Cocaine: How addiction develops

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Permanent drug seeking and relapse after renewed drug administration are typical behavioral patterns of addiction. Molecular changes at the connection points in the brain's reward center are directly responsible for this. This finding was published by a research team from the Institute of Mental Health (ZI) in Mannheim, the German Cancer Research Center (DKFZ) in Heidelberg and the University of Geneva, Switzerland, in the latest issue of *Neuron*. The results provide researchers with new approaches in the medical treatment of drug addiction.

Addiction leaves detectable traces in the brain: In particular regions of the central nervous system, which produce the messenger substance dopamine, the drug cocaine causes molecular restructuring processes at the synapses, the points of connection between two neurons. As a reaction to the drug, protein subunits are exchanged in specific receptor complexes. As a result, the modified synapse becomes able to transmit nervous signals with enhanced strength – a phenomenon that has been termed 'drug-induced synaptic plasticity'. Researchers have suspected for many years that drug-induced synaptic plasticity plays a crucial role in addiction development. However, this hypothesis has not yet been proven experimentally.

Using genetic engineering, researchers headed by Professor Dr. Günther Schütz at the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) have now been able to selectively switch off those protein components in dopamine-producing neurons that are integrated into the receptor complexes under the influence of cocaine. Jointly with the team of Professor Dr. Rainer Spanagel at the

Central Institute of Mental Health (Zentralinstitut für Seelische Gesundheit, ZI) in Mannheim and the research group of Professor Dr. Christian Lüscher at Geneva University, the Heidelberg researchers studied the changes in physiology and behavior of the genetically modified animals.

The scientists performed standardized tests to measure addictive behavior in the animals. At first sight, both the genetically modified and the control animals displayed the usual behavior under the influence of cocaine. Forced to increase their agility, the lab animals covered significantly greater running distances and preferentially frequented those places where they had been conditioned to be regularly administered the drug.

If normal mice do not find drugs at the familiar places over a longer period of time, their addictive behavior and preference for the cocaine-associated places subside. However, this is not true for animals whose receptor subunit GluR1 has been switched off: These mice invariably frequent the places where they expect to find the drug, i.e., their addictive behavior persists.

Mice whose NR1 protein has been switched off have surprised scientists with a different conspicuous behavior. If control animals withdrawn from cocaine are readministered the drug after some time, addictive behavior and drug seeking are reactivated. In contrast, NR1 deficient animals proved to be resistant to relapsing into the addiction.

"It is fascinating to observe how individual proteins can determine addictive behavioral patterns," says Günther Schütz, and his colleague Rainer Spanagel adds: "In addition, our results open up whole new prospects for treating addiction. Thus, blocking the NR1 receptor might protect from relapsing into addiction. Selective activation of GluR1 would even contribute to 'extinguishing' the addiction."

Source: Helmholtz Association of German Research Centres