocaine-related cues. During each test session, participants first viewed the neutral cues, including videotaped images of pine cones and seashells, and then handled rocks, pine cones, and seashells and smelled a fragrant spice. Participants then completed a survey that asked them to describe their mood—for example, “anxious,” “nervous,” or “irritated”—and rate the intensity of their desire to use cocaine and the likelihood that they would use cocaine if it were available. Following exposure to neutral cues, participants were randomly given either

mecamylamine or placebo. Two hours later they were exposed to a series of cocaine-related cues, which included videotaped scenes in which actors simulated purchasing and smoking crack cocaine and scenes of actual crack smoking. The participants then handled drug paraphernalia and a substance that looked like crack cocaine, and smelled a crack pipe that had been treated with an artificial residue with the same aroma as crack cocaine. As before, they rated their mood and desire to use cocaine. The procedure was repeated 2 to 3 days later, with patients who had received mecamylamine during the first session receiving placebo during the second session, and vice versa.

Cue-induced Craving for Cocaine Is Reduced in Mecamylamine Recipients



Twenty-three patients were asked to rate the intensity (on a scale ranging from 0 to 100) of their craving for cocaine and their feeling of anxiety after viewing and handling cocaine-related objects like those shown in the background of the graph. Patients who received mecamylamine before exposure to the objects reported significantly less anxiety and craving for the drug.

“Those who received mecamlamine reported significantly less intense cocaine craving—only half as strong on average.”

“All the patients reported that they felt an increased craving for cocaine after the cocaine-related cue sessions, but those who received mecamlamine reported less anxiety and significantly less intense cocaine craving—only half as strong on average—than did the patients who received placebo,” Dr. Reid says. “In addition, the patients who received the medication reported less intense symptoms of tobacco withdrawal prior to being exposed to cocaine-related cues.”

The success of mecamlamine in reducing both cue-induced craving for cocaine and the rewarding effects of nicotine has important implications in treatment. Epidemiologic studies show that smoking is more prevalent among cocaine-addicted persons than in the general population and that cocaine-addicted smokers begin using cocaine at an earlier age and use it more frequently than cocaine-addicted nonsmokers. “In earlier studies we found that nicotine may intensify cue-induced craving for

cocaine, which can make it difficult for cocaine addicts to stop using the drug. We now know that mecamlamine may reduce cue-induced cocaine craving and it does so even when subjects do not have nicotine in their system,” Dr. Reid says.

“Previous clinical and preclinical studies have suggested that mecamlamine has therapeutic potential in the treatment of smoking cessation and alcoholism,” Dr. Reid notes. “Our current findings indicate it could also play an important role in reducing the risk of relapse for patients in treatment for cocaine addiction.” To further investigate this possibility, Dr. Reid is now conducting a clinical trial of mecamlamine treatment of cocaine addiction at the New York Veterans Affairs Medical Center.

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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 D₃ receptor agonists, or D₃ agonists for short.

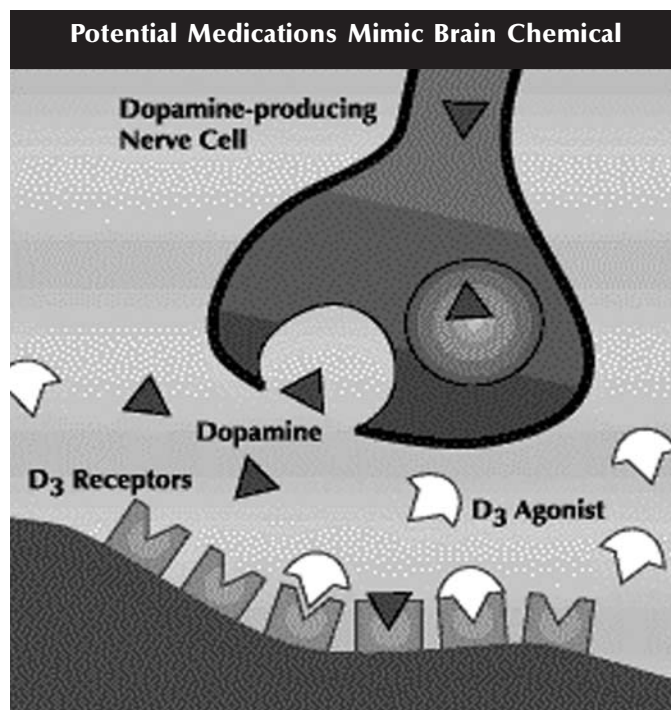
Dopamine is one of several chemicals called neurotransmitters that carry messages between the brain's nerve cells, or neurons. After being released by a transmitting neuron, neurotransmitters interact with molecules called receptors on the surface of a receiving neuron, affecting the neuron's activity. 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 D₁ through D₅, have been identified.

Agonists are compounds not normally found in the body that stimulate receptors in the same way that neurotransmitters do. Consequently, D₃ agonists are compounds that stimulate D₃ receptors.

The PCP-Schizophrenia Connection

Dr. Jeffrey Witkin, Dr. Maciej Gasior, 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 D₃ 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 D₃ agonists—stimulate molecules on nerve cells that receive dopamine messages—called dopamine D₃ receptors. Scientists have yet to learn how this action reduces psychotic symptoms and seizures.

The Witkin group's discovery of the potential of D₃ agonists for treating PCP psychosis and schizophrenia sprang from their exploration into another property of D₃ 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 are sedate. Also, their movements are normal. In contrast, other sedative-like compounds tend to make animals uncoordinated.”

Because the D₃ 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 D₃ 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 D₃ receptors might be involved in seizures and deaths among cocaine abusers.

Again, (+)-PD 128,907 proved effective, and so did the other D₃ 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 D₃ 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 D₃ 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.

Patients who received combined individual and group drug counseling used less cocaine than did patients who received other forms of treatment.

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 manuals, 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, behavioral

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

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**

Even though our worst fears about prenatal cocaine exposure have not been realized, we should not be complacent.

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,



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.

which has important implications for learning and memory. 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 prena-

tal 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



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.

children in the course of normal clinical practice, Dr. Arendt notes. “These kids can be helped with physical 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

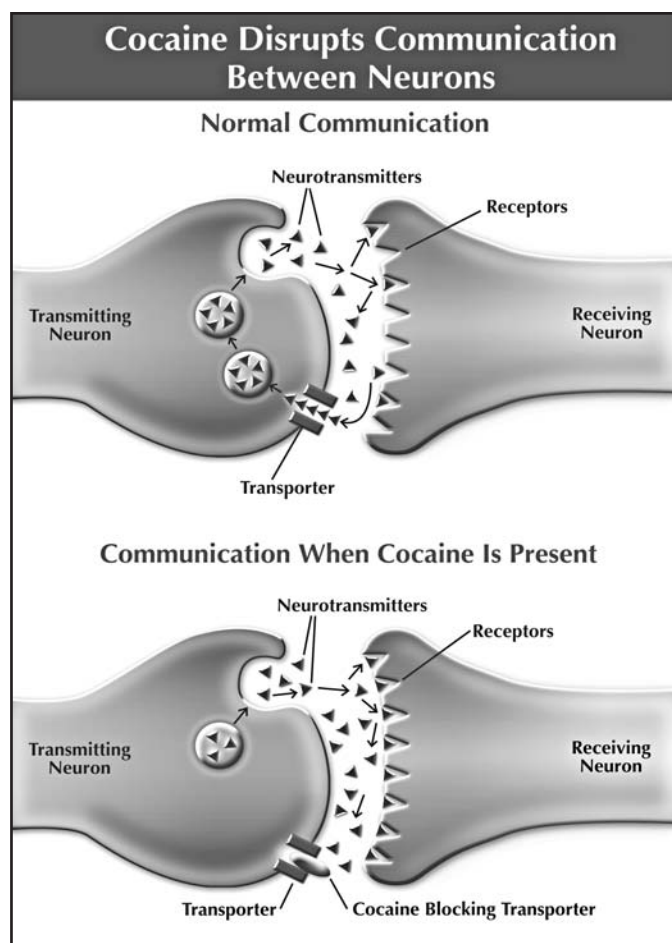
Recent studies with genetically altered mice have suggested that cocaine's euphoric effects may involve not just one, but several, chemical sites in the brain. These studies indicate that medications for treating cocaine addiction may need to target these multiple sites just as cocaine does.

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 compartment 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.

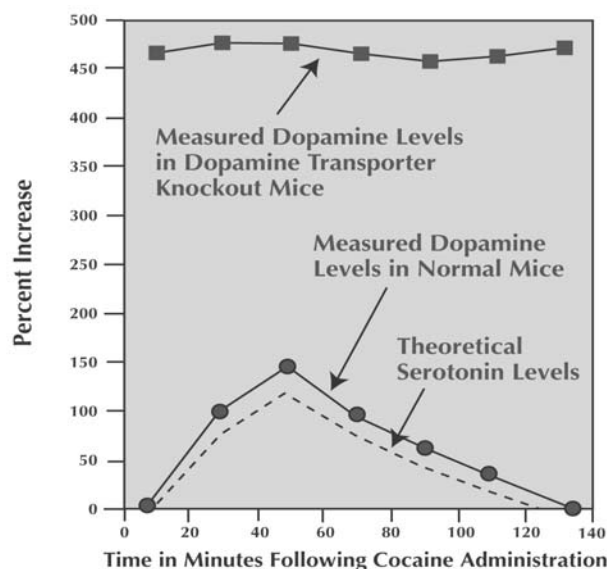
If the dopamine transporter is not the crucial site for producing cocaine reward, then what is? Apparently not the serotonin transporter, because Dr. Uhl’s group also studied serotonin transporter knockout mice and found that these mice also found cocaine rewarding.

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.

The explanation for cocaine’s powerful attraction may be that it affects several neurotransmitters, all of which are involved in mediating pleasure.

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

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.

decreased as other studies have shown they do in normal mice because knocking out the dopamine 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 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 transporters 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.

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.

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 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.

Coping skills training can help patients identify situations that trigger their urges to use cocaine and modify their behavior to avoid drug use.

The patients were evaluated at 1 and 3 months following 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.

Source

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Compounds May Treat Cocaine-induced Heart Disease

Cocaine abuse has been associated with a variety of cardiovascular diseases—including cardiac arrhythmia, in which the normal rhythm of the heart beat is disrupted. In severe cases of cardiac arrhythmia, death can occur, even in young people with no history of heart disease.

