REVIEW

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Astrocytic neurotransmitter receptors (astro-glioreceptors) and their role in neuroplasticity

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Astrocytes express a set of neurotransmitter receptors (glioreceptors) that enable them to regulate synaptic transmission and neuroplasticity, and to function as integral partners in synaptic signaling and the modification of neural circuits. This review presents the current understanding of how glioreceptors on astrocytes (astro-gliorecptors) mediate bidirectional communication between neurons and glia across major neurotransmitter systems. The review focuses on receptors for glutamate, GABA, acetylcholine, monoamines, neuropeptides, opioids, and purines. Through these receptors, astrocytes can modulate synaptic strength, LTP and LTD expression, network dynamics, and state-dependent modulation of arousal and reward circuits. Despite potentially having lower receptor density than neurons, astrocytes can amplify their functional impact through unique structural properties, such as extensive process arborisation, contact with thousands of synapses, and the formation of electrically coupled syncytia that propagate calcium waves across neural networks. Metabolic integration *via* glycogen regulation, lactate production, and gliotransmitter release modulates neuronal excitability and synaptic strength. Therefore, astrocytes can be viewed as integrators of neuronal activity patterns and gatekeepers of experience-dependent plasticity, essential for maintaining synaptic homeostasis and enabling adaptive behavioral responses. Astro-glioreceptors dysfunctions contribute to neurological and psychiatric disorders, including Alzheimer's disease, Parkinson's disease, epilepsy, and depression. Therefore, targeting specific glioreceptor subtypes represents a promising therapeutic strategy for modulating neural circuits while minimizing neuronal side effects.

Key words: astrocytes, neurotransmitter receptors, glioreceptors, astro-glioreceptors, plasticity

INTRODUCTION

The involvement of neurotransmitter receptors on glial cells in brain plasticity is an effect expected from theoretical perspectives and empirical observations, yet remains underexplored in the literature. While the term "gliotransmitters" has become well-established in neuroscience literature to describe neurotransmitter-like substances released by glial cells, the functional counterpart—neurotransmitter receptors expressed on these cells—has not yet been formally unified under a single nomenclature. We propose the term "glioreceptors" (by analogy with gliotransmitters) to denote neurotransmitter receptors on glial cells, thereby establishing a conceptual framework that reflects the active role of these cells as both receivers and integrators of synaptic signals. As the understanding of glioreceptors expression patterns, signaling cascades, and functional consequences continues to expand, mounting evidence demonstrates that neurotransmitter signaling *via* these receptors can profoundly influence neuroplasticity—spanning from local dendritic remodeling to large-scale network reorganization. Astrocytes, in particular, represent key cellular targets for multiple neurotransmitter systems and exhibit a remarkable capacity for integrating synaptic information through diverse receptor repertoires. In this review, we synthesize current knowledge of astrocytic glioreceptors

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(astro-glioreceptors) across the major neurotransmitter systems and discuss emerging evidence for their roles in various forms of neuroplasticity.

Astrocytes in Neuroplasticity

Astrocytes, which are increasingly recognized as important players in synaptic plasticity, learning, and memory, play a critical role in synaptogenesis during brain development (Pfrieger & Barres, 1997), and shape brain connectivity by the developmental elimination of excessive innervation (Nimmerjahn et al., 2009). However, the importance of astrocytes for synapse regulation is not limited to developmental stages, as they are also involved in learning–related phenomena and reactive, trauma-induced synaptogenesis (Falo et al., 2008).

The role of astrocytes in cortical plasticity was first demonstrated by pioneers in the field, Muller and Best (1989), who injected immature astrocytes into the visual cortex of adult cats. This approach enabled them to restore juvenile-like ocular dominance plasticity. Yang et al. (2003) demonstrated in cell cultures that synaptic plasticity depends on D-serine release from astrocytes, thereby controlling NMDA receptor activation. In 2018, Adamsky and colleagues showed that astrocyte activation can induce NMDA-dependent LTP *via* increased spontaneous release of synaptic vesicles in hippocampal slices *in vitro*.

