How the brain puts the brakes on the negative impact of cocaine

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Research published by Cell Press in the January 12 issue of the journal *Neuron* provides fascinating insight into a newly discovered brain mechanism that limits the rewarding impact of cocaine. The study describes protective delayed mechanism that turns off the genes that support the development of addiction-related behaviors. The findings may lead to a better understanding of vulnerability to addiction and as well as new strategies for treatment.

Drug addiction is associated with persistent and abnormal changes in the reward circuitry of the brain, and drug-induced changes in gene expression are thought to contribute to addiction behaviors. Recent research with rodent models of addiction has implicated histone deacetylases (HDACs), which are modulators of gene expression, in the regulation of cocaine-induced behaviors. However, how cocaine regulates the function of HDACs and whether this regulation can modify addiction-related behaviors was not known.

"HDAC5 in the nucleus accumbens, a key brain region involved in drug abuse, limits the rewarding impact of cocaine and the long-lasting memory of places where the drug was taken, particularly after prior cocaine exposure," explains senior study author Dr. Christopher W. Cowan from the University of Texas Southwestern Medical Center. "However, it was not clear whether this was a passive role for HDAC5 or whether drugs of abuse might regulate its function after drug exposure." In the current study, Dr. Cowan and colleagues explored how cocaine might regulate HDAC5 and the development of drug reward-associated behaviors.

Using a rodent model, the researchers discovered that cocaine triggered a novel signaling pathway that caused HDAC5 to move to the cell nucleus, where gene expression occurs, and they found that this process was essential for HDAC5 to limit the development of cocaine reward-associated behaviors. "Our findings reveal a new molecular mechanism by which cocaine regulates HDAC5 function to antagonize the rewarding impact of cocaine, likely by putting a brake on drug-stimulated genes that would normally support drug-induced behavioral changes," concludes Dr. Cowan. "Deficits in this process may contribute to the development of maladaptive behaviors associated with addiction following repeated drug use in humans and may help to explain why some people are more vulnerable to addiction than others."

More information: Taniguchi et al.: "Histone deacetylase 5 limits cocaine reward through cAMP-induced nuclear import." DOI:10.1016/j.neuron.2011.10.032

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