Dr. Donald Ohuoha, formerly with NIDA's Intramural Research Program (IRP) in Baltimore and now at St. Elizabeths Hospital in Washington, D.C., and Dr. Charles Schindler and Dr. Richard Rothman at IRP, have discovered that certain compounds may be useful for treating cocaine-induced cardiac arrhythmia. The compounds block some of the actions of the chemical messenger serotonin in the heart.

Other researchers have shown that serotonin can elicit arrhythmia in human hearts. Because cocaine raises sero-



Dr. Donald Ohuoha (center), formerly with NIDA's IRP, draws a compound for preventing cocaine's damaging effects on the heart into a hypodermic needle. He is watched by Dr. Richard Rothman (left) and Dr. Charles Schindler, both with IRP.

tonin levels, among other actions, the IRP investigators reasoned that the serotonin-blocking compounds might be useful treatments for cardiac arrhythmia caused by cocaine abuse.

The IRP researchers found that when the compounds were given to rats before the rats were given cocaine, the compounds could prevent cocaine's effects on the cardiovascular system, including changes in blood pressure and heart rate, as well as arrhythmia. When the rats were given the compound after they were given cocaine, the compounds reversed the drug-induced arrhythmia. If these

findings are confirmed in other animals and in humans, the compounds eventually might be used for treating cocaine-induced cardiac arrhythmia in humans. These results were reported in the October 2, 1998, issue of *Life Science*. **NN**

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."

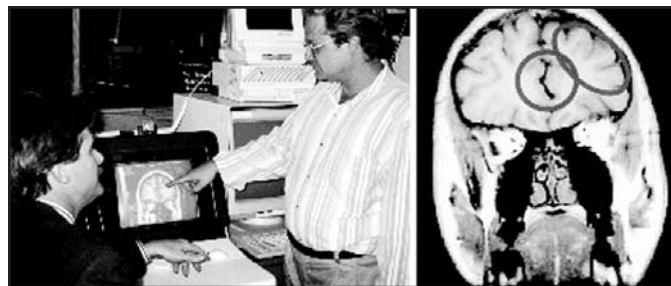
These results bear out similar findings in animals. Some of the regions of activity that were associated with rush or craving have been implicated in animal studies as being important in producing the pleasurable feelings associated with cocaine use. The regions include the ventral tegmentum, nucleus 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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Prenatal Cocaine Exposure Costs at Least \$352 Million Per Year

Prevention of cocaine or crack use during pregnancy could save \$352 million per year, according to a study by researchers at Brown University in Providence, Rhode Island. The research, which analyzed data from eight longitudinal studies of school-age children prenatally exposed to cocaine, was reported in the October 23 issue of *Science*.

The study, funded by the Robert Wood Johnson Foundation, found that up to 80,550 children will have subtle deficits in IQ and language development as a result of prenatal exposure to cocaine. Special education to keep them from failing in school will cost at least \$352 million per year nationwide, researchers estimate.

“These figures are underestimates,” notes Dr. Barry Lester, NIDA grantee and lead member of the research team.

“These are costs attributable only to new cases each year, and do not include the accumulating costs and burdens associated with annual additions.”

“Every dollar of prevention saves five times that amount in treatment and other costs to society,” says NIDA Director Dr. Alan I. Leshner. “This study emphasizes the need for more drug abuse prevention efforts, particularly those directed at women of child-bearing age. The findings also argue for early identification and intervention for children most at risk for developing these problems.” **NN**

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



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.

colleagues at McLean Hospital in Belmont, Massachusetts, 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.

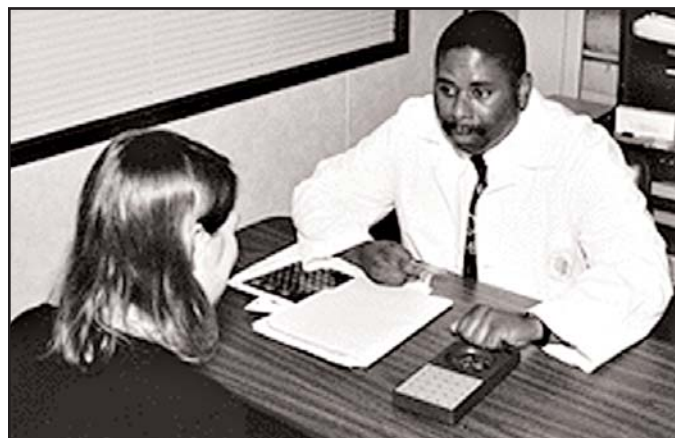
The more often the men had used cocaine in the past, the more likely the drug was to narrow blood vessels, which suggests that cocaine has a cumulative effect on brain arteries. "This cumulative effect may start with as few as 5 to 10 exposures to cocaine," says Dr. Kaufman. "As a result, people who 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



Dr. Tony Strickland of Charles R. Drew University of Medicine and Science tests a volunteer for cocaine-related mental deficits.

showed that the abusers still had blood flow deficits compared to control subjects, suggesting that the 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 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 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.

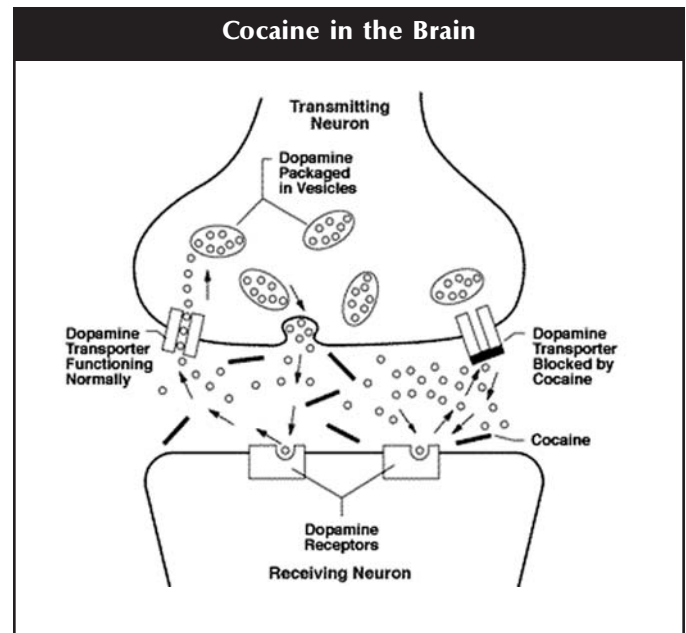
Dopamine flows from neurons into the synapses, or spaces between neurons, to form a temporary link that serves to transmit signals between neurons. Then, normally, after it has transmitted its signal to the neighboring neuron, it vacates these spaces, returning to the same neuron that released it in 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.

“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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MERIT Awardee Examines Long-Term Effects of Prenatal Cocaine Exposure in Rats

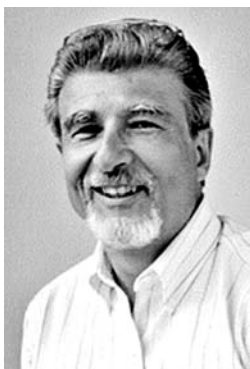
By Steven Stocker, *NIDA NOTES* Contributing Writer

NIDA MERIT (Method to Extend Research In Time) Award winner Dr. Sheldon Sparber, at the University of Minnesota Medical School in Minneapolis, studies the effects of prenatal drug exposure on the fetus and newborn and the effects that may continue into adulthood. His animal studies on opiates and opiate withdrawal have greatly influenced the treatment of opiate-addicted pregnant women in methadone maintenance programs and their newborns, and his current research on cocaine could prove to be just as important.

In the 1980s, Dr. Sparber's animal studies provided a new perspective on whether opiate-addicted women should be treated with methadone. Earlier research findings had suggested that methadone is dangerous to the fetus and probably should not be given to pregnant heroin addicts. However, Dr. Sparber's group showed that the toxic effects on the offspring demonstrated in the earlier studies were due to excessively high doses of methadone and the stress of sudden withdrawal from methadone. "Unlike with adults, severe sudden withdrawal can be deadly for fetuses and infants," explains Dr. Sparber. "This is true for both animals and humans. But if you maintain human pregnant mothers on low but adequate doses of methadone and provide the newborns with medications, if necessary, to allow them to go through slow, mild withdrawal, their prognosis can be quite good."

In his current research, Dr. Sparber is investigating the effects of prenatal cocaine exposure in chickens and rats. He has found that cocaine injected into chicken eggs interferes with the hatching of the chicks, probably by restricting blood flow to the embryos. He also has discovered that this effect could be blocked with a medication called ritanserin, which, according to Dr. Sparber, opens up the possibility of a treatment to prevent the adverse effects of prenatal cocaine exposure.

In his studies with rats, Dr. Sparber is finding that prenatal cocaine exposure causes only minimal effects on brain chemistry and behavior—until the rats reach middle age. When tested at age 10 months to a year, rats that were exposed to cocaine during the last trimester of pregnancy start to show serious learning and memory deficits. "If the data from our animal studies are real and can be generalized



Dr. Sheldon Sparber

to humans exposed to cocaine in utero, it would mean that those people might start showing learning and memory deficits at about age 30 to 40 or perhaps later," says Dr. Sparber.

As part of the research funded by the MERIT Award, Dr. Sparber will be investigating whether cocaine's long-term effects can be prevented by altering the rearing environment of the infant rats or by treating the pregnant mothers with medications such as ritanserin.

According to Dr. Sparber, the MERIT Award with its longer period of funding will allow him to take risks in his research that he might not be willing to take with a conventional grant. "The MERIT Award gives you the opportunity to do innovative work that you wouldn't normally do if you had a 3-year grant," says Dr. Sparber. He adds that many important discoveries in biomedicine are made through serendipity. "If you have your eyes open and don't have any preconceived notions about what you're going to see, you might come up with some very exciting observations."

Dr. Sparber has been funded continuously by NIDA since 1972. Dr. Jerry Frankenheim of NIDA's Division of Basic Research describes Dr. Sparber as being "at the cutting edge of his field." He salutes Dr. Sparber's "willingness to tackle the truly relevant questions in psychopharmacology, no matter how tough."

Dr. Sparber is a professor of pharmacology, psychiatry, and psychology at the university. He has published more than 150 scientific papers and has edited two books.

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Compounds Show Strong Promise for Treating Cocaine Addiction

By Steven Stocker, *NIDA NOTES* Contributing Writer

NIDA-supported animal research is finding a number of compounds that show particular promise as treatment medications for cocaine addiction. The compounds significantly reduce the amount of cocaine animals will give themselves, sometimes for long periods of time. The research is furthering the Institute's wide-ranging quest for a viable cocaine treatment medication.

