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REVIEW ARTICLE

Astrocyte-neuron signaling in the mesolimbic dopamine system: the hidden stars of dopamine signaling

Michelle Corkrum [1,2] and Alfonso Araque [2]✉

Astrocytes are fundamental components of brain information processing and possess the ability to respond to synaptic signaling with increases in cytoplasmic calcium and modulate neuronal activity with the subsequent release of neuroactive transmitters. Dopamine signaling is essential for brain physiology and pathology, participating in learning and memory, motor control, neurological diseases, and psychiatric diseases, and astrocytes are emerging as a key cellular target of dopamine signaling. The present review will examine evidence revealing that astrocytes respond to dopamine and modulate information processing in the primary brain regions implicated in the mesolimbic dopamine system. Astrocytes exhibit circuit-specific modulation of neuronal networks and have the potential to serve as a therapeutic target for interventions designed for dopamine pathologies.

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INTRODUCTION

Astrocytes are among the most abundant cell types in the mammalian brain and garnered their name due to their star-like shape with a cell body and processes that can extend to contact thousands of synapses [1]. In Ramón y Cajal's (1899) rendition of human astrocytes, he illustrated that the cells manifest integral connections with both blood vessels and neuronal synapses. Ramón y Cajal's observations align with the traditional view of astrocytes as support cells and the more recent lines of evidence revealing astrocytes as active regulators of synaptic transmission and plasticity [2–4]. Astrocytes contribute to maintaining brain homeostasis via maintenance of extracellular ion concentration, providing trophic factors and metabolic support to neurons, preserving the blood–brain barrier, regulating blood flow, and contributing to synaptogenesis [2–7]. Traditionally, support roles were the only function attributed to astrocytes because astrocytes are not electrically excitable—they do not generate action potentials in response to stimuli [5]. However, in the recent decades, researchers have found that astrocytes display excitability and responsiveness to neuronal activity via increases in intracellular calcium [2–8]. Astrocytes contain both inotropic and metabotropic receptors for neurotransmitters [9, 10] and multiple transmitters have been shown to increase calcium in astrocytes including: glutamate, ATP, epinephrine, norepinephrine, GABA, acetylcholine, serotonin, and substance P [10, 11]. In turn, astrocytes can release neuroactive substances, termed gliotransmitters, such as glutamate, GABA, D-serine, and ATP to modulate synaptic transmission and plasticity [2, 5]. This signaling interaction represents the basis of bidirectional communication between astrocytes and neurons, which is conceptualized by the tripartite synapse model [2, 5].

While different non-neuronal cells, such as oligodendrocytes and microglia also express dopamine receptors [12–15], this review will focus on astrocyte-neuron signaling in the mesolimbic dopamine system and the implications for understanding brain physiology and pathology as it relates to dopamine signaling. The review provides insight into the active role of astrocytes in dopaminergic signaling to both respond to dopamine with increases in calcium and modulate synaptic transmission (Fig. 1) and proposes the targeting of astrocytes for novel treatments of disease processes involving the mesolimbic dopamine system.

Dopamine signaling contributes to key neural functions including learning and memory, movement, neuroendocrine signaling, and reward-related behaviors [16]. Diseases associated with disrupted dopamine signaling include Parkinson's disease, schizophrenia, depression, and substance use disorders [16–18]. The vast array of brain functions involving dopamine signaling relies on the existence of multiple dopaminergic circuits implicated in numerous behaviors. The mesolimbic system, with dopaminergic signaling from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), amygdala, and hippocampus [17, 19], is associated with reward and motivated related behavior; the mesocortical system, with ventral tegmental dopamine signaling to the cortex, modulates cognition and executive function; the nigrostriatal pathway, comprising dopaminergic projections from the substantia nigra pars compacta to the dorsal striatum, is involved in motor control; and the tuberoinfundibular pathway, which comprises dopaminergic signaling from the arcuate nucleus and periventricular nucleus to the infundibular region of the hypothalamus, is involved in modulating prolactin release from the anterior pituitary gland [20] to regulate neuroendocrine signaling.

Signaling within the mesolimbic dopamine system encompasses multiple neurotransmitter systems, such as neuromodulators dopamine or acetylcholine and fast neurotransmitters glutamate and GABA, within the circuit [18]. Dopaminergic

[1]Medical Scientist Training Program, University of Minnesota, Minneapolis, MN, USA. [2]Department of Neuroscience, University of Minnesota, Minneapolis, MN, USA. ✉email: araque@umn.edu

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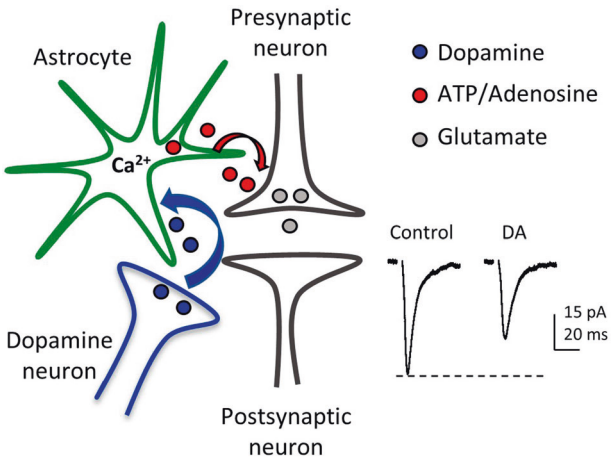


Fig. 1 Dopaminergic tripartite synapse. Illustration representing astrocyte responsiveness to dopamine and the bidirectional communication flow between astrocytes and neurons with depression of excitatory post synaptic currents. DA dopamine.

neurons in the VTA receive glutamatergic input from the bed nucleus of the stria terminalis, pedunculopontine tegmentum, dorsal raphe nucleus, periaqueductal gray, medial prefrontal cortex, laterodorsal tegmentum nucleus, and lateral habeula (reviewed by Morales and Margolis [21]). GABAergic inputs to dopamine neurons in the VTA include the dorsal raphe nucleus, periaqueductal gray, rostromedial mesopontine tegmental nucleus, ventral pallidum, and lateral hypothalamus (reviewed by Morales and Margolis [21]). The interactions between signaling molecules and the mesolimbic brain regions integrate dopamine signaling and contribute to the physiologic and pathologic dopamine signaling circuitry. To fully examine astrocytes role in dopamine signaling and the mesolimbic dopamine system, it is important to evaluate if astrocytes exhibit calcium transients in response to stimuli in the mesolimbic dopamine system and if astrocytes release neuroactive substances to modulate synaptic transmission and plasticity in the mesolimbic dopamine system. This review will specifically assess literature investigating astrocyte-neuron signaling in the VTA and the NAc to synthesize work on the key role astrocytes play in brain circuitry related to motivated behaviors and reward.

ASTROCYTES EXPRESS DOPAMINE RECEPTORS

A key component of dopaminergic signaling is the activation of dopamine receptors and the downstream signaling cascades associated with dopaminergic transmission. Dopamine receptors are G protein-coupled receptors that have been classified into five subtypes belonging to the subcategories of D_1-like (D_1R; D_1 and D_5) receptors and D_2-like (D_2R; D_2, D_3, D_4) receptors [16]. Downstream signaling for D_1Rs includes the coupling to the Gs protein and activation of adenylyl cyclase and the increase in cAMP production. D_2Rs are coupled to Gi/o proteins that inhibit adenyl cyclase and lead to the decrease of cAMP production. Interestingly, the activation of D_1Rs and D_2Rs can manifest as elevations of intracellular calcium via PLC signaling [20]. Using numerous techniques including culture studies, immunohistochemistry, electron microscopy, and signaling cascades, researchers have found that astrocytes express dopamine receptors in multiple brain regions (Table 1). Astrocytes from the striatum [22–25], substantia nigra pars reticulata [23], NAc [26], and cortex [23, 24, 27] were found to express D_1Rs.

