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Astrocytic G Protein-Coupled Receptors in Drug Addiction

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Abstract

Understanding the cellular mechanisms of drug addiction remains a key task in current brain research. While neuron-based mechanisms have been extensively explored over the past three decades, recent evidence indicates a critical involvement of astrocytes, the main type of non-neuronal cells in the brain. In response to extracellular stimuli, astrocytes modulate the activity of neurons, synaptic transmission, and neural network properties, collectively influencing brain function. G protein-coupled receptors (GPCRs) expressed on astrocyte surfaces respond to neuron- and environment-derived ligands by activating or inhibiting astrocytic signaling, which in turn regulates adjacent neurons and their circuitry. In this review, we focus on the dopamine D1 receptors (D1R) and metabotropic glutamate receptor 5 (mGLUR5 or GRM5)—two GPCRs that have been critically implicated in the acquisition and maintenance of addiction-related behaviors. Positioned as an introductory-level review, this article briefly discusses astrocyte biology, outlines earlier discoveries about the role of astrocytes in substance-use disorders (SUDs), and provides detailed discussion about astrocytic D1Rs and mGLUR5s in regulating synapse and network functions in the nucleus accumbens (NAc)—a brain region that mediates addiction-related emotional and motivational responses. This review serves as a stepping stone for readers of *Engineering* to explore links between astrocytic GPCRs and drug addiction and other psychiatric disorders.

Keywords

Astrocyte; GPCR; Nucleus accumbens; Addiction; mGLUR5; Dopamine

1. Introduction

Humans have been consuming psychoactive substances since the beginning of recorded history. In contemporary societies, caffeine and nicotine are regularly used to increase cognition and alertness, opioids are prescribed to ease patients' pain, and drugs such as cannabis and alcohol are consumed recreationally by large portions of the population.

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Compliance with ethics guidelines

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Nevertheless, we still have incomplete knowledge of the brain mechanisms that drive certain individuals to develop substance-use disorders (SUDs), which are currently defined as behavioral states wherein an individual continues to seek out and use substances despite negative consequences. Targeting this brain disease, neuroscience research has largely remained within the framework that repeated drug-seeking and drug-taking behaviors result from drug-induced adaptations in neurons within the brain's reward circuitry. This neural adaptation has been partly concentrated on the actions of individual neurotransmitters, such as dopamine and glutamate, within the mesolimbic and corticostriatal projections to the nucleus accumbens (NAc). The NAc is a key brain region wherein cortical and subcortical inputs converge and integrate to regulate reward- and motivation-related behaviors. Over the years, numerous adaptive changes have been identified in the neuronal populations that constitute the NAc and several other reward-related brain regions. However, it has become increasingly apparent that neurons are not the only players in drug-induced adaptations and drug-motivated behaviors.

In addition to neurons, the central nervous system (CNS) contains an almost equivalent number of glial cells, which not only provide structural and homeostatic support to adjacent nerve cells but also regulate their function. Astrocytes, the most abundant glial cells, have been increasingly recognized for their roles in regulating synaptic transmission and neurocircuit function. In the mammalian brain, astrocyte processes are located near synapses and dendrites—an anatomical arrangement that potentially facilitates bidirectional communication between neurons and astrocytes. Over the past two decades, increasing evidence has suggested that this crosstalk serves as a fundamental mechanism underlying learning and memory processes associated with motivated behaviors.

Glutamatergic and dopaminergic neurotransmission are two primary targets by which drugs of abuse induce drug-seeking and -taking behaviors. The metabotropic receptors for these neurotransmitters—namely, glutamatergic and dopaminergic G protein-coupled receptors (GPCRs)—have been critically implicated in drug-related memories. However, compared with those of their neuronal counterparts, the cellular and behavioral functions of these GPCRs expressed on astrocytes remain poorly understood. In this review, we summarize what is known about astrocyte-expressed glutamatergic and dopaminergic GPCRs and discuss how astrocytes communicate with neurons through these GPCRs to facilitate behavioral changes in the context of SUDs.

2. A brief history of astrocytes in SUDs

Since the advent of the operant conditioning box by B.F. Skinner, neuroscientists have been able to study the neural effects of repeated, voluntary drug use in rodents. The operant responding-based drug self-administration (SA) model allows researchers to examine the rewarding and motivational aspects of drug use and provides a controlled laboratory setting to test causal links between drug-associated behaviors and drug-induced neural adaptations. Using this model, early behavioral neuroscientists demonstrated that rats repeatedly chose to electrically self-stimulate brain regions that either send or receive dopaminergic projections [1,2]. Furthermore, stimulants, which increase or prolong the effects of dopamine, increased the frequency of electrical self-stimulation [3]. Subsequently, researchers found that

dopaminergic transmission from the ventral tegmental area (VTA) in the midbrain to the forebrain NAc is increased by all drugs that cause addiction in vulnerable humans [4]. Thus, the hypothesis that addiction is a result of the dysfunctional rewarding/reinforcing properties of dopamine [5,6] became a mainstay in the neuroscience community [7] (interested readers can see earlier reviews of dopaminergic adaptations in SUDs for more in-depth discussions [8–10]). The involvement of NAc astrocytes in drug-induced adaptations and dopaminergic transmission was discovered very recently and is discussed below.

