RESEARCH HIGHLIGHT

Disinhibitory feedback loops for reward and aversion

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The nucleus accumbens (NAc) region of the brain's ventral striatum plays a central role in the regulation of appetitive and aversive motivations. A new study finds that medium spiny neurons in the NAc regulate the activity of ventral mesencephalic dopamine neurons to drive reward or aversion through direct or indirect projections.

Dopamine is a potent modulatory neurotransmitter in the brain that regulates multiple aspects of learning, memory, and motivation.[1] Dopamine neurons of the ventral mesencephalic (VM), project to numerous striatal, cortical, and limbic structures involved in the processing of rewarding and aversive stimuli to promote approach and avoidance behavior and facilitate learning about cues that predict appetitive and aversive outcomes. Of the structures innervated by the VM dopamine neurons, the striatum receives the densest inputs from these cells and emerging evidence suggests both cellular and anatomical specialization in these striatal structures for promoting approach and avoidance behavior.[2]

Dopamine released in the striatum acts on stimulatory dopamine D1 receptor or inhibitory dopamine D2 receptor expressing medium spiny neurons (MSNs) (D1R-MSN or D2R-MSN). The canonical view of this circuitry is that activation of D1R facilitates activation of D1R-MSNs to promote approach behavior and facilitate reward learning.[2] Within the nucleus accumbens (NAc) region of the ventral striatum, the reinforcing effects of D1R-MSN activation is further boosted by a positive feedback loop in which these inhibitory GABAergic projection neurons of the NAc synapse onto local inhibitory neurons in the VM to suppress their activity and disinhibit dopamine projection neurons to the NAc boosting the dopamine signal.[3,4] In response to aversive stimuli dopamine release is suppressed, promoting the activation of D2R-MSNs by relieving dopamine-induced inhibition to promote the avoidance of the behavior that resulted in the negative outcome.[5] This simplified view of the NAc has been evolved due to the emergence of tools that allow for the precise monitoring and manipulation of these cell types, revealing more nuanced micro- and macrocircuit complexity and function.[6,7]

In addition to their projections to the VM, D1R-MSNs of the NAc also project to the ventral pallidal (VP) region of the basal ganglia.[7,8] The VP consists largely of glutamatergic and GABAergic neurons that share similar projection patterns to the ventral tegmental area (VTA) in the VM, lateral habenula, and rostromedial tegmental area.[9] The function of D1R-MSN projections to the VP in regulating appetitive and aversive motivations has been relatively obscure. To address this, Liu et al.[10] first imaged calcium dynamics in the projections of D1-MSNs to the VM ($D1^{NAc\rightarrow VM}$) or VP ($D1^{NAc\rightarrow VP}$) in response to a variety of appetitive and aversive stimuli. They observed opposing responses of these pathways, with rewarding stimuli activating $D1^{NAc\rightarrow VM}$ neurons and inhibiting $D1^{NAc\rightarrow VP}$ neurons as well as aversive stimuli inhibiting $D1^{NAc\rightarrow VM}$ neurons and activating $D1^{NAc\rightarrow VP}$ neurons. Consistent with these observations, Liu et al.[10] demonstrated using inhibitory and excitatory optogenetic strategies that activation or inhibition of these D1R-MSN populations resulted in opposing effects on positive and negative reinforcement. Interestingly, the authors also found that activation of $D1^{NAc\rightarrow VP}$ neurons reduced cocaine-conditioned place preference, which is consistent with previous observations that D1 receptive MSN projections to the VP regulate behavioral adaptations to cocaine.[8] This highlights the potential importance of these connections in substance use disorder.

To further resolve the differences between $D1^{NAc\rightarrow VM}$ and $D1^{NAc\rightarrow VP}$ neurons, Liu et al.[10] mapped specific inputs to the cells and performed differential gene expression analysis. They demonstrate that $D1^{NAc\rightarrow VP}$ neurons received greater inputs from the basolateral amygdala (BLA) and thalamus, whereas the $D1^{NAc\rightarrow VM}$ neurons received more innervation from the medial prefrontal cortex. The authors further observed that among the differentially expressed genes, D1R gene (*Drd1*) expression and prodynorphin gene (*Pdyn*) expression were lower in $D1^{NAc\rightarrow VP}$ neurons relative to $D1^{NAc\rightarrow VM}$ neurons. Additionally, there were fewer *Pdyn*-positive $D1^{NAc\rightarrow VP}$ neurons overall relative to $D1^{NAc\rightarrow VM}$ neurons. These data suggest that $D1^{NAc\rightarrow VP}$ neurons may be less sensitive to dopamine and may provide less inhibitory dynorphin tone onto kappa opioid receptor expressing inputs from the VTA and BLA. Liu et al.[10] also observed that $D1^{NAc\rightarrow VP}$ neurons received less inhibitory inputs than $D1^{NAc\rightarrow VM}$ neurons, suggesting that these cells may receive less lateral inhibition from D2R-MSNs in the NAc,[11] which is further evidence in support of these neurons regulating aversive responses.

