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Journal
Neuron, 105(6)

ISSN
0896-6273

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Publication Date
2020-03-01

DOI
10.1016/j.neuron.2020.02.031

Peer reviewed

HHS Public Access

Author manuscript

Neuron. Author manuscript; available in PMC 2021 March 18.

Published in final edited form as:

Neuron. 2020 March 18; 105(6): 954–956. doi:10.1016/j.neuron.2020.02.031.

Dopaminergic control over the tripartite synapse

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Abstract

In this issue of *Neuron*, Corkrum, Covelo *et al*. demonstrate an unexpected role for dopamine D_1 receptors on astrocytes located in the nucleus accumbens, a key structure of the brain's reward system. Activation of these receptors mediates dopamine-evoked depression of excitatory synaptic transmission, which contributes to amphetamine's psychomotor effects.

Keywords

dopamine; astrocytes; nucleus accumbens; amphetamine; reward

Astrocytes have classically been thought to support various physiological functions in the central nervous system, including the establishment of the blood-brain barrier and the regulation of the extracellular ion balance. However, evidence is emerging that astrocytes also directly mediate neuronal excitability (Araque et al., 2014), thus playing a role in cognition and behavior. In addition to controlling the metabolic milieu of a neuron, astrocytes may also directly secrete chemical transmitters including glutamate, TNF-α, and ATP (Araque et al., 2014). In line with these findings are several recent papers that showed that astrocytes can directly affect cognition, including reward-related behaviors. For example, astrocytes mediate approach and avoidance through action in the ventral tegmental area (Gomez et al., 2019), depression-like behavior through the lateral habenula (Cui et al., 2019), and the rewarding effects of morphine through the striatum (Skupio et al., 2019).

While relatively little is known about the function of astrocytes in the reward system, the role of the neurotransmitter dopamine (DA) in reward-related behaviors is well established. In particular, midbrain DA neurons projecting to the nucleus accumbens (NAc) in the ventral striatum are known to play a key role in motivation and reward learning. Within the NAc, DA directly binds to D_1-like or D_2-like receptors on medium spiny neurons (MSNs) — the GABAergic neurons that comprise the majority of cells in the striatum — to establish motivated action through basal ganglia output structures (Bariselli et al., 2019).

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DECLARATION OF INTERESTS

The authors declare no competing interests.

In addition to the direct effects of DA on striatal MSNs, it has long been known that DA affects local glutamate release within the NAc, which is secreted by axon terminals of corticolimbic brain structures, including the amygdala, prefrontal cortex and hippocampus. For instance, slice electrophysiology experiments have shown that extracellularly applied dopamine depresses glutamatergic neurotransmission within the NAc (Harvey and Lacey, 1997), a phenomenon that is thought to be involved in the development of drug addiction (Wolf, 2016). However, the exact mechanism behind this DA-induced glutamatergic synaptic depression was not fully understood. In this issue of *Neuron*, Corkrum, Covelo *et al.* (Corkrum et al., 2020) demonstrate that these effects are mediated by local astrocytes, forming a tripartite synaptic complex with glutamatergic projection neurons and MSNs within the NAc core that is under direct control of midbrain DA cells (Figure 1).

Corkrum, Covelo *et al.* start their paper with a surprising observation: optogenetic stimulation of VTA DA neurons in mice robustly increased Ca^{2+} levels within astrocytes in the NAc — an effect that was abolished after treatment with a DA D_1 (but not D_2) receptor antagonist. In addition, the authors used electron microscopy to show that D_1 receptors are located directly on the astrocytic membrane. These findings suggest that VTA DA neurons activate astrocytes through direct effects of DA on astrocytic D1 receptors. To confirm this notion, the authors showed that viral deletion of the D_1 receptor under control of the astrocyte-specific promotor *GFAP* prevented DA from increasing Ca^{2+} levels in astrocytes.

In an elegant set of follow-up experiments, the authors followed the neuronal cascade downstream of the astrocytic D_1 receptor, to define the functional role of these receptors on the tripartite synaptic complex. Towards this aim, the authors simultaneously recorded from astrocytes and MSNs *ex vivo*, to demonstrate that the increase in astrocytic Ca^{2+} (observed after DA release) scales with the level of depression of glutamatergic synapses. This shows, perhaps unexpectedly, that astrocytes may be directly involved in regulating glutamatergic neurotransmission in the NAc core. To test this notion, the authors showed that chemogenetic activation of astrocytes alone was able to evoke depression of presynaptic glutamatergic terminals, demonstrating that astrocyte activation is sufficient for DA-dependent modulation of glutamatergic synaptic physiology. In addition, DA-evoked glutamatergic synaptic depression was abolished after interfering with the normal functioning of astrocytic D_1 receptor signaling, including the use of a mouse line with impaired astrocytic Ca^{2+} dynamics and the genetic deletion of astrocytic D_1 receptors. This suggests that astrocytes are also necessary for DA-dependent depression of glutamatergic synapses.