D_2Rs are expressed on astrocytes from the striatum [24, 28] and cortex [24, 29]. D_3Rs have been localized to astrocytes in the midbrain [30, 31], striatum [25, 30, 31], and cortex [32]. Astrocytes were found to express D_4Rs in the mesencephalon [25], striatum [25], and NAc [33]. D_5Rs were found on astrocytes in the mesencephalon [25], striatum [25], and cortex [27, 32]. Therefore, astrocytes express several subtypes of dopamine receptors in multiple brain regions suggesting that they contain the sensing machinery to contribute to dopamine signaling. Evidence suggests that astrocytes and neurons express similar types of dopamine receptors including congruent molecular methods used for the localization of dopamine receptors on both neurons and astrocytes. In addition, the downstream consequences of dopamine receptor activation such as changes in cAMP signaling [22, 34, 35] and cytoplasmic calcium [16, 26, 29] have also been shown in astrocytes (Table 2 and Fig. 2).

ASTROCYTES HAVE FUNCTIONAL CHANGES IN RESPONSE TO DOPAMINE

While dopamine signaling has been reported to impact astrocyte morphology and gene expression [36, 37], the following paragraphs will specifically focus on the dopamine effects on functional astrocytic signaling events. Functional changes in astrocytes that can contribute to synaptic transmission and plasticity include modulation of downstream signaling events such as the cAMP pathway, increases in cytoplasmic calcium and gliotransmission signaling following dopamine activation. Multiple assays can be used to assess the functional consequences of astrocytic activation by dopamine. For cAMP measurements, the amount of cAMP can be assessed in the supernatant of cultured astrocytes after experimental manipulations [22], importantly cAMP levels can also be assessed in vivo utilizing a Pink Flamindo viral vector with an astrocytic specific GFAP promoter [38]. Similarly, astrocyte calcium elevations can be assessed in culture, in acute brain slices or in vivo utilizing calcium indicators directed to astrocytes combined with imaging techniques such as confocal microscopy [39], two-photon imaging [40, 41], fiber photometry [26, 42], and miniscopes [40, 43]. Early experiments found that cultured astrocytes exposed to dopamine increased their cAMP levels, which was blocked when dopamine receptor antagonists were present (Table 2), suggesting the functional activation of astrocytes in response to dopamine via dopamine receptor activation. Moreover, cultured striatum astrocytes displayed a more robust response to D_1R activation when compared to cortical cultured astrocytes indicating a regional difference in astrocyte responsiveness to dopamine [22, 35]. In addition to responding to dopamine, researchers found that neuronal signaling contributes to astrocytic responsiveness to dopamine. Co-cultures of astrocytes and neurons enhanced cAMP signaling with D_1R activation when compared to astrocytes cultured alone [35], suggesting that there is astrocyte-neuron signaling with regard to the downstream effects of dopaminergic exposure. Dopamine exposure has also been shown to increase cytoplasmic calcium levels in astrocytes (Fig. 2). Cultured cortical astrocytes demonstrated increases in cytoplasmic calcium in response to dopamine receptor activation (Table 2). In addition to these receptor-mediated effects, an independent mechanism of astrocyte calcium increases in response to dopamine exposure via reactive oxygen species resulting from the breakdown of dopamine by monoamine oxidase has also been reported [44]. Therefore, astrocytes have multiple mechanisms for responding to dopamine signaling and manifesting downstream signaling events. Astrocytes may respond in varying ways depending on the type of receptor activated, the extracellular environment such as the concentration of dopamine present, the source of dopamine, the brain region investigated, and the ultimate downstream signaling consequences.

The complexity of the astrocyte responsiveness to dopamine is exemplified by a recent study on hippocampal astrocytes in situ. Rusakov's group found that astrocyte calcium increases can result

Table 1. Astrocyte dopamine receptor evidence.

Dopamine receptor subtype	Brain region	Subregion	Species	References
D_1R	Mesencephalon	–	Rat	Miyazaki et al., 2004 [25]
D_1R	Striatum	–	Rat	Miyazaki et al., 2004 [25]; Zanassi et al., 1999 [22]; Reuss et al., 2000 [24]
D_1R	Striatum	–	Mouse	Nagatomo et al., 2017 [23]
D_1R	Cortex	Visual cortex [23]	Mouse	Nagatomo et al., 2017 [23]; Shibasaki et al., 2017 [27]
D_1R	Cortex	–	Rat	Reuss et al., 2000 [24]
D_1R	Substantia nigra pars reticulata	–	Mouse	Nagatomo et al., 2017 [23]
D_1R	Nucleus Accumbens	Nucleus accumbens core [26]	Mouse	Corkrum et al., 2020 [26]
D_2R	Striatum	–	Rat	Miyazaki et al., 2004 [25]; Bal et al., 1994 [28]; Reuss et al., 2000 [24]
D_2R	Cortex	Prefrontal cortex (layer I, III, V) [100]	Human	Mladinov et al., 2010 [100], Khan et al., 2001 [101]
D_2R	Cortex	–	Mouse	Qiu et al., 2016 [29], Khan et al., 2001 [101]
D_2R	Cortex	–	Rat	Reuss et al., 2000 [24], Khan et al., 2001 [101]
D_2R	Cortex	–	Monkey	Khan et al., 2001 [101]
D_2R	Mesencephalon	–	Rat	Reuss et al., 2000 [24]
D_2R-A2A heteromerization	Striatum	–	Rat	Pelassa et al., 2019 [102]; Cervetto et al., 2017 [103]; Cervetto et al., 2018 [104]
D_3R	Midbrain and Striatum	–	Mouse	Montoya et al., 2019 [30]; Elgueta et al., 2017 [31]
D_3R	Cortex	Frontal cortex [32]	Human	Kumar and Patel, 2007 [32]
D_3R	Striatum	–	Rat	Miyazaki et al., 2004 [25]
D_4R	Mesencephalon	–	Rat	Miyazaki et al., 2004 [25]
D_4R	Striatum	–	Rat	Miyazaki et al., 2004 [25]
D_4R	Nucleus Accumbens		Rat	Svingos et al., 1999 [33]
D_5R	Mesencephalon	–	Rat	Miyazaki et al., 2004 [25]
D_5R	Striatum	–	Rat	Miyazaki et al., 2004 [25]
D_5R	Cortex	Frontal cortex [32]	Human	Kumar and Patel, 2007 [32]
D_5R	Cortex	–	Mouse	Shibasaki et al., 2017 [27]

from dopamine receptor activation or occur independently from dopamine receptor activation [45]. Hippocampal astrocytes located in the stratum radiatum responded to dopamine in a biphasic manner with increases or decreases in astrocytic calcium associated with D_1R or D_2R activation, respectively. In contrast, astrocytes in the hippocampal stratum lacunosum, responded to dopamine in a receptor independent manner [45]. Moreover, we have recently shown that astrocytes in the NAc respond to synaptic dopamine signaling with increases in intracellular calcium mediated by D_1R activation without conspicuous involvement of D_2Rs [26]. The data suggest that astrocytes within separate brain regions may respond and modulate dopaminergic signaling in distinct manners.

Finally, the fact that astrocyte calcium responses were found to be evoked by synaptically released dopamine through specific optogenetic stimulation of dopaminergic inputs and that they occurred in freely behaving animals [26] indicate that in conserved circuits astrocytes physiologically respond to dopaminergic signaling (Fig. 2).

