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NIDA NEWS SEARCH

[NIDA Home](#) > [Publications](#) > [NIDA Notes](#) > [Vol. 21, No. 1](#) > Research Findings

Brain Mechanism Turns Off Cocaine-Related Memory in Rats

Research Findings
 Vol. 21, No. 1 (October 2006)

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

BY PATRICK ZICKLER, *NIDA Notes* Contributing Writer

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

The NIDA-funded scientists, Drs. Courtney Miller and John Marshall, focused on the enzyme in an attempt to elucidate the ways cellular activities promote cue-induced drug-seeking.

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

Days 1-9	Day 10	Day 11	Day 26	Conclusions
 Researchers trained rats to associate cocaine with a specific setting. The animals signaled their successful conditioning by exhibiting conditioned place preference—spending more time in a chamber where they had received cocaine injections over 9 days.	Group 1 Rats received infusions of U0126 or a control vehicle. After 30 minutes, they were tested for CPP. Rats given U0126 showed no preference for a cocaine-associated chamber. Control rats did show preference for the cocaine-associated chamber.	Rats given U0126 still exhibited no CPP. Control rats retained CPP.		Inhibiting ERK activity can block retrieval of cocaine-associated memories for 24 hours.
	Group 2 Rats were tested for CPP and immediately infused with either U0126 or the control vehicle.	Rats given U0126 showed no CPP. Control rats showed CPP.		Inhibiting ERK activity immediately after cocaine-associated memories are retrieved can

Group 3	Rats were tested for CPP and immediately infused with either U0126 or the control vehicle.		Rats given U0126 showed no CPP. Control rats showed CPP.	make the memories unavailable for subsequent retrieval at 24 hours and for at least 2 weeks.
Group 4	Rats received an infusion of U0126 and remained in their home cage with no testing and therefore no opportunity for memory retrieval.	Rats showed a strong CPP for the cocaine-associated environment.		ERK inhibition is effective only when induced at the time of memory formation or memory retrieval.

"Although studies have established that nerve cells in the core of the nucleus accumbens are critically involved," Dr. Miller says, "we haven't had much information about the molecular mechanisms that transform environmental cues into an urge to repeat drug-associated behavior." One likely candidate for a role in the process, however, was extracellular signal-regulated kinase (ERK). This enzyme is known both to foster the new cellular connections that register emotional and object recognition memories in the brain and to be affected by cocaine.

The researchers explored ERK's role in a behavior called conditioned place preference (CPP). By exhibiting CPP—lingering in a part of a cage where it has had a drug experience—an animal indicates that it remembers the experience, associates it with the preferred cage area, and is seeking to have it again (for more on CPP, see "[Animal Experiments in Addiction Science](#)"). In previous research, blocking ERK activity in the nucleus accumbens (NAc) prior to exposing rats to drugs prevented them from developing CPP. Drs. Miller and Marshall reasoned that if blocking ERK forestalls initial formation of the memory links underlying CPP, it might also weaken links that had already been formed. The potential therapeutic implications would be significant if this were so; they would suggest that manipulating ERK might be a means to disrupt drug-environment associations that are already established by the time patients begin therapy.

New Findings on Memory Have Implications For Treatment

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

Dr. Karim Nader of McGill University in Montreal, Canada, explained the process of reconsolidation and how interventions based on that process

might work. The goal, he said, is not to simply erase memory, but rather to modulate the memory so that its effects are more manageable in conditions such as PTSD or addiction. "Our research shows that when a consolidated long-term memory is reactivated, it returns to a labile state similar to short-term memory. Neurons must synthesize new proteins in order for the memory to persist. If protein synthesis is inhibited after reactivation, reconsolidation can't occur," he said.

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

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

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

- CPP involves activation of ERK: Rats that lingered in the cocaine-associated area of the test cage had higher ERK levels in the core area of the NAc than a group of rats that had not been exposed to cocaine or a third group exposed to cocaine but not trained to exhibit CPP.
- Inhibiting ERK activity can block retrieval of cocaine-associated memories for 24 hours: The investigators infused a compound called U0126, which reduces ERK activity, directly into the NAc cores of some of the CPP-trained rats. When placed in the test cage 30 minutes later, these rats gravitated to the cocaine-associated area much less consistently than did a group of CPP-trained rats that were injected with saline rather than U0126. Tested again 24 hours later, they still exhibited little or no preference for the area.
- Inhibiting ERK activity at the time cocaine-associated memories are retrieved can make them unavailable for subsequent retrieval for at least 2 weeks: Rats were placed in the test cage and given U0126 immediately after exhibiting CPP. When retested the following day, they showed no partiality to the drug-associated cage area, nor did a similarly treated group of animals tested 2 weeks later. "These animals had effectively recollected their cocaine experience on day 1, but on day 2 and even 14 days later, there was no evidence that the memory was active," Dr. Miller notes.

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

linking the cue to craving.

