Commentary

Biological Psychiatry

Tipping the Scales Toward Addiction

William J. Wright and Yan Dong

Despite diverse acute pharmacological actions, all drugs of abuse produce many similar behaviors, such as psychomotor sensitization, conditioned drug taking, drug seeking, and relapse (1). The development of these addiction-related behaviors is thought to arise from diverse molecular and cellular adaptations, which collectively result in convergent long-term functional alterations of the striatum. However, at the cellular level, on the one hand, exposure to different classes of drugs, such as stimulants versus opioids (2), induces distinct and often opposing forms of adaptations in striatal medium spiny neurons (MSNs). On the other hand, exposure to alcohol promotes alcohol consumption by simultaneously activating both excitatory and inhibitory synaptic signaling, two seemingly opposing mechanisms, in the striatum (3,4). It remains underexplored how such opposing synaptic mechanisms contribute to the same behavioral states induced by drugs of abuse.

The striatum is composed of two distinct circuits in parallel, termed the direct and indirect pathways (5). MSNs expressing the dopamine D_1 receptor (D1-MSNs) form the direct pathway, whereas MSNs expressing the dopamine D_2 receptor (D2-MSNs) form the indirect pathway. These two MSN subpopulations preferentially mediate different aspects of motivated behaviors, such that, under certain conditions, D1-MSNs promote, while D2-MSNs suppress, behavioral responses (5). Recent studies have started to identify cell type–specific adaptations within the striatum following exposure to drugs of abuse. Such cell type–specific adaptations may partially explain how opposing synaptic mechanisms coordinate to induce common circuit and behavioral consequences. The role of these MSN subpopulations remain a mystery in alcohol-induced behaviors, as does whether exposure to alcohol does indeed induce cell type–specific adaptations in the striatum and, if so, how distinct MSN subpopulations contribute to alcohol seeking and consumption.

In this issue of *Biological Psychiatry,* Cheng *et al.* (6) directly address these important questions by identifying specific alcohol-induced adaptations in D1- and D2-MSNs and determining how these MSN subpopulations contribute to alcohol consumption. Cheng *et al.* (6) first examined whether *N*-methyl-D-aspartate receptor (NMDAR)–mediated excitatory synaptic transmission in the dorsomedial striatum (DMS) is altered in a cell type–specific manner following prolonged alcohol exposure. Following 8 weeks of intermittent access to alcohol, which resulted in excessive alcohol consumption, NMDAR-mediated excitatory postsynaptic currents were selectively increased in D1-MSNs of mice 24 hours after the last self-administration session. In contrast, D2-MSNs showed a reduction in the current mediated by extrasynaptic NMDARs. Subsequent examination revealed that the strengthening of NMDAR-mediated excitatory postsynaptic currents in D1-MSNs stemmed, in part, from the enhancement of GluN2B subunit–containing NMDAR function. In contrast, gamma-aminobutyric acid (GABA)–mediated inhibitory postsynaptic currents were selectively increased in D2-MSNs. Taken together, these findings demonstrate that prolonged alcohol exposure induces differential synaptic adaptations in D1-MSNs versus D2-MSNs within the DMS. These adaptations may ease the activation of D1-MSNs through enhanced excitation, while suppressing the activation of D2-MSNs through enhanced inhibition, tipping the balance of activity between these two MSN subpopulations in favor of the direct pathway.

Does the altered balance between D1- and D2-MSNs within the DMS contribute to the excessive consumption of alcohol? To address this question, Cheng *et al.* (6) manipulated the activity levels of D1- and D2-MSNs within the DMS of animals during alcohol drinking sessions through chemogenetic approaches. Shifting the balance of striatal activity in favor of the direct pathway through chemogenetic activation of D1-MSNs or inhibition of D2-MSNs resulted in the same behavioral consequence—increasing the consumption of and preference for alcohol. In contrast, shifting the balance of striatal activity in favor of the indirect pathway through chemogenetic suppression of D1-MSNs or activation of D2-MSNs attenuated the consumption of and preference for alcohol. These findings indicate that the altered balance between the direct and indirect pathways resulting from alcohol-induced cell type–specific adaptations drives excessive alcohol consumption.