IMPLICATIONS FOR ASTROCYTE FUNCTIONAL RESPONSES TO DOPAMINE SIGNALING

Dopamine signaling in the mesolimbic system exhibits unique characteristics depending on the context and neural environment. The majority of D_1Rs have a low affinity for dopamine and are activated by fast phasic signaling (from presynaptic VTA dopaminergic neurons firing action potentials at >15 Hz) associated with memory consolidation, positive reinforcement and negative reinforcement (reviewed by Volkow et al. [46]), whereas most D_2Rs have a high affinity for dopamine and are activated by low concentrations of dopamine and the tonic firing of dopaminergic neurons (1–8 Hz). D_2R activation is associated with motivational sensitivity to a stimulus (reviewed by Volkow et al. [46]). Salient stimuli result in fast phasic signaling and activation of D_1Rs, and do not solely include rewarding reinforcing elements, but also novel stimuli and aversive stimuli. Tonic versus phasic dopamine signaling are implicated in distinct behavioral phenomenon and information processing.

We have recently reported that dopamine-evoked calcium responses in NAc astrocytes were associated with the depression of excitatory synaptic transmission [26] (Fig. 1), suggesting that astrocytes mediate dopaminergic neuromodulation through gliotransmitter release (see below), and that astrocytes contribute to the synaptic and behavioral effects of the psychostimulant amphetamine known to act via dopamine signaling [20]. It may be that astrocytes differentially contribute to the distinct phases of dopamine signaling, given the evidence that astrocytes respond to dopamine in a dose-dependent manner [22, 26, 35]. Future work investigating if a dopamine concentration threshold is needed to activate astrocytes and gliotransmission will provide further insight into dopamine-evoked astrocyte modulation of synaptic transmission. There may be a possibility that astrocytes only respond to dopamine when a specific concentration is met to

Table 2. Astrocyte dopamine receptor activation signaling events.

Dopamine receptor subtype	Brain region	Species	Method	Findings	References
D_1R	Cortex	Mouse	Culture	Bidirectional change in NADH fluorescence in response to dopamine. Response attenuated by D_1R antagonist SCH23390	Requardt et al., 2010 [105]
D_1R	Nucleus Accumbens	Mouse	In vivo calcium imaging and acute brain slices	Astrocytes respond to dopamine signaling with increases in cytoplasmic calcium mediated by D_1R	Corkrum et al., 2020 [26]
D_1R	Cortex, Striatum	Rat	Culture	Increased cAMP after exposure to dopamine and D_1R agonist SK&F 82526-J and SK&F 383 93A. In a dose-dependent manner No change seen in hippocampus and brainstem cultures	Hansson and Rönnbäck, 1988 [35]
D_1R	Cortex, Striatum	Rat	Culture	Increased cAMP after exposure to dopamine, D_1R agonist (SKF 38393) and the D_1R/D_2R agonist apomorphine Dose dependent	Zanassi et al., 1999 [22]
D_1R	Cortex	Rat	Culture	Increase calcium in astrocytes after exposure to the D_1R agonist SKF83959 and response was attenuated by the D_1R antagonist SCH23390 and by PLC inhibitor (U73122,) exposure suggesting that the signaling was via a PLC pathway	Liu et al., 2009 [106]
D_2R	Cortex	Human, monkey, rat, mouse	Culture	Specific binding to ligands with high D_2R affinity such as spiperone, raclopride, haloperidol, and YM-09151	Khan et al., 2001 [101]
D_2R	Cortex	Rat, mouse	Culture	Increase in calcium levels in response to D_2R agonist quinpirole that is ablated with exposure to the D_2R antagonist raclopride	Khan et al., 2001 [101]
D_2R	Ventral tegmental area, hippocampus	Mouse	Acute brain slices (calcium imaging with 2-photon microscopy)	Decrease in cytoplasmic calcium in astrocytes with exposure to quinpirole (D_2R/D_3R agonist) with regional differences	Xin et al., 2019 [107]
D_1R and D_2R	Hippocampus	Rat	Culture	Dopamine increases duration and frequency of astrocyte calcium transients	Galloway et al., 2018 [36]
D_1R and D_2R	Cortex	Rat	Culture	Dose-dependent increase in astrocyte calcium in response to the D_1R and D_2R agonist SKF83959	Liu et al., 2009 [106]
D_1R and D_2R	Hippocampus	Mouse	Acute hippocampal slices	Dopamine associated bidirectional calcium changes, with calcium increase mediated by D_1R/D_2R and calcium decrease in astrocytes mediated by D_2R	Jennings et al., 2016 [45]
Nonspecific dopamine receptor	Cortex, striatum	Rat	Culture	Dopamine elicited calcium increases	Reuss and Unsicker, 2001 [108]
Nonspecific dopamine receptor	Cortex, hippocampus, striatum	Rat	Culture	After dopamine exposure there is an increase in cAMP levels in cultures. No examination of dopamine receptor subtype involved	Hansson et al., 1984 [34]
Nonspecific dopamine receptor	Striatum, spinal cord	Rat	Culture	Intracellular recordings from cultured astrocytes revealed a hyperpolarization of membrane potential in response to dopamine	Hosli et al., 1987 [109]
No involvement of D1R or D2R indirect calcium signaling	Hippocampus, cortex, midbrain	Rat	Culture	Dopamine induces astrocyte calcium elevations in cultured cells not mediated by D_1R or D_2R receptors. Calcium elevations via intracellular calcium stores,	Vaarman et al., 2010 [44]