"This research provides important new understanding of the processes that take place when the brain is manipulating memories, and it identifies specific molecules that help shape those processes," comments Dr. Jerry Frankenheim of NIDA's Division of Basic Neuroscience and Behavioral Research. "The fact that the intervention with U0126 came after the animals had already learned the cocaine-place association may be important for translating this research to possible clinical application. There are many ways to block the initial consolidation of memory, but the approach used in this research—interrupting reconsolidation—is much more relevant to intervening in cocaine abuse," he adds.

SOURCE

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

Blocking Protein Also Stops Drug-Linked Memory

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

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

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

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

SOURCE

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

Volume 21, Number 1 (October 2006)

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[Home](#) > [Publications](#) > [NIDA Notes](#) > [Vol. 19, No. 6](#) > [Research Findings](#)

A Single Cocaine "Binge" Can Establish Long-Term Cue-Induced Drug-Seeking in Rats

Research Findings
Vol. 19, No. 6 (May 2005)

By Lori Whitten, *NIDA NOTES* Staff Writer

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

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

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

The researchers hypothesized that during this initial session, the rats learned to seek out the cocaine experience and the rats' brains established a link between white noise and the drug experience similar to the environmental cues learned by people addicted to cocaine. Their next experimental step would put the rats into a state corresponding to abstinence in a former cocaine abuser. To accomplish this, they returned the animals to the test cage, now with the white noise turned off and the lever disconnected from the infusion device. The rats obtained nothing when they pressed the lever that previously had delivered cocaine, and they gradually gave up. When a rat had pressed the lever five or fewer times in three consecutive 1-hour sessions, the researchers concluded that its drug-seeking behavior was "extinguished." The animal's motivation was not strong enough for it to keep pressing a lever that had not delivered an infusion in many tries.

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

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

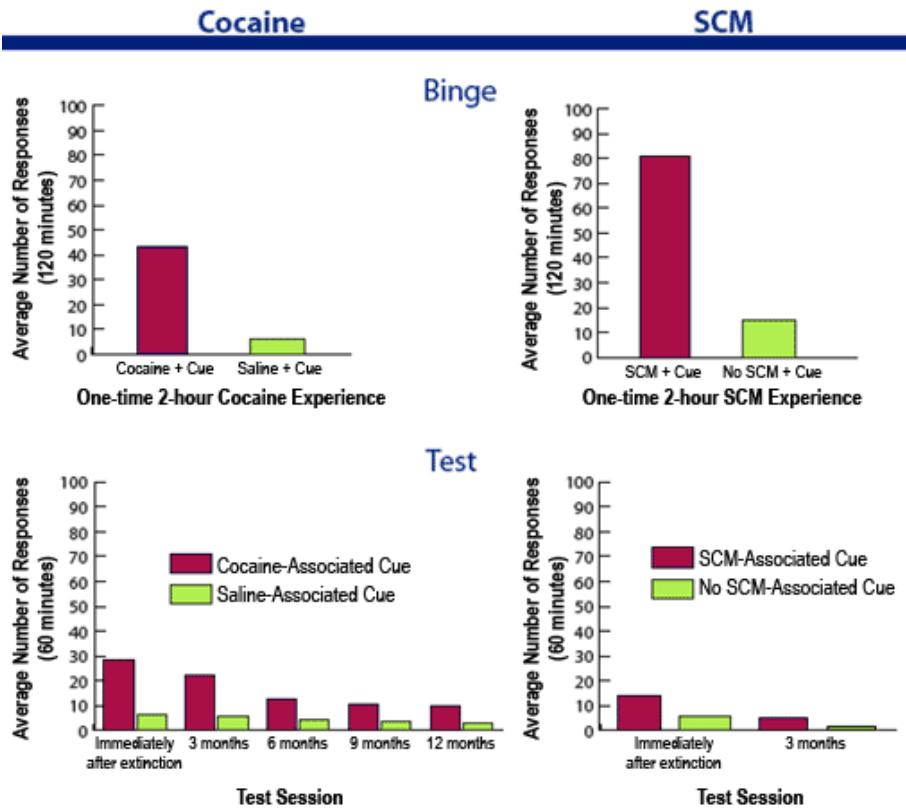
only a few lever presses throughout the experiment.

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

Food Doesn't Elicit the Same Cue Response

In a second experiment that demonstrated the unique reinforcing power of drugs, Dr. Weiss and colleagues showed that a highly palatable food did not produce persistent motivating effects. Following the same procedures they used in the cocaine experiment, the investigators trained a different group of rats to associate white noise with access to sweetened condensed milk (SCM). During access to SCM, rats pressed the lever 80 times on average. Subsequent sessions in the test cage extinguished the rats' SCM-seeking. The investigators then tested white noise's ability to induce the now "abstinent" rats to resume pressing the lever. It did not, either immediately or 3 months after extinction. The results indicate that a "natural" reinforcer does not have cocaine's ability to produce a long-lasting motivational association in a single session of exposure.

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



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

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

Scientists don't yet know the exact neurobiological mechanisms that form learned associations from drug experiences. However, researchers have observed that drugs induce changes in brain cells, or neural adaptations, similar to those underlying normal

learning. These adaptations result in a modification of the brain's neural circuitry—the interconnected networks of neurons responsible for behavioral, cognitive, and emotional and motivational processes.

