Sensitivity to alcohol odors may indicate a genetic predisposition to alcohol dependence

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Single nucleotide polymorphisms (SNPs) are DNA sequence variations that occur when a single nucleotide in the genome sequence is altered. Prior research suggested an association between SNPs in a gene that encodes aspects of the brain's gamma-amino butyric acid (GABA)-A receptors (the GABRA2 gene) and alcohol dependence. A study of responses to the aromas of alcoholic drinks according to subjects' genotyping at a SNP in GABRA2 has found that this genotype can affect the brain's reward responses to cues such as alcohol odors.

Results will be published in the December 2010 issue of *Alcoholism: Clinical & Experimental Research* and are currently available at Early View.

"After repeatedly drinking alcohol, individuals learn to associate alcohol's appearance, taste and smell with its intoxicating properties," explained David A. Kareken, director of the department of neurology's neuropsychology section at Indiana University School of Medicine and corresponding author for the study. This is very similar to what happened when Ivan Pavlov repeatedly rang a bell to call his dogs to their meal, he said, leading to the bell's ability to provoke salivation in the absence of food itself.

"Humans learn at this physiological level as well," Kareken said. "The smell of an alcoholic drink carries little significance to someone who does not drink, but experienced drinkers develop associations between alcohol's taste and smell, and the intoxication that follows soon

thereafter." For those individuals who find alcohol's intoxicating effects particularly rewarding - as do alcoholics or those who abuse alcohol - the sight or smell of alcohol can produce strong desires to drink, known as cravings.

"Rather than examine salivation, however, we studied activity in the brain's reward system— the neural circuitry that recognizes and encodes the presence of something rewarding," added Kareken. "We also wanted to know if variation in one gene - the GABRA2 gene, a form of which has been shown to be more common in alcoholics - affected the brain's response to these potent alcohol cues."

Kareken and his colleagues recruited 36 participants: 13 had two copies of the high-risk allele, while 23 had one high-risk and one low-risk allele. During functional magnetic resonance imaging (fMRI), participants were exposed to the aromas of their preferred alcoholic drink odors, as well as food and environmental odors.

"One of the important features of this study was the opportunity to seek evidence for a gene-environment interaction," noted Sullivan. "Homozygous GABRA2 carriers - that is, participants with a double dose of this gene - showed activations in selective brain regions including medial frontal cortex, which is part of the brain's reward evaluation system. By contrast, heterozygous GABRA2 carriers - that is, participants with only a single dose of the gene - activated a different component of the brain's reward system. These differential patterns endured even when participants were intoxicated. Thus, the difference in brain activation patterns was not dependent on the presence of alcohol in the system per se and so appears to mark a fundamental, genetically linked physiological response to alcohol in homozygous carriers of the GABRA2 gene."

"Alcoholism is a very complex disease that involves both genetics and

the environment, and it is highly unlikely that we will ever discover 'the gene' that controls who will or will not become alcoholic," said Kareken. "However, this study adds to our understanding of how certain genes might influence how the brain's reward system responds to cues in the environment. It suggests that the GABRA2 gene may affect how strongly the brain's reward system responds to the sights and smells that motivate us to use, or over-use, the things that make us feel good."

"While research focused on the genetic foundations of behavior is growing rapidly," agreed Edith V. Sullivan, a professor in the department of psychiatry and behavioral sciences at Stanford University School of Medicine, "most targeted behaviors are highly complex and, despite genetic predisposition, are likely modified by the environment."

"Being a carrier of genetic markers of a complex behavioral disorder such as alcoholism is not necessarily a sentence to expressing the disorder," added Sullivan, "but it may serve as a biological warning to be aware of the liability of harmful drinking by genetically predisposed individuals and could also provide leads to pharmacological treatment focused on this gene and brain system."

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