Over time, increasing evidence has also implicated long-lasting adaptations in glutamatergic transmission in driving the acquisition and maintenance of addiction-related behaviors [11–15]. In 2009, a focus on glutamate homeostasis in addiction was expanded to include a central role for astrocytes. This hypothesis proposed that addiction arises from a drug-induced imbalance in glutamate release/reuptake in the corticostriatal projections terminating in the NAc [16]. As these projections are responsible for generating learned behaviors, as well as changing those behaviors in response to a shifting environment [17], the hypothesis suggested that addiction can result from ① a strengthened and learned drug-seeking behavior, ② a weakened ability to suppress drug-seeking behavior, or ③ a combination of the two. It is important to note that many subsequent studies on glutamate homeostasis utilized the reinstatement model of drug relapse in rodents. As such, some of the identified adaptations may only occur after extinction training [18]—a form of forced abstinence in which the operant responses that previously produced a drug reward and its paired cues (reinforcing conditioned stimuli) no longer produce either [19]. Once SA behavior is stably extinguished, re-exposure to the drug or to the cues that were previously associated with drug taking can elicit drug-seeking behavior, even after extended periods of abstinence [20].

Following chronic cocaine SA and extinction, dysregulation of glutamate homeostasis in the corticostriatal pathway stems from several adaptations in the perisynaptic processes of NAc astrocytes [21–24]. The first is a reduction in the expression of GLT1, which is a glutamate transporter responsible for > 90% of synaptic glutamate clearance in the CNS [25–31]. The second is impaired function of xCT (a cystine/glutamate exchanger), which regulates ambient glutamate levels in the extrasynaptic space [32,33]. While decreased GLT1 impairs the clearance of glutamate from the synapse, downregulation of xCT lowers extrasynaptic levels of glutamate that normally drive presynaptic inhibition by activating metabotropic glutamate receptors 2 and 3 (mGLUR2/3) on nerve terminals, resulting in increased glutamatergic transmission [34,35]. Lastly, extinction training produces a significant retraction of the astrocytic processes that insulate the NAc synapses [18,36]. Together, these adaptations exacerbate glutamate spillover from the synaptic cleft into the extrasynaptic space [16,24], thereby triggering non-specific neuronal activity at neighboring synapses [37–40] and promoting drug-seeking behaviors [24,41,42]. *N*-acetylcysteine, a cysteine prodrug that restores GLT1 and xCT function, is effective in reducing cue-induced drug seeking in extinction and abstinence models of cocaine addiction [21,43–45], raising hope that astrocytes may serve as a novel target for therapeutic intervention in human patients. Thus far, the use of *N*-acetylcysteine to stimulate xCT-mediated glutamate clearance has shown mixed results in preliminary clinical studies [46]. In a double-blind, placebo-controlled study of 111 individuals with cocaine use disorder, *N*-acetylcysteine

was only effective in increasing the time to relapse or reducing cocaine craving in the small subset of subjects who were already abstinent from cocaine, with no effect on abstinence rates in patients actively using the drug [47]. While the outcomes of this study were primarily negative, they do warrant further clinical studies with better inclusion of cocaine-abstinent individuals to further investigate the impact of *N*-acetylcysteine on relapse prevention.

Drug seeking and relapse are often triggered by stress or intense drug craving. In many cases, drug craving is elicited by encountering a person, place, or object a user has learned to associate with the drug experience. During repeated drug-taking episodes, previously neutral cues are conditioned by drug experiences to be predictive of drug availability. Conditioned cues can thus reinforce drug-seeking/taking behavior, in that re-exposure to them during abstinence can trigger an intense craving that leads to continued drug use. This memory-dependent phenomenon raises an important question: How are the memories associated with drug use encoded in the brain, and why—despite prolonged periods of abstinence—can they trigger self-sabotaging behaviors such as relapse? Could the role of astrocytes in SUDs extend beyond a dysfunction in homeostatic maintenance? Could astrocytes, in fact, reshape the nervous system to accommodate and maintain these long-lasting memories?

An important conceptual development came from evidence that drugs of abuse act upon, and utilize, the same cellular mechanisms that underlie learning and memory processes in brain regions such as the NAc [17,48–52]. The principal neurons within the NAc are medium spiny neurons (MSNs), which receive extensive glutamatergic projections from several cortical and subcortical structures [8,9]. These projections provide the relevant contextual and emotional information that is integrated at the level of the NAc to guide motivated behaviors [53,54]. The NAc has two subregions: The core is preferentially involved in the acquisition and initiation of motor functions related to reward seeking, while the shell preferentially influences motivation and associative memory dynamics [55]. Within several projections to the NAc shell, a unique population of glutamatergic synapses is generated *de novo* by cocaine SA. Several cellular features make these synapses distinct from other glutamatergic synapses, a prominent one being a lack of functionally stable α-Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors (AMPARs). At first, these “AMPAR-silent” synapses contain only functional NMDA receptors (NMDARs), but they mature during withdrawal by recruiting atypical, Ca^{2+}-permeable AMPARs (CP-AMPARs), which lack the GLUA2 AMPAR subunit. Once matured, these synapses contribute to cocaine-associated memories, with their dynamic states regulating the retrieval, destabilization, and reconsolidation of cocaine memories [56,57].