One of the most promising of these compounds is GBR 12909. Synthesized in the late 1970s, GBR 12909 was tested initially in Europe as a potential antidepressant. In 1989, Dr. Richard Rothman, then at the National Institute of Mental Health, and colleagues proposed that GBR 12909 and related compounds might be useful medications for treating cocaine addiction.

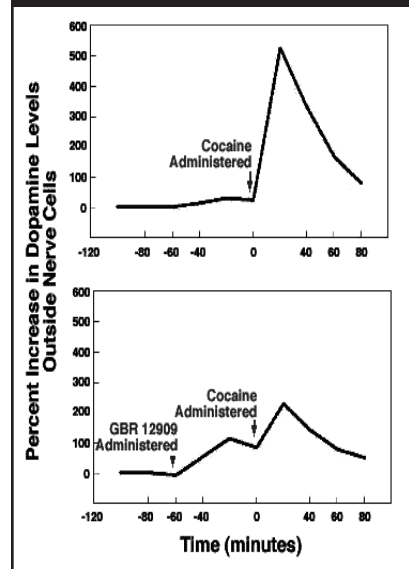
In 1995, Dr. John Glowa, then at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), studied the effects of GBR 12909 on cocaine self-administration by rhesus monkeys. In these NIDA-funded studies, Dr. Glowa found that an injection of GBR 12909 could substantially decrease cocaine self-administration by the monkeys.

"Under the right conditions, we completely eliminated cocaine-seeking behavior for about 2 hours without affecting food-seeking behavior," says Dr. Glowa. This suggests that GBR 12909 reduces cocaine craving while not suppressing normal desires such as hunger. This selectivity is desirable for potential treatment medications.

More recently, Dr. Rothman proposed a long-acting derivative of GBR 12909. The derivative, called compound 5, subsequently was developed by Dr. Kenner Rice and colleagues at NIDDK and then tested by Dr. Glowa, now at the Louisiana State University Medical Center in Shreveport. The derivative is formulated to be released slowly into the blood over several weeks. In a NIDA-funded study, Dr. Glowa determined that compound 5 could substantially reduce cocaine self-administration by monkeys for nearly a month with only one injection. At the highest dose tested, a single injection reduced cocaine self-administration by nearly 75 percent for 24 days without affecting food-seeking behavior.

Studies have shown that both GBR 12909 and cocaine inhibit the action of a protein called the dopamine transporter. By inhibiting the transporter, both GBR 12909 and cocaine elevate the levels of the pleasure-inducing

Promising Cocaine Treatment Compound Blocks Cocaine's Action



Cocaine causes a large spike in the levels of the chemical messenger dopamine outside the nerve cells in the brain, which cocaine users experience as euphoria. The graph at the top shows this dopamine increase in rats when they are administered cocaine. The graph at the bottom shows that treatment with the compound GBR 12909 reduces this dopamine increase caused by subsequent cocaine use and thus dampens cocaine's euphoric effects.

chemical messenger dopamine outside the nerve cells, a process that increases and prolongs dopamine's pleasurable effects. However, according to Dr. Rothman, who is now in NIDA's Division of Intramural Research, GBR 12909 acts more slowly and elevates dopamine levels less than does cocaine.

"Cocaine causes a huge spike of dopamine that goes up to a very high level, which you can think of as a burst of pleasure," explains Dr. Rothman. "GBR 12909, on the other hand, produces a relatively modest and long-lasting increase in dopamine, which may not cause the same degree of euphoria but might be good for treating cocaine craving." By attaching to the dopamine transporter, GBR 12909 also blocks cocaine from binding there, he adds. "GBR 12909's affinity [chemical attractiveness] for the transporter is 500 times that of cocaine, so it binds to the transporter and stays there for a long time. While it's sitting on the transporter, cocaine has no access to the transporter, so the cocaine can no longer act to induce euphoria," says Dr. Rothman.

Dr. Srihari Tella, a NIDA grantee at Georgetown University in Washington, D.C., has discovered that prolonged treat-

ment with GBR 12909 might actually reverse the addiction process. In Dr. Tella's study, rats that were allowed to self-administer cocaine for about 3 weeks had significantly increased dopamine transporter levels in several areas of the brain. According to Dr. Tella, the brain increases dopamine transporter levels to compensate for cocaine inhibiting the activity of the existing transporters. Because of the increased transporter levels, dopamine levels outside nerve cells were reduced, creating a dopamine "deficit." This deficit might be responsible for the feelings of depression and craving that cocaine abusers often describe. When the animals were switched from cocaine to water, the dopamine transporter levels stayed elevated, but if they were switched instead to GBR 12909, their transporter levels returned to normal.

"This benefit for patients may come only with prolonged treatment with GBR 12909. Prolonged treatment would be necessary to give the medication time to bring the dopamine transporter levels back to where they were before the patient started taking cocaine," says Dr. Tella.

An injection of GBR 12909 can substantially decrease cocaine self-administration by monkeys.

Based on this and other research, Dr. Rothman concludes that GBR 12909 is the best candidate so far for treating cocaine addiction. "If you survey the animal literature, I don't think you'll come up with anything that looks as good as GBR 12909," says Dr. Rothman. "It just eliminates cocaine taking without any side effects."

Dr. Frank Vocci, acting director of NIDA's Medications Development Division, agrees that GBR 12909 is a promising compound. He also notes that in tests using nondrug-abusing human volunteers, doses of GBR 12909 in the range that might be given to cocaine-abusing patients did not cause behavioral symptoms such as those of cocaine, which suggests that GBR 12909 does not have the abuse potential that cocaine does. Dr. Vocci adds that NIDA will continue to support research on several other compounds that act on the dopamine transporter.

One of these is PTT, which is being studied by Dr. Michael Nader at Wake Forest University in Winston-Salem, North Carolina. Dr. Nader found that a single injection of PTT could significantly reduce cocaine self-administration by rhesus monkeys for more than 4 hours. PTT appears not to have abuse potential, as indicated by the fact that the monkeys will not self-administer it more than a few times. "When you give the animals almost unlimited access to PTT, they don't take very much of it," says Dr. Nader. He calls PTT "an excellent candidate" for treating cocaine dependence.

GBR 12909, compound 5, and PTT are currently undergoing toxicity testing to determine if they would be safe for humans. GBR 12909 was previously tested in humans in connection with its possible use as an antidepressant, but further safety testing is considered necessary. If no safety issues arise with these compounds, the next step will be to test them in clinical trials with cocaine abusers.

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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.



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.

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 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.

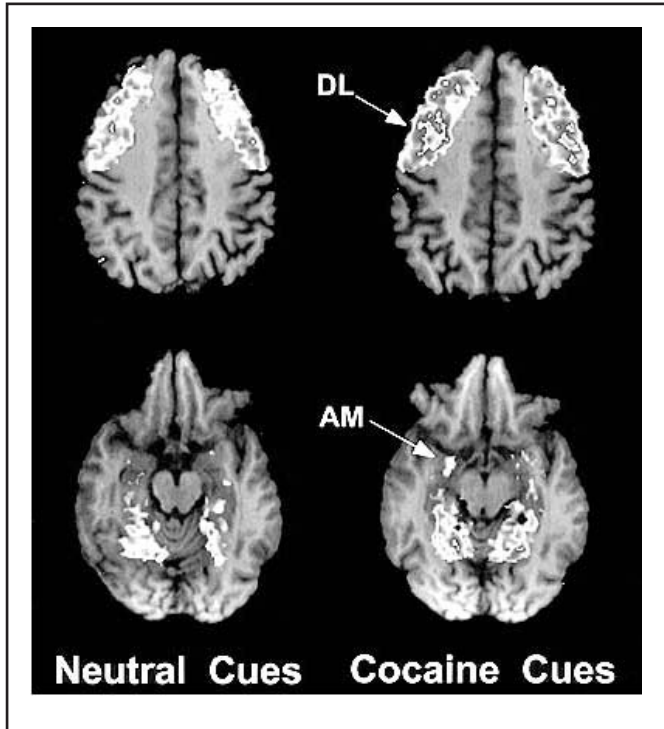
The cocaine-user group responded to the cocaine-related cues, but not to the neutral cues, with increased glucose metabolism, which was visible in the PET images and with their own reports that they were experiencing craving. The greater the reports of craving, the greater the metabolic activity in three 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



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).

system for testing potential interventions. This system overcomes the limitations of an addict's own subjective evaluations of craving sensations by using the PET scanner 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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Type A or B? Classification May Help in Treating Cocaine Abuse

By Neil Swan, NIDA NOTES Staff Writer

For a number of years, researchers have been testing the concept of classifying, or subtyping, alcoholics as Type A or Type B. Now they are finding the concept useful in studying cocaine abusers, too.

Subtyping is a system for classifying and studying individuals who share one or more common characteristics. Subtyping alcoholics provides a greater understanding of the complex interactions between genetic, personality, and environmental risk factors in the development of alcoholism, as well as resiliency against succumbing to these risk factors.

This typing process for alcoholics assesses multiple characteristics of each client, such as factors leading to abuse, severity of symptoms, and consequences of heavy drinking. By typing alcoholics as A or B using defining characteristics, researchers can better sort out the factors associated with their abuse problems and devise appropriate treatment strategies.

Alcohol abuse is more severe among Type B alcoholics than among those who are Type A. Type B alcoholism appears to be more related to hereditary factors than Type A and to be more likely to occur among men than women. Type Bs are more impulsive and tend to have a stronger family history of alcohol abuse; they have more childhood conduct problems and more severe alcohol dependence, polydrug abuse, and psychiatric disorders, especially antisocial personality.

Inspired by advances in subtyping alcoholics, Dr. Samuel A. Ball of Yale University School of Medicine and his colleagues conducted a NIDA-funded study examining whether subtyping is valid for cocaine abusers as well. They found strong evidence that it is.