Lastly, Cheng *et al.* (6) identified a mechanism underlying the alcohol-induced reduction in GABAergic transmission to D2-MSNs. Acute stimulation of D2-receptors reduced the amplitude of inhibitory postsynaptic currents in D2-MSNs, which was due to the activation of glycogen synthase kinase-3β (GSK3β), a downstream signaling target of G_i-coupled D_2 receptors. Subsequent investigation demonstrated that following prolonged alcohol self-administration, there was an increase in the inactive form of GSK3β in the DMS, which was associated with increased expression of $GABA_A$ receptors, indicating a possible mechanism for alcohol-induced enhancement of inhibition to D2-MSNs. Indeed, when D_2 receptors were stimulated in the DMS in vivo, alcohol consumption was significantly attenuated, which was dependent on GSK3β activity as well. Similar behavioral effects were observed when GABA signaling in general was inhibited in the DMS. These findings suggest that decreased GSK3β activity in the DMS may serve to enhance the inhibition of D2-MSNs to tip the balance between D1- and D2-MSNs for the excessive consumption of alcohol.

These findings by Cheng *et al.* (6) provide significant insight into the circuit mechanisms within the DMS that contribute to alcohol addiction. These findings also highlight how differential or opposing synaptic adaptations induced by drugs lead to common circuit level alterations in the striatum to produce

SEE CORRESPONDING ARTICLE ON PAGE 918

http://dx.doi.org/10.1016/j.biopsych.2017.02.009
ISSN: 0006-3223

similar circuit and behavioral outcomes. Recently, it has been demonstrated that exposure to cocaine and morphine induces opposite synaptic adaptations in ventral striatal MSNs, with cocaine promoting synaptogenesis and morphine promoting synaptic elimination (7). However, cocaine preferentially targets D1-MSNs, while morphine targets D2-MSNs, which results in the same net shift in balance of excitation to D1- and D2-MSNs (7). These findings, together with the findings of Cheng *et al.* (6), suggest that cocaine, morphine, alcohol, and likely other drugs of abuse all produce the same circuit shift, albeit through distinct mechanisms. It will be important to determine if this circuit shift also holds for other commonly abused drugs, such as nicotine, amphetamine, and marijuana.

In addition to providing circuit-level insight, the findings of Cheng *et al.* (6) provoke several important questions for future studies. First, are there additional cell type–specific adaptations in the DMS following prolonged withdrawal from alcohol that may contribute to relapse? It has been well documented for many drugs of abuse, including alcohol, that during protracted withdrawal, there is a progressive intensification in cue-induced drug seeking, a phenomenon termed the "incubation of drug craving" (8). A possible cellular process underlying incubation of drug craving is the generation of new synapses in D1-MSNs, as has been suggested for cocaine (7). The synaptogenesis process induced by cocaine exposure is initiated by insertion of GluN2B-containing NMDARs to new synaptic locations (7). Therefore, the enhanced function of GluN2B-containing NMDARs in D1-MSNs observed 24 hours after cessation of alcohol consumption may represent the initiation of synaptogenesis. The potential alcohol-induced synaptogenesis in D1-MSNs may profoundly remodel the DMS circuits, and on maturation during drug withdrawal, they may further enhance the D1-MSN circuit to aggravate relapse, as has been demonstrated for incubated cocaine seeking (9).

Second, do these alcohol-induced synaptic adaptations occur in specific glutamatergic projections to the striatum? The striatum receives glutamatergic inputs from diverse and distinct brain regions, including cortical, thalamic, and amygdalar areas. Projections from these different regions are thought to convey different information to the striatum and thus may regulate specific aspects of behavior. After exposure to cocaine, distinct synaptic adaptations are detected in different glutamatergic afferents to the ventral striatum, which can exert differential effects over drug seeking (9). A projection-specific characterization of alcohol-induced synaptic adaptation will greatly extend the understanding of circuit-based mechanisms underlying alcohol seeking and relapse.

