Scripps research team finds stress hormone key to alcohol dependence

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A team of scientists from The Scripps Research Institute has found that a specific stress hormone, the corticotropin-releasing factor (CRF), is key to the development and maintenance of alcohol dependence in animal models. Chemically blocking the stress factor also blocked the signs and symptoms of addiction, suggesting a potentially promising area for future drug development.

The article, the culmination of more than six years of research, will appear in an upcoming print edition of the journal *Biological Psychiatry*.

"I'm excited about this study," said Associate Professor Marisa Roberto, who led the research. "It represents an important step in understanding how the brain changes when it moves from a normal to an alcohol-dependent state."

The new study not only confirms the central role of CRF in alcohol addiction using a variety of different methods, but also shows that in rats the hormone can be blocked on a long-term basis to alleviate the symptoms of alcohol dependence.

Previous research had implicated CRF in alcohol dependence, but had shown the effectiveness of blocking CRF only in acute single doses of an antagonist (a substance that interferes the physiological action of another). The current study used three different types of CRF antagonists, all of which showed an anti-alcohol effect via the CRF system. In addition, the chronic administration of the antagonist for 23

days blocked the increased drinking associated with alcohol dependence.

Out of Control

Alcoholism, a chronic disease characterized by compulsive use of alcohol and loss of control over alcohol intake, is devastating both to individuals and their families and to society in general. About a third of the approximately 40,000 traffic fatalities every year involve drunk drivers, and direct and indirect public health costs are estimated to be in the hundreds of billions of dollars yearly.

"Research to understand alcoholism is important for society," said Roberto, a 2010 recipient of the prestigious Presidential Early Career Award for Scientists and Engineers. "Our study explored what we call in the field 'the dark side' of alcohol addiction. That's the compulsion to drink, not because it is pleasurable—which has been the focus of much previous research—but because it relieves the anxiety generated by abstinence and the stressful effects of withdrawal."

CRF is a natural substance involved in the body's stress response. Originally found only in the area of the brain known as the hypothalamus, it has now been localized in other brain regions, including the pituitary, where it stimulates the secretion of corticotropin and other biologically active substances, and the amygdala, an area that has been implicated in the elevated anxiety, withdrawal, and excessive drinking associated with alcohol dependence.

To confirm the role of CRF in the central amygdala for alcohol dependence, the research team used a multidisciplinary approach that included electrophysiological methods not previously applied to this problem.

The results from these cellular studies showed that CRF increased the strength of inhibitory synapses (junctions between two nerve cells) in neurons in a manner similar to alcohol. This change occurred through the increased release of the neurotransmitter GABA, which plays an important role in regulating neuronal excitability.

Blocking the Stress Response

Next, the team explored if the effects of CRF could be blocked through the administration of CRF antagonists. To do this, the scientists tested three different CRF1 antagonists (called antalarmin, NIH-3, and R121919) against alcohol in brain slices and injected R121919 for 23-days into the brains of rats that were exposed to conditions that would normally produce a dependence on alcohol.

Remarkably, the behavior of the "alcohol-dependent" rats receiving one of the CRF antagonists (R121919) mimicked their non-addicted ("naďve") counterparts. Instead of seeking out large amounts of alcohol like untreated alcohol-dependent rats, both the treated rats and their non-addicted brethren self-administered alcohol in only moderate amounts.

"This critical observation suggests that increased activation of CRF systems mediates the excessive drinking associated with development of dependence," said Roberto. "In other words, blocking CRF with prolonged CRF1 antagonist administration may prevent excessive alcohol consumption under a variety of behavioral and physiological conditions."

Importantly, in the study the rats did not exhibit tolerance to the suppressive effects of R121919 on alcohol drinking. In fact, they may have become even more sensitive to its effects over time—a good sign for the efficacy of this type of compound as it might be used repeatedly in a clinical setting.

The scientists' cellular studies also supported the promising effects of CRF1 antagonists. All of the CRF antagonists decreased basal GABAergic responses and abolished alcohol effects. Alcohol-dependent rats exhibited heightened sensitivity to CRF and the CRF1 antagonists on GABA release in the central amygdala region of the brain. CRF1 antagonist administration into the central amygdala reversed dependence-related elevations in extracellular GABA and blocked alcohol-induced increases in extracellular GABA in both dependent and naive rats. The levels of CRF and CRF1 mRNA in the central amygdala of dependent rats were also elevated.

Roberto notes that another intriguing aspect of the work is that it provides a possible physiological link between stress-related behaviors, emotional disorders (i.e. stress disorders, anxiety, depression), and the development of alcohol dependence.

More information:
www.ncbi.nlm.nih.gov/pubmed/20060104?log$=activity

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