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A Third-Party Facilitator of Bipartisanship

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Often times, biological processes are reminiscent of a two-party system, wherein two differential or opposing forces must coordinate to achieve a balanced output, and drug addiction is no exception. In the nucleus accumbens (NAc), the two parties in play are D1 and D2 dopamine receptor-expressing medium spiny neurons (MSNs). Differentially embedded in NAc circuits, D1 and D2 MSNs regulate different aspects of motivated behaviors related to drug addiction, very often, in an opposing manner (1). To form coherent and reliable behavioral outputs, e.g., persistent cue-induced drug seeking, cooperative, as opposed to individualistic, adaptations between these two neuronal types is required. However, as we've witnessed with many two-party systems, reaching any sort of bipartisan deal is difficult when left to the two insiders.

In this issue of *Biological Psychiatry* (2) Chioma and colleagues report a surprising third party, the matrix metalloproteases (MMPs), that act as an external coordinator for D1 and D2 NAc MSNs. MMP2/9 are two brain-enriched subtypes of MMPs, activation of which may loosen up the extracellular matrix (ECM), thereby opening synapses for modification. Results from this study show that MMP2/9 exhibited two temporally dynamic activity patterns around D1 versus D2 MSNs, unique to cue-induced heroin seeking versus extinction/refraining of heroin seeking, respectively. These cell type-specific dynamics of MMPs may induce sequential morphologic changes of glutamatergic synapses on D1 and D2 MSNs in order to facilitate the transition between states of drug seeking and extinction/refraining. While recent work by the same research group established a role for the ECM in drug-seeking (3), the newly identified cell type-specific feature of the ECM raises the possibility that, at least within the realm of drug-induced plasticity, bipartisanship can be achieved with a little outside help.

To begin, Chioma and colleagues visualized the catalytic activity of MMPs that closely (within a 300-nm radius) surrounded NAc core MSNs after withdrawal from heroin self-administration. This local activity of MMP-2/9 was selectively increased around D1 MSNs in rats that performed cue-induced heroin seeking. A subsequent 10-day extinction training, which refrained the drug-seeking behavior, normalized the D1 MMP2/9 activity to levels comparable to that of saline-yoked control rats. On the other hand, the D2 MMP2/9 activity, while remaining constant upon cue-induced heroin seeking, was increased following heroin extinction and refraining. Furthermore, these D1 versus D2 MSN-specific changes of

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MMP2/9 activities were transient and sharply correlated to heroin seeking versus refraining, leading to a hypothesis that MMP2/9 is integral to the extracellular signaling coordinating the functional outputs of D1 and D2 MSNs under different behavioral conditions.

To test this hypothesis, the authors focused on MMP2/9-mediated regulation of glutamatergic synapses, which are the primary driving force activating NAc MSNs. Without distinguishing cell types, previous studies show that extinction from heroin self-administration decreases, while cue-reinstated heroin seeking increases, the head diameter of dendritic spines on NAc MSNs (4). Dendritic spines are postsynaptic structures of glutamatergic synapses, with the head size predicting the abundance of AMPA receptors and, thus, synaptic strength(5). In line with these findings, Chioma and colleagues observed that reinstatement of cue-induced heroin seeking increased the head diameter of dendritic spines on D1, but not D2 MSNs, in parallel with a D1 MSN-selective increase in MMP2/9 activities. Furthermore, a pharmacological analysis revealed that heroin seeking elevated MMP9 activities around D1 dendritic spines, whereas MMP2 activities increased around D2 MSN spines during extinction/refraining. Thus, with such a refined division of labor, MMP2 and 9 differentially associate with D1 or D2 MSN synapses to coordinate their functional outputs during heroin seeking or refraining.

As in most sophisticated systems, each player works within a hierarchy of influence. To unravel who pulls the strings of MMP, Chioma and colleagues focused on TIMP1 and 2, two endogenous inhibitors of MMP2/9. They observed that heroin extinction increased levels of TIMP2 around synapses on D1, but not D2, MSNs, an effect that restrains MMP9-mediated synaptic changes in D1 MSNs, thus allowing D2 MSNs to take center stage during drug extinction. On the other hand, reinstatement of cue-induced heroin seeking increased TIMP1/2-mediated inhibition around synapses on D2, but not D1, MSNs, thereby restraining MMP2/9-mediated synaptic changes in D2 MSNs during drug seeking. In this case, TIMP1/2 create a push-n-pull mechanism through MMP2/9 to shift the activity level of D1 and D2 MSNs under different behavioral conditions.