The *de novo* nature of these synapses and the findings that they are generated using cellular mechanisms normally reserved for early development provides support for the Neural Rejuvenation Hypothesis of Addiction [58,59]. In this hypothesis, repeated cocaine exposure brings otherwise dormant cellular mechanisms normally associated with developmental synaptogenesis back online to restructure the synaptic architecture of the brain’s reward circuitry. The integral role of astrocytes in developmental synaptogenesis prompted a study to investigate whether astrocytes contribute to the generation of cocaine-specific synapses. This work revealed that astrocyte-released thrombospondin 2 (TSP2) activates the neuronal

receptor α2δ1 (CACNA2D1; the target for gabapentin and related medications), which then promotes the generation of silent synapses after cocaine SA [60,61]. Thrombospondin (TSP) expression is highest during early development and declines to low levels with age [62]. These low levels are detected in the adult NAc in close proximity to α2δ1 [61,63], the expression of which remains robust despite the decline of TSPs. Although cocaine SA does not upregulate TSP2 levels in the NAc, short hairpin RNA (shRNA)-mediated knockdown of TSP2 or of α2δ1 is sufficient to prevent silent synapse generation [61], indicating that low levels of TSP2 from astrocytes are sufficient for synaptogenesis to occur. Furthermore, pharmacological inhibition of the TSP2-α2δ1 signaling with gabapentin is sufficient to prevent silent synapse generation and the corresponding increase in NAc dendritic spine density, as well as decrease cue-induced cocaine seeking [61]. Thus, an age-related decline in astrocyte-derived signaling does not equate to a loss in function. Rather, it appears that astrocyte-mediated developmental signals persist into adulthood and can actively remodel the surrounding synaptic environment during learning. The ability of astrocytes to utilize signaling pathways despite low expression levels will be further discussed in the following sections, which cover astrocyte biology, the roles of GPCRs in astrocyte function, and the role of astrocyte GPCRs in SUDs.

3. Astrocyte biology

Individual astrocytes have a highly complex anatomy, often described as “spongiform” due to the cloudlike appearance formed by their distal processes. A typical protoplasmic astrocyte comprises a central soma, 1–3 endfeet that enwrap nearby vasculature, several thicker primary branches, and a large web of intricate branchlets and leaflets (perisynaptic processes) that contact thousands of synapses within its territory [64–68]. Perhaps due to the complexity and size of these distal processes (e.g., an individual leaflet can range from 10 to 100 nm [69]), an astrocyte’s territory shows minimal overlap (less than 5%) with the territory of neighboring astrocytes [70–72], resulting in a highly complex, tiling arrangement in which astrocyte processes extend and cover the entire CNS while minimizing overlap [73]. Astrocytic tiling is a robust feature of both rodent and human astrocytes, although human astrocytes display a greater degree of territorial overlap [74–76]. Furthermore, neighboring astrocytes are extensively connected with gap junctions, resulting in large-scale, electrically coupled reticular networks known as syncytia [77–79]. The syncytium structure allows coupled astrocytes to constantly equalize their membrane potentials and function as a singular unit [80]. This feature, together with a low membrane resistance and high permeability to potassium, prevent large deviations in membrane potential [27] and can contribute to the electrically non-excitable feature of astrocytes [81]. Nevertheless, although astrocytes do not produce action potentials like neurons, they can respond to neurotransmitters through dynamic intracellular Ca^{2+} fluctuations in their soma and processes [82,83].

Astrocytes express both ionotropic and metabotropic receptors and have been shown to respond to glutamate, γ-aminobutyric acid (GABA), adenosine triphosphate (ATP), dopamine, serotonin, acetylcholine, norepinephrine, endocannabinoids, and other transmitters [84,85]. While a consensus is lacking on the downstream consequences of astrocytic intracellular Ca^{2+} fluctuations [86,87], it is clear that these Ca^{2+} activities are

