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COMMENTARY

From synaptic gatekeepers to affective-cognitive modulators: The astrocyte D1 receptor−D-serine axis in the prefrontal cortex

KEY WORDS

Gliotransmission;
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Tripartite synapse

The recent study by the lab of Tianming Gao from the Southern Medical University in Guangzhou (China) presents a major advance in our understanding of the interplay between astrocytic dopamine signaling and higher-brain function. Specifically, the work elegantly uncovers how dopamine D1 receptors (DRD1) located on astrocytes, rather than on pyramidal neurons, regulate synaptic transmission and plasticity in the medial prefrontal cortex (mPFC) by modulating D-serine availability. This orchestrates a cascade that ultimately shapes emotional and cognitive behaviors[1]. Below, we position these findings into the landscape of astrocytic dopamine signaling, highlight the novel insights from the Gao's study, and speculate on future implications, including open questions.

1. The current status of dopaminergic gliotransmission at the tripartite synapse

Over the past two decades, Alfonso Araque and many colleagues[2-4] have fundamentally transformed our view of astrocytes—from passive support cells into dynamic regulators of synaptic transmission and neural circuit function. Central is the concept of the "tripartite synapse," where astrocytes sense neurotransmitters *via* their repertoire of receptors, trigger glutamatergic, GABAergic, or purinergic (*e.g.*, ATP/adenosine) gliotransmission, and hence modulate neuronal excitability and synaptic plasticity). A key extension of this concept, as summarized in recent reviews led by Araque, is that astrocytes themselves express functional dopamine receptors (including D1, D2, and others), and respond to synaptically released dopamine with calcium signaling. This has been directly demonstrated in various structures integral to reward and motivation, such as the nucleus accumbens, as well as the cortex — which is also the principal focus in the present work. So far, the following critical points have been identified[4-6]: (1) Astrocytes express multiple dopamine receptor subtypes (D1, D2, etc.) in region- and circuit-specific patterns. (2) Dopamine modulates astrocytic Ca^{2+} signaling through context-dependent mechanisms. (3) Dopamine-evoked astrocyte activation can regulate synaptic transmission acutely—for instance, *via* ATP/adenosine release subsequently depressing presynaptic transmitter release. (4) Astrocyte-neuron dopaminergic signaling is behaviorally relevant, and astrocyte-specific manipulations can modulate drug seeking and other motivational behaviors.

However, the field has primarily focused on reward- and motivation-related circuitry. The precise cellular, molecular, and behavioral implications of astrocytic dopamine receptor signaling in regions controlling or modulating cognition and emotion, such as the mPFC, remained largely uncharted.

2. Dopaminergic activation of astrocytes and elevated levels of D-serine as novel pathway in brain homeostasis, anxiety and cognition

Now, the Yin et al. study marks a significant departure from this earlier focus, venturing into the complex terrain of higher-order cortical functions, with a rigorous, multipronged approach. The most striking and novel findings include: (1) *Astrocytic DRD1 acts as a gatekeeper of glutamatergic synaptic activity.* Where prior

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work largely concerned the modulation of synaptic depression (via ATP/adenosine release) in reward circuits, Yin et al. demonstrate that in the mPFC, deletion of DRD1 specifically from astrocytes leads to *increased* glutamatergic synaptic transmission and enhanced long-term potentiation (LTP). This is in stark contrast to the lack of effect observed when DRD1 is deleted from pyramidal neurons, underlining the unique, astrocyte-centered mechanism. (2) *D-Serine modulates synaptic transmission.* Moving beyond generic gliotransmitter concepts, the authors identify extracellular D-serine — a co-agonist of the NMDA receptor — as the key effector[1]. Astrocytic DRD1 deletion elevates D-serine levels, boosting NMDAR-dependent presynaptic glutamate release and postsynaptic plasticity. The behavioral and physiological phenotypes are reversed by local application of D-serine-degrading enzyme (DAAO), elegantly establishing causality. This mechanistic clarity represents a major advance over previous astrocyte-dopamine studies, which often left the identity of the gliotransmitter ambiguous (ATP, glutamate, etc.) or relied exclusively on in vitro models or reward circuitry. (3) *Astrocytic DRD1 is a pivotal regulatory element of synaptic plasticity and linked to cognitive/emotional behaviors.* Perhaps most impactful is the demonstration that astrocytic DRD1 signaling tunes behaviors ranging from anxiety-like states and coping responses (forced swim) to working memory[1]. Excess D-serine, and hence heightened plasticity, paradoxically impairs cognition despite increased LTP, paralleling findings from epilepsy models and supporting the need for homeostatic regulation of plasticity. This confirms the behavioral reach of astrocytic dopamine signaling into domains of emotion and executive function. (4) *Mechanistically astrocytic DRD1 signaling can be linked to D-serine pathways.* RNA-seq of astrocytes reveals that DRD1 deletion does not affect D-serine synthesis or degradation per se, but modulates genes involved in serine racemase phosphorylation, NO signaling, and vesicular and non-vesicular D-serine release[1]. This hints at a multi-level control, opening new targets for pharmacological intervention. And indeed, since the authors could directly demonstrate that the behavioral abnormalities in anxiety and cognition could be reversed by enzymatic modulation of D-serine in the mutant mice with astroglial DRD1 deficiency, the astrocyte DRD1—D-serine axis emerges as a viable therapeutic target, particularly for disorders of prefrontal function.