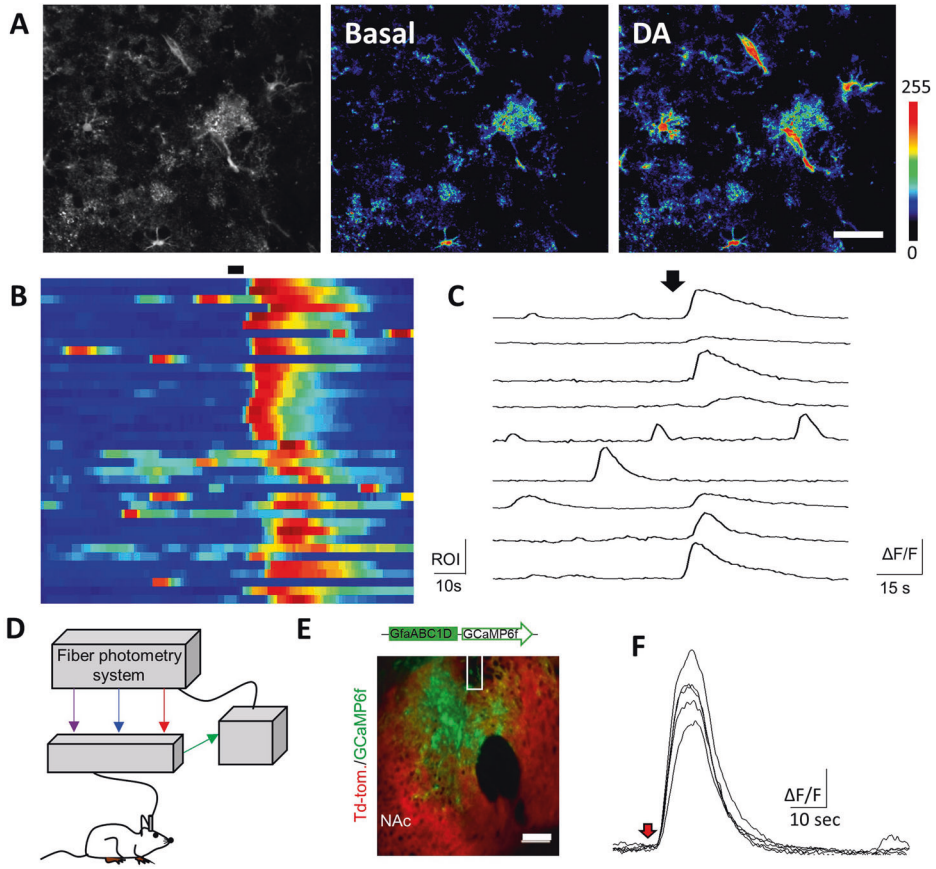


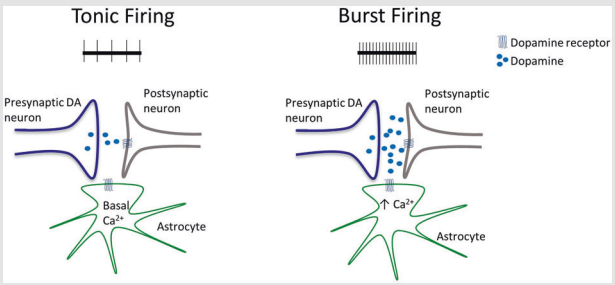
Fig. 2 Astrocytes respond to dopamine with increases in cytoplasmic calcium. A Pseudo color image of astrocytes in the nucleus accumbens (acute slices) in basal conditions and after local application of dopamine (500 µM for 5 s) Scale bar 25 µm. **B** Heatmap of astrocyte relative fluorescence levels (black bar indicates dopamine exposure). **C** Astrocyte relative fluorescence traces (black arrow indicates dopamine exposure). **D** Scheme of fiber photometry setup to examine astrocyte responsiveness to dopamine in awake-behaving animals. **E** Immunohistochemistry image demonstrating astrocytes with the calcium indicator GCaMP6f and dopaminergic terminals in the nucleus accumbens expressing ChrimsonR (Td-tom), and optic fiber tract. Scale bar 500 µm. **F** Astrocyte relative fluorescence traces after optogenetic stimulation of dopaminergic terminals (5 s, 30 Hz). DA dopamine, NAc nucleus accumbens.

modulate aberrant dopamine concentrations or phasic burst dopamine signaling [46], but at baseline and tonic dopamine levels [46], astrocyte calcium signaling may have an alternative role in dopamine neuromodulation (Box 1). Further molecular research is needed to determine if there are molecular distinctions between dopamine receptors on neurons and astrocytes. It may be possible to specifically target dopamine receptors on astrocytes utilizing an astrocytic specific promoter such as GFAP or aldehyde dehydrogenase (with the utility and caveats of these promoters reviewed by Yu et al. [47]). It may also be possible to target dopamine receptors specifically on astrocytes utilizing activity-dependent targeting of astrocytes based on dopamine concentrations (Box 1). The signaling and context-specific response of astrocytes to dopamine may provide specific intervention windows to combat pathologies implicated in disrupted dopamine signaling.

ASTROCYTE-NEURON SIGNALING AND GLIOTRANSMISSION IN THE MESOLIMBIC DOPAMINE SYSTEM

While gliotransmission was a hotly debated topic in the field of astrocyte physiology and signaling [48, 49], there are extensive studies illustrating the ability of astrocytes to respond to multiple neurotransmitters with increases in cytoplasmic calcium [2, 10]

Box 1. Hypothesis for astrocyte responsiveness to dopamine signaling in tonic firing and burst firing



Dopamine exhibits both tonic and burst firing to modulate neuronal networks and behavioral outcomes (reviewed by Volkow et al. [46]). Astrocytes exhibit the ability to preferentially respond to distinct neuronal signals. Work from our lab has shown that astrocytes respond to dopamine in a dose-dependent manner (Corkrum et al. [26]) and that astrocytes preferentially regulate distinct dopamine circuits (Martin et al. [110]), suggesting that neuronal firing cues may contribute to astrocyte calcium signaling dynamics. Furthermore, given the dose response nature of astrocyte calcium responsiveness to dopamine, we hypothesize that astrocytes preferentially increase calcium signaling in response to high-frequency burst dopaminergic transmission and in states with aberrant dopaminergic signaling such as after psychostimulant exposure (Corkrum et al. [26]). DA dopamine.

and to release neuroactive substances, such as glutamate, ATP, and GABA [9], that regulate synaptic transmission and plasticity in multiple brain areas [2, 50]. Yet, the specific mechanisms and consequences of this bidirectional astrocyte-neuron communication remain to be fully evaluated. The following paragraphs will review studies demonstrating astrocyte-neuron signaling in the mesolimbic dopamine system, specifically focusing on the VTA and NAc, illustrating astrocytic calcium elevations and the modulation of synaptic transmission and plasticity via astrocytic release of gliotransmitters.

Astrocyte-neuron signaling in ventral tegmental area

In the VTA, astrocytes have been shown to exhibit calcium transients in response to neurotransmitters and signaling molecules such as neurotensin [51], baclofen [52], and glutamate [52]. In the classical tripartite synapse model, astrocyte calcium elevations are associated with subsequent gliotransmitter signaling to modulate synaptic transmission and plasticity. Researchers found that although acute baclofen exposure increases astrocyte calcium levels, there was no change in NMDAR-mediated slow inward currents (SICs) [52], a biological assay of glutamate gliotransmission [53]. Interestingly, prolonged baclofen exposure decreased spontaneous astrocyte calcium activity and was associated with a decrease in SICs [52], indicating that the same signaling molecule may elicit variable astrocyte responses depending on the time course of the exposure, and suggesting that astrocytes integrate synaptic information to generate calcium responses (Box 1). The ability of astrocytes to modulate synaptic transmission based on contextual cues was further illustrated by work conducted in the VTA that demonstrated astrocyte activation specifically modulated GABAergic excitatory currents, but not inhibitory currents [54], indicating that astrocytes discern and modulate specific circuits within the VTA.

Astrocyte-neuron signaling in the nucleus accumbens

Astrocytes in the NAc respond to various neurotransmitters and signaling molecules with intracellular calcium increases including ATP [26, 55–57], gamma-hydroxybutyrate [55], succinic acid [56], the $GABA_B$ agonist, baclofen [57], the class I mGluR agonist (RS)-3,5-dihydroxyphenylglycine, DHPG [57], dopamine [26], and the mu opioid receptor agonist, DAMGO [58].

In response to activation, astrocytes have been shown to be able to release glutamate and ATP/adenosine. In terms of astrocyte-neuron signaling, astrocytic calcium responsiveness to mGluR5 receptor activation was associated with glutamate gliotransmission as manifested by SICs [57] and the modulation of neuronal excitability [57]. Further evidence revealing glutamate gliotransmission resulted from experiments that specifically targeted astrocytes in the NAc with "designer receptor exclusively activated by designer drugs" (DREADDs), which upon activation increased glutamate concentration levels [58]. Additional evidence for glutamate gliotransmission in the NAc came from studies activating mu opioid receptors, which are known to be expressed by astrocytes [58, 59]. Stimulation of these receptors elevated cytoplasmic calcium in astrocytes and stimulated the release of the gliotransmitter glutamate [58], which activating neuronal NMDARs evoke SIC that are known to regulate neuronal excitability and synchronization [60, 61]. These studies indicate that astrocytes respond to various stimuli in the NAc with increases in calcium and glutamate gliotransmission to modulate neuronal activity.

