UT SOUTHWESTERN MEDICAL CENTER NEWS

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EMBARGOED UNTIL 5 P.M. CST TUESDAY, MARCH 14, 2006

Strength of cocaine cravings linked to brain response

DALLAS – March 14, 2006 – Rats that have a strong craving for cocaine have a different biochemical response to the drug than their less-addicted counterparts, researchers at UT Southwestern Medical Center have found.

The difference lies in the pleasure-seeking area of the brain, according to a study available online and appearing in a future issue of the journal *Neuropsychopharmacology.*

"This work shows that there are profound alterations in the brain mechanisms that regulate motivated behavior with addiction," said Dr. David Self, associate professor of psychiatry at UT Southwestern and senior author of the paper.

"It really shows that the addicted person is ill-equipped to cope because the brain is now wired to make them crave drugs more and get less satisfaction out of the drug or other life events that may be rewarding, and this study found biological changes that would explain these behavioral changes," said Dr. Self.

The researchers looked at dopamine receptors – molecules on cell surfaces that are activated when dopamine or other molecules bind to them. They focused on two types of receptors called D_1 and D_2.

Molecules that activate D_1 are believed to decrease the craving response, while D_2 activators are believed to increase it. Both of the receptors bind to the neurotransmitter dopamine in a part of the brain called the mesolimbic dopamine system.

In the study, rats had tubes surgically implanted that fed into their bloodstream, through which they could give themselves cocaine injections by pressing a lever. Some rats voluntarily gave themselves higher doses of cocaine than others did, an indication that they were more addicted to the cocaine.

The rats then went through three weeks of cocaine withdrawal, during which time they ceased to press the lever. At the late stages of withdrawal, a drug that specifically activated the D_2 receptor was given to see if it would prompt the rats to press the lever again in search of cocaine. In another

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experiment, the rats were given a small dose of cocaine and a drug that activated the D_1 receptor to see if the drug would block them from seeking more cocaine.

The strongly addicted rats responded more aggressively to the craving-enhancing D_2 activator than the less-addicted rats did, and were not as strongly deterred by the D_1 activator.

"It's as if the cocaine-addicted animal is less easily satisfied and more easily induced to seek drugs due to alterations in these receptors," Dr. Self said.

Before the researchers administered cocaine, the rats were tested to see how much they moved around when given D_1 or D_2 activator drugs. Before getting the cocaine, their responses to each drug were the same. After being trained to take the cocaine, the strongly addicted rats were much more sensitive to the D_2 activator but less sensitive to the D1 activator. These tests showed that the difference in sensitivity developed during the addiction process, rather than being already present in the animals from the beginning.

The researchers don't know, however, whether the responses in the rats they studied were due to changes in the numbers of the receptors or to the biochemical actions of the receptors already present. Future research may help clarify those different scenarios, Dr. Self said.

Understanding how receptors control cravings may be applicable to humans, although addiction is a complicated mix of brain biochemistry and learned responses to environmental cues, as well as stress, Dr. Self said.

"If people do become addicted and say they want to quit, their brain system for inhibiting craving is weaker. We want to try to strengthen those systems that help them inhibit their craving," he said.

The lead author in the study was Scott Edwards, a neuroscience graduate student at UT Southwestern. Other UT Southwestern researchers involved in the study were Kimberly Whisler, a research associate in psychiatry, Dwain Fuller, faculty associate in psychiatry, and Dr. Paul Orsulak, professor of psychiatry and pathology.

The work was supported in part by the National Institute on Drug Abuse.

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