

Science Now

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A shocking reversal of cocaine's effect on brain

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FEBRUARY 5, 2015, 7:03 PM

We are starting to know a lot of detail about how cocaine alters the brain's pleasure circuitry. Finding ways to try to undo the drug's microscopic mayhem has been another matter.

This week, researchers may have moved a small step closer, using a combination of an already approved drug and some low-frequency electrical stimulation. The experiments on mice reversed the effect cocaine has on the signaling of neurons in the brain's reward center, according to a study published online Thursday in the journal **Science**.

Researchers at University of Geneva have been probing at neurons in the nucleus accumbens, a kind of hub that mediates information from areas involved in planning and cognition and those involving emotions and context. Its reward-reinforcement role has long been connected with addictive behavior, largely through circuits running on dopamine, a chemical that helps pass signals across the synapses between neurons.

Over the last five years, researchers have used optogenetics to delve into the synapse changes induced by cocaine in one particular class of neurons. The technique, which directs tiny pulses of light at brain cells genetically altered to be light-sensitive, helped demonstrate not only **how cocaine alters signaling** of neurons, but how to reverse the effect.

Unfortunately, optogenetic tinkering is not ready for prime time in humans, said University of Geneva neuroscientist Christian Luscher, who led the research. He set out to adapt the same technique to a less

precise tool -- deep brain stimulation with electrical pulses. Using implanted electrodes, deep brain stimulation has been used widely to treat Parkinson's disease, but had shown less success with addiction.

"It's still invasive, but we have 25 years of experience," said Luscher, who uses the therapy regularly. At the same high frequency as used in Parkinson's patients, the stimulation had only a temporary effect, according to the study. He applied it at frequencies closer to those used in optogenetics.

"It still didn't work," he said.

A closer look, however, revealed that the electrical pulses were tamping down on the cocaine-related signaling changes but simultaneously stimulating dopamine signaling.

"When we then added a pharmacological substance that would block the effect of the dopamine, then we got the result," he said. Neither the drug alone nor the electrical stimulation were enough to work, according to the study.

The effects of the therapy on the brain activity of mice was monitored only a short time, so it is unclear how long it might last.

"After one day it's totally gone, and after one week it's partially coming back but it's still very much suppressed," Luscher said.

The proof of concept in mice suggests human trials might be worthwhile, Luscher said.

"We have FDA approval to implant electrodes. The antagonist we used is also FDA approved ... so I think all the ingredients could be there and one could try that," Luscher said.

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