In addition to glutamate gliotransmission, astrocyte-neuron signaling in the NAc can also be mediated by ATP/adenosine signaling. Dopamine-evoked astrocyte calcium elevations [26] (Fig. 2) is associated with the depression of excitatory synaptic transmission [26]. Moreover, the astrocyte calcium signal has been shown to be both sufficient and necessary for dopamine-evoked depression of excitatory transmission [26]. This synaptic regulation occurs via astrocytic release of ATP (which is extracellularly converted to adenosine [62, 63]) or adenosine that activates presynaptic type 1 adenosine receptors [26]. These signaling events have also been found to mediate the effects of amphetamine on astrocyte calcium levels, gliotransmission, and synaptic regulation [26]. Astrocytes respond to synaptic dopamine with increases in cytoplasmic calcium and modulate synaptic transmission with ATP/adenosine signaling revealing a prominent role not only in dopamine signaling, but also within mesolimbic dopamine circuitry illustrating the vital role astrocytes play in the dopamine network.

Together, these studies indicate that NAc astrocytes respond to various neurotransmitters with calcium increases that stimulate the release of different gliotransmitters and modulate neuronal activity and synaptic transmission. Remarkably, these studies also show that astrocyte-neuron signaling events can be triggered by drugs of abuse like amphetamine [26], suggesting that astrocytes may be mediating the effects of substances of abuse and may be targets for therapeutic approaches to treat brain disorders associated with reward dysfunction and addiction.

In addition to these receptor-mediated events, further astrocytic mechanisms contribute to regulate neuronal and synaptic function in the mesolimbic system. Astrocytes express excitatory amino acid transporters (EAATs) that bind and uptake the synaptically released glutamate to terminate synaptic signaling [64–71]. Among the five subtypes of EAATs [64–66, 72], EAAT1 (or GLAST) and EAAT2 (or GLT-1) are mainly expressed in glial cells, being responsible for taking up the majority of synaptically released glutamate and maintaining its extracellular levels [64–71]. The expression of these transporters can be regulated by growth factors and signaling molecules, such as PACAP, estrogen, glucocorticoids, ATP, adenosine, or dopamine [73–77], as well as by drugs of abuse such as cocaine, opioids, ethanol, nicotine, or amphetamines. They have also been found to be altered in several animal models of drug addiction [78]. Based on the considerable evidence (whose discussion is beyond the scope of this review, and that has been reviewed elsewhere [79]), the Kalivas group has proposed the glutamate homeostasis hypothesis of addiction, in which the imbalance between synaptic and non-synaptic glutamate, i.e., the glutamate homeostasis hypothesis, causes neuroplasticity changes that impair the proper communication between cortical and mesolimbic brain areas [79–82].

Implications for astrocyte-neuron signaling in the mesolimbic dopamine system

Astrocytes respond to synaptic signaling in the VTA and the NAc with increases in cytoplasmic calcium. Astrocytes also exhibit the ability to release neuroactive substances in the mesolimbic dopamine system, revealing astrocyte-neuron signaling and the tripartite synapse in the mesolimbic dopamine network (Fig. 1). This bidirectional communication is a complex phenomenon. First, astrocytes in the mesolimbic system respond with calcium elevations to different neurotransmitters, including glutamate, dopamine, and opioids [26, 57, 58] through activation of G protein-coupled receptors. Notably, such calcium responses occur regardless of the type of G protein activated. Unlike neurons, which exhibit excitation in response to Gq receptor activation and inhibition in response to Gi/o receptor activation, our group has found that both Gq and Gi/o receptor activation elicits increases in calcium in hippocampal astrocytes that stimulate gliotransmitter release [83]. Similarly, we have found that both D_1 dopamine receptors, primarily coupled to the Gs family of G proteins, and μ-opioid receptors, mainly coupled to Gi/o proteins, elevate astrocyte calcium in the NAc [26, 58]. Second, the downstream effects of the astrocyte calcium signaling may have diverse consequences. Indeed, astrocyte calcium elevations in different brain areas have been shown to stimulate the release of different gliotransmitters such as glutamate, GABA, ATP, or D-serine [2, 5].

Astrocytes in the NAc have been found to be able to release ATP/adenosine in response to dopamine [26] and glutamate in response to opioids [58]. Whether the ability to release different gliotransmitters depends on the astrocytic receptors activated remains to be investigated. Perhaps, it may depend on the specific properties of the synaptic inputs, as recently shown in the hippocampus [84]. Future experiments investigating if a single astrocyte can release multiple neuroactive substances [84] depending on the stimulus or in response to the same stimulus will provide further insight into the role of astrocytes within the system.

The studies reviewed illustrate exciting evidence that astrocytes contribute to the modulation of information processing in the mesolimbic dopamine system and provide insight into gaps in the current knowledge for future experiments to investigate the precise role of astrocyte calcium in the modulation of synaptic transmission and plasticity.

ASTROCYTES CONTRIBUTE TO DOPAMINE-RELATED BEHAVIORS IN THE MESOLIMBIC DOPAMINE SYSTEM

Investigating the role of astrocytes in dopamine signaling and the mesolimbic dopamine system provides insight into the role astrocytes play in physiologic and pathologic conditions associated with the mesolimbic dopamine system. Research has shown that astrocytes not only participate in the cellular signaling associated with the mesolimbic dopamine system, but also the behavioral output of the system, specifically reward-related and motivated behaviors. Multiple studies have investigated the consequences of drugs of abuse on GFAP expression levels (reviewed by Haydon et al. [85], Bachtell et al. [86], and Kim et al. [87]) and modulation of astrocytic glutamate transporters associated with drug exposure (reviewed by Scofield and Kalivas [82] and Wang et al. [88]). Recent studies have also reported the effects of the acute activation of astrocytes with pharmacogenetics on reward-related behaviors. Selective activation of astrocytes with cell-specific DREADDs was associated with decreased ethanol consumption [89, 90]. Interestingly, in the study that investigated NAc astrocytes, the effect selectively took place upon activation of astrocytes in the NAc core, whereas the ethanol-seeking behavior was unaffected upon activation of astrocytes in the NAc shell [89] suggesting a region-specific effect. However, researchers also found that acute activation of the basolateral amygdala attenuated ethanol consumption [90] suggesting that astrocytes in multiple mesolimbic structures modulate drug-seeking behavior. In addition to ethanol-related behaviors, selective activation of astrocytes with DREADDs is also associated with the attenuation of cue-induced cocaine-seeking behavior via group II metabotropic glutamate receptors (mGluR2/3), suggesting that astrocyte activation can serve as a potential therapeutic intervention for cocaine-seeking behavior [91]. In addition, acute activation of astrocytes with designer receptors was also associated with attenuated cued methamphetamine-seeking behavior [92]. Our work has also shown that astrocyte calcium signaling and astrocytic dopamine receptors contribute to the behavioral psychostimulant effects of amphetamine [26]. The results indicate that astrocytes contribute to the behavioral output of the mesolimbic dopamine system and can serve as potential targets for the development of therapies targeting the mesolimbic dopamine circuit. Importantly, astrocytes have been shown to be modulated in the mesolimbic dopamine system of humans. In the NAc, astrocytes exhibited increased GFAP levels in human patients with alcohol use disorder [93]. These results indicate that findings in the preclinical literature are supported by clinical literature and position astrocytes as promising therapeutic targets for disrupted dopamine signaling. Astrocyte gene expression in the NAc has also been modulated in other diseases process associated with disrupted dopamine signaling with researchers documenting an upregulation of astrocyte gene expression in postmortem tissue from patients with schizophrenia and bipolar disorder [94]. Future studies aimed at investigating alterations in astrocytes in the VTA will provide further insight into the clinical role astrocytes play in mesolimbic dopamine signaling. Researchers have reported the existence of calcium signaling and gliotransmission in human cortical and hippocampal brain tissue, [95] but whether these phenomena also occur in other human brain areas and relate to dopamine signaling remains to be explored.