Finally, Chioma and colleagues made an attempt to determine whether TIMP1/2 can be used as a handle to manipulate the local MMP2/9 activity and heroin seeking. They observed that delivering antibodies against TIMP1/2 in the NAc core during a heroin seeking test further elevated both NAc MMP2/9 activities and rats' seeking response. However, TIMP-inhibition did not affect heroin refraining or baseline MMP activity levels during extinction, suggesting that, in addition to TIMP1/2, other unveiled 'special interest groups' also kick in to regulate NAc MMPs during the coordination of MSN dynamics.

These new findings are exciting and inspiring in several dimensions. First, it has long been known that D1 and D2 NAc MSNs exhibit different synaptic responses in motivated behaviors and undergo differential drug-induced synaptic adaptations. However, many of these unique cellular properties and adaptations are difficult to link directly to D1/D2 receptors or other neuron-embedded substrates. The current findings, together with a growing body of related evidence, indicate that part of the secret resides outside of neurons. Among many outstanding questions, findings by Chioma and colleague exemplify the

importance of understanding how extracellular components are organized to achieve such a cell type-specific regulation in response to drug experiences.

Second, several forms of NAc adaptations are induced in animals that have only experienced drug administration and withdrawal (without extinction or drug seeking). These adaptations are typically long-lasting and often differ substantially among drugs of different classes. For example, synapse formation versus elimination is induced in NAc MSNs after withdrawal from cocaine versus morphine, respectively (6, 7). Focusing on extinction and reinstatement of heroin seeking after withdrawal from heroin self-administration, the current study demonstrates a ‘transient’ form of synaptic plasticity in NAc MSNs. This extinction/reinstatement-induced transient plasticity exhibits striking similarities among drugs of different classes (5) and, when considered together with withdrawal, raises important questions for future studies. For example, how is such ‘generic’ transient plasticity established at synapses that have different prior histories, or do transient and withdrawal-associated forms of plasticity actually occur at different sets of synapses? Regardless of these unknowns, demonstration of the transient plasticity provides a significant insight in understanding the dynamics of drug-associated memories. Specifically, the withdrawal-associated, long-lasting adaptations are thought to set the basal patterns of NAc circuits that encode several aspects of drug-associated memories (8). During refraining or reinstatement, an animal’s behavior is independent of drug influence, relying instead on established cue-conditioned responding, a behavioral output common to drugs of different classes. Transient forms of plasticity may underlie a common mechanism to temporarily add new circuit features specific for the expression or modification of cue-conditioned responding. In this case, the critical roles of MMP2/9 demonstrated in the current and previous studies (3, 5) raise the possibility that extracellular matrices are the essential partner of the neural network that encodes memory dynamics.

Third, glutamatergic projections from multiple limbic and paralimbic brain regions often times converge onto the same dendrites of NAc MSNs (9). Synapses within these projections undergo differential drug-induced adaptations, which contribute differentially to cue-induced drug seeking. For example, potentiated synaptic transmission is observed in both the projections from the basolateral amygdala (BLA) and infralimbic prefrontal cortex (IL-PFC) after withdrawal from cocaine self-administration, but the BLA adaptation promotes, whereas the IL-PFC adaptation reduces, cue-induced drug seeking (8). In the spine-MMP co-localization experiment, Chioma and colleagues provided images in which MMP2/9 or TIMP were not evenly distributed but appeared to be ‘selective’ for certain spines or dendritic regions. This anecdotal observation raises the possibility that MMP2/9-mediated regulation of NAc synapses is not only cell type- but also projection-specific. As such, although BLA, IL-PFC, and other projections exhibit largely unbiased innervation of D1 versus D2 NAc MSNs (10), MMP2/9-mediated transient plasticity could coordinate the output of functionally clustered synapses almost as a “transitional team”, resulting in specific patterns of circuit dynamics for each given behavioral output. It is tempting to speculate that such an MMP-mediated mechanism of synapse/projection selection operates as a common mechanism for behavioral output of memories in general.

To a certain extent, the brain operates within the philosophy of Yin-and-Yang. Exemplified in the NAc, D1 and D2 MSNs do not directly oppress one-another, but alternate predominance for different situations. Such temporal dynamics require mechanisms that shift the excitation and inhibition of the two parties in a timely manner. While several circuit-based mechanisms have been proposed, Chioma and colleagues identified extracellular signaling as a third-party coordinator that may time the activation/inhibition of D1 and D2 MSNs to support different behaviors. About 160 years ago, Schwann and Schleiden proposed that all the secrets of life can be found in the cell. In line with a growing body of evidence, the results from Chioma and colleagues indicate that the keys to unlocking these secrets may lie just outside it.

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