Brain DNA 'remodeled' in alcoholism

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Reshaping of the DNA scaffolding that supports and controls the expression of genes in the brain may play a major role in the alcohol withdrawal symptoms, particularly anxiety, that make it so difficult for alcoholics to stop using alcohol.

The finding is reported by researchers at the University of Illinois at Chicago and the Jesse Brown VA Medical Center in the April 2 issue of the *Journal of Neuroscience*.

DNA can undergo changes in function without any changes in inheritance or coded sequence. These "epigenetic" changes are minor chemical modifications of chromatin -- dense bundles of DNA and proteins called histones.

"This is the first time anyone has looked for epigenetic changes related to chromatin remodeling in the brain during alcohol addiction," said Dr. Subhash C. Pandey, professor and director of neuroscience alcoholism research at the UIC College of Medicine and the Jesse Brown VA Medical Center in Chicago, the lead author of the study.

Chemical modification of histones can change the way DNA and histones are wound up together. Histone acetyltransferases (HATs) are enzymes that add acetyl groups to histones and loosen the packing, promoting gene expression. On the other hand, histone deacetylases (HDACs) remove acetyl groups from histones, causing them to wrap with DNA more tightly, decreasing gene expression.

The UIC researchers had previously shown in an animal model that levels of neuropeptide Y in the amygdala modulate anxiety and alcohol-drinking behavior. In the new study, they looked at the HDAC activity, acetylation of histones, and expression of the genes for NPY in the amygdala and the anxiety-like behaviors associated with withdrawal from chronic alcohol use.

Pandey and his colleagues found that acute exposure to alcohol decreases HDAC activity; increases the acetylation histones; increases levels of NPY -- and reduced anxiety in the animals.

Conversely, anxiety-like behaviors during withdrawal in animals with chronic alcohol exposure was associated with an increase in HDAC activity and decrease in histones acetylation and NPY levels.

Importantly, blocking the observed increase in HDAC activity using an HDAC inhibitor during alcohol withdrawal brought up histone acetylation and NPY expression levels in the amygdala and prevented the development of anxiety-like behaviors.

"Our findings suggest that HDAC inhibitors may have potential as therapeutic agents in treating alcoholism," Pandey said.

The researchers also found that levels of a protein known as CREB binding protein, which has HAT enzymatic activity, were increased by acute alcohol but were decreased during ethanol withdrawal.

They concluded that the enzymes that are involved in remodeling of chromatin play an important role in the anxiety that accompanies alcohol withdrawal as well as in the anti-anxiety effects of acute alcohol use.

"We need new strategies to treat alcoholism that are directed toward the prevention of withdrawal symptoms," Pandey said. "Anxiety associated

with withdrawal from alcohol abuse is a key factor in the maintenance of alcohol addiction."

Source: University of Illinois at Chicago