FUTURE DIRECTIONS

One of the hallmarks of brain signaling is the ability of the system to integrate information and manifest plasticity to adapt to a constantly changing environment. This review has assessed evidence illustrating that astrocytes respond to dopamine and contribute to synaptic transmission and plasticity in the mesolimbic dopamine system. Plasticity is a key component of brain information processing and future experiments specifically investigating astrocyte plasticity may also provide insight into potential treatment targets and developments for dopamine-related pathologies. Specific types of plasticity that can be investigated in astrocytes include calcium plasticity (does astrocyte calcium change over time—in terms of the astrocytes that are exhibiting calcium signals—are there population changes in the responding astrocytes, the localization of calcium signaling within astrocytes and the characterization of the astrocyte calcium response over time with regard to frequency, amplitude, and duration).

In addition to investigating astrocyte plasticity, developing therapies that specially target astrocytes will also advance therapies targeted toward pathologies of the mesolimbic dopamine system. Manipulation of dopaminergic transmission for therapeutic interventions can result in serious side effects for patients. Given that astrocytes express dopamine receptors and contribute to dopaminergic signaling transmission, it may be advantageous to selectively target only astrocyte or only neuronal dopamine receptors for treatment interventions. Targeting a select cell type may reduce side effects and advance patient care. As discussed in previous reviews [82, 88], astrocyte glutamate homeostasis is disrupted upon exposure to drugs of abuse. Astrocytes express the cystine-glutamate exchanger and glutamate transporters, such as GLT-1. Psychostimulants and opioids downregulate these regulatory mechanisms, resulting in increased extracellular glutamate and dysregulated synaptic transmission and plasticity [96]. Researchers have found the normalization of astrocyte glutamate transporters with ceftriaxone (a commonly used antibiotic) and n-acetyl-cysteine (a readily available nutritional supplement)—both drugs normalize the system via increasing cystine-glutamate exchanger and GLT-1 expression levels and exhibit functional outcomes of decreased drug-seeking behavior [97].

In addition to pharmacologic interventions, non-invasive neuromodulation therapies may also result in cell-specific target for treatment interventions. Preclinical models have demonstrated that modulation of astrocytic activity may be efficacious for attenuating drug seeking and reinstatement of drug-related behaviors [89, 91]. Although these studies utilized invasive approaches via pharmacogenetics, non-invasive modulation of astrocytes may also provide a potential avenue to treating diseases associated with dopamine disruption. For example, transcranial direct current stimulation (tDCS) has been shown to stimulate astrocyte calcium signaling [98]. Although tDCS is not yet an FDA-approved treatment, it has potential therapeutic effects for enhancing cognition and treating neuropsychiatric disorders such as depression, chronic pain, and addiction. Monai et al. [98] found that tDCS induced calcium elevations in astrocytes. Importantly, the researchers did not observe elevations in neuronal calcium suggesting that tDCS exerts its effects directly

on astrocytes to modulate synaptic plasticity. Importantly, Monai and Hirase [99] also observed alleviation of depression symptoms in mice with tDCS that was not observed in mice with deficient astrocyte calcium signaling, suggesting that astrocytes play a role in the therapeutic effects of tDCS as well as the plasticity inducing components of tDCS. Overall, the results provide evidence that astrocytes may be modulated by non-invasive neuromodulation and serve as important targets for the development of therapeutics to treat neuropsychiatric disorders.

CONCLUSIONS

Astrocyte contribution to mesolimbic dopamine signaling includes both (1) evidence for astrocyte expression of dopamine receptors and the ability to respond to dopamine signaling with downstream signaling events and (2) evidence of gliotransmission in the mesolimbic dopamine system. Showing that astrocytes not only respond to dopamine signaling, but also modulate neuronal signaling in the dopamine system, illustrating the key role astrocytes play in dopamine neuromodulation and the mesolimbic dopamine system.