The importance of astrocytic contribution to the learning process was further documented by Han et al. (2013), who observed an increase in synaptic plasticity and learning in mice implanted with human astrocytes, which propagate calcium waves much faster than rodent astrocytes. These mice exhibited improved learning and memory in the auditory and contextual fear conditioning paradigms, as well as better performance in the Barnes maze and the object-location memory task. Moreover, several other studies demonstrated that astrocytes play a significant role in memory formation. For example, *in vivo* activation of astrocytes using the DREADD technique during memory acquisition has been shown to improve contextual memory and cognitive performance in mice, whereas their inhibition impairs remote memory, affecting neighboring neurons based on their projection targets (Adamsky et al., 2018; Kol et al., 2020). Additionally, recent findings by Williamson et al. (2025) suggested that conditioning learning activates a specific population of astrocytes positioned adjacent to the neurons that form the memory engram. The reactivation of these astrocytes increased the frequency of postsynaptic potentials in engram-integrated neurons, thereby triggering recall of the memory.

The strongest interactions between astroglia and neurons are most likely to occur in tripartite synapses, where astrocytes ensheath neurons, thereby having a better position to modulate synaptic activity and control synaptic structure (Araque et al., 1999; Murai et al., 2003). The activation of neurotransmitter receptors in astrocytes increases intracellular calcium levels, which, in turn, triggers the release of gliotransmitters (Fellin, 2009). Even though there are fewer astrocytes than neurons in the brain (Gundersen et al., 2015; Shapson-Coe et al., 2024), their structure and presence of fine perisynaptic processes strongly potentiate their action. Since they form extensive, electrically coupled syncytia, astrocytes can amplify and extend the effects of glioreceptors stimulation, spreading the calcium waves, which gives them the power to monitor and modulate enormous numbers of synapses. It is estimated that one astrocyte in the human brain cortex can contact approximately 2 million synapses (Oberheim et al., 2009). The integrity of the astrocytic syncytium is crucial for neuroplasticity, as decoupling of astrocytes within the syncytium in the hippocampus impairs sensorimotor performance, spatial learning, and memory (Hosli et al., 2022).

Possessing an extensive set of neurotransmitter receptors, astrocytes can register both the direct and indirect effects of neuronal activity, and they can function as signal integrators. Results by Lines et al. (2024) demonstrated that the sensory-evoked calcium signal, which was initially limited to separate domains of astrocytic arborisation, dynamically propagated throughout the entire astrocyte after reaching a spatial threshold defined as approximately 23% of subcellular domains being co-active. This means that astrocytic response reflects the activity of a population of neurons and integrates many inputs distributed over space and time within seconds-long windows (Lines, 2025).

Astro-glioreceptors in Brain Plasticity

Through a wide range of neurotransmitter receptors, astrocytes can detect neuronal activity and respond by releasing gliotransmitters (e.g., glutamate, ATP/adenosine, D-serine, GABA), taking part in bidirectional communication between neurons and glia (Porter & McCarthy, 1997; Araque et al., 2001; Verkhratsky & Nedergaard, 2018). Therefore, although once considered mere supporting cells, astrocytes are now recognized as active regulators of synaptic function and plasticity (Perea et al., 2009), playing a crucial role in synaptic signaling and long-term synaptic changes (Araque et al., 1999).

Below, we review recent advances for each central neurotransmitter system, highlighting how astrocyte receptor activation influences synaptic plasticity, and cognitive functions. It is essential to note that the effects of activating glioreceptors may vary depending on the brain region, the specific receptors involved, and the context of neurotransmitter release.