Dr. Volman explains, "Drugs may produce such rapid and long-lasting learning because they have a double effect: They produce intense pleasure that reinforces behavior and they enhance neural adaptations at the same time. These brain changes might underlie sustained drug-directed behavior and the ability of cues to prompt drug-seeking." In future studies, Dr. Weiss and his colleagues intend to address the physiological mechanisms underlying the different behavioral responses to drugs and to natural reinforcers.

"...an exceptionally strong association is established when cocaine is paired with a cue."

Source:

- Ciccocioppo, R.; Martin-Fardon, R.; and Weiss, F. Stimuli associated with a single cocaine experience elicit longlasting cocaine seeking. *Nature Neuroscience* 7(5):1-2, 2004.
[\[Abstract\]](#)

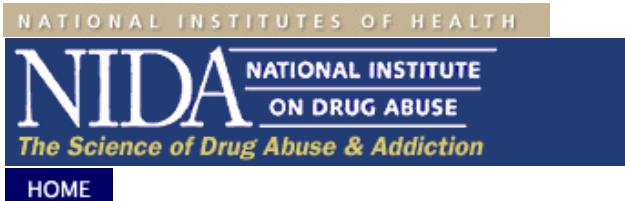
Volume 19, Number 6 (May 2005)

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[NIDA Home](#) > [Publications](#) > [NIDA Notes](#) > [Vol. 20, No. 5](#) > [Research Findings](#)

Cocaine Abuse and HIV Are Linked With Coronary Calcification

Research Findings
Vol. 20, No. 5 (April 2006)

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

By Lori Whitten, NIDA NOTES Staff Writer

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

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

The results revealed coronary calcification in almost one-third (31 percent) of the participants. The prevalence was twice as high in the HIV+/cocaine+ group (38 percent) as in the HIV-/cocaine- group (19 percent). In the other two groups, the proportion of participants with the condition fell in between, with 29 percent of the HIV+/cocaine- and 30 percent of the HIV-/cocaine+ groups showing coronary calcification (see [chart](#)). In the U.S. population as a whole, the prevalence of coronary calcification among 25- to 45-year-olds is about 18 percent.

Participants with HIV infection and/or a history of cocaine abuse had more calcium deposits and a greater volume of calcification than nonabusers without the infection. Compared with the HIV-/cocaine- group, the total volume of coronary calcium was 2.9 times as high in the HIV+/cocaine- group, 2.6 times as high in the HIV-/cocaine+ group, and 3.5 times as high in the HIV+/cocaine+ group. The associations held when the researchers took into account cardiovascular disease risk factors, including age, body mass index, lipid levels, blood pressure, and whether patients were taking HIV medication. The study was too small to determine whether HIV and cocaine contribute independently to calcification when both are present, or whether they interact physiologically to promote it even more.

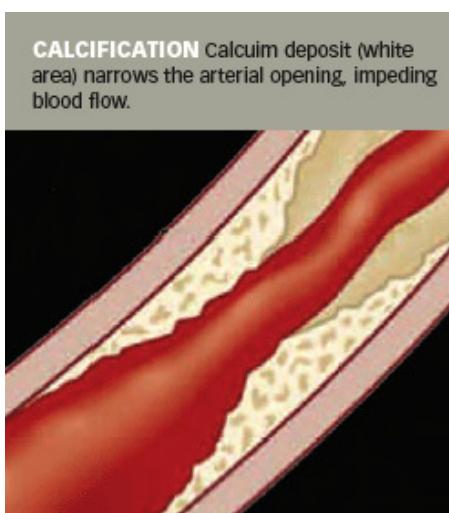
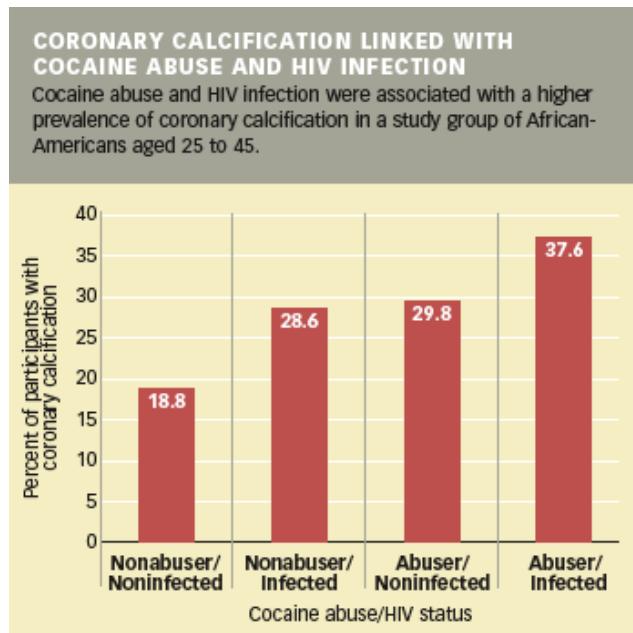
Cardiovascular complications have been well documented in patients who abuse

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

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

SOURCE

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



Volume 20, Number 5 (April 2006)

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