Targeting dysregulated kappa-opioid receptors reduces working memory deficits in alcohol use disorder

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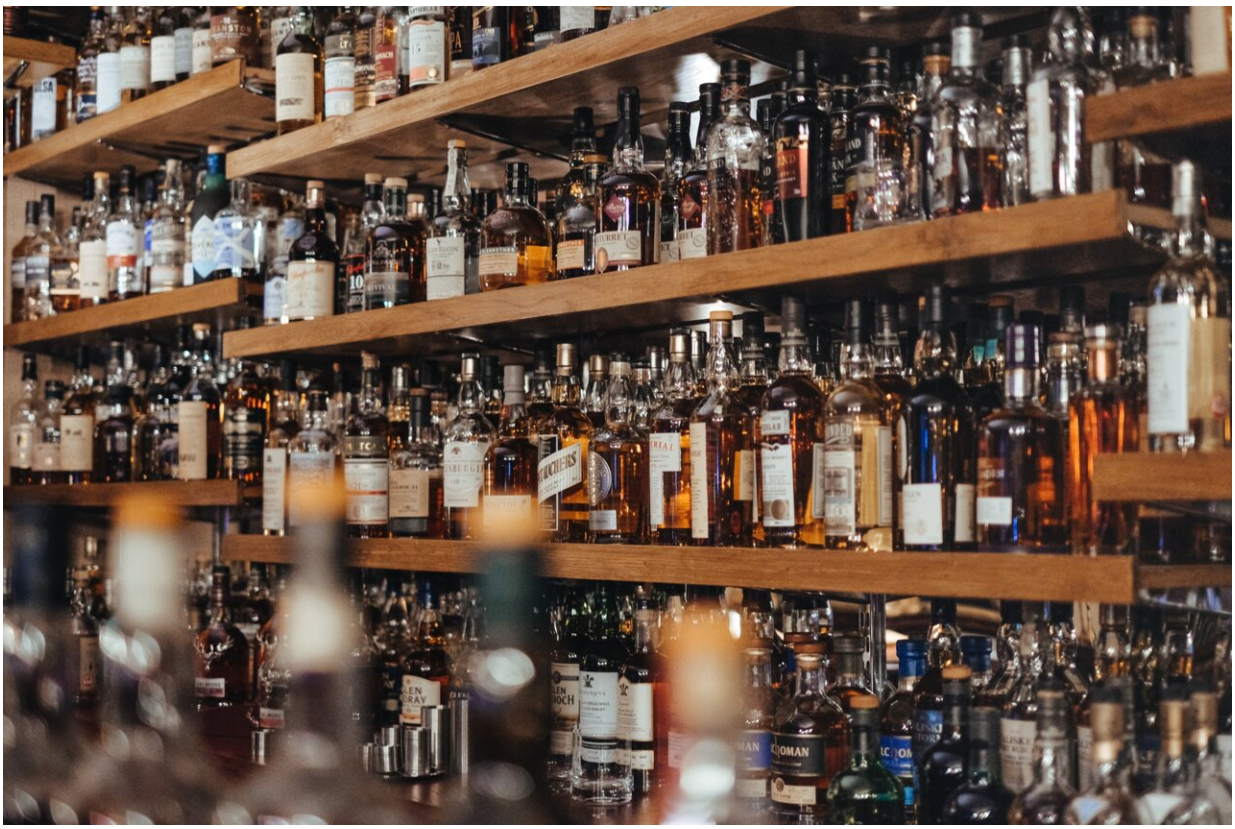

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As heavy or frequent alcohol use escalates, some people continue to drink despite increasingly negative consequences such as poor job or

school performance, unraveling family or personal relationships and declining physical health.

Impaired working memory, a common problem for those with alcohol use disorder (AUD), can interfere with recovery and disease management, and contribute to the risk of relapse. Working memory is one of the processes of executive function, a set of high-level mental skills (also encompassing flexible thinking and self-control) needed to learn and to manage daily life.

