New mechanism underlying cocaine addiction discovered

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Researchers have identified a key epigenetic mechanism in the brain that helps explain cocaine's addictiveness, according to research funded by the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health.

The study, published in the January issue of the journal *Science*, shows how cocaine affects an epigenetic process (a process capable of influencing gene expression without changing a gene's sequence) called histone methylation. These epigenetic changes in the brain's pleasure circuits, which are also the first impacted by chronic cocaine exposure, likely contribute to an acquired preference for cocaine.

"This fundamental discovery advances our understanding of how cocaine addiction works," said NIDA Director Dr. Nora D. Volkow. "Although more research will be required, these findings have identified a key new player in the molecular cascade triggered by repeated cocaine exposure, and thus a potential novel target for the development of addiction medications."

Researchers gave one group of young mice repeated doses of cocaine and another group repeated doses of saline with a final dose of cocaine to determine how the effects of chronic cocaine exposure differed from one-time exposure. The study confirms that one of the mechanisms by which cocaine alters the reward pathway is by repressing G9A, a histone demethylating enzyme that plays a critical role in epigenetic control of gene expression.

As previously observed, animals exposed to chronic cocaine displayed dramatic alterations in gene expression as well as a strong preference for cocaine. For the first time, the authors were also able to show that by experimentally reversing the cocaine induced repression of G9a, they could block the changes in gene expression and inhibit the enhanced preference for cocaine.

"The more complete picture that we have today of the genetic and epigenetic processes triggered by chronic cocaine give us a better understanding of the broader principles governing biochemical regulation in the brain which will help us identify not only additional pathways involved but potentially new therapeutic approaches," said Dr. Eric J. Nestler, study investigator and director of the Brain Institute at Mount Sinai School of Medicine.

Provided by NIH/National Institute on Drug Abuse