It will also be of interest to determine the sources that provide enhanced inhibition to D2-MSNs after exposure to alcohol. Major sources of GABA-mediated inhibition to striatal MSNs arise from local inhibitory interneurons that form a local feedforward inhibitory circuit and axon collaterals from neighboring MSNs providing lateral inhibition (10). Feedforward and lateral inhibition influence the circuit activity in fundamentally different ways, such that feedforward inhibition may serve to gate the activation in response to excitatory inputs, whereas lateral inhibition may confer winner-take-all properties to competing neurons (10). Therefore, understanding how alcohol affects these different inhibitory circuits will add another piece of the puzzle underlying the circuit mechanisms of alcohol addiction.

Collectively, Cheng *et al.* (6) report a series of cell type–specific adaptations induced by prolonged alcohol exposure that shifts the balance between the direct and indirect pathways that drive alcohol consumption. These findings contribute to the growing body of evidence identifying common circuit-based mechanisms of drug addiction and open up the possibilities for many exciting future studies.

Acknowledgments and Disclosures

This work was supported by National Institutes of Health National Institute on Drug Abuse Grant Nos. R01DA023206 (to YD), R01DA034856 (to YD), and R01DA040620 (to YD) and National Institute of Neurological Disorders and Stroke Grant No. T32NS007433 (to WJW).

The authors report no biomedical financial interests or potential conflicts of interest.

Article Information

From the Department of Neuroscience, University of Pittsburgh, Pittsburgh, Pennsylvania.

Address correspondence to Yan Dong, Ph.D., Department of Neuroscience, University of Pittsburgh, A210 Langley Hall, 5th and Ruskin Avenue, Pittsburgh, PA 15260; E-mail: yandong@pitt.edu.

Received Feb 11, 2017; accepted Feb 13, 2017.

References

1. Nestler EJ (2005): Is there a common molecular pathway for addiction? Nat Neurosci 8:1445–1449.
2. Russo SJ, Dietz DM, Dumitriu D, Morrison JH, Malenka RC, Nestler EJ (2010): The addicted synapse: Mechanisms of synaptic and structural plasticity in nucleus accumbens. Trends Neurosci 33:267–276.
3. Wang J, Lanfranco MF, Gibb SL, Yowell QV, Carnicella S, Ron D (2010): Long-lasting adaptations of the NR2B-containing NMDA receptors in the dorsomedial striatum play a crucial role in alcohol consumption and relapse. J Neurosci 30:10187–10198.
4. Nie H, Rewal M, Gill TM, Ron D, Janak PH (2011): Extrasynaptic delta-containing GABAA receptors in the nucleus accumbens dorsomedial shell contribute to alcohol intake. Proc Natl Acad Sci U S A 108:4459–4464.
5. Smith RJ, Lobo MK, Spencer S, Kalivas P (2013): Cocaine-induced adaptations in D1 and D2 accumbens projection neurons (a dichotomy not necessarily synonymous with direct and indirect pathways). Curr Opin Neurobiol 23:546–552.
6. Cheng Y, Huang CCY, Ma T, Wei X, Wang X, Lu J, Wang J (2017): Distinct synaptic strengthening of the striatal direct and indirect pathways drives alcohol consumption. Biol Psychiatry 81:918–929.
7. Graziane NM, Sun S, Wright WJ, Jang D, Liu Z, Huang YH, *et al*. (2016): Opposing mechanisms mediate morphine- and cocaine-induced generation of silent synapses. Nat Neurosci 19:915–925.
8. Pickens CL, Airavaara M, Theberge F, Fanous S, Hope BT, Shaham Y (2011): Neurobiology of the incubation of drug craving. Trends Neurosci 34:411–420.
9. Ma Y-Y, Lee BR, Wang X, Guo C, Liu L, Cui R, *et al*. (2014): Bidirectional modulation of incubation of cocaine craving by silent synapse-based remodeling of prefrontal cortex to accumbens projections. Neuron 83:1453–1467.
10. Wright WJ, Schlüter OM, Dong Y (2017): A feedforward inhibitory circuit mediated by CB1-expressing fast-spiking interneurons in the nucleus accumbens. Neuropsychopharmacology 42:1146–1156.