“Our research may prove useful in explaining different causes of abuse in different types of cocaine abusers,” says Dr. Ball. “We found that certain vulnerability factors, such as family history, sensation-seeking behavior, and childhood conduct problems, seem to predispose cocaine users to a more virulent form of cocaine dependence—Type B,” he explains. “Other cocaine abusers who don’t have these characteristics [Type As] may develop their cocaine

Classifying Cocaine Abusers		
	TYPE A	TYPE B
Cause of Abuse Problem	More Environmental	More Genetic
Gender	Equal Male/Female	More Male
Personality	Low Impulsivity and Sensation Seeking, High Harm Avoidance	High Impulsivity, Sensation Seeking
Childhood Factors	Few Early Risk Factors	Conduct Disorder
Age of Onset	Later	Earlier
Substance Abuse Severity	Less Severe, More Episodic	More Chronic and Severe; Polydrug
Psychopathology	Lower Severity, More Affective	Higher Severity, More Antisocial

After years of studies, researchers are able to identify factors that classify alcoholics as Type A or Type B. Recent NIDA-funded studies show that, in general, the same multiple criteria are valid in classifying cocaine abusers. Results may prove useful in explaining different causes of abuse and in designing specific prevention and treatment interventions.

dependence more from social or environmental influences relative to inherited, temperamental, or psychiatric influences.”

The researchers studied abuse characteristics in 399 cocaine abusers, 69 percent of whom were male. Of these, 298 had sought treatment, 149 in an outpatient treatment program and another 149 in an inpatient, hospital-based program. The remaining 101 were cocaine abusers not in treatment. The study participants had a median age of 28 and were, generally, single, high school graduates, and had a low socioeconomic status. Fifty percent were white, 48 percent were African American, and 2 percent were Hispanic.

As part of a larger diagnostic study of cocaine abusers, for which Yale University’s Dr. Bruce J. Rounsaville was principal investigator, participants were given a battery of standard assessment tests that included the Sensation Seeking Scale, the Addiction Severity Index, the Schedule for Affective Disorders and Schizophrenia, and Family History Research Diagnostic Criteria tests. Subsequently, Dr. Ball and his colleagues sorted these measures into three variables, similar to the factors generally used to categorize alcoholics:

- predisease risk factors, such as family history of substance abuse, childhood conduct disorder and attention-deficit disorder, sensation-seeking traits, and age when drug abuse began;
- substance abuse variables, including frequency of cocaine use, years of heavy cocaine use, cocaine dependence symptoms, alcohol dependence symptoms, polydrug use, and medical and social consequences; and
- psychiatric problems, such as symptoms of depression and antisocial personality disorder, and the severity of these psychiatric problems.

Based on placement within the variables identified by the assessment tests, the researchers classified the cocaine-abusing study participants as either Type A or Type B and then examined differences in behavioral and other characteristics between the two groups.

Researchers found that cocaine abusers classified as Type B scored higher than Type As in assessments of sensation seeking, aggression, criminality, violence, and impairment of social adjustment. Type Bs also used greater amounts of cocaine more frequently and for longer durations than Type A cocaine abusers. Type Bs also suffered more adverse effects from their drug use, such as unconsciousness, chest pain, and violence, and they reported a greater degree of additional drug abuse to relieve withdrawal distress. Type B abusers became involved with cocaine at younger ages for: first use, first binge, first regular use, first daily use, and first symptoms of addiction.

No differences were found between the two subtypes in regard to the length of time between first use of cocaine and first symptoms of dependence; route of use, such as snorting, smoking, or injection; number of strategies used in attempting to control use; and previous periods of abstinence from illicit drugs or alcohol.

Overall, more than half of the participants were classified as Type As, but among those in inpatient treatment, there were nearly equal numbers of Type As and Bs. Among the outpatient and not-in-treatment participants, 75 percent were Type A. This suggests that studies assessing only cocaine abusers who are enrolled in inpatient treatment may not provide valid estimates of the relative proportion of Type A and B abusers who are in outpatient treatment or not in treatment, Dr. Ball warns.

With few exceptions, the classification model assessment results seemed consistent across gender and race. Although women and African Americans were Type As more often than men and whites were, a significant number of women and African Americans showed the kind of Type B abuse risk factors, severity, impairment, and antisocial

Percentages of Type A and Type B Cocaine Abusers		
	TYPE A	TYPE B
Males	61%	39%
Females	79%	21%
African American Males	68%	32%
African American Females	86%	14%
White Males	57%	43%
White Females	78%	22%

A classification of cocaine abusers by Dr. Samuel A. Ball shows results similar to those found in many studies of alcoholics. Although women and African Americans are more often Type As compared to men and whites, a significant number of women and African Americans nevertheless show the kind of Type B abuse risk factors, severity, impairment, and antisocial behavior thought by some earlier researchers to be related to alcoholism among men and among whites.

behavior that some researchers had previously thought were related to alcoholism among men and among whites.

“If Type A substance abuse is in fact more influenced by social relationships and environment, relative to genetic and personality factors, then we might speculate that women and African Americans might be more susceptible to developing alcohol or cocaine addictions for more socially, environmentally, or culturally determined reasons,” says Dr. Ball. But future research is needed on this topic to determine if this typology holds in other ethnic groups such as Latinos/Hispanics, Asians, and Native Americans, as well as in other cultures and countries, he adds.

Dr. Rounsaville, who coauthored the study, notes that while there has been some experimental work using typology-based treatment and prognostic findings, the practice of assessing and classifying substance abusers as Type A or B is not now widely practiced in drug abuse treatment programs. For one thing, classification procedures must be validated and made suitable for simple, routine use in treatment programs. But typology research continues with hope that advances can lead to new insights for evaluating causes of substance abuse and for preventing and treating it in the treatment program setting, he adds.

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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.

The stressed rats in the experiment learned to self-administer cocaine twice as fast as did animals that were not exposed to the stressor.

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.

Research also is important for understanding how external factors may make some individuals more vulnerable to cocaine abuse.

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.

“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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NIDA-Funded Studies Shed Light on Neurobiology of Drug Craving

By Michael D. Muller, NIDA NOTES Staff Writer

How do environmental cues trigger drug craving in a recovering drug abuser? Is it possible to block the effects of those cues? These are key questions faced by clinicians and researchers wrestling with the problem of relapse to drug use. The answers may lie within the extended amygdala, a neural circuit that connects several structures in the lower front of the brain.

“We’ve known for some time that elements of the environment become tied to drug use and prompt drug craving,” says Dr. Roger Brown of NIDA’s Division of Basic Research. “Now, NIDA-supported investigations of the extended amygdala are telling us how this happens. They’re a new and exciting approach to the issue of relapse, and this information may be important for treatment compliance.”



The work of Dr. Athina Markou and Dr. George Koob at Scripps Research Institute is helping to explain why drug abusers relapse and how to keep them from relapsing.

The extended amygdala is part of the limbic system—a seat of memories and emotions—and is connected to other brain systems as well. “We believe that it is in the extended amygdala that memories relating to drug abuse are transformed into craving to use a drug again,” says Dr. George Koob, director of the Division of Psycho-pharmacology in the Department of Neuropharmacology at the Scripps Research Institute in La Jolla, California.

How do memories give rise to craving? “Imagine a drug user who usually buys cocaine at a particular subway stop and typically experiences a drug effect shortly after the purchase,” says Dr. Koob. “Eventually, the subway stop—

normally a neutral part of the environment—becomes linked in the mind of the drug user to the positive rewarding effects of cocaine.” Later, even after successful treatment for drug abuse, the sight of the subway stop can bring on craving for cocaine. That is, the subway stop has become a conditioned stimulus that may trigger relapse.

“Basically, we are investigating the extended amygdala and adjoining structures to figure out why drug abusers relapse and how to keep them from relapsing,” says Dr. Koob. “These studies are giving rise to a better understanding of the neuro-circuitry of craving, which is getting us closer to our goal.” Chronic drug use and conditioning may bring about changes that can be detected by brain scans, and these changes might be reversible through medication, psychotherapy, or both, he says.

Dr. Koob and his colleagues began their investigations of the extended amygdala by first determining whether it plays a role in the effects of drugs. Those investigations built on research by Dr. David C.S. Roberts, currently of Carleton University in Ottawa, and others. The research took two approaches.

In the first approach, the researchers inactivated the dopamine component in areas of the extended amygdala in rats after training them to self-administer cocaine. These rats significantly reduced the amount of cocaine they gave themselves. Dopamine is a chemical messenger associated with pleasure and movement. Cocaine prevents the brain cells that release dopamine from collecting it again. The resulting high levels of dopamine overstimulate the dopamine receptors—the molecules to which dopamine binds—causing the cocaine “high.” This process accounts for cocaine’s addictive effects, scientists believe.

Inactivation of the dopamine component of the extended amygdala reduced the rewarding effects of cocaine, an indication that the extended amygdala may be important in processing information about the rewarding effects of the drug.

In the second approach, Dr. Koob and his colleagues studied the effects on cocaine self-administration in rats when dopamine receptors in various areas of the extended amygdala were blocked by cocaine. The investigators found that the rats compensated by giving themselves

larger amounts of cocaine. This research provides further evidence of a role for the extended amygdala in the rewarding effects of the drug.

“This basic neuroscience research showed us that the structures believed to form the extended amygdala not only resemble each other in design but may have similar functions,” explains Dr. Athina Markou, Dr. Koob’s colleague at Scripps.

Now, the Scripps investigators are pursuing lines of investigation to determine if the extended amygdala also plays a role in linking environmental stimuli to both the rewarding effects of drugs and to withdrawal.

In a series of collaborative studies with Dr. Barry Everitt from Cambridge University in England, the Scripps investigators have begun to examine the role of the basolateral nucleus (BLA) of the amygdala—a small adjoining brain structure that sends information to the extended amygdala—in conditioned drug effects, those triggered by environmental cues. In a study currently in progress, rats are exposed to light and sound cues during withdrawal from morphine. Later, when presented with the light and sound cues only, rats with inactivated BLAs are significantly less likely than rats whose BLAs are not altered to experience withdrawal. In other words, the BLA seems to play an important role in linking environmental cues to withdrawal.

In recent years, Dr. Everitt, Dr. Trevor Robbins, and other researchers at Cambridge University have found that inactivation of the BLA in rats disrupts the association of environmental stimuli with the rewarding effects of food, water, and sex. Today, Dr. Markou, in collaboration with the Cambridge researchers and with the support of a NIDA Career Development Award, is developing an animal model based on the design of the British studies for studying whether the BLA plays the same role with drugs.

Dr. Markou and colleagues have found that inactivation of the BLA interrupts the association between light and the rewarding effects of cocaine. Thus, the BLA appears to link environmental stimuli not only to withdrawal, but also to the positive effects of drugs.

“Our research is still in the early stages,” Dr. Markou says. “First, we have to develop a model that allows us to study the formation of these associations. Then, we will continue to investigate the neurobiology and psychopharmacology underlying these associations and the effects of these associations on motivated behaviors.”