"People with severe alcohol dependence have reduced ability to make sound decisions, or good choices," said Brendan Walker, Ph.D., a professor of psychiatry and behavioral neurosciences at the University of South Florida Health (USF Health) Morsani College of Medicine. "They ignore the problems created by excessive drinking and give up things of importance to satisfy their craving to drink more."

Dr. Walker studies the biological brain changes that drive addictive behaviors with the aim of finding ways to improve treatment outcomes. A major obstacle to recovery, even months or years after rehabilitation and prolonged abstinence, appears to be physical changes in neurotransmitters and their receptor targets as the brain adapts to abuse of alcohol or other drugs.

Dr. Walker's laboratory and others have focused on the interaction of alcohol-induced "feel bad" brain peptides (neurotransmitters) known as dynorphins that bind with kappa-opioid receptors (KORs), naturally occurring receptors for opioids in brain cells.

Now, for the first time, a preclinical study led by Dr. Walker shows that dysregulated KORs in the brain's medial prefrontal cortex region (part of the frontal lobe) contribute to working memory deficiencies in alcohol dependence. Furthermore, the researchers discovered that a compound

used to block KORs (an antagonist) alleviated these working memory deficits and may help restore "normal" executive function in those with severe AUD, Dr. Walker said.

The USF Health findings were reported Jan. 20, 2022, in *Addiction Biology*.

"Collectively, our research is helping establish that targeting the dynorphin-KOR system could be a viable treatment strategy for simultaneously managing the hallmark symptoms of alcohol dependence—increased motivation for drinking, increased negative emotional states and compromised executive function (decision-making)," said Dr. Walker, the study's principal investigator.

Earlier preclinical studies looked at how abnormal regulation of the dynorphin-KOR system in another brain region called the amygdala increases both motivation for alcohol consumption and negative emotional states like depression and anxiety that are amplified during sudden withdrawal from drinking.

In a series of experiments, the USF Health researchers used a rat model mimicking severe human AUD, which was induced by cycles of intoxication (long-term intermittent ethanol vapor exposure) and alcohol withdrawal (exposure to air only). This group of alcohol-dependent rats was compared with two other groups: nondependent rats (a model mimicking social drinking in humans) and alcohol-naïve rats (a control group never exposed to ethanol vapor.) All were trained and tested in a working memory task (delayed nonmatching-to-sample task) involving a T-maze.

Among the key findings:

- The alcohol-dependent rat model the researchers developed

proved very effective for measuring working memory deficits.

- Medial prefrontal cortex KORs in the alcohol-dependent rats were overactivated (abnormally increased) in dependence, compared to those same opioid receptors in the nondependent and alcohol-naïve rats. This dysregulation of the dynorphin-KOR system in a brain region critical for the control of working memory correlated with worse working memory performance by the alcohol-dependent rats during acute withdrawal.
- When researchers stimulated KORs in the medial prefrontal cortex of nondependent rats with a KOR agonist mimicking dynorphin, they were able to produce profound working memory deficits like those observed in alcohol-dependent rats.
- Conversely, administering KOR antagonist norbinaltophimine (nor-BNI) to block activation of the brain KORs significantly reduced alcohol-induced impaired working memory. Alcohol-dependent rats showed working memory performance comparable to the nondependent rats.

More studies are needed, including in humans, but previous laboratory research has already shown that KOR antagonists curb the desire to excessively consume alcohol and the negative emotions that can drive self-medication with alcohol. This latest USF Health study suggests such a compound also holds promise for restoring executive function needed for people to make better decisions about their alcohol intake and improve their quality of life, Dr. Walker said.

There is "no magic bullet" for AUD, Dr. Walker emphasized, but identifying and developing one medication that alleviates multiple symptoms could make it easier for patients to cut back or quit drinking when combined with cognitive behavioral therapy.

More information: Gengze Wei et al, Dysregulated kappa-opioid receptors in the medial prefrontal cortex contribute to working memory

deficits in alcohol dependence, *Addiction Biology* (2022). DOI: 10.1111/adb.13138