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## Aripiprazole Prevents Rats From Resuming Cocaine Seeking

Research Findings  
Vol. 22, No. 2 (December 2008)

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

By **LORI WHITTEN**, *NIDA Notes* Staff Writer

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

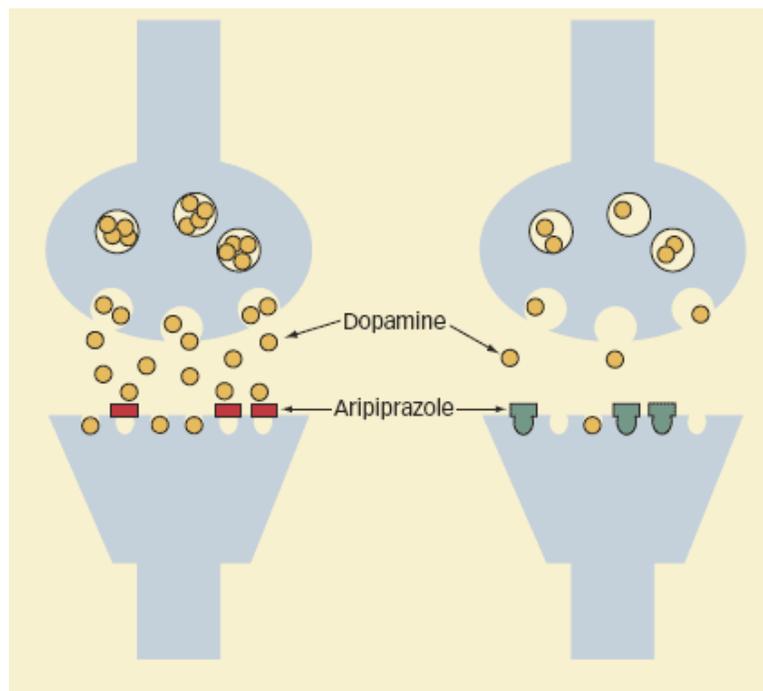
Drs. Ronald See and Matthew Feltenstein of the Medical University of South Carolina found that rats treated with aripiprazole were less likely than untreated rats to resume cocaine self-administration after a period of abstinence. The finding indicates that the medication reduces cocaine seeking directly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

### INDIFFERENCE TO COCAINE WITH FEW SIDE EFFECTS

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

#### **ARIPIPRAZOLE ALLEVIATES DOPAMINE IMBALANCE THAT PROMOTES RELAPSE**

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



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

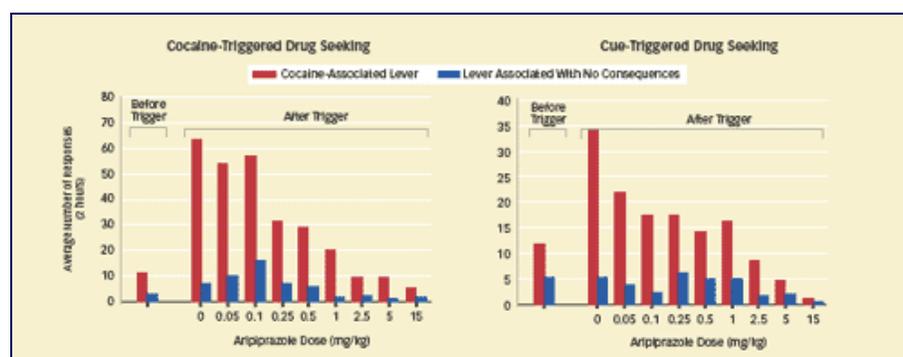
To rule out the possibility that aripiprazole reduced the rats' cocaine seeking through general effects—such as sedation or lethargy—that would be undesirable in a medication, the investigators conducted further trials that showed:

- *Aripiprazole does not sedate animals to the point where they are too tired to approach and press levers for rewards.* During the protocol that mimicked relapse, the lowest medication doses that attenuated lever pressing did not suppress locomotor activity. Higher doses (1 mg/kg and 5 mg/kg) reduced spontaneous and cocaine-induced locomotor activity only modestly. Furthermore, while aripiprazole-treated rats pressed the drug-linked lever less often, they continued to press another lever, which delivered nothing at all, as often as before.
- *Aripiprazole does not make rats indifferent to rewards from all activities, including natural, healthy ones.* Aripiprazole did not reduce the enthusiasm with which rats pressed levers to obtain food, so it did not seem to blunt their natural pleasure responses. In addition, when the researchers put animals through a protocol that simulates ongoing drug use, rather than recovery from an addiction, the animals pressed levers to obtain cocaine infusions just as avidly after receiving aripiprazole as after saline. This result indicates that while the medication may help individuals maintain abstinence, it is unlikely to diminish ongoing binge cocaine abuse.