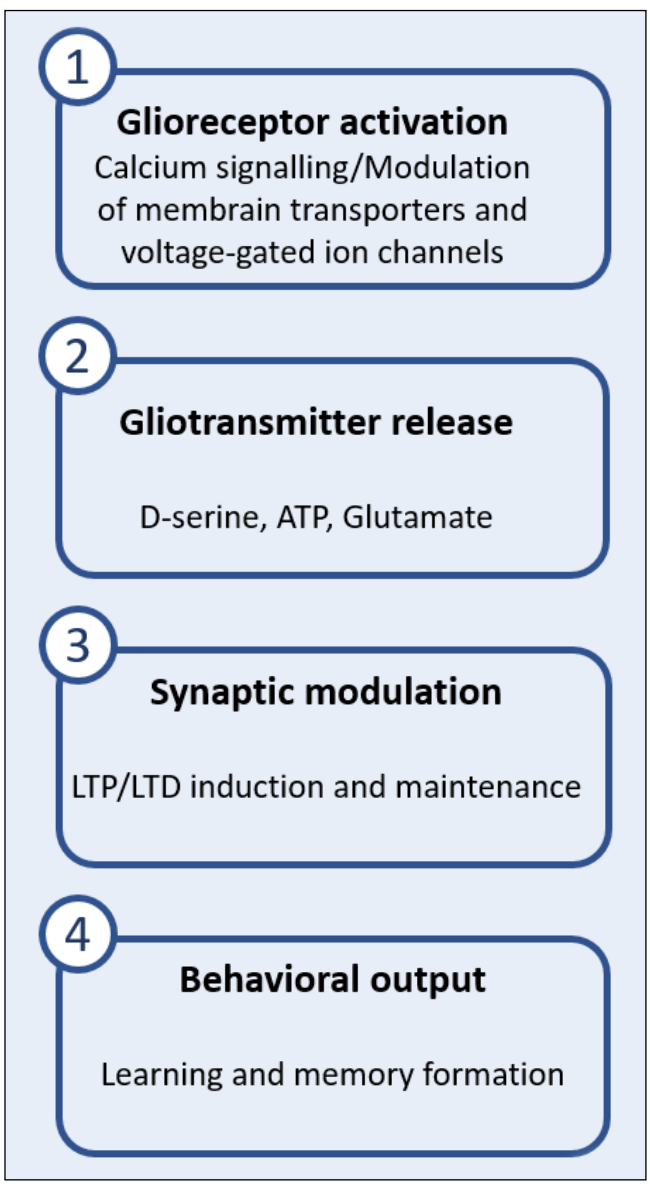

Fig 1. Glioreceptors-to-behavior signaling.

Historically, the story of glioreceptors began several decades ago, with pioneering studies by Bowman and Kimelberg (1984), Kettenmann et al. (1984), and Gilbert et al. (1984). They demonstrated electrophysiological responses to glutamate in astrocytic and oligodendrocytic cell cultures. This research confirmed the presence of neurotransmitter receptors on glial cells and laid the groundwork for subsequent investigations that identified and characterized several neurotransmitter receptors on astrocytic membranes. Further studies demonstrated their active participation in neurotransmission (Deitmer et al., 1998; Araque et al., 1999; Nedergaard et al., 2003; Perea & Araque, 2005; Volterra & Meldolesi, 2005; Verkhratsky, 2006).

It was also documented that neurotransmitter signaling through glioreceptors can influence various aspects of astrocyte activity, mainly calcium influx and release from intracellular stores (Perea & Araque, 2007), but also the release of gliotransmitters (Santello et al., 2019), and other neuroactive molecules (Pascual et al., 2005), which are able to affect astrocytic morphology and neurovascular coupling. These findings emphasize the essential role of astrocytes in regulating neural circuits and maintaining homeostasis within the central nervous system. Obviously, not only is the number of receptors important, but also their allocation to different subcellular compartments. Moreover, the density of receptors at a given site may be significant for particular neuronal-glial interactions.

Glutamate Receptors

Astrocytes demonstrate a strong reactivity to extracellular glutamate by engaging both metabotropic and ionotropic glutamate receptors.

Ionotropic Glutamate Receptors

All three types of glutamate ionotropic receptors (AMPA, NMDA, and kainate receptors) are expressed in astroglia, although this expression differs across brain regions. Early experiments by Bowman and Kimelberg (1984) and Kettenmann et al. (1984) revealed that excitatory amino acids depolarize rat brain astrocytes in primary culture, and in 1988, Sontheimer et al. recorded AMPA receptor currents from cultured astrocytes. Subsequent studies using intracellular recordings in brain slices have shown that functional AMPA receptors are present in most brain structures (Burnashev et al., 1992; Droste et al., 2007; Höft et al., 2014); however, their subunit composition varied across brain regions. For example, the expression of the GluR2 subunit, which regulates calcium permeability, was strong in the hippocampus (Seifert & Steinhauser, 2001), but not in the cortex, where GluR1 and GluR4 predominated (Conti et al., 1994). The hippocampal CA1 field was initially found to lack astrocytic AMPA receptors (Berglas & Jahr, 1998).