After establishing the necessity and sufficiency of D_1 receptor signaling on the astrocytic membrane to modulate glutamatergic signaling, the authors go one step further down the neuronal cascade, by identifying the receptor target on the glutamatergic presynapse in the NAc, downstream of the astrocyte. By combining *ex vivo* optogenetics, calcium imaging, electrophysiology and pharmacology, the authors provided compelling evidence that the effects are mediated by presynaptic activation of the adenosine A_1 receptor by ATP/adenosine released from astrocytes.

Finally, the authors emphasized the relevance of their findings by demonstrating a role for astrocytic D_1 receptors in behaviors that are known to rely on DA. They did this by showing that activation of astrocytic D_1 receptors contributes to the locomotor hyperactivity observed after a systemic injection of amphetamine — a psychostimulant that increases monoaminergic transmission in the brain. Thus, impairing D_1 receptor signaling in astrocytes within the NAc reduced hyperlocomotion of mice that were injected with amphetamine, while it had no effect on movement in animals that were injected with saline. This hints towards a role of astrocytic D_1 receptors in mediating aspects of reward-related behaviors.

Together, Corkrum, Covelo *et al.* highlight an unexpected role for astrocytes in DA-dependent synaptic plasticity in the NAc. By carefully examining the action of DA on the tripartite synapse, the authors demonstrate that DA evokes depression of excitatory synaptic transmission onto striatal MSNs through consecutive action on the astrocytic D_1 receptor, intra-astrocytic Ca^{2+} signaling, and action of ATP/adenosine on the A_1 receptor on presynaptic glutamatergic terminals.

As with many innovative papers, the findings of Corkrum, Covelo *et al.* open many avenues for future research. The most important one in this regard is to what extent astrocytes in the NAc contribute to the development of addiction. Importantly, the authors show that amphetamine-evoked hyperlocomotion is reduced, but not completely abolished, after disruption of the D_1-receptor machinery in astrocytes, indicating that astrocytes are just one of several elements that contribute to the acute behavioral effects of amphetamine. Does deletion of astrocytic D_1 receptors also prevent (or attenuate) the development of addictive-like behaviors in a drug self-administration paradigm? And what is the role of astrocytic D_1 receptors in the physiological processes in which DA is involved, such as reinforcement learning?

Another important follow-up study would be to assess whether the effects observed by the authors extend beyond the core subregion of the NAc. The NAc comprises at least two additional subregions, the NAc medial shell and NAc lateral shell, which have been shown to be heterogeneous in terms of anatomy, connectivity and function (de Jong et al., 2019), and the direct rewarding effects of psychostimulants are usually attributed to the NAc medial shell. In addition, the experimental setup of the current study involved electrical stimulation of excitatory inputs to the NAc and consequently the identity of their anatomical origin remains unknown. Different NAc afferents are also known to target distinct NAc subregions and may play different roles in the behavioral responses to drugs of abuse (Pascoli et al., 2014). Thus, future experiments may explore whether the DAergic modulation of the tripartite synaptic complex occurs throughout the NAc and whether differences exist between glutamatergic afferents from distinct brain regions. In sum, the findings by Corkrum, Covelo *et al.* provide important new insights into the diverse modulatory effects of DA on the brain's reward circuitry, and may spark a search for an entirely new branch of astrocyte-directed pharmacotherapies for addiction.

