

PRIZE ESSAY

NEUROMODULATION

Toward a targeted treatment for addiction

Cocaine-induced synaptic plasticity can be reversed in mice with optogenetically inspired deep brain stimulation

By Meaghan C. Creed

A major challenge in treating many neuropsychiatric disorders is that diagnoses are regularly based on behavior rather than on biomarkers, as well as the fact that such conditions are often not associated with gross structural brain changes. Addiction is one example of a disorder defined by pathological behavior (drug seeking despite harmful consequences) in which there is no significant loss of neurons and for which there is no cure.

How is it possible that changes in brain function lead to symptoms of addiction? And can we modulate brain activity to develop therapies for this disorder? To answer these questions, we turned to the study of neural circuits: networks of neurons that work in concert and are connected by specialized structures called synapses.

Synapses are specialized structures where communication between neurons occurs. They are dynamic and can undergo increases or decreases in strength, a process that alters the function of the entire neural circuit, which can manifest as changes in behavior. In the case of addiction, exposure to addictive drugs induces a characteristic “memory trace” in the brain’s reward system by increasing levels of the neurotransmitter dopamine. This synaptic plasticity persists in the reward system even after prolonged periods of abstinence and underlies drug-adaptive behaviors such as drug seeking and anhedonia during withdrawal (1, 2).

MANIPULATING THE ADDICTED BRAIN: EASIER SAID THAN DONE

Restoring normal synaptic transmission, and thus abolishing pathological behavior

in addiction, would be difficult to achieve using classical pharmacology. When drugs are injected or swallowed, they are distributed throughout the entire body and change the function of many systems. This makes side effects likely and makes it difficult to determine how (or if) a drug exerts a therapeutic effects.

A more targeted way to influence brain circuits would be to use deep brain stimulation (DBS). In DBS, electrodes are implanted into specific brain areas to deliver electrical stimulation. This technique has been used for more than 20 years to reduce symptoms of movement disorders such as Parkinson’s disease. However, the mechanisms by which DBS works remain unclear, making its optimization difficult.

Optogenetic interventions, on the other hand, work through a well-defined mechanism. With this technique, light-sensitive proteins are introduced into specific populations of neurons, and the activity of these neurons is precisely controlled by delivering light into the brain with an optic fiber.

A NEW PROTOCOL FOR STUDYING PLASTICITY TAKES SHAPE

Although optogenetics is a powerful experimental approach in invertebrates, rodents, and even primates, it cannot yet be used in humans. However, we can use insights from optogenetic circuit dissection in a model of disease to design novel DBS protocols.

The first step in such a protocol would be to determine how addictive drugs alter plasticity in the reward system in a rodent model of addiction using optogenetics. The second step would be to find a way to restore normal transmission. In the third step, this protocol would need to be applied in vivo to measure the effect on drug-adaptive behavior. Finally, the optogenetic protocol could be emulated with electrical stimulation, yielding an optogenetically inspired form of DBS.

THE CHALLENGE: REDUCE THE SYNAPTIC STRENGTH, REDUCE THE REWARD

From previous work, we know that drug-adaptive behavior is mediated by synaptic plasticity in the nucleus accumbens (NAc) (3), a structure in the basal ganglia composed of two populations of medium-sized spiny projection neurons (MSNs) that express either the dopamine D1 or D2 receptor (D1-MSNs and D2-MSNs, respectively) (Fig. 1A). MSNs integrate excitatory inputs from several brain areas, including the medial prefrontal cortex (PFC), and receive dopaminergic fibers from the ventral tegmental area (VTA).

All addictive drugs increase dopamine release in the NAc, which mediates their rewarding effects and increases synaptic strength between the PFC and D1-MSNs (3). Usually, excitatory transmission in the NAc is mediated by classical AMPA receptors (Fig. 1B). But upon exposure to cocaine, atypical AMPA receptors are inserted at synapses between the PFC and D1-MSNs. These atypical AMPA receptors flux more current than classical AMPA receptors, so their insertion



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increases the strength of synaptic transmission. Removing atypical AMPA receptors from the synapse, which is most efficiently accomplished by activating metabotropic glutamate receptors (mGluRs) (4), leads to a weakening of transmission between the PFC and D1-MSNs in the NAc.

IT WORKS! (SORT OF)

For the current experiments, we began by treating mice with cocaine for 5 days and measuring their locomotor response. This response successively increased with each dose, an effect which persisted for a week after stopping treatment.

Using optogenetics to selectively target PFC inputs to the NAc, we found that 12-Hz stimulation activated mGluRs, which led to the removal of atypical AMPA receptors and weakened synaptic transmission at PFC to D1-MSN synapses (1, 3). This stimulation reversed cocaine-evoked synaptic plasticity and, importantly, abolished behavioral sensitization to cocaine.

We then attempted to emulate this protocol using DBS, but our initial attempts were unsuccessful. We stimulated the NAc at 12 Hz—the frequency identical to the successful optogenetic protocol—but there was no effect. The mice still expressed drug-evoked plasticity in the NAc and showed robust locomotor sensitization to cocaine.

