MedicalXpress

How genetic variations in neuroactive steroid-producing enzymes may influence drinking habits

February 15 2011

One of the ways in which alcohol dependence (AD) may develop is through alcohol's effects on neural signaling, such as modulation of γ-aminobutyric acid type A (GABAA) receptors. Alcohol may indirectly modulate GABAA receptor function by increasing levels of neuroactive steroids in blood. A new study has found linkages between AD and single nucleotide polymorphisms (SNPs) in the genes encoding two key enzymes required for the generation of endogenous neuroactive steroids, which suggests a genetic link between neuroactive steroids and risk for AD.

Results will be published in the May 2011 issue of *Alcoholism: Clinical & Experimental Research* and are currently available at Early View.

"Although alcohol's biochemical effects on the nervous system are not completely known, the immediate effect of alcohol on how we feel and function as well as the long-term development of tolerance to alcohol are thought to be mediated by neurotransmitter receptors, especially GABAA receptors," said Jonathan Covault, associate professor of psychiatry at the University of Connecticut Health Center and corresponding author for the study.

GABAA receptors are primarily responsible for dampening brain activity, Covault explained, and balance the other major class of neurotransmitter receptors – glutamate receptors – that are responsible

for enhancing excitatory brain activity. Healthy brain function relies on a relative balance of these two signaling systems.

"For example," he said, "excess excitatory relative to inhibitory receptor activity can result in seizures. The acute dampening effects of alcohol, such as disinhibition and sedation, are in large part due to alcohol effects on enhancing GABAA receptor function. Changes in the production of GABAA and glutamate receptors after chronic alcohol use also contribute to withdrawal symptoms, which can be medically serious and include delirium or seizures. The mainstay of medical treatment for alcohol withdrawal is to replace the effects of alcohol on stimulating GABAA receptors with medications – valium, librium or other benzodiazapines – that have similar effects as alcohol on enhancing GABAA receptor activity but can be gradually reduced in a controlled fashion."

"Previous studies have shown that neuroactive steroids contribute to alcohol sensitivity in rats and subjective feelings produced by alcohol in humans," said A. Leslie Morrow, John Andrews Distinguished Professor in the departments of psychiatry and pharmacology, and associate director of the Bowles Center for Alcohol Studies, both at the University of North Carolina School of Medicine. "Since low alcohol sensitivity has been linked to risk for alcoholism in humans, it is possible that low neurosteroid responses to alcohol may be linked to this disease."

"The detailed mechanisms by which alcohol modulates GABAA or glutamate receptors are still not well understood," added Covault. "How the body controls the production of neuroactive steroids is poorly understood, but stress and alcohol are two triggers shown to increase neuroactive steroids in the bloodstream and brain of laboratory rats. Laboratory studies suggest that many of the immediate effects of alcohol may be the result of alcohol on the production and metabolism of neuroactive steroids."

Covault and his colleagues genotyped SNPs in the genes encoding two key enzymes – 5α-reductase, type I (5α-R) and 3α-hydroxysteroid dehydrogenase, type 2 (3α-HSD), both of which are expressed in the human brain – in 1,083 participants living in Connecticut (583 males, 500 females): 531 with AD, and 552 individuals without AD.

"Results indicate that naturally occurring common genetic variations in two key enzymes required for the production of neuroactive steroids may influence the risk of developing AD," said Covault. "This finding is among the first evidence that some behavioral effects of alcohol are related to the production of neuroactive steroids. Specifically, genetic variation in each of two genes coding neuroactive steroid biosynthetic enzymes was more common in controls than AD participants, suggesting that protective genetic variations may result in more neuroactive steroids being produced in response to alcohol, thereby increasing the acute effects of alcohol – particularly sedating effects – which tend to limit a person's use of alcohol."

"This study brings scientists one step closer to understanding genetic and biochemical factors that underlie risk for alcoholism," said Morrow. "Such advances will surely lead to better treatments for alcoholism. We now have both genetic and behavioral studies linking neuroactive steroids to alcohol effects in humans. More studies of neuroactive steroids in humans are needed.

Covault concurs. "While much more work is needed to understand how variation in neuroactive steroid metabolism may influence an individual's predisposition to alcohol use problems, this report opens the door to new avenues of investigation and the potential development of new medical interventions for alcohol use problems."

Provided by Alcoholism: Clinical & Experimental Research