Scientists uncover molecular roots of cocaine addiction in the brain

May 22 2013

Researchers at Johns Hopkins have unraveled the molecular foundations of cocaine's effects on the brain, and identified a compound that blocks cravings for the drug in cocaine-addicted mice. The compound, already proven safe for humans, is undergoing further animal testing in preparation for possible clinical trials in cocaine addicts, the researchers say.

"It was remarkably serendipitous that when we learned which brain pathway cocaine acts on, we already knew of a compound, CGP3466B, that blocks that specific pathway," says Solomon Snyder, M.D., a professor of neuroscience in the Institute for Basic Biomedical Sciences at the Johns Hopkins University School of Medicine. "Not only did CGP3466B help confirm the details of cocaine's action, but it also may become the first drug approved to treat cocaine addiction." Details of the research appear May 22 on the website of the journal *Neuron*.

Snyder, who won a 1978 Lasker Award for identifying the brain's own opiate receptors, and his team have been studying the brain for decades. Twenty years ago, they discovered that the gas nitric oxide (NO) is a major player in the complex signaling network that lets our neurons coordinate activity with one another. Snyder and his team have since studied many of the proteins in that network that interact with NO, including GAPDH, a protein best known for regulating how cells store and use sugars.

A few years ago, Snyder's team and other researchers found that if NO

reacts with GAPDH, GAPDH can then bind to another protein that whisks GAPDH away from its humdrum sugar metabolism tasks and into the nucleus, the cell's control center. There, depending on what other chemical signals are present, the GAPDH can either stimulate the neuron's growth or activate a self-destruct program—called apoptosis—that will kill the neuron.

In his research on GAPDH, Snyder came across a paper published in 1998 by scientists at Novartis. The company had identified a molecule, CGP3466B, that in laboratory tests protected neurons from degeneration by inhibiting apoptosis, and had tested it in clinical trials on patients with Parkinson's disease and amyotrophic lateral sclerosis, or ALS. But while the drug had few side effects, it wasn't an effective treatment for either of the diseases. Before Novartis gave up on the drug, however, its scientists investigated which molecules it interacted with in the brain, hoping to learn the reasons for its neuroprotective effects. Their only hit was GAPDH, a result that no doubt left the researchers scratching their heads, Snyder says. After all, CGP3466B seemed so promising partly because its effects were so specific—it appeared to do nothing except protect neurons from self-destructing. How would it accomplish that by acting on GAPDH, a signaling molecule with such a broad role in sugar metabolism? Though the study seemed like a dead end, the researchers published it anyway.

When Snyder saw the paper, he connected it to his team's findings, inferring that CGP3466B might work by preventing GAPDH from entering the nucleus to trigger cell death. In a study published in 2006, he and other Johns Hopkins researchers tested two compounds similar to CGP3466B to see if they would block GAPDH from triggering cell death under the types of highly stressful conditions that would normally cause apoptosis. The protective drugs worked, the team found, by disrupting with extraordinary potency the reaction between NO and GAPDH, which ultimately blocked GAPDH from binding to the protein

that ferries it into the nucleus.

In the most recent study, M.D./Ph.D. student Risheng Xu worked with other members of Snyder's team to investigate whether cocaine works through the NO signaling network, and if so, how. Using mice, they found that cocaine induces NO to react with GAPDH so that GAPDH moves into the nucleus. At low doses of cocaine, the GAPDH in the nucleus will stimulate the neuron, but at higher doses it activates the cell's self-destruct pathway. "This explains why cocaine can have very different effects depending on the dosage," Xu says.

The team then did experiments to see whether CGP3466B, which blocks the reaction between NO and GAPDH, would also block the effects of cocaine. In one experiment, they placed mice in a cage with two rooms, and trained them to expect occasional doses of cocaine in one of the rooms. When the mice began spending most of their time in that room, it showed they had become addicted to cocaine. But when treated with CGP3466B, the mice went back to spending roughly equal amounts of time in both rooms: Their cravings had abated, Xu says.

"What's exciting is that this drug works at very low doses, and it also appears only to affect this specific pathway, making it unlikely to have unwanted side effects," Xu notes. "We also know from Novartis' early-stage clinical trials that the drug exhibits few documented side effects in people."

CGP3466B is now owned by a different company. With the results of the current study in hand, Snyder has brokered a deal between that company and the National Institute on Drug Abuse (NIDA) for NIDA to test CGP3466B as a treatment for cocaine addiction. NIDA will first conduct more animal trials, and then, if all goes well, move on to clinical trials in addicts. "Our study's results provide a direct demonstration that actions of a major psychotropic drug are mediated by the NO-GAPDH

system and afford an unprecedented, straightforward approach to the treatment of cocaine abuse and neurotoxicity," Snyder says.

Another member of the research team, Nilkanta Sen, Ph.D., cautions that more research is needed to see whether CGP3466B will fulfill its apparent promise. But, says Sen, now an assistant professor at Georgia Regents University, "what we cannot deny is that this study provides a new hope in the field of addiction research."

Provided by Johns Hopkins University School of Medicine