3. Future implications and speculations

The findings from Yin et al. provoke several far-reaching questions and opportunities for future investigation. Are there distinct populations of astrocytes in the mPFC, or even subdomains within astrocytes, that possess unique dopamine receptor signatures and preferentially modulate specific microcircuits. Advanced imaging, single-cell transcriptomics, and genetically targeted interference will be pivotal in dissecting these nuances. Astrocytes differentiate phasic from tonic dopamine depending on receptor subtype affinity and local conditions. Here, in the cortex, does DRD1 on astrocytes act preferentially during high-frequency (burst) dopaminergic signaling typical of salient stimuli, as in striatum? Or could alterations in tonic signaling contribute to chronic behavioral deficits? Astrocytes are responsive to a plethora of neurotransmitters. Does cross-talk between dopaminergic, glutamatergic, and cholinergic signaling at the level of astrocytic processes fine-tune the gain and timing of prefrontal circuits underlying flexible cognition? Can maladaptive integration of these signals underpin psychiatric disease? The dissociation between enhanced LTP and impaired working memory in the DRD1-astrocyte knockout is reminiscent of findings across epilepsy and memory disorder models. This underscores the emerging concept that synaptic plasticity must be homeostatically maintained, not

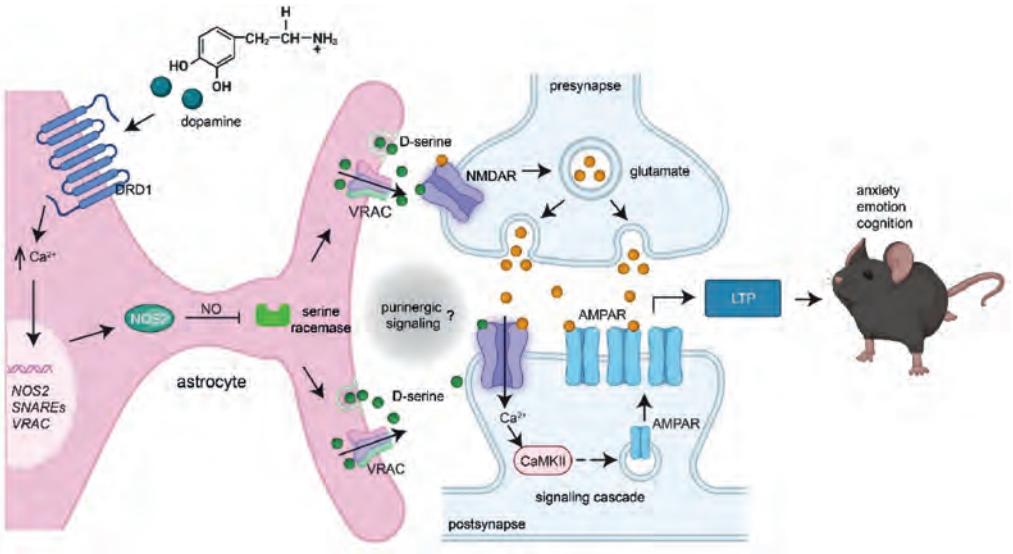

Figure 1 Linked signaling of astroglial dopamine receptors and D-serine release modulate synaptic transmission and affective-cognitive brain functions. Astrocytic dopamine D1 receptor (DRD1) signaling precisely regulates extracellular levels of the NMDA receptor co-agonist D-serine by modulating its synthesis and release. Activation of DRD1 controls the expression of both vesicular and non-vesicular D-serine release machinery, while the activity of nitric oxide synthase 2 (NOS2) acts as a negative regulator of D-serine synthesis by inhibiting serine racemase. When D-serine synthesis and release are upregulated, elevated extracellular D-serine enhances glutamatergic transmission and NMDAR-dependent plasticity, leading to anxiolytic effects but also cognitive deficits. It will be exciting to explore how the abundant purinergic signaling within the central nervous system interacts with this pathway.

