The neuropeptide Y system is linked to a more severe form of alcohol dependence

September 23 2008

Previous animal research showed an association between the neuropeptide Y (NPY) pathway and its three receptor genes and response to alcohol and cocaine. A new study has examined the relationship of the human NPY system with alcohol dependence (AD), with and without withdrawal symptoms, and cocaine dependence. Two receptor genes in particular, NPY2R and NPY5R, were found to be associated with a more severe subtype of AD – characterized by withdrawal symptoms or coexisting alcohol and cocaine dependence – and cocaine dependence.

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

"Very little is known about the association of the NPY system and alcohol dependence and withdrawal in humans," said Tatiana M. Foroud, director of the division of hereditary genomics at the Indiana University School of Medicine and senior author of the study. "The majority of information comes from studies done on rats and mice, research which suggests that animals that prefer alcohol are genetically different in their expression of NPY in the brain."

These animals, she added, are selectively bred to prefer drinking alcohol and are meant to mimic AD in humans. "Rats that prefer alcohol have lower levels of NPY, which makes them more excitable and thus more likely to experience seizures when they are not allowed to drink alcohol," said Foroud. "When doses of NPY are administered to alcohol-drinking

rats that are experiencing withdrawal, the withdrawal seizures are reduced. Since rats are genetically very similar to humans, these results could implicate that variants of the NPY gene or the receptor genes may be associated with alcohol dependence and seizures in humans."

"Recent human genetic linkage studies have suggested that polymorphisms of the NPY gene may contribute to risk of increased alcohol use, but these results have been inconsistent," added Todd E. Thiele, professor and director of research services in the department of psychology at the University of North Carolina at Chapel Hill. "What is novel about the present paper is that the authors have taken the human genetic linkage studies a step further by examining polymorphisms of NPY receptor genes."

Researchers genotyped 39 single nucleotide polymorphisms (SNPs) across NPY and its three receptor genes (NPY1R, NPY2R and NPY5R) in a sample of 1,923 subjects from 219 multiplex alcoholic families of European-American descent participating in the Collaborative Studies on the Genetics of Alcoholism (COGA) study. Variation in these genes was first analyzed for any association with AD, and second, analyzed for associations with symptoms of alcohol withdrawal, cocaine dependence, and coexisting alcohol and cocaine dependence.

"We found an association with the NPY2R and NPY5R receptor genes and alcohol withdrawal," said Foroud. "In other words, certain alleles are genetically transmitted more often to, and are more common in, AD people who experienced alcohol-withdrawal symptoms compared to AD people who did not experience any symptoms. That means that alcoholics who suffer withdrawal symptoms when they try to stop drinking may be genetically different than alcoholics who do not suffer these symptoms when they cut down or stop drinking."

"While these receptors have been implicated in animal work," noted

Thiele, "this is the first observation with human genetic data. While results from this study do not provide a cure for alcoholism, they do show us a potential avenue for future clinical work. In other words, while much work is yet needed, the present study suggests that pursuing the Y2 receptor may be fruitful."

Foroud wholeheartedly concurs. "First, we know from the animal research how alcohol and NPY interact. Second, we know from our research that NPY1R and NPY2R are associated with withdrawal symptoms and seizures in humans. Knowing both pieces of information supports what researchers in the animal literature have been saying in their articles for several years, namely, that treatments for AD should target antagonists in the NPY2R gene and agonists in the NPY1R gene. This pharmacological treatment would not eradicate AD or cure it, in fact it might only help those people who consume more alcohol and/or experience seizures or other withdrawal symptoms. But it's a start."

Foroud and her colleagues have begun to further examine NPY, NPY receptor genes, anxiety and drinking. "This also derives from the animal literature," she said. "Rats that prefer drinking alcohol have lower levels of NPY in their brain, and express higher levels of stress in tests compared to rats that do not like to drink alcohol. If you translate this finding to humans, the NPY gene could be associated in human beings who perhaps slipped into AD because they could not adapt to stressful situations. They gradually increased their alcohol consumption to deal with increasing stress."

Source: Alcoholism: Clinical & Experimental Research