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Distinct Synaptic Strengthening of the Striatal Direct and Indirect Pathways Drives Alcohol Consumption

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ABSTRACT

BACKGROUND: Repeated exposure to addictive drugs or alcohol triggers glutamatergic and gamma-aminobutyric acidergic (GABAergic) plasticity in many neuronal populations. The dorsomedial striatum (DMS), a brain region critically involved in addiction, contains medium spiny neurons (MSNs) expressing dopamine D_1 or D_2 receptors, which form direct and indirect pathways, respectively. It is unclear how alcohol-evoked plasticity in the DMS contributes to alcohol consumption in a cell type–specific manner.

METHODS: Mice were trained to consume alcohol using an intermittent-access two-bottle-choice drinking procedure. Slice electrophysiology was used to measure glutamatergic and GABAergic strength in DMS D_1- and D_2-MSNs of alcohol-drinking mice and control mice. In vivo chemogenetic and pharmacologic approaches were employed to manipulate MSN activity, and their consequences on alcohol consumption were measured.

RESULTS: Repeated cycles of alcohol consumption and withdrawal in mice strengthened glutamatergic transmission in D_1-MSNs and GABAergic transmission in D_2-MSNs. In vivo chemogenetic excitation of D_1-MSNs, mimicking glutamatergic strengthening, promoted alcohol consumption; the same effect was induced by D_2-MSN inhibition, mimicking GABAergic strengthening. Importantly, suppression of GABAergic transmission via D_2 receptor–glycogen synthase kinase–3β signaling dramatically reduced excessive alcohol consumption, as did selective inhibition of D_1-MSNs or excitation of D_2-MSNs.

CONCLUSIONS: Our results suggest that repeated cycles of excessive alcohol intake and withdrawal potentiate glutamatergic strength exclusively in D_1-MSNs and GABAergic strength specifically in D_2-MSNs of the DMS, which concurrently contribute to alcohol consumption. These results provide insight into the synaptic and cell type–specific mechanisms underlying alcohol addiction and identify targets for the development of new therapeutic approaches to alcohol abuse.

Keywords: Alcoholism, Dopamine D_2 receptor, Dorsomedial striatum, DREADDs, GABAergic plasticity, GSK3β

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Addiction is considered to arise from maladaptive learning and memory processes, involving various forms of aberrant synaptic plasticity in different neuronal populations within unique neural circuits (1–3). The striatum, a major area of the basal ganglia, is essential for drug and alcohol addiction (1–3). For instance, human imaging studies have indicated that the striatum is linked to cocaine and alcohol addiction (4,5). Moreover, rodent studies revealed that striatal glutamatergic inhibition attenuated cocaine sensitization and alcohol intake (6,7). Similarly, striatal knockdown of gamma-aminobutyric acid (GABA) receptors or inhibition of GABAergic transmission also reduces alcohol consumption (8,9). These studies indicate that both excitatory glutamatergic and inhibitory GABAergic activities in the striatum positively control alcohol consumption, although the underlying mechanisms are poorly characterized.

Increasing evidence suggests that the dorsal part of the striatum is essential for drug and alcohol addiction (5,10,11). The dorsal striatum can be subdivided into the dorsolateral striatum, which is involved in habit formation (10,12), and the dorsomedial striatum (DMS), which mediates goal-directed behaviors (10,12). The DMS has been strongly implicated in drug and alcohol abuse (6,13–16). The principal cells of the striatum are medium spiny neurons (MSNs). MSNs expressing dopamine D_1 receptors (D_1-MSNs) project directly to the substantia nigra pars reticulata (SNr); this constitutes the direct pathway, which mediates "Go" actions in rewarding behaviors (17–19). In contrast, D_2-MSNs express dopamine D_2 receptors (D_2Rs) and connect indirectly to the SNr; this indirect pathway regulates "NoGo" behaviors (17,18). In MSNs, there are two major neurotransmissions: glutamatergic and GABAergic (20). They are known to be regulated by alcohol in the DMS and other brain regions (6,21,22). However, it is unclear whether these two types of neurotransmissions are modulated by alcohol in a cell type–specific manner and it is not known how D_1- and D_2-MSNs distinctly influence alcohol consumption.

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In this study, we measured both glutamatergic and GABAergic activity in D_1-MSNs and D_2-MSNs and found that *N*-methyl-D-aspartate receptor (NMDAR) activity in D_1-MSNs and GABAergic activity in D_2-MSNs were selectively potentiated following cycles of alcohol consumption and withdrawal. Using a chemogenetic approach employing designer receptors exclusively activated by designer drugs (DREADDs), which allowed selective manipulation of D_1- or D_2-MSN activity (23), we discovered that both of these cell types were not only necessary, but also sufficient, to drive alcohol consumption. Furthermore, we observed that D_2R-glycogen synthase kinase-3β (GSK3β) signaling regulated GABAergic activity and thus alcohol consumption. The findings of this study provide detailed mechanistic information indicating how different forms of neuroplasticity in distinct neuronal populations of the striatal direct and indirect pathways drive alcohol consumption.