critically regulated by GPCRs expressed on astrocytes [84,88–92]. Such Ca^{2+} fluctuations, in either the soma or branches, are often induced by GPCR-mediated activation of phospholipase C (PLC) and inositol 1,4,5-triphosphate (IP3) [93]. When IP3 binds to its primary intracellular receptor (IP3R2) in astrocytes, it triggers the release of Ca^{2+} from internal stores within the endoplasmic reticulum (ER). IP3R2-independent Ca^{2+} waves are also detected in distal processes, but these are relatively small and localized within microdomains adjacent to neuronal synapses [94–99]. IP3R2-independent Ca^{2+} fluctuations are readily observed *in vivo* and can arise from external sources such as transmembrane Ca^{2+} diffusion [100]. *In vivo* studies have also revealed that the bulk release of neuromodulators can drive large-scale Ca^{2+} events spanning entire brain regions [101–104]. While neuronal responses (e.g., synaptic transmission and action potential firing) occur in the order of milliseconds, astrocytic Ca^{2+} responses are much slower, typically lasting hundreds of milliseconds to seconds [97,103,105]. It is possible that the longer timescales for astrocytic Ca^{2+} fluctuations have significant behavioral relevance. For instance, in larval zebrafish, repeated attempts to swim against a current generates a behavioral mismatch signal that leads to the progressive accumulation of Ca^{2+} in radial astrocytes. These long Ca^{2+} signals correlate with the onset and maintenance of behavioral passivity between bursts of vigorous swim attempts, suggesting that the temporal dynamics of astrocytic Ca^{2+} are part of the CNS computation for behavioral state switching [104].

There is strong evidence that astrocytes and neurons are in constant communication and that this reciprocal communication is important for behavior [106–108]. As mentioned previously, astrocytes express numerous types of neurotransmitter receptors that allow for neuron-to-astrocyte communication. In return, astrocytes can transfer information to neurons through a process named gliotransmission, which is thought to be partly driven by the stimulation of GPCRs on astrocytes [86,87,97,109]. In response to experimenter-induced or neuronal stimulation, astrocytes can release a myriad of neuroactive molecules, including ATP/adenosine [110–121], glutamate [122–126], GABA [127–132], and *D*-serine [133–135]. Notably, a single astrocyte can release different gliotransmitters (i.e., glutamate and ATP/adenosine) in a biphasic manner depending on the intensity and duration of stimulation [136]. This feature suggests that astrocytes can perform complex signal integration and processing.

Astrocytes contain multiple mechanisms for gliotransmission, including Ca^{2+}-dependent exocytosis and various forms of Ca^{2+}-independent transmitter release. Glutamate, for example, can be released through Ca^{2+}-dependent exocytosis [137,138], BST1 anion and TREK-1 potassium channels [139], hemichannels [140], volume-regulated anion channels (VRACs) [141], and several transporters, antiporters, and exchangers [142]. The prominence of Ca^{2+}-dependent exocytosis in adult astrocytes has been the subject of continuing debate in astrocyte biology. Both cultured and acutely isolated astrocytes have been found to contain the molecular machinery necessary for Ca^{2+}-dependent vesicle exocytosis, including the SNARE proteins synaptobrevin II, SNAP 23, VAMP 2 and 3, and Syntaxin 1, as well as several synaptotagmin isoforms and VGLUT1 and 2 [143–148]. VGLUT1 and 2 are essential for packaging glutamate into vesicles and for the exocytotic release of glutamate. For example, immunogold labeling and single-cell reverse-transcription polymerase chain reaction (RT-PCR) have verified the presence of VGLUT1 and 2 in cultured and acutely

isolated astrocytes from the dentate gyrus (DG) of the hippocampus. VGLUT1 and 2 are expressed in diffusely distributed vesicles that resemble neuronal vesicles but differ in the molecular composition of their fusion proteins. Stimulation of endogenous, astrocytic GPCRs with *S*-3,5-dihydroxyphenylglucine (DHPG)—a potent agonist at metabotropic glutamate receptors 1 and 5 (mGLUR1 and mGLUR5)—results in fast, SNARE-mediated vesicle fusion and glutamate release. Importantly, VGLUT1 and 2 are only found in approximately 25%–40% of isolated astrocytes, suggesting the existence of a specialized subpopulation of astrocytes that can undergo Ca^{2+}-dependent exocytosis [138]. However, it is possible that a larger portion of astrocytes express lower levels of VGLUT1 and 2 that are difficult to detect. Furthermore, this study did not detect glutamate release from astrocytes in response to chemogenetic-mediated increases in internal Ca^{2+} levels [149]. To address such contradictory findings, the researchers, who had previously demonstrated Ca^{2+}-dependent exocytosis in the DG, re-examined their findings using updated bioinformatic and imaging methods [150]. Their studies revealed nine molecularly distinct populations of astrocytes, with only one subpopulation expressing the necessary machinery for the vesicular exocytosis of glutamate [150]. While being somewhat surprising, these results suggest a pronounced regional and molecular heterogeneity of astrocytes, which may underlie many of the earlier inconsistencies that sparked debates on the role of Ca^{2+} signals and gliotransmission [151–154]. Indeed, other groups have found that chemogenetic stimulation of astrocytes in other brain regions (e.g., the NAc core and somatosensory cortex) triggers glutamate release [155–158]. For instance, in the context of SUDs, glutamate released (presumably via exocytosis) by astrocytes stimulates neuronal mGLUR2/3 in the NAc core and attenuates cue-induced reinstatement of cocaine, methamphetamine, and ethanol seeking [155,157,158]. These findings highlight the complexity and diversity of astrocyte mechanisms, which should be taken into consideration when interpreting positive and negative results across brain regions and behavioral contexts.

