Study identifies peptide as key mediator in heavy alcohol drinking

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Alcohol is the most common addictive substance in the world. Every year in the U.S. excessive alcohol use costs $249 billion and causes approximately 88,000 deaths, as well as various chronic diseases and

social issues. Alcohol use disorder, a highly prevalent, chronic, relapsing disorder, affects more than 14 million people in the U.S. alone, in addition to being severely under-treated, with only three modestly effective pharmacological therapies available.

Chronic exposure to alcohol has been shown to produce profound neuroadaptations in specific brain regions, including the recruitment of key stress neurotransmitters, ultimately causing changes in the body that sustain excessive drinking. The area of the brain known as the "bed nucleus of the stria terminalis" (BNST) is critically involved in the behavioral response to stress as well as in chronic, pathological alcohol use.

Researchers from Boston University Chobanian & Avedisian School of Medicine have identified that a peptide called pituitary adenylate cyclase-activating polypeptide (PACAP), is involved in heavy alcohol drinking. In addition, they have discovered that this peptide acts in the BNST area.

Using an established experimental model for heavy, intermittent alcohol drinking, the researchers observed that during withdrawal, this model showed increased levels of the stress neuropeptide PACAP selectively in the BNST, compared to the control model.

Interestingly, a similar increase was also observed in the levels of another stress neuropeptide closely related to PACAP, the calcitonin gene-related peptide, or CGRP. Both peptides have been implicated in stress as well as pain sensitivity, but their role in alcohol addiction is less established.

The researchers then used a virus in a transgenic model to block the neural pathways containing PACAP that specifically arrive to the BNST. "We found that inhibiting PACAP to the BNST dramatically reduced heavy ethanol drinking," explained co-corresponding author Valentina

Sabino, Ph.D., co-director of the School's Laboratory of Addictive Disorders as well as professor of pharmacology, physiology & biophysics.

According to the researchers, these results provide evidence that this protein mediates the addictive properties of alcohol. "We found a key player, PACAP, driving heavy alcohol drinking, which can be targeted for the development of novel pharmacological therapies," added co-corresponding author Pietro Cottone, Ph.D., associate professor of pharmacology, physiology & biophysics and co-director of the Laboratory of Addictive Disorders.

These findings appear online in the journal *eNeuro*.

More information: Pituitary Adenylate Cyclase Activating Polypeptide (PACAP) of the Bed Nucleus of the Stria Terminalis Mediates Heavy Alcohol Drinking in Mice, *eNeuro* (2023). doi.org/10.1523/ENEURO.0424-23.2023

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