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REFERENCES

1. Bushong EA, et al. Protoplasmic astrocytes in CA1 stratum radiatum occupy separate anatomical domains. J Neurosci. 2002;22:183–92.
2. Perea G, Navarrete M, Araque A. Tripartite synapses: astrocytes process and control synaptic information. Trends Neurosci. 2009;32:421–31.
3. Vasile F, Dossi E, Rouach N. Human astrocytes: structure and functions in the healthy brain. Brain Struct Funct. 2017;222:2017–29.
4. Allen NJ, Lyons DA. Glia as architects of central nervous system formation and function. Science. 2018;362:181–5.
5. Araque A, et al. Tripartite synapses: glia, the unacknowledged partner. Trends Neurosci. 1999;22:208–15.
6. Khakh BS, Deneen B. The emerging nature of astrocyte diversity. Annu Rev Neurosci. 2019;42:187–207.
7. Allen NJ, Eroglu C. Cell biology of astrocyte-synapse interactions. Neuron. 2017;96:697–708.
8. Bezzi P, Volterra A. A neuron-glia signalling network in the active brain. Curr Opin Neurobiol. 2001;11:387–94.
9. Araque A, et al. Gliotransmitters travel in time and space. Neuron. 2014;81:728–39.
10. Bazargani N, Attwell D. Astrocyte calcium signaling: the third wave. Nat Neurosci. 2016;19:182–9.
11. Verkhratsky A, Orkand RK, Kettenmann H. Glial calcium: homeostasis and signaling function. Physiol Rev. 1998;78:99–141.
12. Huck JH, et al. De novo expression of dopamine D2 receptors on microglia after stroke. J Cereb Blood Flow Metab. 2015;35:1804–11.
13. Färber K, Pannasch U, Kettenmann H. Dopamine and noradrenaline control distinct functions in rodent microglial cells. Mol Cell Neurosci. 2005;29:128–38.
14. Bongarzone ER, et al. Identification of the dopamine D3 receptor in oligodendrocyte precursors: potential role in regulating differentiation and myelin formation. J Neurosci. 1998;18:5344–53.
15. Rosin C, et al. Dopamine D2 and D3 receptor agonists limit oligodendrocyte injury caused by glutamate oxidative stress and oxygen/glucose deprivation. Glia. 2005;52:336–43.
16. Missale C, et al. Dopamine receptors: from structure to function. Physiological Rev. 1998;78:189–225.
17. Pierce RC, Kumaresan V. The mesolimbic dopamine system: the final common pathway for the reinforcing effect of drugs of abuse? Neurosci Biobehav Rev. 2006;30:215–38.
18. Nestler EJ, Carlezon WA Jr. The mesolimbic dopamine reward circuit in depression. Biol Psychiatry. 2006;59:1151–9.
19. Wightman RM, Robinson DL. Transient changes in mesolimbic dopamine and their association with 'reward'. J Neurochem. 2002;82:721–35.
20. Beaulieu JM, Gainetdinov RR. The physiology, signaling, and pharmacology of dopamine receptors. Pharm Rev. 2011;63:182–217.
21. Morales M, Margolis EB. Ventral tegmental area: cellular heterogeneity, connectivity and behaviour. Nat Rev Neurosci. 2017;18:73.
22. Zanassi P, et al. Pharmacological and molecular evidence for dopamine D(1) receptor expression by striatal astrocytes in culture. J Neurosci Res. 1999;58:544–52.
23. Nagatomo K, et al. Dopamine D1 receptor immunoreactivity on fine processes of GFAP-positive astrocytes in the substantia nigra pars reticulata of adult mouse. Front Neuroanat. 2017;11:3.
24. Reuss B, et al. Regionally distinct regulation of astroglial neurotransmitter receptors by fibroblast growth factor-2. Mol Cell Neurosci. 2000;16:42–58.
25. Miyazaki I, et al. Direct evidence for expression of dopamine receptors in astrocytes from basal ganglia. Brain Res. 2004;1029:120–3.
26. Corkrum M, et al. Dopamine-evoked synaptic regulation in the nucleus accumbens requires astrocyte activity. Neuron. 2020;105:1036–47. e5
27. Shibasaki K, et al. Glycine release from astrocytes via functional reversal of GlyT1. J Neurochem. 2017;140:395–403.
28. Bal A, et al. Evidence for dopamine D2 receptor mRNA expression by striatal astrocytes in culture: in situ hybridization and polymerase chain reaction studies. Brain Res Mol Brain Res. 1994;23:204–12.
29. Qiu J, et al. Sinomenine activates astrocytic dopamine D2 receptors and alleviates neuroinflammatory injury via the CRYAB/STAT3 pathway after ischemic stroke in mice. J Neuroinflammation. 2016;13:263.
30. Montoya A, et al. Dopamine receptor D3 signalling in astrocytes promotes neuroinflammation. J Neuroinflammation. 2019;16:1–19.
31. Elgueta D, et al. Pharmacologic antagonism of dopamine receptor D3 attenuates neurodegeneration and motor impairment in a mouse model of Parkinson's disease. Neuropharmacology. 2017;113:110–23.
32. Kumar U, Patel SC. Immunohistochemical localization of dopamine receptor subtypes (D1R-D5R) in Alzheimer's disease brain. Brain Res. 2007;1131:187–96.
33. Svingos AL, Periasamy S, Pickel VM. Dopamine D4 receptors are strategically localized for primary involvement in the presynaptic effects of dopamine in the rat nucleus accumbens shell. Ann N Y Acad Sci. 1999;877:679–83.
34. Hansson E, Rönnbäck L, Sellström Å. Is there a "dopaminergic glial cell"? Neurochem Res. 1984;9:679–89.
35. Hansson E, Rönnbäck L. Neurons from substantia nigra increase the efficacy and potency of second messenger arising from striatal astroglia dopamine receptor. Glia. 1988;1:393–7.
36. Galloway A, et al. Dopamine triggers CTCF-dependent morphological and genomic remodeling of astrocytes. J Neurosci. 2018;38:4846–58.
37. Koppel I, et al. Dopamine cross-reacts with adrenoreceptors in cortical astrocytes to induce BDNF expression, CREB signaling and morphological transformation. Glia. 2018;66:206–16.
38. Oe Y, et al. Distinct temporal integration of noradrenaline signaling by astrocytic second messengers during vigilance. Nat Commun. 2020;11:1–15.
39. Pérez-Alvarez A, Araque A, Martín ED. Confocal microscopy for astrocyte in vivo imaging: recycle and reuse in microscopy. Front Cell Neurosci. 2013;7:51.
40. Yu X, et al. Reducing astrocyte calcium signaling in vivo alters striatal microcircuits and causes repetitive behavior. Neuron. 2018;99:1170–87. e9
41. Lines J, et al. Astrocytes modulate sensory-evoked neuronal network activity. Nat Commun. 2020;11:1–12.
42. Qin H, et al. Monitoring astrocytic Ca2+ activity in freely behaving mice. Front Cell Neurosci. 2020;14:410.
43. Ingiosi AM, et al. A role for astroglial calcium in mammalian sleep and sleep regulation. Curr Biol. 2020;30:4373–4383. e7
44. Vaarmann A, Gandhi S, Abramov AY. Dopamine induces Ca2+ signaling in astrocytes through reactive oxygen species generated by monoamine oxidase. J Biol Chem. 2010;285:25018–23.
45. Jennings A, et al. Dopamine elevates and lowers astroglial Ca(2+) through distinct pathways depending on local synaptic circuitry. Glia. 2017;65:447–59.
46. Volkow ND, Wise RA, Baler R. The dopamine motive system: implications for drug and food addiction. Nat Rev Neurosci. 2017;18:741–52.
47. Yu X, Nagai J, Khakh BS. Improved tools to study astrocytes. Nat Rev Neurosci. 2020;21:121–38.
48. Savtchouk I, Volterra A. Gliotransmission: beyond black-and-white. J Neurosci. 2018;38:14–25.
49. Fiacco TA, McCarthy KD. Multiple lines of evidence indicate that gliotransmission does not occur under physiological conditions. J Neurosci. 2018;38:3–13.
50. Halassa MM, Fellin T, Haydon PG. The tripartite synapse: roles for gliotransmission in health and disease. Trends Mol Med. 2007;13:54–63.
51. Trudeau LE. Neurotensin regulates intracellular calcium in ventral tegmental area astrocytes: evidence for the involvement of multiple receptors. Neuroscience. 2000;97:293–302.