4. Roles of astrocyte GPCRs in SUDs

Two representative astrocytic GPCRs that are implicated in SUDs are mGLUR5 and the dopamine D1 receptor (D1R). Although extensive research has been conducted on neuronal mGLUR5 and D1R, far less is known about the contributions of their astrocytic counterparts. Following a brief discussion of GPCR function, we will summarize below what we know about the expression of these receptors on astrocytes and their contributions to SUDs.

GPCRs are a class of receptors that trigger multi-stepped signaling cascades within a cell upon activation by transmitter binding. In neurons, these signaling cascades are triggered by the dissociation of the Gα subunit from the βγ subunits that together comprise the G protein heterotrimer [159]. There are at least four classes of G proteins (G_q, $G_{i/o}$, G_s, and $G_{12/13}$) [160,161]. In neurons, activation of G_q- and G_s-coupled second messenger systems generally increases internal Ca^{2+} and neuronal excitability, while activation of the $G_{i/o}$ pathway causes the opposite effects. In astrocytes, however, this functional dichotomy does not appear to be clearcut [156,162]. Recent studies have demonstrated that both “excitatory” (G_q-coupled) and “inhibitory” ($G_{i/o}$-coupled) designer receptors exclusively activated by designer drugs (DREADDs) can increase astrocytic Ca^{2+} levels in the striatum [106,149].

In the hippocampus, G_q activation reliably increases astrocytic Ca^{2+} levels [149,156,163], while the effects of $G_{i/o}$ activation vary among studies, with no impact on internal Ca^{2+} levels [149,164], increases in Ca^{2+} levels [156], and biphasic responses (an initial increase followed by subsequent decrease) in basal Ca^{2+} levels [165] all having been observed. Although the precise mechanisms underlying these discrepant observations are unclear, these discrepancies may be a result of regional and molecular heterogeneity of astrocyte GPCR function. Historically, neuronal GPCRs were believed to only couple to a single G protein. However, we now know that GPCRs display conformational plasticity, which allows them to couple to multiple G proteins [166–169] and activate them sequentially in a time-dependent manner [170,171]. Thus, it is possible that astrocytic GPCRs can also activate multiple signaling pathways and that these responses may show regional heterogeneity.

An important consideration is that astrocytic GPCRs are scarcer and more diffuse than their neuronal counterparts. However, astrocytic GPCRs maintain robust functionality, as has been demonstrated with endogenous cannabinoid receptor CB1 [172–174]. In fact, astrocytic GPCRs exhibit certain features—including serial amplification, higher ligand-binding affinities, and lower desensitization rates [84,109]—that allow for reliable sampling and integration of neuronal activity at multiple synapses despite low expression levels.

4.1. mGLUR5

In both mice and humans, astrocytic expression of mGLUR5 peaks during early development and then declines upon entering adulthood [149,175–177], a developmental feature that is partly driven by increased expression of adenosine A_2B receptor [178]. The coinciding increase in mGLUR2/3 [176,179] expression has been interpreted as a compensation for the reduction in mGLUR5 functionality in adulthood. Despite low expression levels, astrocytic mGLUR5 remains functional in adult wild-type mice [180] and is even increased in response to insult or disease states [181–184]. On astrocytes, mGLUR5 has been observed on the fine peripheral processes associated with pre- and post-synaptic terminals with little expression on the soma [119,185], making detection difficult through light-based microscopy. However, a recent study detected mGLUR5 proteins on the soma and primary branches of adult, s100β-labeled hippocampal astrocytes [186], and another study detected the colocalization of immunogold-labeled mGLUR5 with GFAP in the somatosensory cortex following nerve ligation [187]. Thus, the expression and relative levels of mGLUR5 are heterogeneous both at the subcellular level within individual astrocytes and at the population level between astrocytes of different brain regions (Fig. 1).

Interestingly, knockout of mGLUR5 in the adult mouse hippocampus increased the expression and intensity of the astrocyte marker s100β [186]. This result suggests that astrocytic mGLUR5 negatively regulates astrocyte proliferation and activation in adulthood. However, the researchers acknowledged that this finding contrasts with other findings showing that mGLUR5 positively regulates astrocyte branching during development [188,189]. Exploration is necessary to determine whether mGLUR5 is localized with s100β or with the striatal astrocyte marker μ-crystalline in the NAc, as previous attempts to localize mGLUR5 expression to astrocytes in this brain region utilized glail fibrillary

acidicprotein (GFAP) [190], which is expressed at very levels in striatal astrocytes compared with hippocampal astrocytes [149].

