Brain mechanism may explain alcohol cravings that drive relapse

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New research provides exciting insight into the molecular mechanisms associated with addiction and relapse. The study, published by Cell Press in the March 11 issue of the journal *Neuron*, uncovers a crucial mechanism that facilitates motivation for alcohol after extended abstinence and opens new avenues for potential therapeutic intervention.

Previous work has suggested that people, places, and objects associated with alcohol use are potent triggers for eliciting relapse and that cravings for both alcohol and drugs can increase across protracted abstinence. However, the specific molecular mechanisms that underlie pathological alcohol seeking are not well defined.

"Animal paradigms can model crucial aspects of human addiction, and these paradigms will help elucidate the molecular and cellular mechanisms that drive drug-seeking behaviors and, as a consequence, facilitate the development of novel therapeutic interventions for addiction," explains lead study author Dr. F. Woodward Hopf from the Ernest Gallo Clinic and Research Center at the University of California, San Francisco.

Dr. Hopf and colleagues were particularly interested in studying how alcohol addiction impacted a part of the brain called the nucleus accumbens (NAcb) core that is known to be important for allowing stimuli to drive motivated, goal-directed behaviors. The researchers examined the brains of rats that had experienced nearly 2 months of alcohol or sugar self-administration followed by a 3□□ week abstinence

period.

The rats who had consumed alcohol, but not those who had consumed sugar, exhibited an increased electrical activity in the NAcb core after abstinence. The increased activity was due to an inhibition of small-conductance calcium-activated potassium channels (SK).

Importantly, pharmacological activation of SK channels produced greater inhibition of NAcb activity in the alcohol- versus sucrose-abstinent rats and significantly reduced alcohol but not sucrose seeking after abstinence. The authors concluded that decreased SK currents and increased excitability in the NAcb core represents a critical mechanism that facilitates motivation to seek alcohol after abstinence.

"Our findings are particularly exciting because the FDA-approved drug chlorzoxazone, which has been used for more than 30 years as a muscle relaxant, can activate SK channels," says Dr. Antonello Bonci, a senior author on the project. "Although SK channels are not the only target of this drug and it can present a variety of clinical side effects, it provides an unexpected and very exciting opportunity to design human clinical trials to examine whether chlorzoxazone, or other SK activators, reduce excessive or pathological alcohol drinking."

More information: Bonci et al.: “Reduced Nucleus Accumbens SK Channel Activity Enhances Alcohol Seeking during Abstinence.” Publishing in *Neuron* 65, 682-694, March 11, 2010. DOI 10.1016/j.neuron.2010.02.015

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