Experimental treatments for cocaine addiction may prevent relapse

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Doctors have used the drug disulfiram to help patients stay sober for several decades. It interferes with the body's ability to metabolize alcohol, giving a fierce hangover to someone who consumes even a small amount of alcohol.

More recently, disulfiram was shown to be effective in treating cocaine addiction as well, even though alcohol and cocaine affect the nervous system in different ways.

Now, researchers at Emory University School of Medicine have identified how disulfiram may exert its effects, and have shown that a newer drug with fewer side effects works by the same mechanism.

The results are published online this week by the journal Neuropsychopharmacology. Research assistant professor Jason Schroeder, PhD, and graduate student Debra Cooper are co-first authors of the paper, and the research also involved collaborations with P. Michael Iuvone, PhD, director of research at the Emory Eye Center, Gaylen Edwards, DVM, PhD, head of the department of physiology and pharmacology at the University of Georgia's College of Veterinary Medicine, and Philip Holmes, PhD, professor of psychology at the University of Georgia.

"Disulfiram has several effects on the body: it interferes with alcohol metabolism, but it inhibits several other enzymes by sequestering copper, and can also damage the liver," says senior author David Weinshenker,

PhD, associate professor of human genetics at Emory University School of Medicine. "We wanted to figure out how disulfiram was working so we could come up with safer and potentially more effective treatments."

In treating cocaine addiction, there are several challenges: not only getting people to stop taking the drug, but also preventing relapse. Cocaine boosts the levels of several neurotransmitters, including dopamine and norepinephrine, at the junctions between nerve cells by blocking the machinery the brain uses to remove them.

Under normal conditions, dopamine is important for the sensation of pleasure produced by natural rewards such as food or sex, Weinshenker says. Cocaine "hijacks" the dopamine system, which plays a large role in addiction. Similarly, norepinephrine has a role in attention and arousal, but its overactivation can trigger stress responses and relapse, he says.

Weinshenker's team showed that disulfiram prevents rats from seeking cocaine after a break, a model for addicts tempted to relapse. At the same time, it doesn't stop them from taking cocaine when first exposed to it, or from enjoying their food.

Disulfiram appears to work by inhibiting dopamine beta-hydroxylase, an enzyme required for the production of norepinephrine. A dose of disulfiram that lowers the levels of norepinephrine in the brain by about 40 percent is effective, while doses that do not reduce norepinephrine have no effect on relapse-like behavior in rats.

To confirm that the beneficial effects of disulfiram were because of dopamine beta-hydroxylase inhibition, the researchers turned to a drug called nepicastat, which was originally developed for the treatment of congestive heart failure in the 1990s.

"Nepicastat is a selective dopamine beta-hydroxylase inhibitor that does

not sequester copper or impair a host of other enzymes like disulfiram," Weinshenker says. "We reasoned that if disulfiram is really working through dopamine beta-hydroxylase, then nepicastat might be a better alternative."

Researchers at the University of Texas Medical Branch at Galveston have recently completed a Phase I safety trial studying nepicastat for the treatment of cocaine addiction in human subjects.

More information: J.P. Schroeder et al. Disulfiram Attenuates Drug-Primed Reinstatement of Cocaine Seeking via Inhibition of Dopamine β-Hydroxylase. *Neuropsychopharmacology*, 35, page numbers TK (2010).

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