Enzyme regulates brain pathology induced by cocaine, stress

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Researchers have uncovered a key genetic switch that chronic cocaine or stress influences to cause the brain to descend into a pathological state. In studies with mice they showed how chronic cocaine changes gene activity to enhance the addictive reward from the drug. And they showed similarly how chronic stress induces the same kinds of changes that hypersensitizes the brain, causing depression-like symptoms.

The researchers said their basic finding in the animals could lead to better treatments for addiction, depression and other psychiatric disorders.

Eric Nestler and colleagues published their findings in the November 8, 2007, issue of the journal *Neuron*, published by Cell Press.

In their experiments, the researchers explored how chronic cocaine or stress exerts “epigenetic” control of genes in the brain. Such control involves repressing or activating genes by altering the structure of the chromatin that enwraps genes. Specifically, the researchers explored whether chronic cocaine or stress affect an enzyme called histone deacetylase 5 (HDAC5). Normally, HDAC5 represses specific genes by removing molecules called acetyl groups from the histone proteins that make up the chromatin surrounding them. The researchers’ previous studies had shown that chronic cocaine administration in mice caused an increase in acetyl groups in a brain region called the nucleus accumbens (NAc), known to be involved in response to cocaine or stress.

The researchers' studies showed that giving mice chronic cocaine led to a reduction in HDAC5, allowing some 172 genes to be activated. What's more, they found that this loss of HDAC5 in the NAc made the mice more sensitive to the reward of chronic cocaine. They determined the animals' reward-sensitivity to cocaine by measuring the mice's preference for an area of a box that they were taught to associate with receiving cocaine.

The researchers also studied whether the animals' adaptation to chronic stress involved HDAC5 levels. In these experiments, they exposed mice to aggressive mice and measured the resulting depressive behavior. The researchers found that such stress also reduced HDAC5 function, although through a different mechanism than for chronic cocaine.

"These data demonstrate a crucial role for HDAC5 in regulating behavioral adaptations to chronic stress as well as chronic cocaine and suggest that HDAC5 contributes to a molecular switch between acute stress responses and more long-lasting depression-like maladaptations," wrote the researchers.

"The functions of HDAC5 described here provide new insight into the pathogenesis of drug addiction, depression, and other stress-related syndromes," they wrote. "This fundamentally new insight into the molecular underpinnings of chronic maladaptation in brain could lead to the development of improved treatments for addiction, depression, and other chronic psychiatric disorders."

Source: Cell Press

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