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Scientists Identify a Brain Mechanism Underlying Persistent Cocaine Craving
Finding May Lead to New Treatments to Decrease Risk of Relapse

Scientists have identified a mechanism in the brain that helps to explain why craving for cocaine, and the risk of relapse, seems to increase in the weeks and months after drug use is stopped. The research was supported by the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health.

The study¹ published in the May 25 issue of the journal *Nature*, “reveals a novel mechanism for why cocaine craving intensifies after cessation of drug use and suggests a new target for the development of medications to decrease the risk of relapse in abstinent cocaine abusers,” says NIDA Director Dr. Nora Volkow.

Exposure to environmental cues (e.g., people, places, things) previously associated with drug use can trigger drug craving, often leading to relapse. Previous NIDA-funded research using a rat model of drug craving and relapse (published in *Nature* in 2001²) has shown that the responsiveness of rats to cocaine cues progressively increases, rather than decreases, over the first 60 days after cessation of intravenous cocaine self-administration.

In the current study, also in rats, researchers demonstrate that after prolonged periods of forced abstinence from cocaine self-administration, there is an increase in the number of proteins called AMPA glutamate receptors in a brain region known as the nucleus accumbens (a brain area involved in motivation and reward). “The additional AMPA receptors increase the reactivity of the nucleus accumbens to cocaine-related environmental cues, explaining the intensified cue-induced cocaine seeking that occurs after prolonged abstinence from the drug,” explains lead investigator Marina E. Wolf, Ph.D., Professor and Chair of Neuroscience at the Rosalind Franklin University of Medicine and Science in North Chicago. “This happens not only because

¹ Conrad KL, Tseng KY, Uejima JL, Reimers JM, Heng LJ, Shaham Y, Marinelli M, Wolf ME. Formation of accumbens GluR2-lacking AMPA receptors mediates incubation of cocaine craving. *Nature*, May 25, 2008

² Grimm JW, Hope BT, Wise RA, Shaham Y. Incubation of cocaine craving after withdrawal. *Nature* 2001;412(6843):141-2.

there are more AMPA receptors, but also because the new AMPA receptors are atypical - they are missing a particular subunit, and therefore enable stronger stimulation of the nucleus accumbens than typical AMPA receptors,” adds Wolf.

When the investigators blocked these atypical receptors (termed GluR2-lacking AMPA receptors) after prolonged abstinence from cocaine, they were able to substantially decrease intensified cue-induced craving in the rat model. “The finding suggests,” says Wolf, “that medications could be developed to block the atypical GluR2-lacking AMPA receptors in the nucleus accumbens, thus reducing drug craving and the risk for relapse, without interfering with neurotransmission at typical AMPA receptors, which are important for normal brain functions such as learning and memory.”

The research was performed in the laboratories of Wolf, Michela Marinelli, Ph.D., and Kuei Y. Tseng, M.D., Ph.D., at Rosalind Franklin University of Medicine and Science and Yavin Shaham, Ph.D., of the NIDA Intramural Research Program in Baltimore, Maryland.

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