“These findings are very exciting because they help us understand relapse behavior,” says Dr. Koob. “What we’re learning about the extended amygdala and its connecting structures is allowing us for the first time to identify the neurocircuits involved in conditioning processes.”

“We’re working from the perspective of drug abuse, but the results apply to a wide range of compulsive behaviors that disrupt and destroy a great many lives each year,” says NIDA’s Dr. Brown. The research may help explain the neurobiological mechanisms and brain changes associated with compulsive overeating, alcohol abuse, drug addiction, smoking, compulsive gambling, and other behaviors driven by reward, withdrawal effects, and elements in the environment, he says. “This research also focuses on learning and memory,” he says. “There are relatively few people working in this area of drug abuse research.”

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Rats Immunized Against Effects of Cocaine

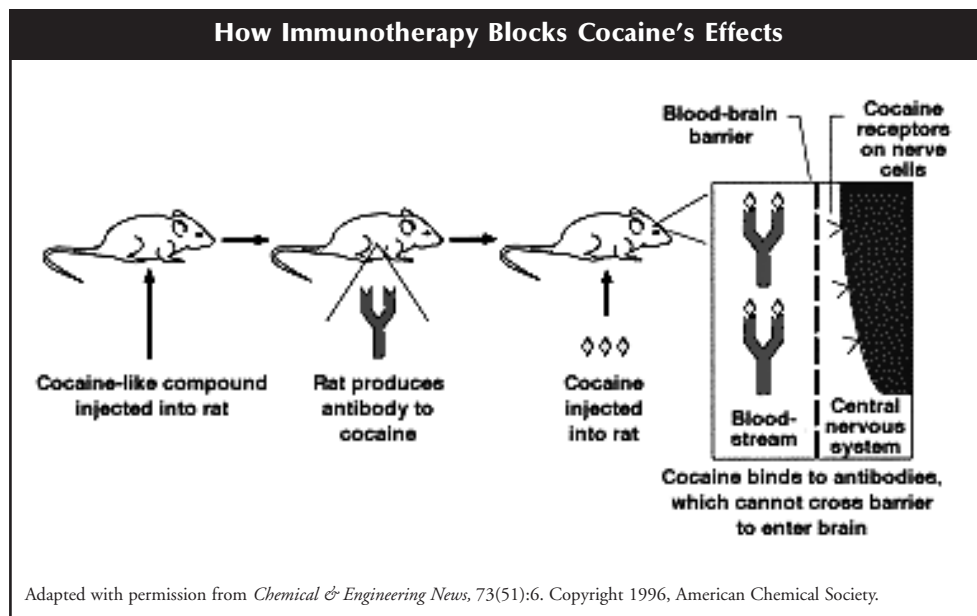
By Neil Swan, NIDA NOTES Staff Writer

NIDA-funded researchers have moved closer to finding a new approach to treating cocaine addiction by developing a cocaine-like compound that immunizes rats against many of the stimulant effects of cocaine. Acting like a vaccine that mobilizes the body's immune system to fight off diseases, the cocaine-like compound produces antibodies that reduce the amount of cocaine that can enter the brain. This research is one of the first to show how the body's immune system might be utilized to treat drug addiction.

"We have created a new scientific approach for potential treatment of cocaine abuse and maybe drug abuse in general," says the study's lead investigator, Dr. Kim D. Janda of Scripps Institute in San Diego. "We see a great deal of promise in this immunotherapy approach to drug treatment."

NIDA Director Dr. Alan I. Leshner agrees. "This is an exciting advance for drug abuse treatment research," he says. "Developing medications for the treatment of cocaine addiction is among the Nation's greatest needs, and it is one of NIDA's top priorities. Dr. Janda's research gives a promising new direction to the search for a safe means of blocking the damaging effects of cocaine, including crack."

The Scripps scientists altered the cocaine molecule to create a cocaine-like compound, or analog, that stimulates the production of antibodies to cocaine. These antibodies then act like sponges that bind with cocaine in the bloodstream to reduce the amount of the drug that reaches the brain, says Dr. Janda. Dr. Janda, Dr. George F. Koob, M. Rocio A. Carrera, Dr. Peter Wersching, and their colleagues at Scripps developed a coupled molecule because cocaine itself is unstable in the body, metabolizing so rapidly that it is not capable of generating cocaine-specific antibodies. To do this, the researchers reconfigured cocaine's unstable structure into a stable analog molecule



that, when coupled to a carrier protein, is capable of stimulating the body to produce cocaine-binding antibodies. This is because the stable analog is similar enough to the real cocaine molecule that it is recognized as cocaine by the immune system, which then produces cocaine-specific antibodies.

"Dr. Janda's research gives a promising new direction to the search for a safe means of blocking the damaging effects of cocaine, including crack."

In the study, the researchers inoculated rats three times in a 35-day period with the cocaine analog to develop a concentration of blood antibody. Then they gave the animals a dose of cocaine previously shown to cause behavioral changes in the rats. The inoculated rats displayed significantly less of the type of drug-related behavior typically observed in rodents—sniffing, rearing, and increased movement—than did the rats in the control group, which were not immunized. No unsatisfactory side effects were noted in the initial animal tests. When the rats' brains were later

examined, levels of cocaine found in tissues from different areas of the brain were up to 77 percent lower in the treated animals than in the control animals.

This form of immunotherapy is called “active” immunization because antibodies are produced within the body of the animal that is immunized. Dr. Janda and others are also exploring “passive” immunization, which involves the development and cloning of cocaine-binding antibodies in the laboratory. These antibodies then can be injected into the body. The bee-sting vaccine used to immunize people who are extrasensitive to bee-sting toxin is a type of passive immunization, Dr. Janda explains. He and his colleagues have produced several types of passive antibodies very specific to cocaine. Dr. Janda says that they may be able to develop a cocaine treatment that is a combination therapy, involving both conjugate-produced active antibodies and laboratory-cloned passive antibodies. “Several techniques might be used together to combat cocaine addiction,” he says. “There probably will not be a single ‘magic bullet.’”

A key question posed by the Scripps research is how long immunization against cocaine might be effective. Follow-up animal studies have already produced a more stable type of conjugate.

“We are working to develop a cocaine therapy in which booster immunizations would be required periodically—maybe weeks or months apart. Even so, we realize that for this therapy to work with humans, the patients must be motivated to strive to maintain their immunity with periodic inoculations.”

Immunotherapy against cocaine is distinctive in that it works through the immune system, not the central nervous system. Conventional medication treatment approaches seek to develop chemical variants of a drug, such as heroin, that act within the central nervous system to block or reverse the effects of the illicit drug itself. Because immu-

nization therapy acts outside the central nervous system, it should reduce the potential for adverse side effects. This is because the cocaine antibodies—unlike cocaine itself and other drugs—cannot cross the blood-brain barrier. Cocaine molecules that bind to these antibodies are then blocked by the blood-brain barrier from entering the brain. “The advantage is that immunization should have none of the side effects associated with medications that interfere directly with parts of the brain responsible for cocaine’s action,” says Dr. Koob.

Adds Dr. Leshner, “Our long-term goal would be to use this type of research to develop a medication capable of immunizing cocaine users and addicts against the effects of cocaine.”

In a commentary published in the same issue of *Nature* as the Scripps research, Dr. David W. Self of Yale University notes that the initial research with rats did not determine whether the cocaine immunotherapy reduces cocaine’s reward-producing properties and, accordingly, its addictive potential. He also asks whether the counteractive effect of cocaine antibodies can be overcome by increasing the self-administered dose of cocaine or crack.

The researchers say that this and other issues, such as determining the effects of repeated immunization or booster shots, are now being addressed.

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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

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.

Source

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Studying the Effects of Drugs in Humans

By Robert Mathias & Neil Swan, *NIDA NOTES* Staff Writers

The Clinical Pharmacology Branch conducts studies with human volunteers that are designed to provide basic information about the physiological and psychological effects of drugs. In turn, treatment researchers can use this information to develop and test new pharmacological and behavioral therapies for drug abuse and dependence.

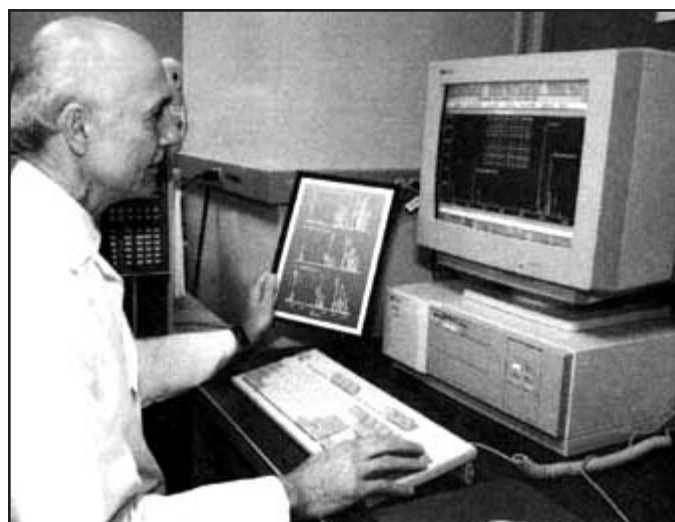
Scientists from the branch's three sections, in collaboration with researchers from other DIR branches and other NIH Institutes, conduct research on methods of measuring drugs in body fluids and hair, the mechanisms by which abused drugs act, ways to measure drug effects, how different methods of drug delivery—such as injecting, inhaling, or smoking—alter those effects, and the abuse liability and therapeutic potential of new drugs.

Studies conducted by the branch's Biology of Dependence Section confirmed that nicotine is highly addictive and that cigarettes are the most toxic and the most addictive way to deliver the drug, says Section Chief Dr. Jack Henningfield, who also directs the branch. "This research has played a major role in providing the scientific evidence used to develop antismoking and nicotine policies," he says.

The finding that the delivery method influences the addictiveness and toxicity of nicotine also provided the basis for developing alternative ways to administer nicotine as a treatment medication. Ultimately, this research led to the development of nicotine gum and the transdermal nicotine patch. These forms of nicotine delivery have proven to be safe and effective treatments for nicotine dependence, and they have very low addiction potential, Dr. Henningfield says.