To establish the neural circuit basis of $D1^{NAc\rightarrow VP}$ and $D1^{NAc\rightarrow VM}$ neurons in regulating appetitive and aversive outcomes, Liu et al.[10] performed a series of synaptic connectivity and in vivo imaging experiments. Through these combined efforts, they demonstrate that $D1^{NAc\rightarrow VP}$ neurons send inhibitory projections to the VP and synapse onto GABA projections to the VM, that in turn synapse onto GABA neurons of the VM (Fig. 1). Conversely, the authors find that $D1^{NAc\rightarrow VM}$ GABA neurons synapse onto VM GABA neurons to disinhibit dopamine-producing cells and increase dopamine release (Fig. 1).

Collectively, the findings of Liu et al. resolve important insights into the functional connectivity of $D1^{NAc\rightarrow VP}$ neurons and their opposition to the reinforcing effects of $D1^{NAc\rightarrow Vm}$ neurons. Future experiments to determine how dopamine release regulates the

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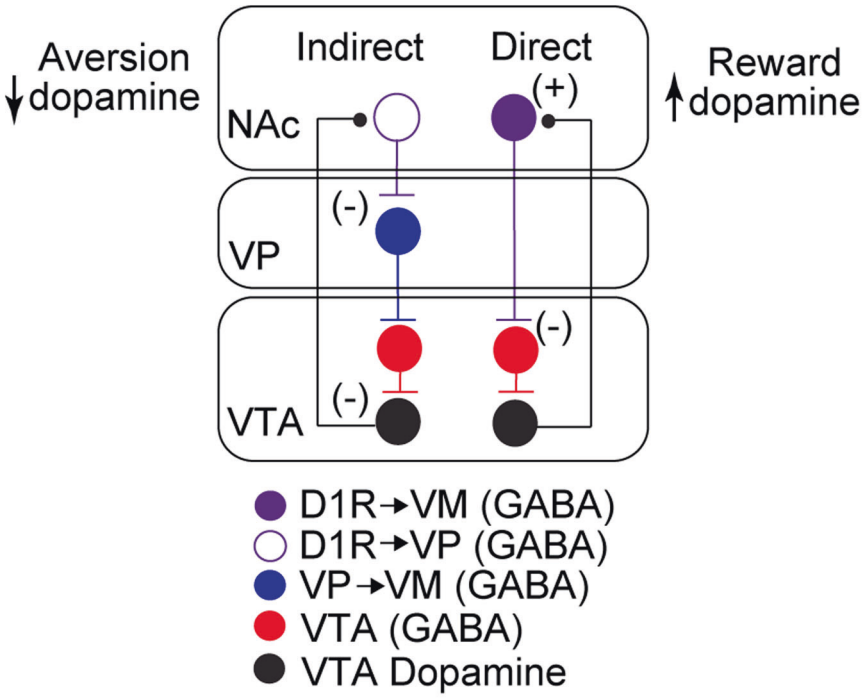

Fig. 1 Disinhibitory loops for reward and aversion. $D1^{NAc→VM}$ neurons send a GABAergic projection to the VTA where they inhibit GABA-releasing neurons that inhibit dopamine-producing cells, setting up a direct NAc→VTA pathway. This disinhibition by $D1^{NAc→VM}$ neurons is enhanced by D1R activation setting up a positive feedback loop that further boosts dopamine release in the NAc leading to rewarding behavior. Conversely, $D1^{NAc→VP}$ neurons send a GABAergic projection to the VP that inhibits VP-GABA projections to the VM. These VP → VM projections inhibit VTA GABA neurons, setting up an indirect NAc→VP → VTA pathway. Thus, activation of $D1^{NAc→VP}$ neurons inhibits VP → VM projection neurons disinhibiting VTA GABAergic neurons that reduces the activity of VTA dopamine neurons and suppresses dopamine release in the NAc leading to aversive response.

function of these cells, the importance of the differential inputs and genetic heterogeneity in regulating these cells, and whether further sub-specialization of these D1R-MSNs exist at the anatomical level within the NAc will provide key insights into the neural circuit basis of approach-avoidance behavior.

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