Commentary

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N-Methyl-D-Aspartate Receptors: "C"ing the Culprits Behind Cocaine-Induced Metaplasticity

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The development of drug addiction involves diverse molecular and cellular adaptations in complex neural circuits. A critical node in these circuits is the nucleus accumbens (NAc). Excitatory inputs that innervate medium spiny projection neurons (MSNs) undergo extensive and dynamic adaptive changes after exposure to drugs of abuse that critically contribute to the expression of addictive behaviors (1). An important adaptation at NAc excitatory synapses after withdrawal from cocaine is the progressive accumulation of synaptic alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPARs), demonstrated by increased AMPAR surface expression and an increase in the relative ratio of AMPAR-mediated to *N*-methyl-D-aspartate receptor (NMDAR)-mediated synaptic responses (1). Although involving different AMPAR subtypes, accumulation of AMPARs occurs after either noncontingent or contingent cocaine administration, and the strengthened responsiveness of the NAc MSNs to excitatory inputs contributes to a variety of withdrawal-associated–motivated behaviors, including intensified/incubated cocaine seeking (1).

While these findings shed significant light on how cocaine experience reshapes the NAc to influence future behaviors, they also raise several key questions. First, the NAc receives excitatory projections from several limbic and paralimbic regions, and each projection plays distinct roles in motivated behaviors (1). Do these projections undergo the same or different adaptations after cocaine exposure? Second, NAc MSNs can be categorized into at least two populations, dopamine D_1-type receptor-expressing (D_1) MSNs and dopamine D_2-type receptor-expressing (D_2) MSNs. These two populations preferentially mediate different aspects of cocaine-motivated behaviors (2). Are excitatory synapses on D_1 and D_2 MSNs affected by cocaine experience similarly or differently? Third, after cocaine withdrawal, experience-dependent plasticity at the NAc excitatory synapses within different projections appears to be impaired or biased toward specific directions. For example, a tetanus protocol that typically induces long-term potentiation (LTP) at hippocampal-to-NAc synapses in drug-naive animals fails to do so in animals withdrawn from noncontingent cocaine exposure (3). Similarly, induction of LTP and long-term depression (LTD) in the NAc is impaired after withdrawal from contingent cocaine exposure in specific projections (4). These findings suggest that, in addition to AMPAR upregulation, the plasticity machinery is also altered after cocaine withdrawal, which may prime or preset NAc synapses to be resistant to certain forms of plasticity while favoring others. What are these alterations affecting plasticity?

In this issue of *Biological Psychiatry*, Joffe and Grueter (5) provide significant insight into these critical questions. Using projection-specific optogenetic approaches in a transgenic mouse line with genetically labeled D_1 MSNs, they identified differential adaptations in synaptic AMPARs and NMDARs within several key excitatory projections to NAc D_1 and D_2 MSNs after cocaine withdrawal. Thus, specific projections to distinct NAc MSN populations do undergo different adaptations after cocaine exposure. Furthermore, these researchers identified a novel and unexpected adaption in NMDAR function involving atypical GluN2C-containing NMDARs. While AMPARs function as the workhorse to mediate most of the excitatory synaptic transmission, NMDARs serve as the plasticity dictator. Depending on the stoichiometric composition, the activation level, and the involvement of additional signaling pathways, synaptic NMDARs can induce different forms of plasticity. As such, NMDARs are one of the key substrates that mediate metaplasticity—plasticity that does not necessarily change synaptic transmission, but alters the induction threshold and biases the direction of subsequent plasticity (6). Along this line of thinking, alterations in synaptic NMDARs after cocaine withdrawal may serve as a metaplastic event dictating the subsequent adaptive changes at NAc synapses in ways already observed and yet to be identified.

Among several projections to the NAc, Joffe and Grueter (5) singled out the midline thalamic (mThal) input to D_1-positive and D_1-negative (putative D_2-expressing) MSNs within the NAc core. To do so, they recorded excitatory postsynaptic currents (EPSCs) in D_1 and D_2 MSNs evoked by optogenetic stimulation of mThal afferents in the NAc core from mice withdrawn from cocaine. They first observed that after 15–19 days withdrawal from 5-day noncontingent cocaine administration, AMPAR function at mThal-D_1 MSN synapses was enhanced, indicated by an increase in the amplitude of quantal-like asynchronous EPSCs. The NMDAR-to-AMPAR ratio at mThal-D_1 MSN synapses was unchanged, however, indicating a concurrent upregulation of synaptic NMDARs. Furthermore, a change in the current-voltage relationship of NMDAR EPSCs revealed a reduced sensitivity to Mg^{2+} blockage of NMDARs, a change suggesting the addition of new GluN2C/D or GluN3 subunit-containing NMDARs. Subsequent pharmacologic examinations identified GluN2C-containing NMDARs as the culprits mediating this change. Interestingly, an upregulation of NMDAR function, but not AMPAR function, was also observed at mThal-D_2 MSN synapses, but this NMDAR upregulation did not involve GluN2C subunits. Taken together, these findings demonstrate that cocaine withdrawal enhances NMDAR function at mThal synapses in the NAc, although through different mechanisms in D_1 and D_2 MSNs.

