Researchers Find Key Mechanism in Transition to Alcohol Dependence

By Jeff Worley and Mika Ono
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"Our focus in this study, like much of our lab's research, was to examine the role of the brain's stress system in compulsive alcohol drinking driven by the aversive aspects of alcohol withdrawal," says Associate Professor Marisa Roberto (back), who authored the study with Research Associate Nicholas Gilpin (front) and colleagues. (Photo by Cindy Brauer.)

A team of Scripps Research Institute scientists has found a key biological mechanism underpinning the transition to alcohol dependence. This finding opens the door to the development of drugs to manage excessive alcohol consumption.

"Our focus in this study, like much of our lab's research, was to examine the role of the brain's stress system in compulsive alcohol drinking driven by the aversive aspects of alcohol withdrawal," said Scripps Research Associate Professor Marisa Roberto, senior author of the study.

"A major goal for this study," added Research Associate Nicholas Gilpin, the paper's first author, "was to determine the neural circuitry that mediates the transition to alcohol dependence."

In the new research, published in the June 1, 2011 issue of the journal *Biological Psychiatry*, the Scripps Research scientists demonstrated the key role of a receptor—a structure that binds substances, triggering certain biological effects—for neuropeptide Y in a part of the brain known as the central amygdala. The amygdala, a group of nuclei deep within the medial temporal lobes, performs an important role in the processing and memory of emotional reactions.

"We've known for quite some time that neuropeptide Y is an endogenous [naturally occurring] anti-stress agent," said Markus Heilig, clinical director of the National Institute of Alcohol Abuse and Alcoholism (NIAAA). "We've also known that development of alcohol dependence gives rise to increased sensitivity to stress. This paper elegantly and logically brings these two lines of research together. It supports the idea that strengthening neuropeptide Y transmission in the amygdala would be an attractive treatment for alcoholism. The challenge remains to develop clinically useful medications based on this principle."

Discovering the Circuitry

Building on Gilpin's previous work on neuropeptide Y, in the new project, Gilpin, Roberto, and colleagues observed the effects of the administration neuropeptide Y in the central amygdala on alcohol drinking in rats. Alcohol-dependent rats were allowed to press levers for ethanol and water during daily withdrawal from chronic alcohol exposure.

"Normally, the transition to alcohol dependence is accompanied by gradually escalating levels of alcohol consumption during daily withdrawals," Gilpin explained. "The aim of this protocol was to examine whether neuropeptide Y infusions during daily withdrawals would block this escalation of alcohol drinking."

The scientists report a suppression of alcohol consumption with chronic neuropeptide Y infusions and detailed some of the neurocircuitry involved. Ethanol normally produces robust increases in inhibitory GABAergic transmission—GABA is another neurotransmitter—in the central amygdala, but this effect is blocked and reversed by neuropeptide Y.

Gilpin notes the scientists were surprised at one aspect of the findings—the role of a subset of neuropeptide Y receptors known as Y2 receptors. "Previous behavioral evidence suggested that antagonism of Y2 receptors in whole brain suppresses alcohol drinking, similar to the effects of neuropeptide Y," he said. "However, our data suggest that Y2 receptor blockade in central amygdala might actually increase alcohol drinking, presumably by affecting pre-synaptic release of GABA. These data also suggest that antagonism of post-synaptic Y1 receptors in central amygdala provides a viable pharmacotherapeutic strategy, a hypothesis supported by previous work from other labs." Two additional aspects of the findings are worth noting, Roberto says. First, repeated neuropeptide Y administration not only blocked the development of excessive alcohol consumption in dependent rats, but also tempered the moderate increase in alcohol consumption following periods of abstinence in non-dependent rats. Second, neuropeptide Y exhibited long-term efficacy in suppressing alcohol self-administration, highlighting the potential of neuropeptide Y treatments for a clinical setting.

In addition to Roberto and Gilpin, authors of this paper, titled "Neuropeptide Y Opposes Alcohol Effects on GABA Release in Amygdala and Blocks the Transition to Alcohol Dependence" and scheduled to appear in the June 1, 2011 print edition of *Biological Psychiatry*, include Kaushik Misra, Melissa Herman, Maureen Cruz, and George Koob, all of Scripps Research. See http://www.ncbi.nlm.nih.gov/pubmed/21459365 .

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