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Critical Involvement of Actin Stabilizer TMOD2 in Cocaine-Induced Neuroadaptations

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Review of Mitra et al.

Repeated exposure to addictive drugs leads to the increase in drug-seeking behavior (the effort to obtain a drug when it is unavailable) and behavioral sensitization (a neuroadaptive process in which repeated drug exposure leads to a progressively stronger and long-lasting behavioral response to a drug). Over the past two decades, extensive research has characterized the drug-induced plasticity that occurs within neural circuits that regulate motivation and reward in parallel with the behavioral changes that occur in animal models of addiction. These structural and functional adaptations are responsible for the persistent craving and reduced regulation of drug use that characterize addiction, as well as changes in the sensitivity to the effects of a drug.

A key hub of the reward system is the nucleus accumbens (NAc). Medium spiny neurons (MSNs) within the NAc display cell-specific adaptations after administration of the psychostimulant drug cocaine. These adaptations vary based on the neuronal inputs and outputs of the MSNs, location within the NAc, and dopamine D1- or D2-receptor expression (Zinsmaier et al., 2022). For example, a cocaine-induced strengthening of synapses between dorsomedial prefrontal afferents and NAc core MSNs promotes cocaine seeking (Zinsmaier et al., 2022). Understanding the mechanisms underlying this plasticity could contribute to the development of effective treatments for cocaine use disorder (CUD), and genes and signaling cascades that are involved may be potential therapeutic targets.

A network of actin filaments beneath the plasma membrane supports the shape of dendritic spines, and rearrangement of this meshwork, mediated by actin binding proteins, produces the structural changes necessary for strengthening or weakening synaptic connections. Actin polymerization is required for long-term potentiation and modulates the function of neurotransmitter receptors at the synapse. Moreover, actin filaments interact with signaling molecules that regulate synaptic plasticity (Pandey and Miller, 2024). Proteins that regulate actin filaments are essential for changes in the morphology of dendritic spines and the formation and stabilization of synapses (Pandey and Miller, 2024). Also, the cytoskeleton and its regulatory proteins are major players in the aberrant plasticity that is observed in substance use disorders (Toda et al., 2006).

Tropomodulin-2 (TMOD2) is a neuron-specific tropomyosin-dependent protein that acts as an actin stabilizer by binding to the slow-growing end of the filament, preventing both destabilization and elongation of actin filaments (Mitra et al., 2024). Drawing from prior studies indicating that actin dysregulation is associated with CUD (Toda et al., 2006), Arojit Mitra and colleagues provide a robust description of how TMOD2 promotes a predisposition to addiction and plays a crucial role in drug-induced synaptic changes (Mitra et al., 2024). The authors chose to focus on this molecule after delving into a publicly available phenotyping database that characterizes single-gene knock-out (KO) mice to evaluate addiction-predictive behavioral traits and found novelty-induced hyperactivity, increased risk-taking, and lower anxiety levels in *Tmod2* KO mice compared with wild-type (WT) animals.

To assess addiction-relevant behavior, the authors observed a decreased locomotor sensitization to cocaine injection (15 mg/kg) in the *Tmod2* KO mice compared with WT animals, which is suggestive of compromised drug-induced neuroadaptations. Furthermore, WT mice readily learned to press a lever to self-administer cocaine, whereas KO failed in this task. Although the latter effect could have been caused by a general learning deficit, the authors showed that *Tmod2* KO mice readily learned to respond for food reward in an operant task, indicating that TMOD2 is uniquely involved in cocaine reinforcement. In addition, the acute psychomotor effects of cocaine and cocaine metabolism were unaltered in *Tmod2* KO mice. Combined, these results suggest that TMOD2 regulates cocaine-induced plasticity but is not involved in the acute pharmacological effects of the drug.