Functionally, astrocytes in the hippocampus and striatum are sensitive to agonists for mGLUR5 and mGLUR2/3, both of which induce Ca^{2+} activity in astrocytic processes, with mGLUR2/3-selective agonists evoking larger responses in the soma compared with mGLUR5-selective agonists [149,156,179]. While mGLUR2/3 is best studied for its role in controlling glutamatergic nerve terminals, as noted above, mGLUR3 is enriched in astrocytes. In theory, astrocytic mGLURs can be stimulated either by synaptically released glutamate or by glutamate from extrasynaptic spillover. Several studies have examined these possibilities. For instance, an mGLUR5-dependent response was observed following a single synaptic stimulation of hippocampal CA1 neurons in young rats [119]. These signals are small and occur in discrete subcellular compartments localized to dendritic spines, supporting the notion that astrocytes receive information directly from neurons. *In vivo*, astrocytic responses to synaptic or ectopic glutamate release were observed following whisker stimulation in awake [191] and anesthetized [91] adult mice. The astrocytic Ca^{2+} responses induced by whisker stimulation were not sensitive to AMPAR or NMDAR antagonists, indicating that they are not an indirect consequence of glutamatergic synaptic transmission onto neurons [91] (but see Ref. [191]). Furthermore, these *in vivo* responses are blocked by the mGLUR5 antagonist 2-Methyl-6-(phenylethynyl)pyridine (MPEP), implicating mGLUR5 in these astrocytic responses. In another study, subpopulations of astrocytes in both the NAc core and shell of adult mice responded to optogenetic stimulation of multiple glutamatergic afferents. These responses, again, required mGLUR5 and were retained in the presence of tetrodotoxin (TTX) and picrotoxin [192], further suggesting that astrocytes respond to stimulated afferents directly, without the involvement of local neurons.

While the above results suggest a functional role for astrocytic mGLUR5 in adulthood, there is also evidence suggesting otherwise. In the hippocampal mossy fiber pathway of adult mice, electric field stimulation (EFS)-induced glutamate release onto astrocytes increased Ca^{2+} activity in astrocyte soma and branches only after burst firing, with no noticeable effect occurring after a single stimulation. These responses were IP3R2-dependent and were prevented by a combination of the mGLUR2/3 antagonist LY341495 (10 $\mu mol \cdot L^{-1}$) and the $GABA_B$ receptor antagonist CGP52432 (10 $\mu mol \cdot L^{-1}$), but not the mGLUR5 antagonist MPEP (50 $\mu mol \cdot L^{-1}$) [193]. However, it is likely that there are different mechanisms underlying the responses to single synaptic events versus large afferent stimulations. Since significant Ca^{2+} events can be observed in the vicinity of dendritic spines following minimal stimulation, whereas a single EFS stimulation has no impact on Ca^{2+} levels in the soma or branches, we speculate that there may be a component of temporal or spatial integration at play.

Take, for example, a study examining the striatum of adult mice, wherein EFS selectively increased Ca^{2+} activity in astrocyte branches, but not soma, within 10 s of a 1-s, four-burst stimulation [179]. In that study, additional but substantial Ca^{2+} activities occurred about 20 s after stimulation—a delay that was initially interpreted as an artifact of stimulation. However, this delayed effect is similar to a recently demonstrated evocation of astrocyte Ca^{2+} signals in the somatosensory cortex, which peaked about 20 s after peripheral sensory

stimulation (hind paw prick) [194]. Thus, this delay could be reinterpreted as an integrated somatic outcome of astrocyte processes. Specifically, if mGLURs are indeed preferentially expressed in the fine processes where they mediate local Ca^{2+} events [185], a delayed somatic response may only occur when sufficient and temporally relevant Ca^{2+} signals from distal processes integrate into a supra-threshold somatic signal. Such a threshold was recently detected in an *in vivo* two-photon study monitoring astrocytic Ca^{2+} activities in the mouse primary somatosensory cortex in response to peripheral sensory stimulation [195]. The study also revealed that the astrocytic Ca^{2+} signals originated from the fine processes and branches and had to pass a specific spatial threshold to trigger a whole-cell, IP3R2-mediated Ca^{2+} surge [195]. In brain slices, ATP-induced stimulation of astrocytes generated slow inward currents, a proxy of gliotransmission, in nearby layer 2/3 cortical neurons once the spatial threshold was passed [195]. While the implications of these findings are exciting, the degree to which this spatial threshold can be generalized across brain regions and astrocyte-expressed GPCRs remains to be determined.

Activation of astrocytic mGLUR5 leads to a range of downstream effects (Fig. 1). In the NAc, astrocytic mGLUR5 regulates Ca^{2+} dynamics that result in gliotransmission onto adjacent MSNs [196]. In the dorsal striatum, astrocytic mGLUR5 regulates long-term depression (LTD) induction at corticostriatal synapses [197]. In the somatosensory cortex, upregulation of astrocytic mGLUR5 by peripheral pain leads to the release of the synaptogenic signaling molecule TSP-1 and the generation of new synaptic connections that underlie neuropathic pain maintenance [187,198].

