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Drinking through the pain

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Abstract

A feature of abusive alcohol drinking has been modeled successfully in experiments with rats. The experiments show that changes in NMDA signaling in specific neural circuits accompany the transition to aversion-resistant drinking.

Most of us drink alcoholic beverages. Unfortunately, some of us overindulge to the point of reaching diagnostic criteria for alcohol dependence. Rodent models have long been used to explore the neurobiology and motivation underlying different aspects of drinking, including binge drinking¹, excessive drinking and relapse drinking during periods of abstinence². One crucial, unanswered question is why people continue to drink excessively in the face of mounting evidence of damage to their health, relationships, work or happiness. Understanding the neurobiological underpinnings of the transition to persistent drinking even after the adverse consequences become evident would offer new potential treatment strategies.

Most rodents, even those that drink a lot, generally seem to avoid drinking beyond the point of intoxication, and it has been a challenge to demonstrate that they will continue to drink despite adverse consequences. In this issue of *Nature Neuroscience*, Seif *et al.*³ show that NMDA-type glutamate receptors (NMDARs) containing the Grin2c (also known as GluN2C) subunit are upregulated in the nucleus accumbens (NAc) core at a specific set of inputs when animals drink intermittently for 2–3 months, at which point neither pairing drinking with electric shocks nor the addition of bitter-tasting quinine to the alcohol suppresses the behavior. Furthermore, the authors use pharmacological, optogenetic, RNA-interference and electrophysiological tools to manipulate these inputs and show that these manipulations selectively affect such aversion-resistant drinking, thus establishing both a circuit and a molecular target that underlies this difficult-to-treat aspect of alcohol abuse.

The authors used an intermittent-access drinking protocol to establish high levels of ingestion⁴. When rats are given a choice between a high concentration (20%) of alcohol and tap water for three 24-hour periods per week, their intake escalates during the first 2–3 weeks. Although the amount of alcohol they drink may or may not be sufficient to induce physical dependence, something about their drinking changes: when bitter quinine is added to the alcohol tube, the animals will continue to drink the alcohol-quinine-water mixture at a quinine concentration they would normally avoid. This has been suggested to be evidence

for the development of resistance to alcohol's aversive effects⁵. Most such studies, however, cannot rule out the possibility that chronic exposure to alcohol has influenced the taste of the combination of quinine and alcohol, reducing quinine's aversive potency. Here, the authors compared each rat's drinking of alcohol (with or without quinine) under different experimental conditions. An important addition was first switching rats to an operant schedule in which they had to press a bar to obtain access to alcohol. The operant sessions were given 5 days a week for short durations; this allowed the addition of a shock paired with some opportunities to access alcohol. Because the stimulus modality was different (shock instead of a bitter tastant), the role of taste in these experiments was irrelevant. This opened the door to interrogating the mechanism underlying this aversion-resistant consumption of alcohol using physiological and optogenetic approaches.

Seif *et al.*³ focused on the NAc. This region is critical in both reward- and aversion-related behavior, and stimulation of a variety of glutamate inputs to this region can motivate behavior^{6,7}. The authors first sought to understand which inputs mediate the aberrant behavior. They homed in on the insular cortex and the medial prefrontal cortex (mPFC), regions that have both been shown to encode aversive stimuli and project to the nucleus accumbens. They found that optogenetically silencing the synaptic inputs from either the insular cortex or the mPFC to the NAc blocked alcohol drinking, but only in an aversive setting (that is, when the alcohol was adulterated with quinine). This suggested that long-term, chronic alcohol drinking leads to a change in how these inputs work.

To examine this, the authors investigated NMDAR-mediated responses at these inputs. The NMDAR has long been thought to have a key function in synaptic plasticity, as it acts as a coincidence detector, allowing ion flux only upon concurrent pre- and postsynaptic activity. Curiously, the NMDAR is both targeted by acute alcohol exposure and dysregulated after chronic alcohol exposure⁸. Using an optogenetic approach to evoke glutamate release at these defined inputs, the authors found that at both the insular and mPFC inputs, there was an NMDAR-mediated response at hyperpolarizing potentials. This suggests that chronic alcohol drinking leads to the presence of a biophysically distinct NMDAR specifically at these synapses in drinking animals—one that could potentially alter the ability of the insular and mPFC inputs to drive firing of NAc neurons. Using a series of approaches, the authors found that *Grin2c* subunits are upregulated at these inputs after chronic alcohol exposure and that these receptors are necessary for aversion-resistant drinking (Fig. 1). Finally, the authors found that stimulation of these inputs can drive firing of NAc neurons in an NMDAR-dependent fashion.

These results are exciting for two reasons. First, they identify a specific receptor target in a specific neural circuit that mediates an aspect of alcohol abuse that is difficult to model in the laboratory and difficult to treat in the clinic. Second, they suggest that *Grin2c*-containing NMDARs may be an effective target for treatment of alcohol addiction. This finding is particularly useful because *Grin2c* mRNA is expressed at relatively low levels throughout the brain, and this subunit may provide more selectivity for choosing drug treatments with greater efficacy and fewer side effects.

Although the authors found an NMDAR-dependent effect on firing in these neurons, they did not explore how the dynamics and summation of this synapse are altered. It may be that these cortical inputs fire at a higher rate after aversion-resistant alcohol drinking, but it also may be that the biophysical properties of these *Grin2c*-containing receptors—for example, the relatively long decay time—lead to enhanced summation, thus allowing a subthreshold signal from the cortex to initiate action potential firing. The behavioral approaches used led to blood alcohol concentrations below the threshold (80 mg ml⁻¹) taken to indicate binge-like drinking⁹, so it will be interesting to see how this neural circuit is affected by other

types of alcohol drinking. The authors note that not all rats developed aversion-resistant drinking, and their exploration of neural circuitry was confined to those that did. These individual differences raise the possibility of genetic contributions to this plasticity, which could be explored in several available rodent models of genetic susceptibility to high levels of alcohol drinking².

The function of some of this circuitry, specifically the mPFC, has also been investigated in models of cocaine addiction¹⁰. The mPFC shows a reduction in excitability after long-term cocaine use in rats that come to seek cocaine even at the cost of an electrical shock. At first glance, this would seem to stand in contrast to the findings of Seif *et al.*³. However, several key differences suggest that the results are more similar than they first appear. In the cocaine study, the authors investigated the properties of all mPFC neurons, regardless of projection pattern, whereas in the alcohol study the authors focused specifically on the pathway from the mPFC to the NAc. This difference is important, as the mPFC projects to many regions of the brain besides the NAc, including the dorsal raphe, the amygdala and the ventral tegmental area. All these regions can shape motivated behavior. It is tempting to suggest that chronic exposure to a drug, be it cocaine or alcohol, leads to a reduction in the excitability of mPFC neurons. For alcohol, this might gate the homeostatic change in NMDAR composition in the NAc that underlies the altered drug-related behavior. There are, however, many procedural differences between the two experimental approaches (for example, several hours of i.v. access to cocaine versus 20 minutes of oral access to alcohol), and these may also contribute to the differences between the studies' mPFC findings. Nonetheless, in both cases, individual rats showed markedly different neural signatures under conditions including occasional punishment by shock, indicating that their drug-taking had become persistent. In this respect, the methods may well provide useful for testing new therapeutic agents.

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Figure 1.

Neural circuitry underlying aversion-insensitive alcohol consumption. Long-term access to alcohol leads to upregulation of Grin2c-containing NMDARs at synapses in the NAc by axons coming from insular cortex and mPFC. These receptors are more active at hyperpolarizing currents, leading to altered firing properties of NAc neurons (inset).