In addition to behavioral effects, differences were observed between WT and KO neurons in NAc neurons. In the absence of cocaine administration, KO neurons showed greater intrinsic excitability, larger-amplitude excitatory synaptic currents, and a greater frequency of inhibitory

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currents than WT neurons, indicating that TMOD2 plays an important role in the normal physiology of MSNs. Although repeated cocaine exposure normally potentiates excitatory synaptic neurotransmission onto NAc MSNs (Zinsmaier et al., 2022), as measured by an increase in the frequency of excitatory postsynaptic currents, this effect was absent in *Tmod2* KO mice. Instead, cocaine exposure potentiated inhibitory postsynaptic currents in NAc MSNs of *Tmod2* KO mice, but did not affect IPSC frequency in NAc MSNs from WT mice. Furthermore, KO mice had a reduced overall brain volume.

Altogether, these results provide a potential mechanistic link for the lack of sensitization and acquisition in cocaine self-administration observed in *Tmod2* KO mice. It is likely that differences in the response to cocaine occurred at the cellular level, since no significant transcriptional changes were observed in KO animals with RNA-seq analysis, except for *Tmod2*. Therefore, it is reasonable to hypothesize that the lack of stabilization of the actin filaments caused by the absence of TMOD2 reduces the potential for aberrant cocaine-induced synaptic plasticity. Indeed, cocaine exposure produces pronounced changes in the density and size of dendritic spines in the NAc (Zinsmaier et al., 2022), which are thought to be correlated with the motivation for the drug (Spencer et al., 2017). In addition, disrupting the actin cytoskeleton-stabilizing process in the NAc during the destabilization and reconsolidation of a cocaine memory can produce a lasting reduction in cocaine seeking (Wright et al., 2020). Thus, the formation and stabilization of dendritic spines are crucial for the motivational processes in the NAc that mediate cocaine addiction. The findings suggest that a lack of TMOD2 likely results in a reduced stabilization of the actin cytoskeleton, which protects KO mice from developing addiction-like behaviors.

Perhaps future studies could examine whether the observed decrease in EPSCs and increase in IPSC effects of *Tmod2* KO are due to compensatory homeostatic adaptations that counteract the increased excitability of MSNs induced by cocaine (Kourrich et al., 2007) or whether cocaine-induced increases in NAc inhibitory neurotransmission contribute to the observed lack of sensitization and cocaine self-administration in KO mice. It would also be important to investigate whether the KO of *Tmod2* differentially affects D1 and D2 MSNs in the NAc and their responses to cocaine using more selective disruptions of TMOD2 expression such as using gene editing approaches and local viral vector injections, since these cells are known to undergo different adaptations with regard to spinogenesis, glutamatergic receptor trafficking, and intrinsic neuronal excitability (Zinsmaier et al., 2022). Additionally, it will be important to discern the role of TMOD2 in cocaine-induced synaptic changes at different NAc inputs (Kauer and Malenka, 2007) and to examine the formation, elimination, density, and size of dendritic spines of NAc D1 and D2 MSN subtypes using imaging techniques to complement electrophysiological findings.

The thorough investigation conducted by Mitra and colleagues in this paper shows the mechanisms, whereby TMOD2 regulates cocaine-associated behaviors and cocaine-induced plasticity. However, there are a few methodological considerations that warrant attention in future research endeavors. Although the study was carried out in both males and females, potential sex differences were not examined. This is particularly important given that a recent study found striking sex differences in cocaine-induced NAc plasticity. Unlike male rats, female rats did not show an increase in NAc excitatory synaptic neurotransmission onto MSNs after the development of cocaine-induced behavioral sensitization (Catalfio et al., 2023). In addition, female sex hormones are well-known regulators of relapse vulnerability (Doncheck et al., 2021). Thus, examining sex as a biological variable remains crucial in future studies on the neurobiology of CUD.

In conclusion, Mitra et al. (2024) demonstrate the pivotal role of TMOD2 in the synaptic changes within the NAc that are linked to cocaine addiction. Their study provides important new details on the cellular and molecular mechanisms underlying cocaine-induced behavioral and synaptic changes and provides insights of the mechanistic underpinnings of CUD. Most importantly, the authors demonstrate that targeting the actin cytoskeleton in the NAc may be a promising strategy to improve understanding of CUD and pave the way for potential treatments to mitigate the maladaptive neurobiological effects of addictive drugs.

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