Scientists in the branch's other sections are also conducting research that demonstrates how important the delivery method is in determining the biological and behavioral effects of abused drugs. Recently, the branch's Chemistry and Drug Metabolism Section, under the direction of Dr. Edward Cone, completed studies of how the body processes "crack" cocaine, which is smoked.

These studies determined that smoking "crack" cocaine produces higher concentrations of cocaine in the blood than does intravenously injecting cocaine, Dr. Cone says. When this cocaine-laden blood arrives at the brain, it produces intense behavioral effects. In fact, people who



Dr. Edward Cone examines hair analyses for cocaine. Scientists in the Clinical Pharmacology Branch develop and assess new technologies to measure abused drugs in body fluids and hair.

received equivalent doses of cocaine in both forms reported a much greater behavioral effect from smoked than from intravenous cocaine. "This means that people who smoke cocaine are going to get higher faster and experience a greater euphoria, which probably accounts for the greater addiction liability of 'crack,'" he says.

The branch's studies on the effects of different drug delivery forms suggest that one important approach to developing medications for cocaine addiction might be searching for slower-acting drugs that would produce weaker, longer-lasting effects than cocaine does, Dr. Henningfield says. Theoretically, such a medication could be used in the same way that methadone is used for heroin, to stabilize people addicted to cocaine and enable them to live without a constant overpowering urge to use cocaine, he says.

Using this hypothesis, scientists in the branch's Clinical Psychopharmacology Section, under the direction of Dr. Richard Rothman, are working with researchers from the laboratory of Dr. Kenner Rice at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to try to develop a compound that could be used as a medication to treat cocaine addiction. "A recent study conducted with Dr. John Glowa of NIDDK showed that acute and chronic treatment of rhesus monkeys with the

cocaine analog GBR 12909 essentially eliminated cocaine self-administration,” Dr. Rothman says. A clinical protocol to begin testing GBR 12909 in humans is under review, he says.

The section is also collaborating with Dr. Rice and other extramural investigators on a large-scale project to produce new opioid treatment agents by developing compounds that act at delta opioid receptors in the brain. The most

exciting part of this project is an attempt to design new compounds that block the delta receptor because researchers have found that such compounds have both anticocaine and antimorphine actions, Dr. Rothman says. “Ultimately, we hope to identify a delta antagonist that we could test clinically here at the ARC in cocaine and opiate users,” he says. **NN**

Molecular Pharmacology, Brain Scans, and Human Attention Spans

By Robert Mathias & Neil Swan, *NIDA NOTES* Staff Writers

The Neuroscience Branch's three sections conduct research into the effects of drugs on the brain. Some researchers study receptors, the molecular sites where drugs bind, to determine the receptors' role in drug-induced euphoria and drug craving. Other scientists study and use brain scans to show how drugs influence the brains of living animals and human volunteers.

The Molecular Pharmacology Section, headed by Dr. Michael J. Kuhar, conducts advanced molecular studies of the actions of drugs, particularly cocaine. Dr. Kuhar, who is also chief of the Neuroscience Branch, says that DIR scientists represent one of the world's leading research efforts in the development of medications and ligands, or binding partners, for receptors for cocaine and other drugs. Scientists also develop techniques for conducting molecular biological studies of how cocaine works. Their goal is to find substances that bear promise as potential cocaine blockers or medications.

The section has studied more than 350 analogs—or chemical cousins—of cocaine. Many of these cocaine analogs are highly selective, both in discerning specific brain binding sites and producing a variety of effects. The selectivity and varying effects of these analogs are keys to understanding and controlling how cocaine works.

The section's molecular research also focuses on the role of the dopamine transporter, which is involved in producing cocaine's distinctive pleasurable "rush." Through radioactive tagging and brain scans, the actions of various cocaine analogs in the brain are converted to images and then digitally recorded by computers.

This use of molecular chemistry to develop and test cocaine analogs, combined with brain imaging and physiological and psychological studies of the effects of these unique compounds, results in the hybrid science sometimes called molecular pharmacology.

Already the section's research has had a serendipitous benefit: the discovery of a compound, RTI 55, that has significant potential as an imaging tool for diagnosing Parkinson's disease.

Another unit of the branch, the Molecular Neuropsychiatry Section headed by Dr. Jean Lud Cadet, a psychiatrist and neurologist, studies the effects of prolonged drug use in humans and animals.

Current research with humans centers on long-term effects of the use of cocaine, heroin, and methadone, a treatment medication for heroin users. Volunteers, recruited from among people identified as having been cocaine users for at least 2 years, live drug free for 30 days in the ARC's 26-bed residential ward. These volunteers are medically and neurologically evaluated when they enter the ward and again when they leave drug free a month later. Tests seek evidence of improved neurological function at the end of the 30-day residential period. Following the studies, volunteers are offered drug abuse treatment.



Dr. Jean Lud Cadet uses a laboratory instrument to amplify DNA to help determine the effects of drugs on human memory and attention span.

Dr. Cadet uses a battery of neurological tests to determine the effects of drugs on human memory, attention, and decision making. Tests of the cerebral vascular effects of cocaine are performed because of concern about the prevalence of strokes among young people who use cocaine. Preliminary data suggest that, after drug abstinence, there might be an improvement in the subjects' ability to maintain their attention spans on a specific concept for longer periods of time, says Dr. Cadet.

The section uses mice as models to study the long-term toxic effects of amphetamines. After prolonged daily use by humans, amphetamines, like cocaine, can produce a psychosis similar to acute schizophrenia. To study the causes of this drug toxicity, researchers use two strains of mice: one that is vulnerable to and another that is protected from the toxic effects of amphetamines.

The Neuroimaging and Drug Action Section uses noninvasive imaging, or PET (positron emission tomography) brain-scanning techniques in human volunteers, and x-ray images of radioisotope tracers in animals, to better understand the mechanisms of drug action and how drugs influence brain functions.

Since 1983, DIR researchers have used these and other scanning techniques to study the acute effects of drug abuse in human volunteers. A key finding—that drugs of abuse reduce the brain’s use of glucose, its main source of energy—led to continuing studies and “mapping” of drug-influenced brain functions.

Molecular biological studies are probing the way that cocaine works, seeking substances that might be used as cocaine blockers or medications.

More recently, researchers began using PET scans to study the patterns of brain metabolism related to long-term use of drugs. Chronic drug abusers—compared with nondrug users of the same age, gender, and education level—

appear to have deficits in the visual-association cortex area of the brain. “This appears to be a part of the brain that is involved in decision making. It is involved particularly in making choices between behavior that is associated simultaneously with reward and the risk of harm,” explains Dr. Edythe D. London, section chief.

Dr. London and her colleagues are now preparing imaging studies to try to determine whether people who are not drug abusers but who have conditions associated with increased frequency of drug abuse, such as antisocial personality disorder (in adults) and conduct disorder (in children), are more prone to drug abuse than individuals who are not afflicted with these disorders, says Dr. London.

The ARC brain scanning facility’s capacity was expanded recently with the installation of a new state-of-the-art PET scanner that can produce brain images with greater detail and clarity. The Siemens high-resolution scanner is the only such device in the world devoted exclusively to drug abuse research. **NN**

Progress and Potential Mark NIDA's Search for a Cocaine Treatment Medication

By Dr. Alan I. Leshner, NIDA Director

I believe this country's single most important need in the fight against drug abuse and addiction is a cocaine dependence treatment agent. Currently, we have no such medication. To address this critical lack in our means to treat drug abuse, NIDA has made the development of a medication to treat cocaine abuse and dependence the Institute's number one priority.

Our sense of urgency is prompted by the fact that cocaine abuse and dependence affect all segments of our society with devastating personal, social, and public health consequences. National surveys indicate that more than 23 million Americans have used cocaine at some time in their lives and an estimated 1.4 million Americans are current cocaine users. Cocaine use is associated with potentially life-threatening cardiovascular and pulmonary effects; possible damage to the health and development of infants born to women who abuse cocaine while they are pregnant; sex-for-crack exchanges that are spreading the AIDS virus among both drug-abusing and non-drug-abusing populations; and violence and neighborhood disintegration related to the cocaine marketplace.

In the last few years, NIDA's intramural and extramural researchers have greatly increased our knowledge about where and how cocaine works in the brain and what the acute and long-term effects of those actions are. At the same time, our Medications Development Division has standardized the process of identifying and assessing potential cocaine treatment compounds and established an outcomes-based structure to decide whether or not to proceed with the development of tested compounds. The progress we have made in building scientific knowledge about cocaine and about how to conduct and evaluate clinical trials of proposed treatment agents has now brought us to the point where the development of effective cocaine treatment medications has become not only conceivable, but achievable.

To make the best use of our resources, we are now working to integrate the relevant research from the Institute's intramural and extramural divisions into the efforts of our medications development program, under the direction of Dr. Charles Grudzinskas, to develop a cocaine treatment medication. We are also working cooperatively with private pharmaceutical firms to obtain promising proprietary compounds for testing and development as cocaine

treatment medications, with the Department of Veterans Affairs to expand our clinical trials capabilities by creating clinical trials sites of excellence, and with the Food and Drug Administration to speed the medications approval process.

Our ultimate goal is to develop integrated treatment approaches combining cocaine treatment medications and behavioral interventions.

Because of our basic research findings about the neurobiology of cocaine addiction, our search for treatment medications has focused on the brain's dopamine system through which we believe cocaine produces its primary rewarding and reinforcing effects. However, we know that cocaine also interacts with two other neurotransmitters, serotonin and norepinephrine, which undoubtedly also play a role in modulating the drug's effects. In addition, recent work by NIDA's intramural and extramural researchers indicates that a number of opiate receptors may also be involved in mediating cocaine's effects.

Nearly 4 years ago, we achieved a significant milestone when intramural and extramural teams of NIDA researchers first cloned the gene for the dopamine transporter, thought to be the primary site of cocaine's action in the brain. Cocaine blocks the transporter from removing dopamine from the space between neurons, initiating a cascade of molecular events that produces euphoria. Other researchers have cloned five dopamine receptors and a number of serotonin receptors. These sites all represent potential molecular targets for medications to either block or attenuate cocaine's effects. In fact, NIDA researchers are currently working on promising experimental treatment compounds, based on new knowledge about the role specific dopamine receptors play in cocaine dependence.

This year, we took another significant step. By manipulating the structure of the dopamine transporter, Dr. George Uhl, who serves as chief of NIDA's Molecular Neurobiology

Branch and acting director of our Division of Intramural Research, has shown that we can develop a compound that will block cocaine's effects while preserving the normal functioning of the dopamine system. Although much developmental work and testing must be done before we can conduct clinical trials of such a compound, this is a tremendously encouraging advance.

