Research reveals secrets of alcohol's effect on brain cells

December 7 2007

Alcohol triggers the activation of a variety of genes that can influence the health and activity of brain cells, and new research from Weill Cornell Medical College in New York City sheds light on how that process occurs.

The findings, published in the Nov. 21 issue of *The Journal of Neuroscience*, may also edge scientists closer to understanding alcohol-linked disorders such as the brain damage associated with chronic alcoholism, and the abnormal brain development seen in the fetal alcohol syndrome (FAS).

"If you are going to understand the biological effects of alcohol on genes within cells, you have to understand the molecular machinery driving the transcription, or activation, of the genes in question. That's what we believe we have done here," says the study's senior author Dr. Neil L. Harrison, professor of pharmacology and pharmacology in anesthesiology at Weill Cornell.

In research conducted in cell cultures and in mouse neurons in vivo, his team found that alcohol stimulates a ubiquitous, stress-linked biochemical cascade -- called the heat shock pathway -- to send a molecule called heat shock factor 1 (HSF1) into the neuron's nucleus. HSF1 then stimulates the transcription of many of the genes known to be activated by alcohol.

The fact that alcohol triggers the activation of genes in the brain is not

new and has long been the subject of intense research.

One gene in particular, called Gabra4, is closely linked to the function (or dysfunction) of receptors for GABA, an important neurotransmitter.

"We knew that levels of expression of Gabra4 fluctuated rapidly in the presence of alcohol, and so we wondered if we could find out how this happens," says lead author Dr. Leonardo Pignataro, instructor in pharmacology in anesthesiology at Weill Cornell.

At the same time, research in Korea with the C. elegans worm (a common tool for genomics research) had discovered that alcohol worked on a particular bit of DNA to trigger activity in the heat shock pathway, finding the same piece of DNA in the Gabra4 gene of mice and humans. "This was all very intriguing, because the heat shock pathway is a biochemical mechanism found in almost all cells and all organisms," says Dr. Harrison. "Scientists believe it helps cells deal with stressors -- including excessive heat or environmental toxins -- substances such as alcohol."

Working with mouse cells in the lab, the researchers used microarray technologies to search for genes other than Gabra4 that might be activated when the heat shock pathway was exposed to alcohol. They found many others.

"The big question that remains is how does this activation occur" The current theory holds that, under conditions of stress, heat shock proteins break away from a key molecule, HSF1. HSF1 then makes its way to the cell nucleus, where it helps stimulate the transcription and activation of a variety of genes that enable the cell to survive stress. We think this may happen with alcohol exposure," Dr. Harrison explains.

This finding, observed in vitro in the cell cultures, was replicated in in

vivo experiments in mice, conducted in the lab of Dr. Daniel Herrera, assistant professor of psychiatry at Weill Cornell and an attending psychiatrist at NewYork-Presbyterian/Weill Cornell.

"It was really exciting to see this mechanism work itself out in an animal model, suggesting that this same pathway may mediate at least some of the effects of alcohol on human brain cells," Dr. Herrera says.

Exactly what those effects might mean clinically remains in the realm of speculation for now, the researchers stress.

"Alcohol can have bad effects -- the well-known effects of alcoholism, such as liver or brain damage, for example -- but moderate alcohol use also has more benign effects, such as the improvement in cardiovascular health observed in drinkers of red wine compared with tee-totallers," Dr. Pignataro points out.

One theory holds that alcohol-mediated stimulation of the heat shock pathway might trigger genes that help mop up mis-folded proteins that can damage cells. This would be a beneficial effect.

"But it might also be possible that inappropriate activity of this pathway -- either during fetal brain development or in the adult brain -- is harmful. We just don't know," Dr. Harrison says. "We'd certainly like to explore these issues going forward, and this research will give us some tools to answer these questions."

Source: New York- Presbyterian Hospital