# Mechanism links substance abuse with vulnerability to depression

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It is well established that a mood disorder can increase an individual's risk for substance abuse, but there is also evidence that the converse is true; substance abuse can increase a person's vulnerability to stress-related illnesses. Now, a new study finds that repeated cocaine use increases the severity of depressive-like responses in a mouse model of depression and identifies a mechanism that underlies this cocaine-induced vulnerability. The research, published by Cell Press in the August 25 issue of the journal *Neuron,* may guide development of new treatments for mood disorders associated with substance abuse.

"Clinical evidence shows that substance abuse can increase an individual's risk for a mood disorder," explains senior study author, Dr. Eric Nestler from Mount Sinai School of Medicine "However, although this is presumably mediated by drug-induced neural adaptations that alter subsequent responses to stress, the mechanisms underlying this phenomenon were largely unexplored."

Dr. Nestler and colleagues examined whether histone H3 lysine 9 dimethylation (H3K9me2), a prominent type of chromatin modification, might be involved in the effects of repeated cocaine use on vulnerability to depressive-like behaviors. Histones are found in the nucleus where they package the DNA into chromatin, and changing the number of histone methyl groups can alter gene expression. A reduction in H3K9me2 reflects a decrease in the number of histone methyl groups, and previous human and animal studies have found a link between histone methylation and mood disorders.

The researchers found that cocaine increases the susceptibility of mice to stress in a well-established model of depression and that decreased H3K9me2 in the nucleus accumbens, a major reward center in the brain, was a central mechanism linking cocaine with stress vulnerability. Importantly, knockout of an enzyme called G9a that controls H3K9me2 in the nucleus accumbens was sufficient to enhance an animal's vulnerability to stress, while excess G9a in the same region blocked the ability of cocaine to increase stress susceptibility.

The researchers went on to show that this G9a-mediated resilience to stress was mediated, in part, through repression of the BDNF-TrkB-CREB signaling pathway. This is significant because BDNF-TrkB-CREB signaling is increased in the nucleus accumbens by exposure to stress or cocaine and promotes both depressive and addictive behaviors. "Together, our results provide fundamentally novel insight into how prior exposure to a drug of abuse enhances vulnerability to depression and other stress-related disorders," concludes Dr. Nestler. "Identifying such common regulatory mechanisms may aid in the development of new therapies for addiction and depression."

Provided by Cell Press