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Adolescent Drinking Affects Adult Behavior Through Long-Lasting Changes in Genes

'Epigenetic' changes interrupt brain development

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Newswise — Binge-drinking during adolescence may perturb brain development at a critical time and leave lasting effects on genes and behavior that persist into adulthood.
The findings, by researchers at the University of Illinois at Chicago College of Medicine using an animal model, are reported online in the journal *Neurobiology of Disease*.

"This may be the mechanism through which adolescent binge-drinking increases the risk for psychiatric disorders, including alcoholism, in adulthood," says lead author Subhash Pandey, professor of psychiatry and director of neuroscience alcoholism research at UIC.

Pandey and his colleagues used experimental rats to investigate the effects of intermittent alcohol exposure during the adolescent stage of development.

On-and-off exposure to alcohol during adolescence altered the activity of genes needed for normal brain maturation, said Pandey, who is also a research career scientist at the Jesse Brown VA Medical Center. The gene alterations "increased anxiety-like behaviors and preference for alcohol in adulthood," he said.

The behavioral effects, he said, were due to "epigenetic" changes -- "which previous research has shown can be influenced through environmental substances, including alcohol." Epigenetic changes can be long-lasting or permanent in an individual. Previous studies have shown that some epigenetic changes can be heritable.

Epigenetic changes are chemical modifications of the DNA or of the proteins around which DNA is wound, like thread on a spool. Modification of these proteins, called histones, can change how loosely or tightly the DNA is wound. Genes that lie within DNA that is tightly wrapped around the histones are less

active than they are if the DNA is loosely wrapped. The looser the DNA is coiled, the more accessible are the genes to the cellular machinery that "expresses" them.

Epigenetic changes regulate many processes, including brain development and maturation during adolescence. Changes to the histones expose the genes needed to form new synaptic connections, or to prune unneeded neurons.

To model adolescent binge-drinking in humans, the researchers gave 28-day-old rats alcohol for two days in a row, followed by two days off, and repeated this pattern for 13 days. Some rats were followed into adulthood and observed for abnormal behaviors. They were offered both alcohol and water, and their alcohol-drinking behavior was monitored.

Rats exposed to alcohol during adolescence exhibited changes in behavior that lasted into adulthood, long after exposure to alcohol ended. They showed increased anxiety-like behaviors and drank more alcohol in adulthood.

When the researchers analyzed tissue from a part of the brain called the amygdala, they found in the exposed rats that the DNA and histones appeared to be tightly wrapped. They also found increased levels of a protein called HDAC2, which modifies histones in a way that causes DNA to be wound tighter around them.

These epigenetic changes in turn were linked to lowered expression of a gene that nerve cells need in order to form new synaptic connections. Pandey believes the lowered activity of this gene may be due to the tighter winding of its DNA. The diminished expression of the gene persisted in adulthood, even if alcohol exposure was stopped weeks before. The researchers observed diminished nerve connectivity in the amygdalae of these affected adult rats.

"Our study provides a mechanism for how binge-drinking during adolescence may lead to lasting [epigenetic] changes ... that result in increased anxiety and alcoholism in adults," Pandey said. Intermittent alcohol exposure "degrades the ability of the brain to form the connections it needs to during adolescence."

"The brain doesn't develop as it should, and there are lasting behavioral changes associated with this."

But a pharmacological experiment hinted at the possibility of a treatment.

When adult rats that had been exposed to alcohol during adolescence were given a cancer drug known to block the activity of HDAC2, the drug restored expression of the gene needed for synapse formation. The DNA was observed to be less tightly coiled, as expected.

Most importantly, the rats exhibited less anxiety and reduced alcohol intake.
"We aren't sure if the drug needs to be given long term during adulthood in order to completely reverse the harmful effects of adolescent alcohol exposure," Pandey said. Further experiments with this and other epigenetic drugs are planned.

Amul Sakharkar, Lei Tang and Huaibo Zhang of the UIC College of Medicine are co-authors on the paper.

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