Bile acids from the gut could help to treat cocaine abuse

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A pile of cocaine hydrochloride. Credit: DEA Drug Enforcement Agency, public domain

Bile acids that aid fat digestion are also found to reduce the rewarding properties of cocaine use, according to a study publishing on July 26 in the open-access journal *PLOS Biology* by India Reddy, Nicholas Smith, and Robb Flynn of Vanderbilt University, Aurelio Galli of the University of Alabama at Birmingham, and colleagues. The results point to potential new strategies for treatment of cocaine abuse.

The study builds on evidence that bile acids influence the brain's reward system. Bile acids are normally released from the gall bladder into the upper part of the small intestine, where they emulsify fats for absorption, before being recycled further down the small intestine. In bile diversion surgery, an experimental treatment for weight loss, bile is released at the end of the small intestine, increasing the amount of bile acids that enter the general circulation. Mice treated with this surgery have less appetite for high-fat foods, which suggests that bile acids affect brain reward pathways.

To test this hypothesis, the authors first showed that surgery produced an elevation of bile acids in the brain, resulting in a reduction in dopamine release in response to cocaine. Mice receiving the surgery also showed less preference for the cocaine-associated chamber, indicating that cocaine was probably less rewarding.

The authors next administered a drug, called OCA, that mimics the effect of bile at its receptor in the brain, called TGR5. They found that OCA mimicked the cocaine-related results of surgery in untreated mice, strengthening the case that the effects of surgery were due to elevated levels of bile acids. Knocking out TGR5 from the brain's nucleus accumbens, a central reward region, prevented bile acids from reducing cocaine's effects, confirming that signaling through this receptor was responsible for the cocaine-related results of bile acid elevation.

"These findings redefine the physiological significance of bile acid signaling and highlight the importance of determining whether bile acid analogues represent a viable pharmacological treatment for cocaine abuse," Galli said. OCA, the compound that activated the bile acid receptor in this study, is approved for the treatment of primary biliary cirrhosis (Intercept Pharmaceuticals) offering fast translational opportunities for pharmacotherapies. This study also contributes to a greater understanding of how gut-based signaling influences higher order central functions such as reward.

The gut-to-brain axis regulates diverse behavioral phenotypes. The authors reveal that a new gut-based bariatric surgical approach chronically elevates systemic bile acids and reduces cocaine reward. These findings redefine the physiological significance of bile acid signaling and highlight the importance of determining whether bile acid analogues represent a viable pharmacological treatment for cocaine abuse.

More information: Reddy IA, Smith NK, Erreger K, Ghose D, Saunders C, Foster DJ, et al. (2018) Bile diversion, a bariatric surgery, and bile acid signaling reduce central cocaine reward. *PLoS Biol* 16(7): e2006682. doi.org/10.1371/journal.pbio.2006682