REFERENCES

Araque A, Carmignoto G, Haydon PG, Oliet SH, Robitaille R, & Volterra A (2014). Gliotransmitters travel in time and space. Neuron, 81(4), 728–739. [PubMed: 24559669]

Bariselli S, Fobbs WC, Creed MC, & Kravitz AV (2019). A competitive model for striatal action selection. Brain research, 1713, 70–79. [PubMed: 30300636]

Corkrum M, Covelo A, Lines J, Bellocchio L, Pisansky M, Loke K, … & Martin ED (2020). Dopamine-Evoked Synaptic Regulation in the Nucleus Accumbens Requires Astrocyte Activity. Neuron. doi: 10.1016/j.neuron.2019.12.026

Cui Y, Yang Y, Ni Z, Dong Y, Cai G, Foncelle A, … & Shen Y (2018). Astroglial Kir4. 1 in the lateral habenula drives neuronal bursts in depression. Nature, 554(7692), 323–327. [PubMed: 29446379]

de Jong JW, Afjei SA, Pollak Dorocic I, Peck JR, Liu C, Kim CK, Tian L, Deisseroth K, and Lammel S (2019). A Neural Circuit Mechanism for Encoding Aversive Stimuli in the Mesolimbic Dopamine System. Neuron 101, 133–151.e7. [PubMed: 30503173]

Gomez JA, Perkins JM, Beaudoin GM, Cook NB, Quraishi SA, Szoeke EA, … & Beckstead MJ (2019). Ventral tegmental area astrocytes orchestrate avoidance and approach behavior. Nature communications, 10(1), 1–13.

Harvey J, & Lacey MG (1997). A postsynaptic interaction between dopamine D1 and NMDA receptors promotes presynaptic inhibition in the rat nucleus accumbens via adenosine release. Journal of Neuroscience, 17(14), 5271–5280. [PubMed: 9204911]

Pascoli V, Terrier J, Espallergues J, Valjent E, O'Connor EC, & Lüscher C (2014). Contrasting forms of cocaine-evoked plasticity control components of relapse. Nature, 509(7501), 459–464. [PubMed: 24848058]

Skupio U, Tertil M, Bilecki W, Barut J, Korostynski M, Golda S, … & Bobula B (2020). Astrocytes determine conditioned response to morphine via glucocorticoid receptor-dependent regulation of lactate release. Neuropsychopharmacology, 45(2), 404–415. [PubMed: 31254970]

Wolf ME (2016). Synaptic mechanisms underlying persistent cocaine craving. Nature Reviews Neuroscience, 17(6), 351. [PubMed: 27150400]

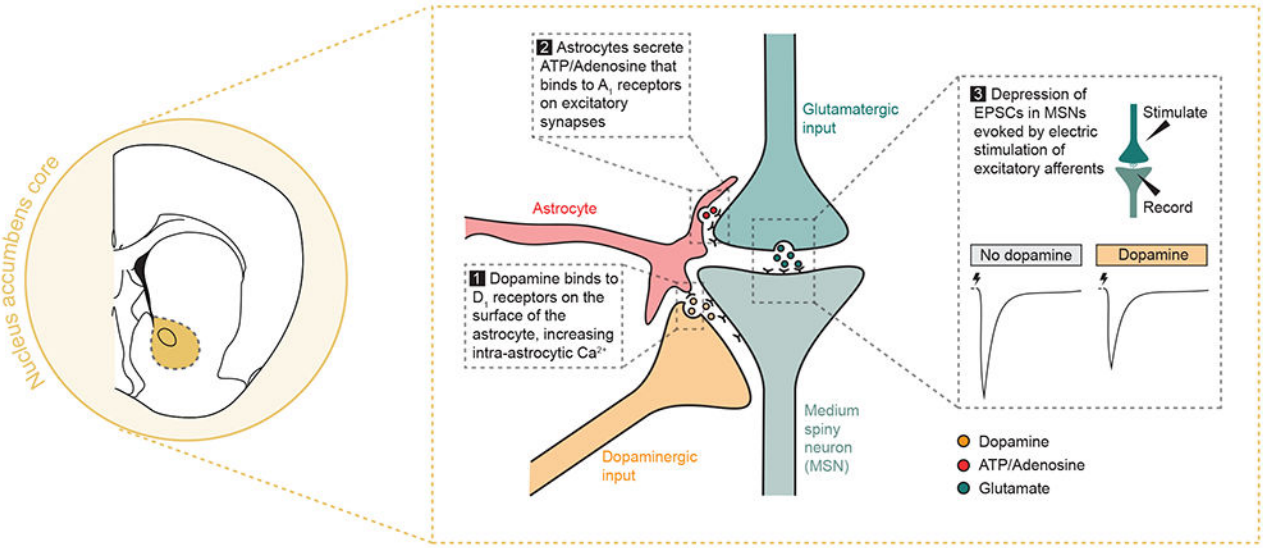

Figure 1.
Schematic representation of dopaminergic control over the tripartite synapse