However, Zhou and Kimelberg (2001) identified two subpopulations of astrocytes in CA1, one with high and the other with negligible AMPAR expression and glutamate-induced membrane currents. In cortical astrocytes, activation of AMPARs produced the fast component of glutamate-induced current (Lalo et al., 2011).

NMDA receptors, on the other hand, were not identified in early electrophysiological studies on astrocytic membranes in primary cell cultures (Backus et al., 1989; Bowman & Kimelberg, 1984). Instead, their presence on astrocytes was detected by immunocytochemistry (Conti et al., 1996) and confirmed by in situ hybridization in many brain structures (Conti et al., 1994). Only later electrophysiological studies by Schipke et al. (2001) showed that activation of NMDARs evoked membrane currents and increased cytosolic Ca^{2+} in cortical astrocytes. Verkhatsy and Kirchoff, in 2007, working with freshly dissociated cortical astrocytes derived from the mouse brain, established that astrocytic NMDRs were modulated by glycine and blocked by MK801 and AP5, mirroring the effects observed in neurons. Interestingly, unlike neuronal NMDRs, astroglial NMDARs were found to be insensitive to magnesium block (Lalo et al., 2006; Ziak, 1998), likely due to the expression of the NR3A subunit (Henson et al., 2010). Studies by Lee et al. (2010) on primary astrocytic cultures from the human cortex demonstrated the astrocytic expression of all known NMDA receptor subunits. As reviewed by Skowronska et al. (2019), the astrocytic NMDAR is composed of the same seven subunits as the neuronal receptor; however, their configuration and assembly can differ across species, brain regions, and astrocyte maturation. Kainate receptors (KARs), assembled as homo- and heteromers from five subunits (GluR5, GluR6, GluR7, KA1, and KA2), represent perhaps the most enigmatic component of the astrocytic glutamate receptor repertoire. While these receptors have been identified in astrocytes at both transcript and protein levels (Jabs et al., 1994; Garcia-Barcina & Matute, 1996; Porter & McCarthy, 1997; Ziak et al., 1998), their functional significance remains largely unexplored. The upregulation of all five KAR subunits observed in reactive astrocytes following status epilepticus suggests that these receptors may serve as sensors of pathological glutamate spillover (Vargas et al., 2013).

Astroglial Ionotropic Glutamate Receptors in Neuroplasticity

Glial AMPARs were shown to be involved in cerebellar neuroplasticity, where their activation can modulate synaptic structure and is necessary for ensheathing Purkinje cell dendrites with fine glial processes (Baltrons & Garcia, 1997; Iino et al., 2001). In adult mice, AMPAR inactivation led to retraction of glial processes, accompanied by behavioral impairments in fine motor coordination (Saab et al., 2012).

The role of CA1 pyramidal neurons' synaptic strength tuning by astrocytic NMDARs was described by Letellier et al. (2016) and Chipman et al. (2021). The first one demonstrated that maintaining differences in the presynaptic strengths of two inputs to a pyramidal neuron relies on calcium signaling in astrocytes, initiated by astrocytic NMDAR activation. When these receptors were blocked or deleted, the strength of the converging inputs quickly became equal, losing their original differences. Chipman and colleagues (2021) suggested that presynaptic strength diversity strongly influences the expression of long-term synaptic plasticity, which is essential for learning and memory. They claim that astrocyte NR2C NMDARs are a key player in linking the regulation of synaptic strength distribution to the expression of synaptic plasticity that promotes optimal circuit performance. In behavioral and pharmacological experiments, astrocytic NMDA receptors with the NR2C subunit facilitated the extinction of conditioned fear in rats (Shelkar et al., 2021). The same group also found that cocaine exposure upregulated NR2C subunit expression and increased NMDAR currents in astrocytes (Shelkar et al., 2022), linking astrocyte receptors to mechanisms of addiction.

Metabotropic Glutamate Receptors

Astrocytic Ca^{2+} responses to neuronal activity are primarily attributed to the activation of metabotropic glutamate receptors (mGluRs) (Pasti et al., 2001), which in turn promote the release of gliotransmitters, thereby providing feedback control of synaptic transmission (Panatier et al., 2011; Covelo & Araque, 2018). Among astroglial metabotropic glutamate receptor (mGluR) subtypes, GluR3 is the most abundant in both young and adult brains (Sun et al., 2013), whereas GluR5 is more prevalent during development and then downregulated in adulthood (Panatier & Robitaille, 2016). It may reappear in pathological conditions, such as allodynia (Danjo et al., 2022) or Alzheimer's disease (Yang et al., 2025). The functional consequence of mGluRs activation is the release of calcium from intracellular stores (Kellner et al., 2021), but Vanzulli and Butt (2015) identified the functional expression of group I mGluRs in white matter astrocytes, whose activation helps protect astrocytes from ischemic damage.