52. Gould T, et al. GABA(B) receptor-mediated activation of astrocytes by gamma-hydroxybutyric acid. Philos Trans R Soc Lond B Biol Sci. 2014;369:20130607.
53. Araque A, et al. SNARE protein-dependent glutamate release from astrocytes. J Neurosci. 2000;20:666–73.
54. Gomez JA, et al. Ventral tegmental area astrocytes orchestrate avoidance and approach behavior. Nat Commun. 2019;10:1–13.
55. Molnár T, et al. Activation of astroglial calcium signaling by endogenous metabolites succinate and gamma-hydroxybutyrate in the nucleus accumbens. Front Neuroenergetics. 2011;3:7.
56. Molnár T, et al. Calcium signals in the nucleus accumbens: activation of astrocytes by ATP and succinate. BMC Neurosci. 2011;12:96.
57. D'Ascenzo M, et al. mGluR5 stimulates gliotransmission in the nucleus accumbens. Proc Natl Acad Sci USA. 2007;104:1995–2000.
58. Corkrum M, et al. Opioid-mediated astrocyte–neuron signaling in the nucleus accumbens. Cells. 2019;8:586.
59. Svingos AL, et al. Ultrastructural immunocytochemical localization of mu-opioid receptors in rat nucleus accumbens: extrasynaptic plasmalemmal distribution and association with Leu5-enkephalin. J Neurosci. 1996;16:4162–73.
60. Perea G, Araque A. Properties of synaptically evoked astrocyte calcium signal reveal synaptic information processing by astrocytes. J Neurosci. 2005;25:2192–203.
61. Fellin T, et al. Neuronal synchrony mediated by astrocytic glutamate through activation of extrasynaptic NMDA receptors. Neuron. 2004;43:729–43.
62. Dunwiddie TV, Diao L, Proctor WR. Adenine nucleotides undergo rapid, quantitative conversion to adenosine in the extracellular space in rat hippocampus. J Neurosci. 1997;17:7673–82.
63. Cunha RA, Sebastião AM, Ribeiro J. Inhibition by ATP of hippocampal synaptic transmission requires localized extracellular catabolism by ecto-nucleotidases into adenosine and channeling to adenosine A1 receptors. J Neurosci. 1998;18:1987–95.
64. Bergles DE, Jahr CE. Glial contribution to glutamate uptake at Schaffer collateral-commissural synapses in the hippocampus. J Neurosci. 1998;18:7709–16.
65. Bergles DE, Diamond JS, Jahr CE. Clearance of glutamate inside the synapse and beyond. Curr Opin Neurobiol. 1999;9:293–8.
66. Conti F, Weinberg RJ. Shaping excitation at glutamatergic synapses. Trends Neurosci. 1999;22:451–8.
67. Huang YH, Bergles DE. Glutamate transporters bring competition to the synapse. Curr Opin Neurobiol. 2004;14:346–52.
68. Marcaggi P, Attwell D. Role of glial amino acid transporters in synaptic transmission and brain energetics. Glia. 2004;47:217–25.
69. Otis TS, et al. Interactions between glutamate transporters and metabotropic glutamate receptors at excitatory synapses in the cerebellar cortex. Neurochem Int. 2004;45:537–44.
70. Tzingounis AV, Wadiche JI. Glutamate transporters: confining runaway excitation by shaping synaptic transmission. Nat Rev Neurosci. 2007;8:935–47.
71. Oliet SH, Piet R, Poulain DA. Control of glutamate clearance and synaptic efficacy by glial coverage of neurons. Science. 2001;292:923–6.
72. Danbolt NC. Glutamate uptake. Prog Neurobiol. 2001;65:1–105.
73. Pawlak J, et al. Regulation of glutamate transporter GLAST and GLT-1 expression in astrocytes by estrogen. Brain Res Mol Brain Res. 2005;138:1–7.
74. Autry AE, et al. Glucocorticoid regulation of GLT-1 glutamate transporter isoform expression in the rat hippocampus. Neuroendocrinology. 2006;83:371–9.
75. Zschocke J, et al. Differential promotion of glutamate transporter expression and function by glucocorticoids in astrocytes from various brain regions. J Biol Chem. 2005;280:34924–32.
76. Frizzo ME, et al. Extracellular adenosine triphosphate induces glutamate transporter-1 expression in hippocampus. Hippocampus. 2007;17:305–15.
77. Wu J, et al. Regulation of ethanol-sensitive EAAT2 expression through adenosine A1 receptor in astrocytes. Biochem Biophys Res Commun. 2011;406:47–52.
78. Roberts-Wolfe DJ, Kalivas PW. Glutamate transporter GLT-1 as a therapeutic target for substance use disorders. CNS Neurol Disord Drug Targets. 2015;14:745–56.
79. Kalivas PW, et al. Glutamate transmission in addiction. Neuropharmacology. 2009;56:169–73.
80. Kalivas PW. The glutamate homeostasis hypothesis of addiction. Nat Rev Neurosci. 2009;10:561–72.
81. Scofield M, et al. The nucleus accumbens: mechanisms of addiction across drug classes reflect the importance of glutamate homeostasis. Pharmacol Rev. 2016; 68:816–71.
82. Scofield MD, Kalivas PW. Astrocytic dysfunction and addiction: consequences of impaired glutamate homeostasis. Neuroscientist. 2014;20:610–22.
83. Durkee CA, et al. Gi/o protein-coupled receptors inhibit neurons but activate astrocytes and stimulate gliotransmission. Glia. 2019;67:1076–93.
84. Covelo A, Araque A. Neuronal activity determines distinct gliotransmitter release from a single astrocyte. Elife. 2018;7:e32237.
85. Haydon PG, et al. Astrocytic control of synaptic transmission and plasticity: a target for drugs of abuse? Neuropharmacology. 2009;56:83–90.
86. Bachtell RK, et al. Glial and neuroinflammatory targets for treating substance use disorders. Drug Alcohol Depend. 2017;180:156–70.
87. Kim R, et al. Astroglial correlates of neuropsychiatric disease: from astrocytopathy to astrogliosis. Prog Neuropsychopharmacol Biol Psychiatry. 2018;87:126–46.
88. Wang J, et al. Astrocytes in cocaine addiction and beyond. Mol Psychiatry. 2021; in press.
89. Bull C, et al. Rat nucleus accumbens core astrocytes modulate reward and the motivation to self-administer ethanol after abstinence. Neuropsychopharmacology. 2014;39:2835–45.
90. Nwachukwu KN, et al. Chemogenetic manipulation of astrocytic signaling in the basolateral amygdala reduces binge-like alcohol consumption in male mice. J Neurosci Res. 2021; in press.
91. Scofield MD, et al. Gq-DREADD selectively initiates glial glutamate release and inhibits cue-induced cocaine seeking. Biol Psychiatry. 2015;78:441–51.
92. Siemsen BM, et al. Effects of methamphetamine self-administration and extinction on astrocyte structure and function in the nucleus accumbens core. Neuroscience. 2019;406:528–41.
93. Sarkisyan D, et al. Damaged reward areas in human alcoholics: neuronal proportion decline and astrocyte activation. Acta Neuropathologica. 2017;133:485–7.
94. Ramaker RC, et al. Post-mortem molecular profiling of three psychiatric disorders. Genome Med. 2017;9:1–12.
95. Navarrete M, et al. Astrocyte calcium signal and gliotransmission in human brain tissue. Cereb Cortex. 2013;23:1240–6.
96. Hearing M, et al. Opioid and psychostimulant plasticity: targeting overlap in nucleus accumbens glutamate signaling. Trends Pharm Sci. 2018;39:276–94.
97. Scofield MD, et al. The nucleus accumbens: mechanisms of addiction across drug classes reflect the importance of glutamate homeostasis. Pharm Rev. 2016;68:816–71.
98. Monai H, et al. Calcium imaging reveals glial involvement in transcranial direct current stimulation-induced plasticity in mouse brain. Nat Commun. 2016;7:11100.
99. Monai H, Hirase H. Astrocytes as a target of transcranial direct current stimulation (tDCS) to treat depression. Neurosci Res. 2018;126:15–21.
100. Mladinov M, et al. Astrocyte expression of D2-like dopamine receptors in the prefrontal cortex. Transl Neurosci. 2010;1:238–43.
101. Khan ZU, et al. An astroglia-linked dopamine D2-receptor action in prefrontal cortex. Proc Natl Acad Sci USA. 2001;98:1964–9.
102. Pelassa S, et al. A2A-D2 heteromers on striatal astrocytes: biochemical and biophysical evidence. Int J Mol Sci. 2019;20:2457.
103. Cervetto C, et al. A2A-D2 receptor–receptor interaction modulates gliotransmitter release from striatal astrocyte processes. J Neurochemistry. 2017; 140:268–79.
104. Cervetto C, et al. Homocysteine and A2A-D2 receptor-receptor interaction at striatal astrocyte processes. J Mol Neurosci. 2018;65:456–66.
105. Requardt RP, et al. The biphasic NAD (P) H fluorescence response of astrocytes to dopamine reflects the metabolic actions of oxidative phosphorylation and glycolysis. J Neurochemistry. 2010;115:483–92.
106. Liu J, et al. Activation of phosphatidylinositol-linked novel D 1 dopamine receptor contributes to the calcium mobilization in cultured rat prefrontal cortical astrocytes. Cell Mol Neurobiol. 2009;29:317–28.
107. Xin W, et al. Ventral midbrain astrocytes display unique physiological features and sensitivity to dopamine D2 receptor signaling. Neuropsychopharmacology. 2019;44:344–55.
108. Reuss B, Unsicker K. Atypical neuroleptic drugs downregulate dopamine sensitivity in rat cortical and striatal astrocytes. Mol Cell Neurosci. 2001;18:197–209.
109. Hösli L, et al. Action of dopamine and serotonin on the membrane potential of cultured astrocytes. Exp Brain Res. 1987;65:482–5.
110. Martin R, et al. Circuit-specific signaling in astrocyte-neuron networks in basal ganglia pathways. Science. 2015;349:730–4.

AUTHOR CONTRIBUTIONS

MC and AA jointly wrote, revised, edited the paper, and approved the final version of the paper.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to A.A.