AN ANTAGONIST TO THE RESCUE

To determine why optogenetic stimulation—but not DBS—could reverse cocaine-evoked plasticity, we turned to patch-clamp electrophysiology. Optogenetic stimulation of PFC afferents at 12 Hz activated mGluRs and removed atypical AMPA receptors from synapses, but—due to the nonspecific nature of electrical stimulation—DBS also activated afferents releasing dopamine that then activated D1Rs on MSNs (Fig. 1B). The resulting activation of two opposing signaling cascades explains the failure of DBS to restore normal synaptic transmission.

To overcome this problem, we combined 12-Hz DBS with a D1R antagonist. Under these conditions, mGluR signaling was unopposed, DBS now efficiently reversed drug-evoked plasticity in the NAc, and the sensitized locomotor response to cocaine was abolished (1).

THE ADVANTAGES OF OI DBS

Our observation provides proof of principle that neuromodulation can eliminate drug-adaptive behavior by altering the function of

synapses. We refer to this combination of 12-Hz DBS and a D1 antagonist as “optogenetically inspired DBS (OiDBS).”

This technique has important advantages over conventional DBS. First, the effects of DBS are typically transient; any therapeutic effects subside when DBS is turned off. One acute, 10-min session of optogenetically inspired DBS, on the other hand, reversed cocaine-evoked plasticity and abolished drug-

D1-MSNs to the VP was strengthened after cocaine treatment, whereas output of D2-MSNs to the VP was depressed. Using patch-clamp electrophysiology to dissect the mechanisms of this plasticity, we were then able to design stimulation protocols that normalized transmission selectively at either D1-MSN to VP or D2-MSN to VP synapses and abolished the behavioral response to cocaine, confirming the importance of D1-MSNs in behavioral sensitization.

Conversely, restoring transmission between D2-MSNs and the VP had no effect on sensitization. Instead, when we selectively normalized transmission at D2-MSN outputs to the VP, we eliminated the anhedonia that emerged after cocaine withdrawal. This finding is consistent with the role D2-MSNs are known to play in negative mood states (6).

Collectively, these results support a circuit model of addiction in which drug-evoked synaptic plasticity in distinct populations of NAc neurons mediates opposing behavioral symptoms of addiction. These findings also suggest that, in addition to the NAc, the VP may be a promising target for future neuromodulation therapies.

WHAT'S NEXT? THE FUTURE OF CIRCUIT-BASED INTERVENTIONS

Going forward, it will need to be established whether optogenetically inspired DBS reduces compulsive drug-seeking behavior in mice, a phenomenon that more closely recapitulates symptoms of addiction in people than behavioral sensitization. Translating our findings to an intermediate primate model would also further strengthen the rationale for advancing this novel therapeutic strategy to patients.

In addition to addictive disorders, optogenetics is also enabling the characterization of the neural circuits involved in anxiety, mood disorders, and obsessive-compulsive disorders. Optogenetically inspired DBS may therefore not be limited to addiction but could be expanded to other neuropsychiatric disorders for which effective therapies are desperately needed. ■

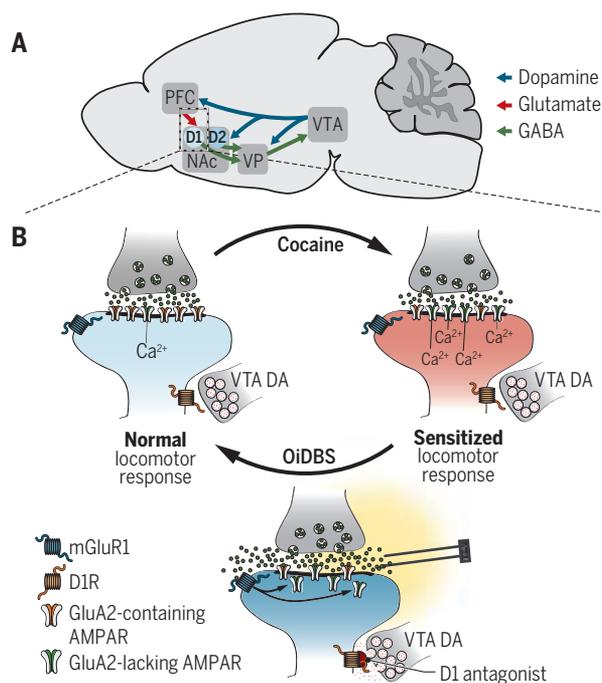
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Optogenetically inspired DBS (OiDBS) reverses cocaine-evoked plasticity

(A) Schematic of reward circuitry, highlighting synapses between the PFC and D1-MSNs in the NAc. (B) Repeated cocaine exposure changes the composition of AMPA receptors at the synapse, which mediates the sensitized locomotor response to cocaine. OiDBS reversed this plasticity and normalized the locomotor response to cocaine.



adaptive behavior for more than a week after its application. Second, the mechanisms exploited by conventional DBS are not well understood, which likely contributes to its variable efficacy (5). With optogenetically inspired DBS, however, the synaptic mechanism can be identified.

BEYOND CRAVING: TREATING NEGATIVE AFFECT IN ADDICTION

Addiction is a syndrome defined not only by craving but also by a negative affective state. In an extension of the work described above, we demonstrated that cocaine-evoked plasticity at D1- and D2-MSN outputs to the ventral pallidum (VP) contributes to behavioral sensitization and to withdrawal-induced anhedonia, respectively (2).

Here, we observed that the output of

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