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Does the altered NMDAR function confer plastic or metaplastic properties to NAc excitatory synapses after cocaine withdrawal? To address this, Joffe and Grueter (5) examined if NMDAR-dependent synaptic plasticity was altered at mThal-D_1 MSN synapses. In drug-naive animals, 1-Hz low-frequency stimulation did not affect mThal-D_1 MSN synapses. However, after cocaine withdrawal, low-frequency stimulation became capable of inducing robust LTD at these synapses. This LTD was then verified to be NMDAR-dependent, narrowing down NMDARs as the culprit. Thus, after being equipped with GluN2C-containing NMDARs and possibly other components, mThal-D_1 MSN synapses become susceptible to LTD induction. This is a typical form of metaplasticity induced after cocaine withdrawal, with the secret possibly hidden behind GluN2C-containing NMDARs.

While the actual mechanisms underlying cocaine withdrawal-induced metaplasticity remain to be determined, one speculation is that synaptic recruitment of GluN2C-containing NMDARs lowers the induction threshold for LTD, turning an otherwise subthreshold induction protocol into an effective one. A defining property of GluN2C subunits is their decreased sensitivity to Mg^{2+}, which allows GluN2C-containing NMDARs to be activated at less depolarized potentials compared with more typical GluN2A- and GluN2B-containing NMDARs (7). As such, a weak induction protocol that minimally depolarizes MSNs and is normally insufficient to activate NMDARs in drug-naive animals becomes sufficient in GluN2C-enriched synapses after cocaine withdrawal, resulting in LTD and possibly other forms of plasticity.

Another unique property of GluN2C-containing NMDARs is their higher binding affinity for glutamate compared with GluN2A- and GluN2B-containing NMDARs (7). This increased affinity may allow GluN2C-containing NMDARs to be activated by weaker synaptic activation where less glutamate is released and possibly even by glutamate spillover from adjacent synapses. Given that cocaine exposure disrupts normal glutamate homeostasis to increase glutamate spillover after withdrawal (8), the increased affinity for glutamate together with decreased Mg^{2+} blockage of GluN2C-containing NMDARs may not only lower the threshold for NMDAR-dependent synaptic plasticity but also facilitate heterosynaptic plasticity, which has been implicated in cocaine reinstatement after extinction training (8).

Another related property of GluN2C-containing NMDARs is the decreased conductance of Ca^{2+} (7). This decreased Ca^{2+} permeability combined with the two other properties mentioned above may on one hand allow for easy activation of NMDARs, while on the other hand limit Ca^{2+} influx. These combined features may preset NAc excitatory synapses to undergo LTD by biasing NMDAR activation for the induction of LTD over LTP. After withdrawal, re-exposure to cocaine rapidly decreases the synaptic levels of AMPARs in NAc MSNs (1). It would be intriguing to determine whether this LTD-like process is preset by GluN2C-mediated metaplasticity.

In addition to GluN2C subunits, other NMDAR subunits may also be involved in cocaine-induced metaplasticity. One example is GluN2B-containing NMDARs, upregulation of which is observed at NAc excitatory synapses 1–2 days after 5 days of noncontingent cocaine administration (9). This GluN2B upregulation may prime NAc excitatory synapses with enhanced GluN2B-coupled signaling that favors the induction of specific forms of plasticity such as LTP (7). Furthermore, in the ventral tegmental area, another component of the mesolimbic dopamine system, a single exposure to cocaine induces synaptic expression of GluN3A-containing NMDARs in dopaminergic neurons (10). GluN3A expression is normally expressed early during development and then declines during the course of development. As such, some developmentally related synaptic plasticity mechanisms can be reactivated through these receptors to tweak ventral tegmental area excitatory synapses by additional cocaine exposure or during withdrawal (10). It is conceivable that there are additional forms of metaplasticity induced within as well as outside of the mesolimbic dopamine system that selectively reshape the pattern or intensity of synaptic transmission on specific external or internal stimulation. The final circuitry effects of cocaine exposure and withdrawal driving addiction-related behaviors are the integrated consequences of all these plastic and metaplastic adaptations.

Collectively, Joffe and Grueter (5) report a series of cell type- and projection-specific synaptic adaptations after cocaine withdrawal. These findings provoke several critical questions for future studies. First, does GluN2C upregulation facilitate experience-dependent synaptic depression in general or selectively for certain types of experience? Second, what are the behavioral consequences of GluN2C upregulation and its related effects on addiction-related behaviors? Third, can synaptic GluN2C-containing NMDARs be targeted to shift the rules of plasticity back to normal for therapeutic benefits? Answering these questions may further expand our mechanistic understanding of drug addiction and may help develop effective treatments for addiction.

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