How neural inhibition could reduce alcohol use

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Neuroscientists at Scripps Research have found that inhibiting neurons involved in the body's stress response may reduce alcohol consumption in people who have both post-traumatic stress disorder (PTSD) and

alcohol use disorder (AUD)—even if they still experience trauma-related anxiety.

The findings were published in *Molecular Psychiatry* in a paper titled "Chemogenetic inhibition of central amygdala CRF-expressing neurons decreases alcohol intake but not trauma-related behaviors in a rat model of post-traumatic stress and alcohol use disorder. "

These discoveries are helping untangle the complex role that stress and trauma play in neurological disorders like PTSD and AUD, while also informing the development of new treatment options for people who experience both these conditions simultaneously.

"Traumatic experiences in life can increase vulnerability to alcohol drinking and exacerbate symptoms of depression and anxiety," says senior author Marisa Roberto, Ph.D., the Schimmel Family Endowed Chair and vice chair of the Department of Molecular Medicine. "Alcohol is often used as a coping strategy to blur trauma-associated memories and diminish negative emotional states."

PTSD and AUD are often comorbid, so understanding their underlying neurological mechanisms in tandem is crucial. About 6% of the U.S. population will develop PTSD at some point, according to the U.S. Department of Veterans Affairs, and people with PTSD have a 30% lifetime prevalence of AUD. However, few pharmaceutical therapies exist to treat the disorders together.

Roberto's team previously created a model in which rats develop symptoms similar to what people with comorbid PTSD and AUD experience: aggression, anxiety, hyperarousal, disturbed sleep and increased alcohol consumption. In this new study, they compared these rats with those that did not exhibit anxiety-like behaviors by giving each group access to both alcohol and water.

Compared with unstressed rats, those that were stressed exhibited higher levels of peripheral stress hormones, and various genes in the central amygdala, including one that encodes for the neuropeptide known as corticotropin-releasing factor (CRF), were also shown to be altered in stressed rats.

CRF exists in the central amygdala, a part of the brain that's altered by excessive drinking and is responsible for processing fear. Stress causes neural release of CRF, which plays a key role in regulating physiological responses to the emotion. Prior research with rats has shown that inhibiting neurons that express CRF reduces alcohol consumption.

After identifying that the stressed rats expressed higher levels of CRF in the amygdala, the researchers then inhibited CRF-producing neurons in the stressed group. As expected, they found that this decreased alcohol consumption—but it didn't mitigate anxiety as they initially thought it would.

"We were surprised to see that the anxiety phenotypes were not reduced when silencing CRF expressing neurons in the central amygdala, suggesting other neuropeptide co-factors might be at play," says the study's first author, Bryan Cruz, Ph.D., a postdoctoral fellow at Scripps Research.

The results suggest that CRF plays a role in alcohol use among those with comorbid PTSD and AUD. Still, the researchers conclude that future studies need to disentangle the neurological mechanisms behind stress-related alcohol consumption and trauma-induced anxiety.

"Understanding the neurobiology of PTSD-AUD is key for development of future intervention strategies for this devastating comorbidity," says Roberto. "We speculate that other neuropeptides with anti-stress properties may be involved in PTSD-AUD."

More information: Bryan Cruz et al, Chemogenetic inhibition of central amygdala CRF-expressing neurons decreases alcohol intake but not trauma-related behaviors in a rat model of post-traumatic stress and alcohol use disorder, *Molecular Psychiatry* (2024). DOI: 10.1038/s41380-024-02514-8

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