Astroglial mGluRs in Neuroplasticity

The role of astroglial metabotropic glutamate receptors in neuroplasticity has been recognized for both synaptic plasticity and developmental changes in synaptic morphology. Their activation in astrocytes leads to Ca^{2}+-dependent release of gliotransmitters, such as D-serine, glutamate, and ATP, which can gate synaptic LTP/LTD and metaplasticity (Cavaccini et al., 2020). Through these mechanisms, astrocytes contribute to learning-related plasticity in memory circuits. Blocking astrocytic mGluR5 or astrocyte Ca^{2}+ signaling prevents adenosine/A1Rs-dependent LTD in corticostriatal synapses. Conversely, chemogenetic stimulation of astrocyte Gq receptors (mimicking mGluR5 activation) is sufficient to induce the phenomenon *via* adenosine A1 receptors (Cavaccini et al., 2020). In the hippocampus, Lalo and Pankratov (2022) reported that mGluRs stimulated the release of ATP from astrocytes, which can directly activate postsynaptic P2X receptors in the hippocampal and neocortical neurons, possibly affecting the formation of LTD. Expression of astrocytic mGluR5 is upregulated early in Alzheimer's disease, and Yang et al. (2025) suggested that it drives the development of the disease. Consequently, they found that reducing astrocytic mGluR5 in mouse models of Alzheimer's disease rescued cognitive functions.

Furthermore, during brain development, astrocytic mGluR5 receptors are essential for the functional maturation of astrocytes. Their removal is associated with deficits in astrocytic process arborisation and in the expression of glutamate transporters (Morel et al., 2014).

In astrocyte culture, mGluR3 and mGluR5, which are localized in fine peripheral astrocyte processes, respond to glutamate by rapidly inducing their motility (Lavialle et al., 2011). Both receptor types are crucial during the early development of auditory pathways, where they detect local glutamate transients associated with spontaneous burst activity, thereby contributing to the maturation and structural completion of tripartite synapses in this sensory pathway (Sanchez et al., 2007).

GABA Receptors

GABA receptors (GABARs) on astrocytes are present in many CNS structures and are located on the soma, the processes surrounding synapses, and the endfeets on blood vessels (Nilsson et al., 1993; Charles et al., 2003; Meier et al., 2008). Astrocytes express both GABAA and GABAB receptors, which enable them to regulate extracellular GABA levels through uptake transporters and catabolic enzymes (Verkhratsky & Nedegaard, 2018). In this sense, astrocytes can be considered GABAceptive cells. The activation of GABAARs on astrocytes opens voltage-gated calcium channels, leading to the influx of extracellular Ca^{2}+ into the cell, which, in turn, affects astroglial glutamate and ATP release (Liu et al., 2022). In contrast, activation of GABABRs induces the release of Ca^{2}+ from the intracellular pool (Perea et al., 2016; Covelo & Araque, 2018). Astrocytes can synthesize and release GABA into the extracellular space, thereby tonically activating high-affinity GABAA receptors by volume transmission (Lee et al., 2010; Ishibashi et al., 2019).

Astroglial GABARs in Neuroplasticity

During brain development, GABA receptor activity promotes astrocyte morphological differentiation, thereby increasing the complexity of astroglial processes (Mong et al., 2002; Runquist & Alonso, 2003). Since this effect can be blocked by GABAAR antagonists, the involvement of those receptors in GABA-induced neonatal astrocyte differentiation is crucial (Matsutani & Yamamoto, 1997).

At the network level, astrocytic GABA signaling contributes to plastic changes in oscillatory activity and neuronal excitability.