The role of neuronal mGLUR5 in SUDs has been rigorously tested, and excellent reviews can be found elsewhere [199–202]. As there are no studies directly examining astrocytic mGLUR5 in SUDs, we extrapolate some potential contributions based on an in-depth literature analysis. Genetic deletion of mGLUR5 abolished the acquisition of cocaine SA and decreased cocaine-induced locomotor sensitization [203]. However, another study showed that genetic deletion of mGLUR5 did not affect cocaine-induced locomotor sensitization, despite blocking cocaine-induced adaptations in the VTA [204]. This discrepancy may stem from the different mouse lines that were used, such that mGLUR5 deletion was differentially affected within different populations of neurons or glial cells. Nonetheless, pharmacological inhibition of mGLUR5 dose-dependently decreased cocaine SA [203] and several forms of reinstated drug seeking, including cue- and cocaine-induced reinstatement [205–208] (but see Ref. [190]). Thus, with some discrepancies, most results indicate that disruption of mGLUR5 function attenuates drug-taking, -seeking, or other addiction-related behaviors.

The disruptions of mGLUR5 function discussed above were achieved by global knockout or pharmacological inhibition, approaches that affect mGLUR5 on all cell types, including neurons and astrocytes. Focusing on neuronal mGLUR5, a recent study showed that the knockdown of mGLUR5 selectively in NAc D1-MSNs affected the cue-induced reinstatement of cocaine seeking to a lesser degree than non-specific pharmacological inhibition, with no impact on SA or extinction [209]. These results raise the possibility that astrocytic mGLUR5 may act in tandem with neuronal mGLUR5 to regulate cue-associated drug memories. In addition, during development, astrocytic mGLUR5 regulates

the functional maturation of both astrocytes and adjacent excitatory synapses [188], while the upregulation of astrocytic mGLUR5 induces TSP1 release and the formation of new excitatory synapses in adulthood [187,198]. Astrocyte-derived TSP2 and its neuronal α2δ1 receptor mediate the formation of cocaine-generated synapses in the NAc, and these synapses undergo dynamic changes regulating the dynamics of cue-associated cocaine memories after cocaine abstinence, as discussed earlier [61]. Interestingly, cocaine SA and extinction increased the expression of TSP1 and α2δ1 in the NAc core, but the administration of gabapentin before reinstatement did not affect cue-induced reinstatement of cocaine seeking [63]. These results suggest that TSP1/2-α2δ1 signaling is required for the formation—but not behavioral expression—of cue-associated drug memories. In line with the neural rejuvenation hypothesis cited above [58], which postulates that drug experience reactivates developmental mechanisms to produce long-lasting cellular adaptations, investigation of whether astrocytic mGLUR5 contributes to drug-induced synaptogenesis is warranted.

4.2. D1R

D1 and D2 dopamine receptors in the NAc are foundational in regulating cell-type-specific glutamatergic adaptations implicated in drug- and cue-associated memories that promote drug seeking [8,9]. D1R protein has been detected in the NAc [110], caudate putamen (dorsal striatum) [210], and (to varying degrees) cerebral cortex [210–213]. In acute NAc slices, astrocytes increased internal Ca^{2+} levels in response to optogenetic stimulation of dopaminergic terminals via D1Rs [110]. In the prefrontal cortex (PFC), however, astrocytes seem to respond to dopamine not through D1Rs but through the G_q-coupled α1-adrenergic receptor [214], suggesting a heterogeneous function of astrocytic D1Rs in different brain regions. In neurons, D1Rs are often regarded as G_s-coupled GPCRs that increase cAMP activity through activation of adenylyl cyclase [215]. However, D1R-mediated Ca^{2+} activity in astrocytes requires IP3R2, indicating the involvement of the G_q-signaling pathway [110,216,217]. Thus, the G_q-Ca^{2+} pathway may be the dominant mediator of D1R signaling in astrocytes. In addition, D1Rs may operate not alone but as heterodimers with other GPCRs in astrocytes. For example, it has been shown that D1Rs can form heterodimers with adrenergic receptors in cell culture [218–221], and the colocalization of these receptors is found in cortical neurons [222]. Such a receptor–receptor interaction has been hypothesized to be a key feature of dopamine receptors in astrocytes but remains to be tested experimentally [223].

NAc astrocytes decrease their basal activity levels after cocaine SA [224], which may be a result of dysregulated dopamine tone after cocaine abstinence [225,226]. In brain slices, acute dopamine exposure—either through optogenetic stimulation of VTA terminals or bath application—increases the probability of Ca^{2+} events in NAc astrocytes [61,110]. While strong evidence indicates that dopamine-induced astrocytic Ca^{2+} activities are mediated by D1Rs, transgenic deletion of D1Rs in astrocytes elevates the basal level of Ca^{2+} events [110], suggesting a complex functionality of astrocytic D1Rs in the NAc. Nonetheless, recent studies have revealed key functional implications of D1R-induced astrocytic activities in the NAc [110,227]. More specifically, activation of astrocytic D1R-IP3 signaling induces adenosine release, which in turn activates A_1 receptors on adjacent presynaptic

nerve terminals, resulting in decreased glutamatergic transmission to NAc MSNs (Fig. 1). Behaviorally, mice that lack functional astrocytic IP3R2 or D1Rs show attenuated behavioral sensitization to amphetamine, indicating that astrocytic D1Rs plays a role in the development of drug-induced neuroplasticity and associated behaviors.