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

## A SELECTIVE STABILIZER

Dr. See and colleagues focused on aripiprazole for practical reasons: It is generally safe, it is already on the market, and its pharmacological action suggests the potential to reduce relapse. Aripiprazole preferentially binds to dopamine receptors  $D_2$  and  $D_3$ , which are proteins on brain cell surfaces that mediate dopamine's effects on cellular activity. The drug has different effects, depending on the amount of dopamine present. The overall effect is neurochemical modulation: Aripiprazole quiets hyperactive neurons and stimulates sluggish ones through both presynaptic and postsynaptic mechanisms, according to Dr. See. Such stabilization seems to account for the efficacy of aripiprazole as a psychiatric medication and may also underlie its benefit as a relapse-prevention agent.



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"As a neurochemical stabilizer, aripiprazole most likely reduces excess dopamine activity in the mesolimbic reward circuit brought about by drug abuse," says Dr. See. "The medication also may simultaneously boost dopamine in the cortex, particularly the prefrontal circuits, thereby enhancing the ability to suppress the desire for drugs." Although aripiprazole also acts at serotonin receptors, pharmacologists currently consider dopamine stabilization to be its main therapeutic action.

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

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

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

### SOURCE

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

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## Methadone Reduces Rats' Cocaine Seeking

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

By **NIDA Notes Staff**

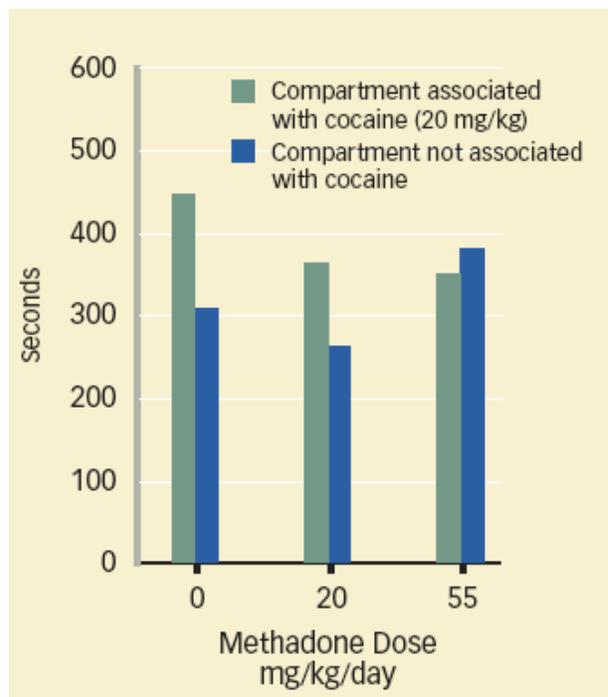
Methadone may prove to be an effective treatment for cocaine as well as opioid abuse, if the results of a recent study with rats, funded by NIDA and the Canadian Institutes of Health Research, can be replicated and applied to people. The animals' cocaine seeking dropped in response to methadone given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

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

### EXTINGUISHING RATS' MOTIVATION

Clinical trials have shown that people who take high-dose methadone for heroin addiction and who are also addicted to cocaine decrease their abuse of both drugs. To Dr. Leri, that observation suggested that methadone might have unexploited potential as a medication to treat cocaine abuse in patients

**COCAINE SEEKING DIMINISHED** In the absence of methadone, each rat in a group of eight spent, on average, more time in a compartment that it associated with cocaine than in one not associated with the drug. When implanted mini-pumps delivered high-dose methadone to the rats, there was no significant difference between the times spent in the two compartments.



both with and without histories of opioid abuse. Accordingly, with colleagues at Concordia University in Montreal and Rockefeller University in New York, Dr. Leri set out to better understand methadone's effect on cocaine seeking.

