Study with rats suggests drinking alcohol increases risk of addiction to cocaine

2 November 2017, by Bob Yirka

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

(Medical Xpress)—A team of researchers working at Columbia University has found a possible link between prior use of alcohol and an increased risk of cocaine addiction. In their paper published on the open access site *Science Advances,* the group describes their study, what they found and why they believe more studies are required to better understand "gateway drugs."

Most everyone knows that cocaine is addictive, but few are aware that it is more addictive for some people than for others. Prior research has shown, for example, that just 21 percent of people who use cocaine become compulsive users. In this new effort, the researchers sought to learn more about the impact of so-called gateway drugs—drugs that lead people to take other, stronger drugs. More specifically, they wondered if alcohol might be a gateway to cocaine use and subsequent addiction.

To better understand the connection between drinking alcohol and taking cocaine, the researchers enlisted the assistance of lab rats—some were given alcohol for 10 days and some were not, then both were given cocaine to see if prior exposure to alcohol impacted their desire for cocaine. The researchers found that it did; those rats that had been drinking prior to being given cocaine were clearly more interested in getting more. This was demonstrated by removing their resource, which was obtained by pressing the lever that normally delivered cocaine. Those rats that were not given alcohol before the cocaine kept pressing the lever on average 18 times. In sharp contrast, those that had been given alcohol pressed the lever on average 58 times—they were also more willing to endure pain to get it. This was shown by attaching a device that delivered a mild shock—those given alcohol were found willing to endure jolts as strong as 0.3 mA to get their fix.

The researchers also found a physical cause for the increased desire for the drug—the brains of those rats that had consumed alcohol for 10 days had reduced levels of two proteins that normally serve as a brake on reward circuitry. With reduced levels of these proteins, the rats had no reason to resist the pleasure the drug gave them.

More information: Edmund A. Griffin et al. Prior alcohol use enhances vulnerability to compulsive cocaine self-administration by promoting degradation of HDAC4 and HDAC5, *Science Advances* (2017). DOI: 10.1126/sciadv.1701682

Abstract

Addiction to cocaine is commonly preceded by experiences with legal or decriminalized drugs, such as alcohol, nicotine, and marijuana. The biological mechanisms by which these gateway drugs contribute to cocaine addiction are only beginning to be understood. We report that in the rat, prior alcohol consumption results in enhanced addiction-like behavior to cocaine, including continued cocaine use despite aversive consequences. Conversely, prior cocaine use has no effect on alcohol preference. Long-term, but not short-term, alcohol consumption promotes

proteasome-mediated degradation of the nuclear histone deacetylases HDAC4 and HDAC5 in the nucleus accumbens, a brain region critical for reward-based memory. Decreased nuclear HDAC activity results in global H3 acetylation, creating a permissive environment for cocaine-induced gene expression. We also find that selective degradation of HDAC4 and HDAC5, facilitated by the class II–specific HDAC inhibitor MC1568, enhances compulsive cocaine self-administration. These results parallel our previously reported findings that the gateway drug nicotine enhances the behavioral effects of cocaine via HDAC inhibition. Together, our findings suggest a shared mechanism of action for the gateway drugs alcohol and nicotine, and reveal a novel mechanism by which environmental factors may alter the epigenetic landscape of the reward system to increase vulnerability to cocaine addiction.

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