Study underlines potential of anti-stress peptide to block alcohol dependence

December 9 2011

New research by scientists at the Scripps Research Institute has underlined the power of an endogenous anti-stress peptide in the brain to prevent and even reverse some of the cellular effects of acute alcohol and alcohol dependence in animal models. The work could lead to the development of novel drugs to treat alcoholism.

The new study, led by Scripps Research Associate Professor Marisa Roberto and now published online ahead of print by the journal *Biological Psychiatry*, illuminates the cellular mechanisms that govern the transition from alcohol use to alcohol dependence. Specifically, the study examined the interaction between two competing agents—one a stress peptide that promotes excessive alcohol drinking, the other an anti-stress peptide that opposes it. The results confirm that drugs derived from the anti-stress peptide nociceptin could play an important role in treating a complex and multi-faceted disease.

"Alcohol affects a lot of systems in the brain, and there won't be a single pill that will cure the multiple and complex aspects of this disease," Roberto said. Instead, scientists are seeking to attack the disease from a variety of angles, and are investigating the many different areas of the brain that appear to play a role in the use and abuse of alcohol.

Alcoholism, a chronic disease characterized by compulsive drinking and loss of control over alcohol intake, is devastating to both individuals and society. Approximately one third of all traffic fatalities involve drunk drivers, and alcohol abuse generates hundreds of billions of dollars in

direct and indirect public health costs.

"Alcoholism is a complex disorder with many contributing factors, one of which is stress," said Maureen Cruz, a research associate in Roberto's lab and first author of the study. "By targeting a particular system that's associated with stress, we can better understand the interaction of alcohol and stress in the brain."

Peptide vs. Peptide

Roberto and her team focus on the central nucleus of the amygdala, a region of the brain that has long been implicated in the elevated anxiety and excessive drinking associated with alcohol dependence and withdrawal.

In previous animal studies, Roberto and her colleagues demonstrated that a particular stress peptide produced in the amygdala, corticotropin-releasing factor (CRF), plays a key role in the transition from alcohol use to alcohol dependence. "This peptide," said Roberto, "drives craving for alcohol." Roberto and her colleagues also demonstrated that nociceptin, a peptide that structurally resembles endogenous opioids, can both prevent and reverse some effects of alcohol.

Intriguingly, CRF and nociceptin exert opposite effects on the inhibitory neurotransmitter, gamma-amino butyric acid (GABA), in central amygdala. CRF stimulates the release of GABA by neurons in the amygdala, while nociceptin inhibits it.

In the new study, Roberto, Cruz, and their colleagues examined how these two competing agents interact. At the behavioral level, nociceptin regulates anxiety and alcohol drinking in rats. "We were interested in seeing if nociceptin blocked the effect of CRF on a cellular level," Roberto said.

To find out if that were indeed the case, the scientists examined amygdala neurons from both alcohol-dependent and control rats. They added CRF and nociceptin and electrically stimulated the neurons to see how they would behave under the influence of both peptides. The result: nociceptin completely blocked the effects of CRF on GABA release.

Winner Takes All

But that was not all. By varying the sequence in which the scientists introduced the two opposing peptides, the researchers established that it did not matter whether they introduced nociceptin before or after CRF had done its work: In either case, nociceptin counteracted CRF and drove GABA levels down. "No matter when CRF is added, nociceptin wins," said Roberto. "That's a really consistent effect."

The researchers also found that both CRF and nociceptin had a more powerful effect on the amygdala neurons of alcohol-dependent rats compared to those from non-dependent animals. Roberto believes that this has to do with cellular changes that alcohol dependence causes in the brain—changes that heighten sensitivity to alcohol, compounding the effects of both drinking and withdrawal.

In addition, the team was able to determine that nociceptin and CRF both rely on the same enzyme, protein kinase A (PKA), to modulate GABA release in the amygdala.

More information: In addition to Roberto and Cruz, the authors of the Biological Psychiatry paper, titled "Nociceptin/Orphanin FQ Blockade of CRF-induced GABA Release in Central Amygdala is Enhanced after Chronic Ethanol Exposure," include Melissa A. Herman and Marsida Kallupi of Scripps Research. See www.sciencedirect.com/science/ … ii/S0006322311010791

Provided by The Scripps Research Institute