It was found that the ablation of GABAB receptors in medial prefrontal cortex astrocytes altered cortical neurons' low-gamma oscillations and firing properties, revealing the importance of GABAB receptors in maintaining brain rhythms (Mederos et al., 2021). This ablation also affected neuroplasticity, disturbed goal-directed behaviors, caused impairment of working memory, enhanced exploration of the arena, and lowered anxiety levels in an elevated plus maze (Mederos et al., 2021). As the main reservoir for extracellular GABA clearance, astrocytes can influence the duration of inhibitory postsynaptic currents and the level of tonic inhibition on neurons (Park et al., 2025). By sensing GABA (and often co-released peptides) from inhibitory neurons, astrocytes can thus trigger many feedback signals – notably ATP/adenosine or glutamate release – that modulate GABAergic synaptic strength over the long term.

Acetylcholine Receptors

Astrocytes express both major classes of acetylcholine receptors (AChRs); however, their distribution and functional properties exhibit significant regional vari-

ation, reflecting the diverse roles of cholinergic signaling in brain plasticity.

Nicotinic Acetylcholine Receptors

Nicotinic acetylcholine receptors (nAChRs) on astrocytes function as ligand-gated ion channels that mediate rapid calcium influx upon activation. Multiple nicotinic receptor subunits have been identified in astrocytes across various brain regions, with α3, α4, β2, and α7 subunits being mostly expressed in cortical and hippocampal astrocytes (Graham et al., 2003; Sharma & Vijayaraghavan, 2001). Predominant β2 subunit expression in the ventral tegmental area (VTA) was found in approximately 45% of astrocytes, while in the locus coeruleus, expression of all nicotinic subunits was lower than in VTA (Gao et al., 2024).

The α7-containing nicotinic receptors on astrocytes play a critical neuroprotective role by inducing the release of glial cell-derived neurotrophic factor and participating in the regulation of synaptic AMPA receptor trafficking (Takarada et al., 2012; Wang et al., 2003).

Astroglial nAChRs in Neuroplasticity

Early research on astrocytic nicotinic receptors focused on the neuroprotective functions of α7-nAChRs. However, recent studies have revealed a crucial role for astrocytic α4-containing nicotinic acetylcholine receptors in the formation of associative memory in the mouse hippocampus. Ma and colleagues (2016) employed a trace fear conditioning paradigm to demonstrate that activation of these receptors in hippocampal astrocytes triggers calcium signaling, thereby regulating the supply of D-serine, a crucial co-agonist of the NMDA receptor. The specificity of this mechanism was revealed by targeted knockdown of α4-nAChRs in CA1 astrocytes, which reduced nicotine-evoked calcium transients and led to deficits in trace fear conditioning and memory, but did not affect contextual memory. The restoration of both LTP and memory formation through exogenous D-serine administration established the astrocytic α4-nAChR--D-serine-NMDA receptor axis as a fundamental mechanism for temporal information processing.

Muscarinic Acetylcholine Receptors

Astrocytes also express all muscarinic acetylcholine receptor (mAChRs) subtypes, including M1, M2, and M3 receptors, with distinct expression patterns across various brain structures (André et al., 1994). Oda et al. (2018) have shown that pial astrocytes demonstrate stronger M1 receptor immunoreactivity compared to protoplasmic astrocytes, suggesting functional specialization within astrocyte populations. The muscarinic receptor profiles of astrocytes differ significantly from those of neurons, indicating cell-specific specialization in cholinergic signaling (Murphy & Pearce, 1986).

Astroglial mAChRs in Neuroplasticity

Araque et al. (2002) demonstrated that hippocampal astrocytes in the stratum oriens region of the CA1 respond to ACh *via* mAChRs, which can evoke glutamate release and modulate neuronal activity. In this way, astrocytic muscarinic receptors may contribute to ACh-dependent synaptic plasticity. Later research has shown that the M3 muscarinic receptor subtype specifically promotes structural plasticity by regulating the expression and release of two extracellular matrix proteins fibronectin and laminin-1 (Guizzetti et al., 2008).

In vivo studies have established astrocytic muscarinic receptors as gatekeepers of cortical plasticity. The direct involvement of astrocytic mAChRs in cortical plasticity has been demonstrated in two experimental models: the responses of the somatosensory cortex to whisker stimulation (Takata et al., 2011) and the responses of the visual cortex to visual stimulation (Chen et al., 2012). The experiments of Takata and colleagues (2011) revealed that combining whisker stimulation with nucleus basalis magnocellularis stimulation augments whisker-evoked local field potentials. During this effect, calcium levels in astrocytes are elevated. Calcium rise is crucial in this type of synaptic plasticity as it does not occur in mice with deletion of astrocytic 1,4,5 triphosphate receptor type 2, in which astrocytic calcium elevations are diminished. This experience-induced astrocytic calcium elevation is blocked by mAChR antagonists.