While NIDA scientists continue to probe cocaine's underlying biological and behavioral mechanisms to gain a better understanding of such addiction-related phenomena as craving, relapse, and withdrawal, we are also supporting completely new approaches to the design of cocaine medications. For example, NIDA researchers are working on medications designed to neutralize the cocaine molecule directly, rather than act on the cocaine receptor in the dopamine system.

Meanwhile, NIDA's Medications Development Division has been applying the scientific advances we have made in basic research to clinical research. In the 5 short years since the Division was mandated by Congress to fill an unmet national need for addiction treatment medications, it has served as the centerpiece of a concerted Institute-wide medications development program that has:

- launched an extensive cocaine medication discovery program in which molecular biologists and medicinal chemists are working together, using the findings from molecular research, to design and systematically test hundreds of compounds for their potential to block or attenuate cocaine's effects;
- held a series of workshops that have helped treatment specialists become experts in conducting clinical trials of cocaine treatment medications. These workshops have also helped to standardize methods of conducting such trials and assessing their results;
- identified and thoroughly evaluated a range of medications already approved for treating other diseases that may offer fast-track potential as cocaine treatment agents;
- conducted comprehensive reviews of the results of these early-stage clinical trials of proposed medications to determine whether or not they should continue to be tested;

- established five Medications Development Research Centers across the Nation where 80 percent of the research is now directed toward finding a cocaine treatment medication; and
- worked with the Department of Veterans Affairs to establish an extensive infrastructure of clinical trials sites of excellence that actively seeks promising clinically available compounds to treat cocaine dependence. These centers will be able to evaluate new cocaine medications that show enough promise to move into large-scale clinical efficacy trials.

At this point, we have tested many proposed treatment medications. A handful of these compounds has shown enough promise to warrant further evaluation to determine whether or not they should go forward in the development cycle. Our Medications Development Division is also planning to test compounds in small, single-site, double-blind, placebo-controlled clinical trials that will give us an indication of their potential treatment efficacy.

While building the scientific and clinical base for developing cocaine medications, we have also made considerable progress in developing nonpharmacological treatments for cocaine abuse and dependence. NIDA-supported treatment researchers have developed behavioral therapies that are showing great promise in helping diverse patient populations achieve initial abstinence from cocaine. NIDA researchers have also developed therapeutic strategies that are helping patients who have stopped using cocaine deal with conditioned responses to stimuli that can trigger the little-understood phenomenon we call craving that often precipitates relapse to cocaine use and dependence.

Combining behavioral therapies with cocaine treatment medications would vastly increase our chances of treatment success. Therefore, our ultimate goal is to develop integrated treatment approaches combining cocaine treatment medications and behavioral interventions to address the biological, behavioral, and social aspects of cocaine addiction. By leveraging our available resources through the broad-based public-private coalition we have put together to develop a cocaine treatment medication, NIDA is working toward the day when effective behavioral therapies and pharmacotherapies will be available to help people recovering from cocaine dependence build productive lives. **NN**

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

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.

given vouchers for clean urines stayed off cocaine for more 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 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.

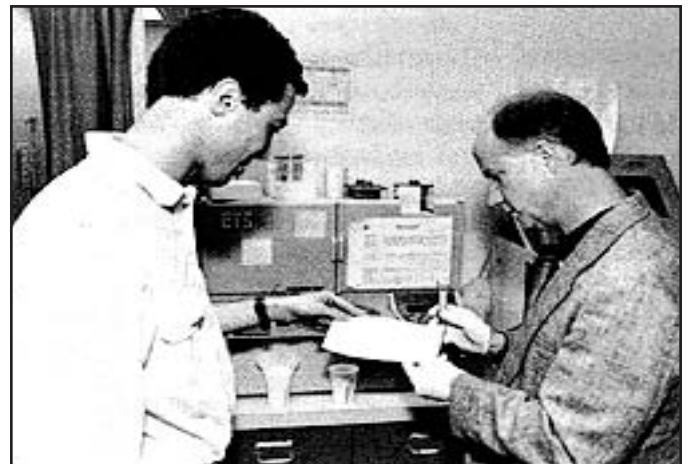
"Cocaine abusers never receive cash-only vouchers," emphasizes Dr. Higgins. "The patients and counselors must agree on the items to be purchased with the vouchers."

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: _____

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

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 Workshops Advance Clinical Trials of Cocaine Treatment Medications

By Robert Mathias, *NIDA NOTES* Staff Writer

One of the most important steps in developing a cocaine dependence treatment medication is conducting human clinical studies to establish a proposed medication's safety and efficacy. Three years ago, when NIDA and leading cocaine researchers first met to look at how clinical trials of potential cocaine treatment medications were being conducted, they found that differences in methodology and outcome measures made it difficult to assess and compare the results of different studies.

Clinical trials of cocaine treatment medications have come a long way since that initial workshop. Dr. Betty Tai of NIDA's Medications Development Division (MDD) told the most recent meeting of NIDA-funded cocaine researchers. NIDA held the workshop last fall to present an overview and update of issues critical to the success of clinical trials of potential cocaine treatment medications. The meeting was the culmination of a series of workshops NIDA's MDD has been holding with its treatment researchers, the Food and Drug Administration (FDA), and members of the pharmaceutical industry since 1992 to identify and resolve practical problems researchers have been confronting in conducting such clinical trials.

Through these meetings, workshop participants have identified issues that are critical to the design, implementation, analysis, and interpretation of the results of clinical trials of medications for cocaine abuse and dependence. The participants have also established and upgraded standards for conducting and evaluating these clinical trials and have developed clinical guidelines for deciding whether or not to take a proposed cocaine treatment medication further down the rigorous and costly path of safety and efficacy testing required for approval of a treatment medication by the FDA. "Probably the most critical elements in clinical trials of cocaine treatment medications are outcome measures," says Dr. Tai. When MDD scientists reexamined data from early clinical trials, they found that individual investigators had used a potpourri of outcome measures to determine whether or not a medication worked, such as self-reported reductions in drug use or improvements in a patient's mental state or well-being. These researchers may have used many of these measures simply because an instrument was available to assess them, but they do not meet current standards for categorizing a drug as therapeutically effective, says Dr. Tai.

Through the clinical workshops, NIDA's MDD and the FDA have established four primary outcomes for assessing the safety and efficacy of a medication to treat cocaine abuse. Clinical trials of proposed cocaine treatment medications now measure patients' drug use by urinalysis or self-report, preferably both; how long patients remain in treatment; the physician's global assessment—a clinician's subjective assessment of how well a patient is progressing to a drug-free state compared to similar patients; and the patients' self-assessment of their own progress to a drug-free state.

The establishment of four core measures does not preclude individual researchers from looking at other outcome measures, such as the medication's effect on depression, that may be related to cocaine abuse, says Dr. Charles Grudzinskas, who directs NIDA's medications development program. However, the use of these four basic measures "will permit us to compare apples to apples, so that when we commission a meta-analysis a few years from now, people will be able to compare results using the same measures," he says. A meta-analysis is a statistical method used to summarize and describe the results of a number of studies.

Many of the workshops have also addressed the difficulties in assessing one of the core outcome measures—cocaine use. Early clinical trials often measured cocaine use with qualitative urinalysis. However, this method, which is used in workplace drug testing, only gives a positive or negative reading based on whether or not a preset amount of benzoylecgonine, a cocaine metabolite, is present in the urine when the test is performed. Because this method does not tell researchers the actual concentrations of benzoylecgonine in the urine, they cannot use it to determine if a medication is having an effect on the amount of cocaine use.

"Methods for conducting clinical trials of proposed cocaine medications have been getting much more sophisticated," says Dr. Tai. Now, almost every NIDA-funded trial is double-blind and placebo controlled. Researchers have also started using quantitative urinalysis to measure precise levels of cocaine in the urine. This method can give researchers a clearer picture of the effect of a medication on the extent of drug use, she says. At the workshop last fall, Dr. Kenzie Preston of NIDA's Division of Intramural Research showed how researchers can take that assessment one step further by using both quantitative

urinalysis and patient self-reports of cocaine use to obtain a more accurate assessment of the timing, episodes, and amount of actual cocaine use than could be determined by either measure alone.

What NIDA has tried to do with this series of meetings, concludes Dr. Peter Bridge, who directs MDD's Clinical Trials Branch, is standardize clinical studies so that there is consistency across study sites. **NN**

New Strategy Would Neutralize Cocaine in the Bloodstream

By John A. Bowersox, NIDA NOTES Contributing Writer

In contrast to cocaine treatment medication development strategies that target dopamine receptors, the brain cell molecules that are overstimulated during cocaine use, other NIDA-funded researchers are investigating ways to neutralize the drug in the bloodstream, reducing the amount available for brain uptake. A main benefit of this approach would be that adverse side effects associated with medications aimed at dopamine receptors, such as disruptions in motor functions, could be avoided. By attacking cocaine directly, this approach also could help reverse some of the drug's toxic effects, such as decreased blood flow and reduced oxygen delivery to the brain.

The primary cocaine-neutralizing tools under investigation are catalytic antibodies, synthetic molecules developed within the past decade by a process involving both synthetic chemistry and immunology. Like natural antibodies, catalytic antibodies are designed to recognize, and bind to, a specific molecule. But unlike naturally occurring antibodies, catalytic antibodies function as enzymes by inducing the molecules to which they bind to undergo a chemical reaction.

Although this research is still in an early stage of development, some researchers envision catalytic antibodies that bind to cocaine in the bloodstream and enzymatically break it down into its nonaddictive components—mimicking the body's natural metabolism of cocaine, but at a much faster rate. The first step toward this goal was reported in 1993 by Dr. Donald Landry, a researcher at the Columbia University College of Physicians and Surgeons in New York, who created a catalytic antibody that was able to break cocaine down in test-tube experiments.

Theoretically, catalytic antibodies are potentially powerful new weapons against cocaine abuse. But even enthusiastic proponents of this approach say that it will take at least several more years of research to determine whether catalytic antibodies can be a viable treatment alternative for cocaine abuse.

"In the next year or two, we're probably not going to see a humanized catalytic antibody that can detoxify cocaine or any other drug of abuse," says Dr. John R. Cashman, a NIDA-funded researcher currently working on these compounds. A humanized antibody, he explains, is one that is able to work safely and effectively in the human body.

