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RESEARCH HIGHLIGHT

The best defense is a strong offense: preventing alcohol abstinence-induced depression

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The march toward alcoholism is a multifaceted and dynamic process. It is characterized by an ever-progressing cycle of anticipation of use, positive reinforcement during intoxication, and a withdrawal-induced negative affective state that, fueled by stress, drives relapse and, ultimately, excessive alcohol consumption. How does one untie this Gordian knot? A good place to start might be targeting a brain region involved in relapse that is stress-sensitive, bi-directionally modulates motivated behavior, and interfaces multiple circuits encoding affect. Thanks to early work, the bed nucleus of the stria terminalis (BNST), which is part of the extended amygdala, fits the bill.

Supporting a role for the BNST in the development of alcohol use disorders is that BNST synapses are under plastic control by alcohol. Chronic alcohol exposure and acute withdrawal upregulate extrasynaptic GluN2B-containing NMDA receptors, which are necessary for BNST long-term synaptic potentiation (LTP) [1]. Supporting the notion that targeting BNST NMDA receptors modulates alcohol withdrawal-induced negative affective states is the finding that ketamine, an NMDA receptor antagonist with rapid-acting antidepressant effects, acutely attenuates depressive-like behavior following withdrawal from alcohol [2].

There is a problem with ketamine however; ketamine is a dissociative drug and is subject to abuse. Thus, repeated ketamine treatments for affective disturbances brought on by withdrawal from alcohol drinking is likely to cause more problems than it solves. An ideal clinical scenario would be one in which a single ketamine treatment could protect against the development of abstinence-induced negative affect that drives relapse.

In the recent article in this issue of *Neuropsychopharmacology*, Vranjkovic and colleagues [3] examined exactly this: whether a prophylactic dose of ketamine protects against depressive-like behavior following withdrawal from a two-bottle choice (alcohol or water) drinking procedure. In untreated mice, withdrawal from alcohol drinking induces an early stage increase in anxiety as measured by the elevated plus maze, followed by a delayed presentation of a negative affective state during protracted withdrawal, as assessed by the forced swim and novelty suppressed feeding tests. Remarkably, the authors demonstrate that a single dose of ketamine administered on the day of withdrawal from chronic alcohol drinking, but not 2 or 6 days later, prevents both the early withdrawal-induced anxiety and late withdrawal (2–3 weeks)-induced negative affective states.

Vranjkovic went on to test the hypothesis that the mechanism underlying this astonishing effect is a modulation of dorsal lateral BNST (dlBNST) synaptic plasticity by ketamine. In control alcohol drinking mice not receiving ketamine treatment, LTP magnitude robustly decreases during two to three week protracted withdrawal compared to that of water-only drinkers. Showing that the timing of ketamine administration matters, treatment during early withdrawal significantly augments the magnitude of both early and late phase LTP recorded during protracted withdrawal. In contrast, ketamine administered six days after withdrawal fails to rescue LTP magnitude. Although these findings do not directly establish causality, they offer a compelling link between dlBNST plasticity and ketamine-mediated prevention of negative affect after withdrawal from alcohol.

These data represent an exciting addition to extant and emerging studies supporting the notion that rapid-acting antidepressants may have wide-ranging efficacy for neuropsychiatric disorders with a significant negative affect component. In light of the psychotomimetic properties of ketamine, a deeper understanding of its actions is required to develop more refined and safer therapeutics. For instance, determining the synapse that mediates dlBNST LTP may narrow the potential target playing field. Candidate glutamatergic afferents to the dlBNST arise from insula, amygdala, hypothalamus, and thalamus. A role for GABAergic circuits cannot be ruled out: these inputs arise primarily from the central amygdala, but also include hypothalamus and intrinsic interneuron populations. Investigation of the circuits mediating the early versus late stage LTP components will provide clarity as to the exact mechanism by which both alcohol and ketamine influence plasticity in the BNST, and therefore, behavior.

If a circuit is identified to underlie the plastic changes observed by Vranjkovic and coworkers then perhaps an underlying molecular mechanism acting at this synapse can be more specifically targeted to limit side-effect potential. Brain-derived neurotrophic factor (BDNF) regulates neuronal plasticity and is strongly implicated in both ketamine's antidepressant effects [4] and prevention of alcohol withdrawal-induced anhedonia [5]. Thus, targeting signaling cascades downstream of the BDNF receptor Tropomyosin receptor kinase B (TrkB) may be an option. Several intracellular pathways activated by TrkB regulate synaptic homeostasis through mammalian target of rapamycin (mTOR), which may serve as a potential therapeutic target [6]. Continued study of ketamine's specific molecular mechanisms of action, particularly in the dlBNST, may facilitate the development of safer therapeutics.

Alternatively, we may be losing the forest for the trees. The ubiquity of NMDA receptors throughout the brain raises the

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possibility that ketamine exerts its effects through global actions on neural networks across the brain. Indeed, ketamine induces a persistent general reconfiguration of neural networks in non-human primates that, strikingly, opposes that of depressed patients [7]. Other rapid-acting means to combat negative affective states such as electro-convulsive therapy [8], the anesthetic isoflurane [9], and the psychedelic serotonin 2a receptor agonist psilocybin [10] share a common feature of global modulation of neuronal activity. Thus, these treatments may reset network activity induced by pathological synaptic plasticity. Owing to the convergence of multiple cortical and subcortical circuits encoding stress-sensitive affective states in the BNST, perhaps ketamine modulation of BNST synaptic plasticity at the time of drinking cessation may aid in breaking the cycle of the march toward a global neural network that encodes the alcoholic brain.

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ADDITIONAL INFORMATION

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