Heavy drinking in young adults tied to endocannabinoid pathway

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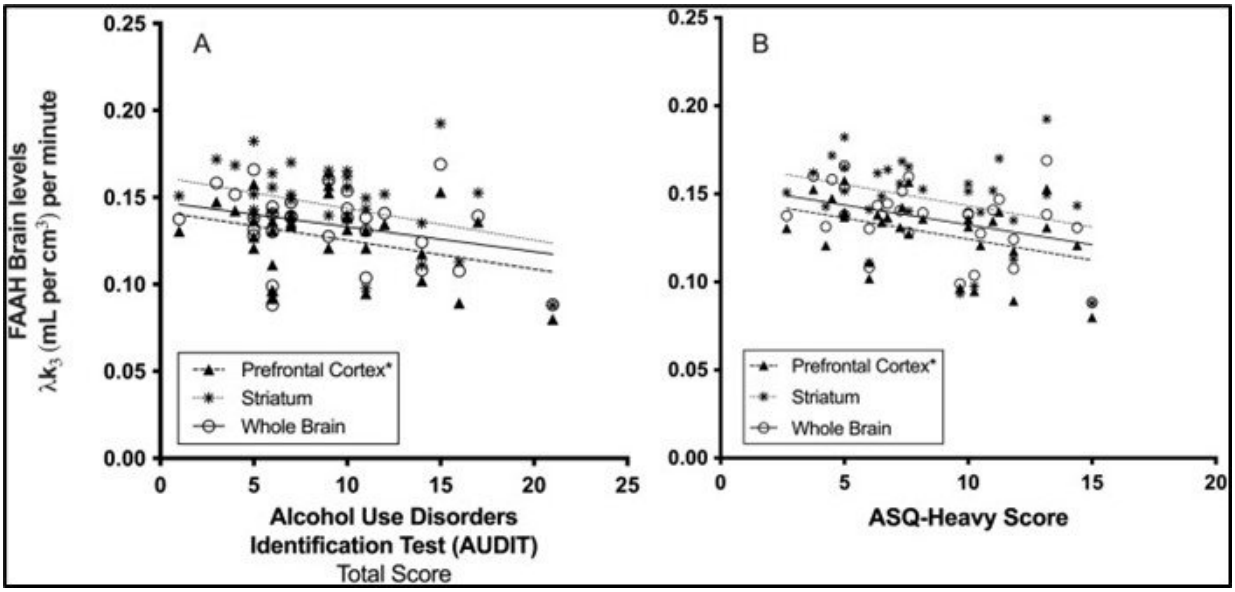

[11C]CURB binding, reflecting brain levels of FAAH, relates to self-reported alcohol outcomes. The AUDIT measures risky or hazardous alcohol use, while the ASQ (Alcohol Sensitivity Questionnaire) measures the effects of alcohol, with higher scores indicating lower sensitivity to alcohol's effects. Credit: Biological Psychiatry

Although heavy drinking in young adulthood increases the risk for alcohol use disorder (AUD), not all young heavy drinkers go on to develop AUD, globally the most common substance use disorder. Research has shown that individual differences in alcohol sensitivity and

cardiovascular responses may predict drinking patterns and progression to AUD. Little is known, however, about the brain-based mechanisms of AUD vulnerability—a better understanding of which could guide preventive interventions against AUD. A new study explores the role of endocannabinoid levels in hazardous alcohol use.

The study appears in *Biological Psychiatry*.

Led by Isabelle Boileau, Ph.D., at the Centre for Addiction and Mental Health and University of Toronto, the new study explores the relationship between fatty acid amide hydrolase (FAAH) levels in heavy drinking youth and alcohol intake, drinking patterns, differential responses to alcohol, and family history of AUD. The researchers hypothesized that lower brain FAAH levels would correlate to heavier and more hazardous drinking.

FAAH is an enzyme that degrades the endogenous cannabis-like substance anandamide, a neurotransmitter that activates the cannabinoid 1 receptor (CB1) and is involved in the regulation of pain, appetite, and mood. Endocannabinoid activity specifically in the brain's striatum and prefrontal cortex regions is thought to modulate the rewarding effects of alcohol. Studies in animals and people have suggested that reduced FAAH activity leads to increased alcohol seeking and consumption and decreased negative effects of intoxication.

The researchers used positron emission tomography imaging of [^{11}C]CURB, a highly specific radiotracer for FAAH, to assess FAAH levels in the striatum, prefrontal cortex, and whole brains of 31 participants aged 19 to 25 who reported at least one occurrence of heavy drinking in the previous 30 days. The researchers also measured behavioral and cardiovascular responses while administering controlled intravenous alcohol infusions to participants.

Lower [^{11}C]CURB binding, reflecting lower FAAH activity and presumably higher anandamide levels, was not related to frequency of alcohol use, but it was associated with more severe use, a greater reported craving for alcohol prior to the infusion, a greater reported "liking" of intoxication during the infusion, and reduced sensitivity to the negative effects of alcohol. "In our study, young adults with lower brain levels of FAAH reported greater stimulation and fewer intoxicating and sedating effects from drinking alcohol," said Dr. Boileau.

Lower FAAH levels were also associated with lower heart-rate variability, a cardiac measure of parasympathetic nervous system activity. A family history of AUD, present in about half the participants, had no relationship to [^{11}C]CURB binding.

"Our findings are important as they suggest that FAAH levels in the brain may contribute to the maintenance of excessive drinking and to susceptibility for developing an AUD and provide a brain-based target for prevention efforts and treatment approaches," Dr. Boileau added.

John Krystal, MD, editor of *Biological Psychiatry*, said of the work, "This fascinating study provides evidence linking increased endocannabinoid levels to reduced sensitivity to the negative effects of alcohol, an important risk factor for heavy drinking and AUD."

This work suggests that FAAH levels may influence a youth's susceptibility to alcohol misuse. These findings may guide researchers toward preventive measures to avoid AUD during this critical developmental stage, or potentially to interventions for treatment of AUD.

More information: Laura M. Best et al, Association between Fatty Acid Amide Hydrolase and Alcohol Response Phenotypes: A PET

Imaging Study with [11C]CURB in Heavy-drinking Youth, *Biological Psychiatry* (2022). DOI: 10.1016/j.biopsych.2022.11.022