simply maximized, for optimal cognitive performance. Astrocytic DRD1, *via* D-serine release, thus may function as a "brake" preventing runaway potentiation. Understanding and harnessing this regulation may allow for the "tuning" rather than global enhancement of plasticity as a therapeutic strategy.

Astrocytic dysfunction is increasingly implicated in schizophrenia, depression, and autism spectrum disorders — all conditions with prefrontal and dopaminergic involvement. Yin et al. provide a concrete molecular axis (astrocyte DRD1−D-serine−NMDAR signaling) that can now be interrogated in patient tissue (*via* transcriptomics and proteomics), in imaging studies (*e.g.*, PET ligands for D1R), and, conceivably, in precision medicine. The possibility of modulating D-serine levels locally, rather than systemically, is especially compelling to minimize off-target effects.

One of the most important translational lessons from this work is the potential for cell-type- and even subcellular domain-specific interventions. If pathological states arise from either insufficient or excessive astrocytic D-serine release, then targeted pharmacological or gene-based therapies could restore balance. Temporally, interventions may need to be matched to windows of dopaminergic activity, leveraging, for example, behavioral states or sleep to optimize therapy.

As stated already at the very beginning, astrocyte physiology is characterized by multiple and complex routes of purinergic signaling. Actually, this point has been largely ignored in this otherwise very careful work. When screening for altered gliotransmitter levels in the brains of mutant mice, the authors did neither present data on ATP nor on adenosine as signaling molecules in the extracellular space, although sensitive detection methods including genetically encoded indicators are available[7]. It is more than tempting to speculate that the astroglial DRD1−D-serine axis will be affected by the ancient purine transmitters. The authors and the glial research community is encouraged to address these limitations in future studies.

4. Conclusions

In summary, the present study by Yin and colleagues pioneers a new frontier in the astrocytic modulation of higher-brain function, bridging a key conceptual gap left by the work from Araque and others. Through exemplary genetic and physiological approaches, the authors explicate a pathway by which astrocytic DRD1 regulates D-serine release, synaptic glutamate transmission, plasticity, and, ultimately, behavior. This work elevates astrocytes from passive participants to dynamic organizers of prefrontal circuit function, reveals underappreciated subtleties of neuromodulation, and paves the way for targeted translational interventions for cognitive and emotional disorders (Fig. 1). The field eagerly awaits subsequent exploration — both mechanistic and clinical — of the astrocytic dopamine axis in health and disease.

References

1. Yin Y, Hu J, Wu H, Yang X, Qi J, Huang L, et al. Astrocytic dopamine D1 receptor modulates glutamatergic transmission and synaptic plasticity in the prefrontal cortex through D-serine. *Acta Pharm Sin B* 2025. Available from: https://doi.org/10.1016/j.apsb.2025.07.034.
2. Perea G, Navarrete M, Araque A. Tripartite synapses: astrocytes process and control synaptic information. *Trends Neurosci* 2009;**32**:421−31.
3. Oliveira JF, Araque A. Astrocyte regulation of neural circuit activity and network states. *Glia* 2022;**70**:1455−66.
4. Lines J, Corkrum M, Aguilar J, Araque A. The duality of astrocyte neuromodulation: astrocytes sense neuromodulators and are neuromodulators. *J Neurochem* 2025;**169**:e70054.
5. Corkrum M, Covelo A, Lines J, Bellocchio L, Pisansky M, Loke K, et al. Dopamine-evoked synaptic regulation in the nucleus accumbens requires astrocyte activity. *Neuron* 2020;**105**:1036−47.
6. Corkrum M, Araque A. Astrocyte-neuron signaling in the mesolimbic dopamine system: the hidden stars of dopamine signaling. *Neuropsychopharmacology* 2021;**46**:1864−72.
7. Lobas MA, Tao R, Nagai J, Kronschläger MT, Borden PM, Marvin JS, et al. A genetically encoded single-wavelength sensor for imaging cytosolic and cell surface ATP. *Nat Commun* 2019;**10**:711.

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