5. Final words

Over the past several decades, enormous strides have been made in neuroscience in terms of our collective understanding of how astrocytes contribute to behavior. Aided by rapid advancements in imaging technologies and astrocyte-specific tools, we are now able to re-examine and bridge previous results through a new lens. As these tools become more precise in their ability to manipulate astrocyte functions in brain slices and *in vivo*, we stand to gain increased insight into how basic biological components, such as GPCRs, differ between neurons and astrocytes. With this new information, we will find ourselves in a better position to understand brain disorders such as SUDs and develop novel therapeutic avenues to treat them.

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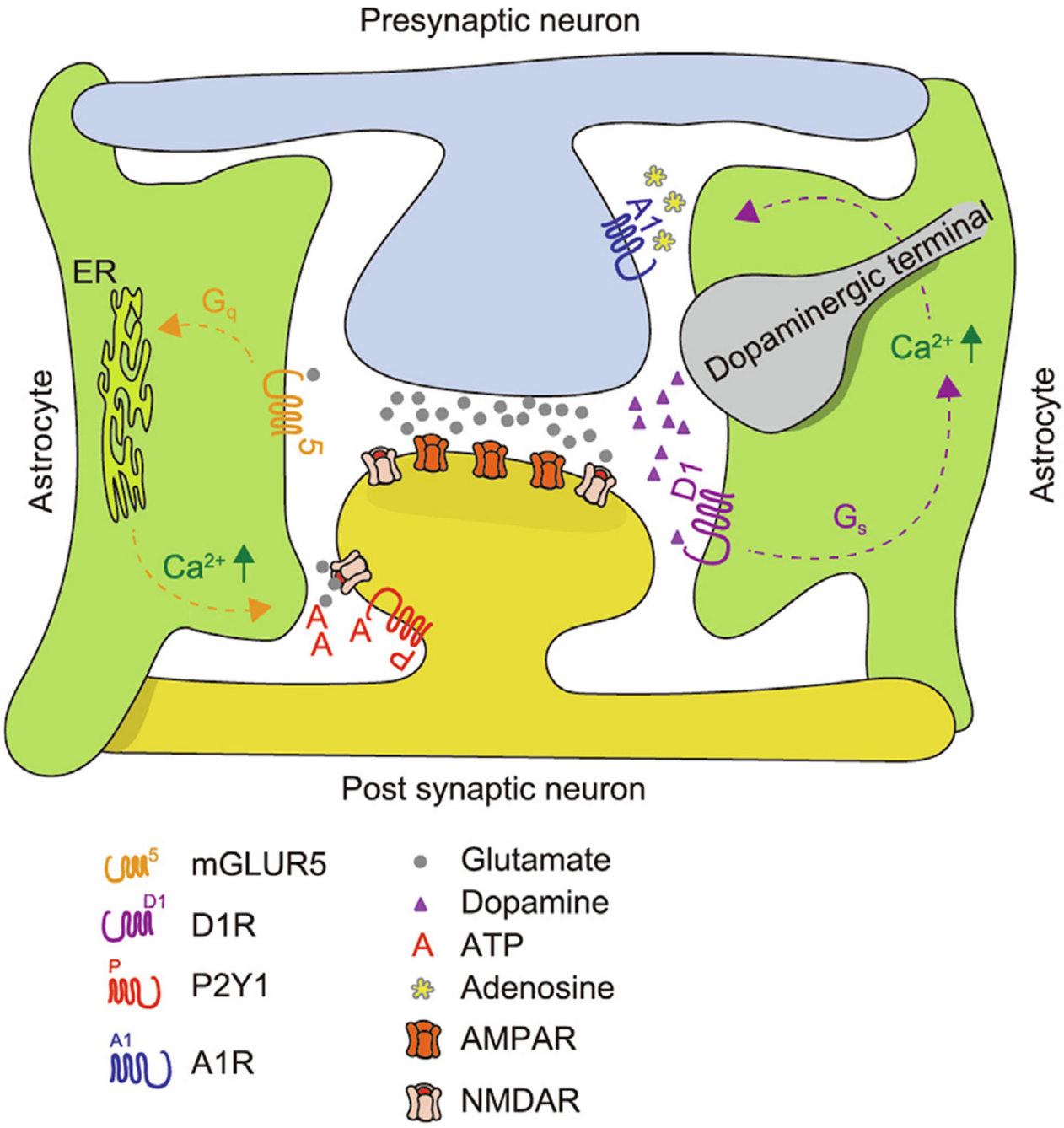

Fig. 1.

Astrocytic mGLUR5 and dopamine D1 signaling. Illustration showing that astrocytically expressed mGLUR5 and dopamine D1R and their coupled Ca^{2+} signaling triggers the release of astrocytic factors (e.g., ATP), which in turn regulate neuronal substrates to influence synaptic transmission.