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

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

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

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

**-Dr. Francesco Leri**

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

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

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

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

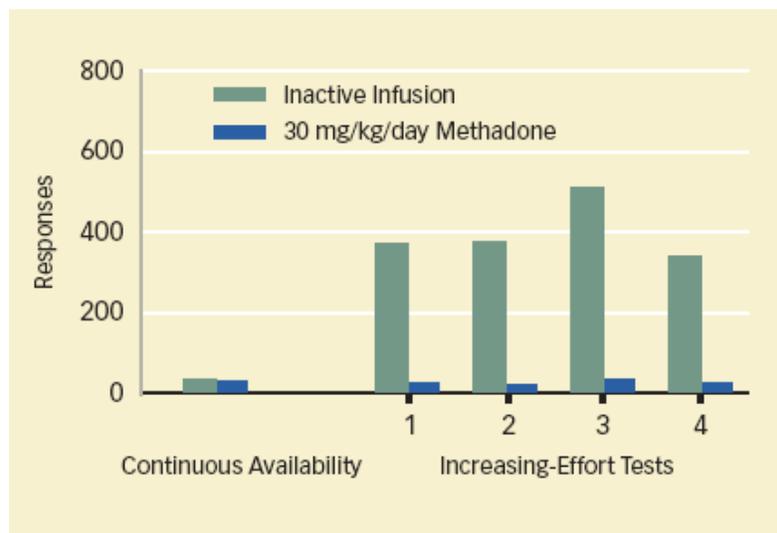
## **BRAIN CORRELATES**

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

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

### **RATS RECEIVING METHADONE EXPEND LITTLE EFFORT TO GAIN COCAINE**

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



In the experiments, rats exposed to three injections of 5 or 20 mg/kg doses of cocaine were found to have more mu-opioid receptor messenger RNA (mRNA)—an indicator of receptor production rates—than animals exposed to three injected doses of the drug at 1 mg/kg. These elevations were less pronounced, however, in rats that were being maintained on 20 mg/day of methadone at the time of the cocaine exposures. Moreover, rats exposed to cocaine while being maintained on 55 mg/kg/day of methadone had mu-opioid mRNA levels that were indistinguishable from those of rats that received no cocaine.

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

methadone brings the endorphins back."

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

## SOURCES

Leri, F., et al. High-dose methadone maintenance in rats: Effects on cocaine self-administration and behavioral side effects. *Neuropsychopharmacology* 32(11):2290-2300, 2007. [[Full Text](#)]

Leri, F., et al. Effects of high-dose methadone maintenance on cocaine place conditioning, cocaine self-administration, and mu-opioid receptor mRNA expression in the rat brain. *Neuropsychopharmacology* 31(7):1462-1474, 2006. [[Full Text](#)]

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Research Findings  
Vol. 21, No. 4 (October 2007)

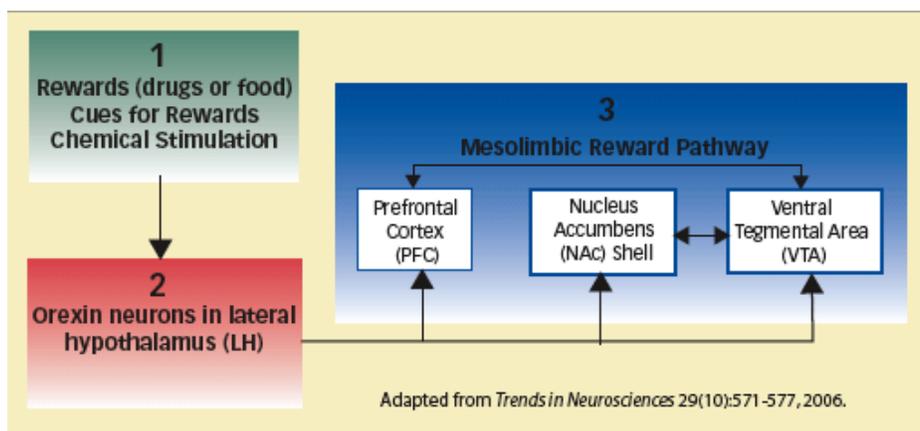
## Neuropeptide Promotes Drug-Seeking and Craving in Rats

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

BY LORI WHITTEN, *NIDA Notes* Staff Writer

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

**OREXIN STIMULATION DRIVES DRUG-SEEKING** Exposure to cues associated with drugs activate the orexin neurons (red), which stimulates neurons in the brain's mesolimbic reward pathway (blue).



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

### OREXIN AND DRUG SEEKING

An observation in animals by Drs. Harris and Aston-Jones also seemed to suggest a possible connection. They noted that lateral hypothalamus (LH) cells

in the same area as orexin neurons were activated during drug seeking using a behavioral assay called conditioned place preference (CPP; for more on CPP, see "[Animal Experiments in Addiction Science](#)"). After repeated morphine injections in one chamber of a test cage and saline in the other, rats gravitate to the drugpaired area in an effort to re-experience the opiate effects. The time they spend in the area—their morphine place preference—indicates how intensely the drug motivates drug seeking. When Drs. Harris and Aston-Jones determined that the LH neurons activated during drug seeking produce orexin, they conducted further experiments.

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

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

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

## **DRUGS MAY USURP FEEDING SYSTEM**

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

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

## **A ROLE IN COCAINE CRAVING?**

Drs. Borgland and Bonci and colleagues at the UCSF Ernest Gallo Clinic and Research Center demonstrated orexin effects on cocaine-related behaviors remarkably consistent with those the Pennsylvania team showed with respect to

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

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

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

## SOURCES

Harris, G.C., Wimmer, M., and Aston-Jones, G. A role for lateral hypothalamic orexin neurons in reward seeking. *Nature* 437(7058):556-559, 2005. [[Abstract](#)]

Borgland, S.L., et al. Orexin A in the VTA is critical for the induction of synaptic plasticity and behavioral sensitization to cocaine. *Neuron* 49(4):589-601, 2006. [[Full Text](#)]

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