Some NIDA-funded researchers envision catalytic antibodies that bind to cocaine in the bloodstream and enzymatically break the drug down into its nonaddictive components.

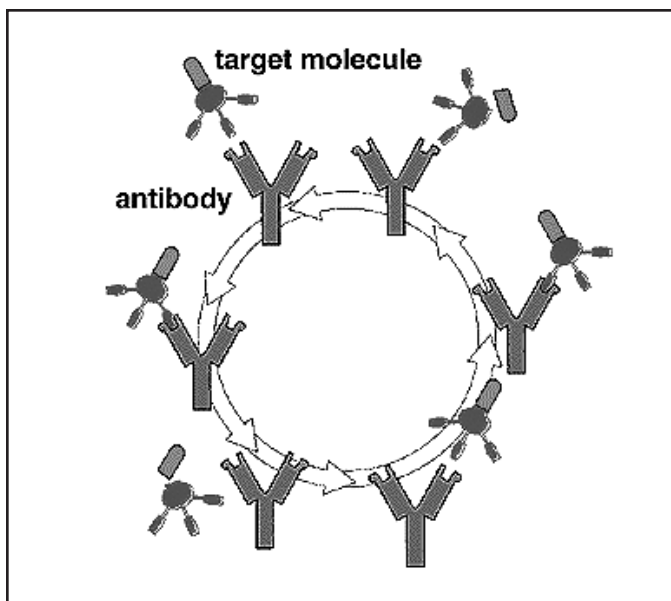
"But what is important," he adds, "is to continue to try to develop new detoxification catalysts that do not currently exist in nature."

Dr. Cashman, a senior scientist at the Seattle Biomedical Research Institute, says that catalytic antibodies ultimately could be used to rescue individuals from acute cocaine overdose. If they work as planned, these specially designed catalysts would quickly reduce the amount of cocaine circulating in the bloodstream of people who overdose.

The plausibility of treating drug addiction with antibodies, an approach known as immunotherapy, was demonstrated in 1974 by former NIDA Director Dr. Charles R. Schuster, currently a professor and director of the Substance Abuse Clinical Research Program at Wayne State University in Detroit, Michigan. Dr. Schuster showed that antibodies to heroin could block its effects in addicted monkeys. This approach, however, only worked for very low doses of heroin since a heroin antibody can only bind to, and neutralize, a single heroin molecule. Administering the large doses of antibody that would be needed to neutralize large doses of heroin is impractical in a clinical setting.

Catalytic antibodies improve on the earlier approach to immunotherapy because the antibodies are not bound permanently to their target molecule. Instead, they are "turned over." After they bind and catalyze the enzymatic breakdown of their target, catalytic antibodies are released and can then bind to another target molecule. Turnover thus prevents the rapid depletion of the antibodies.

Still, some researchers suggest that it is too early to attempt to develop catalytic antibody medications for cocaine abuse. They point to the formidable technical hurdles that must be overcome before these compounds



Scientists are trying to develop catalytic antibodies, synthetic molecules that will target and break down cocaine molecules more quickly than the body's natural cocaine-metabolizing enzymes. This simplified diagram shows how a typical catalytic antibody works. The antibody recognizes (upper left), binds to, and induces the breakdown of a specific target molecule. With the release of the breakdown byproducts, the antibody is recycled and is free, unlike naturally occurring antibodies, to repeat this process with another target molecule.

can be clinically useful as evidence that more basic research is needed.

“It is proving extremely challenging to develop a catalytic antibody with a turnover rate that even approaches the turnover rates of natural cocaine metabolizing enzymes,” says Dr. Michael Owens, a NIDA grantee who also is investigating immunotherapeutic approaches for drug abuse. “Therefore, we should first determine if similar approaches, which are more technically feasible, might serve the same purpose.”

Dr. Owens, a professor of pharmacology and toxicology at the University of Arkansas College of Medicine, says that other approaches might include purifying natural cocaine-metabolizing enzymes from human blood or developing monoclonal, or genetically identical, antibodies that bind to cocaine molecules with a high degree of specificity.

“Nevertheless,” Dr. Owens adds, “basic research on cocaine catalytic antibodies should be pursued since the development of pharmacokinetic and metabolic modifiers of abused drugs is an underexplored area of medications development.”

Dr. Cashman concurs on the need for additional basic research but adds that this should not preclude current efforts to develop clinically useful catalytic antibodies.

“NIDA should be commended for embracing this kind of research activity,” says Dr. Cashman. **NN**

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 reduce

cocaine intake without producing motor side effects. Other medications that target dopamine receptors non-specifically 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.

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31% of New York Murder Victims Had Cocaine in Their Bodies

By Neil Swan, NIDA NOTES Contributing Writer

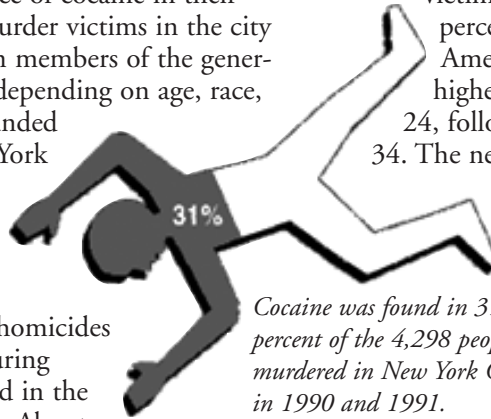
Nearly 3 out of every 10 homicide victims in New York City in the early 1990s had evidence of cocaine in their bodies when they died. Overall, murder victims in the city are 10 to 50 times more likely than members of the general population to be cocaine users, depending on age, race, and gender, according to NIDA-funded research using data from the New York City medical examiner.

Dr. Kenneth Tardiff of Cornell University Medical College in New York City headed a team of researchers that studied the 4,298 homicides that occurred in New York City during 1990 and 1991. Cocaine was found in the bodies of 31 percent of the victims. About three-fourths of all the murders involved firearms.

“Homicide victims may have provoked violence through irritability, paranoid thinking, or verbal or physical aggression, which are known to be pharmacologic effects of cocaine,” the researchers hypothesized. Drug dealers’ efforts to protect their sales territories from invading competitors also promote violence and homicide, they suggested.

Young African-American and Latino men were more likely to be victims of homicide than were members of all other

demographic groups, the study found. Two-thirds of the victims were between the ages of 15 and 34, 86 percent were male, and 87 percent were African American or Latino. The rate of homicide was highest for African-American males ages 15 to 24, followed by African-American males ages 25 to 34. The next highest homicide rates were among young Latino men ages 25 to 34 and 15 to 24, respectively.



Cocaine was found in 31 percent of the 4,298 people murdered in New York City in 1990 and 1991.

African-American women and Latino women had much lower rates of death by homicide than their male counterparts. However, their rates were slightly higher than those of white males, particularly in the 15- to 34-year-old age group. White females had the lowest homicide rates of any demographic group.

Among some of the young demographic groups of victims, cocaine use surprisingly was higher among females than among males. For example, 59 percent of white women and 72 percent of African-American women ages 25 to 34 had been using cocaine before they died compared with 38 percent of white men and 44 percent of African-American men in that age group. This “high proportion”

Percentage of New York City Homicide Victims in 1990 and 1991 Positive for Cocaine Metabolites in Each Age Group by Gender and Race*

Age in Years	White		African American		Latino		Asian/Other		Total
	Male (n=272)	Female (n=74)	Male (n=1,583)	Female (n=276)	Male (n=1,344)	Female (n=184)	Male (n=138)	Female (n=19)	
14 or under	0	25.0	2.4	0	3.7	0	0	0	4.1
15-24	18.4	16.7	18.9	35.6	23.7	28.1	8.6	0	21.5
25-34	37.5	59.1	44.4	71.8	43.4	36.1	4.9	0	43.9
35-44	34.0	26.7	49.3	40.8	42.0	31.0	12.1	0	40.9
45-54	12.2	0	27.8	20.0	26.4	14.3	0	0	20.7
55 or over	2.3	0	14.0	0	16.3	0	0	0	7.2
Total	22.4	25.7	31.6	39.5	39.9	27.7	6.5	0	31.0

* Denominators include only cases in which there were toxicologic analyses for benzoylecgonine, a cocaine metabolite, and in which the interval between injury and death was 48 hours or less.

This table was adapted from an article that appeared in *The Journal of the American Medical Association*, Vol. 272, No. 1, July 6, 1994, pp. 43-46. Copyright 1994, American Medical Association.

Characteristics of Homicide Victims Killed in 1990 and 1991 in New York City (Residents Only)

Characteristics	# of Cases	% of All Homicides
AGE IN YEARS		
Less than 1	46	1.1
1-14	93	2.2
15-24	1,442	33.7
25-34	1,457	34.0
35-44	693	16.2
45-54	289	6.8
55-64	126	2.9
65 and older	132	3.1
Total	4,278*	100.0
GENDER		
Male	3,682	85.7
Female	614	14.3
Total	4,296*	100.0
RACE		
White	402	9.4
African American	2,069	48.2
Latino	1,648	38.4
Asian/other	171	4.0
Total	4,290*	100.0
CAUSE OF DEATH		
Firearms	3,131	72.8
All other methods	1,167	27.2
Total	4,298	100.0

* Numbers are less than 4,298 because of unknowns for age, gender, and race.

This table was adapted from an article that appeared in *The Journal of the American Medical Association*, Vol. 272, No. 1, July 6, 1994, pp. 43-46. Copyright 1994, American Medical Association.

of cocaine users among white and African-American female homicide victims is contrary to surveys showing that women in general are less likely to be drug users and shows that drug use is a key risk factor for homicide victimization among women, the study authors said. "It is possible that female users of cocaine are more likely than nonusers to be victims of violence from spouses, boyfriends, or, in the case of prostitutes, their clients," said the researchers.

The investigators attributed the high homicide rate they found among African Americans and Latinos to the increased availability and abuse of crack cocaine and the increased availability and lethal firepower of guns.

"There is no clear answer as to how we can decrease the heavy use of cocaine, particularly in our cities," the researchers said. "There is a major need for public treatment programs, but these will be very expensive, and treatment for cocaine addiction has no methadone analog yet. Prevention programs aimed at schools require adequate evaluation."

Source

- Tardiff, K.; Marzuk, P.M.; Leon, A.C.; Hirsch, C.S.; Stajic, M.; Portera, L.; and Hartwell, N. Homicide in New York City: Cocaine use and firearms. *JAMA* 272:43-46, 1994. **NN**

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