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New study details how cocaine really works in the brain, suggests possibile addiction treatment

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A research team led by the University of Colorado Boulder has discovered a mechanism in the brain that is key to making cocaine seem pleasurable, a finding that could lead to a drug treatment for fighting addiction.

The findings build on past research also involving CU-Boulder that found the same mechanism in the brain also interacts with heroin, oxycodone, morphine and other opioid drugs to amplify their addictiveness. The latest study suggests that the mechanism plays a key role in the addictiveness of many abused drugs, possibly including methamphetamine and alcohol.

The study, which also involved scientists at the University of Adelaide in Australia and the National Institute on Drug Abuse, is being published today in the *Nature* journal *Molecular Psychiatry*.

Cocaine works by increasing the amount of dopamine, a chemical associated with feelings of pleasure, in the brain. Dopamine is part of the brain's reward pathway, and it's released to encourage animals to repeat behaviors, typically those that are key for survival such as eating and reproduction.

Researchers have known that cocaine blocks the brain's ability to reabsorb dopamine, increasing its excitatory effects on neurons of the

drug reward pathway.

In the new study, the research team shows that cocaine's impact on neurons does not fully explain the drug's dramatic effects on reward. In laboratory studies involving rats and mice, the scientists demonstrated that a second mechanism in the brain potently contributes to the abuse potential of cocaine.

The second mechanism centers on glial cells, the key component of the brain's immune system. Cocaine binds to glial cells at a location called Toll Like Receptor 4 (TLR4). The glial cells then trigger an inflammatory response in the brain, exciting neurons and further increasing the amount of dopamine pumped into the brain.

"We've demonstrated conclusively that cocaine interacts with TLR4 to produce a pro-inflammatory effect in the brain," said Alexis Northcutt, a CU-Boulder research associate in the Department of Psychology and Neuroscience and lead author of the paper. "The effect is necessary to convey the drug's rewarding effects. Without it, reward is greatly reduced."

The research team found that blocking the ability of cocaine to bind to TLR4 dramatically reduces the rewarding effects of cocaine. That finding suggests that blocking TLR4 on glial cells could be a therapeutic approach for treating drug abuse.

Previous research in the lab of CU-Boulder Professor Linda Watkins, the senior author of this study, has shown that a drug known as (+)-naltrexone, can be used to keep opioids from binding to TLR4.

"We found the same results when studying cocaine, which means the same drug, (+)-naltrexone, might be useful for treating a wider range of drug addictions," Watkins said. "The exciting news is that this drug is

already in development by Xalud Therapeutics."

San Francisco-based Xalud Therapeutics, a CU-Boulder spinoff company based on Watkins' research, is currently moving (+)-naltrexone toward human clinical trials.

Provided by University of Colorado at Boulder