Similar mechanisms operate in the visual cortex, where repeated stimulation of the nucleus basalis, paired with visual stimulation, leads to prolonged potentiation of visual responses in V1 excitatory neurons (Chen et al., 2012). Moreover, *in vivo* activation of mAChRs by sensory stimulation or electrical stimulation of the septal nucleus increases Ca^{2+} in hippocampal astrocytes and induces LTP of CA3-CA1 synapses (Navarrete et al., 2012). Those results indicate that the astrocyte Ca^{2+} signal, depending on cholinergic activation, is required for hippocampal LTP, thus proving that astrocytes are essential elements in synaptic plasticity.

Noradrenaline Receptors

Already in the 1990s, electron microscopic studies demonstrated the presence of both α- and β-adrenergic receptors in cortical astrocytic membranes (Aoki, 1992), and this finding was subsequently confirmed in many brain regions (Hertz et al., 2010; Wahis & Holt, 2021). The functional significance of astrocytic noradrenergic receptors (ARs) is highlighted by their greater sensitivity and stronger calcium responses than those of neurons (Pankratov & Lalo, 2015). Astrocytic α1 adrenergic receptors (α1-ARs) mediate widespread calcium waves that propagate throughout cortical networks following sensory stimulation. This mechanism enables noradrenergic signaling to coordinate activity across extensive cortical areas. β-ARs activation and the associated increase in intracellular cAMP levels are, on the other hand, responsible for the so-called "background priming", which is the facilitation of the astrocyte calcium response evoked by a short pulse of NA, designed to mimic local release from locus coeruleus varicosities (Nuriya et al., 2017). Recent transcriptomic analyses have revealed heterogeneity in astrocytic noradrenergic receptor expression, with some cortical astrocytes lacking Adra1a transcripts entirely, suggesting the existence of functionally distinct subpopulations with differential sensitivity to neuromodulators (Reitman et al., 2023). Interestingly, the Human Protein Atlas data from Thul et al. (2017) reveal that neuron-associated RNAs are expressed in glial cells within the human cortex, challenging the traditional view of neuron-exclusive localization and suggesting broader functional roles in cortical cellular interactions. β1-ARs exhibit unique sex-dimorphic patterns in astrocytes, with 20-30% higher expression in females (Shrestha & Briski, 2025), and they play a crucial role in neuroinflammation and Alzheimer's disease pathology.

Astroglial ARs in Neuroplasticity

The functional importance of astrocytic noradrenergic signaling is demonstrated by studies showing that astrocyte-specific deletion of Adra1a impairs arousal-related cortical synchrony while enhancing arousal-driven neuronal activity (Reitman et al., 2023). Such state dependence suggests that noradrenergic α1-ARs activation level may set the "gain" of astrocyte contributions. Moreover, astrocytic noradrenergic receptors are essential for neocortical synaptic plasticity, as α1-ARs-mediated release of ATP from astrocytes can directly activate postsynaptic P2X receptors in neocortical neurons, and this cascade is involved in LTP induction in cortical slices, as it was abolished by the selective α1-adrenoreceptor antagonist (Pankratov & Lalo, 2015).

A recent paper by Dewa et al. (2025) postulates the role of the astrocytic *Adrb1* gene in noradrenergic β1-AR receptors in emotional memory recall. They showed that an ensemble of astrocytes, neighbouring an ensemble of neurons forming the fear memory engram, activates not during memory formation, but during recall. Fear conditioning triggers the expression of adrenoreceptor genes in ensemble astrocytes, which is likely to underlie β-AR-driven cAMP signaling during memory retrieval. Blocking this signaling impaired memory recall. Astrocytic β2-ARs in the hippocampus were found to be necessary for the consolidation of a fear-based contextual memory (Gao et al., 2016). These receptors regulate the learning-dependent release of lactate, which is crucial for forming a memory trace in a fear conditioning paradigm.

β-AR activation also induces a unique form of synaptic plasticity - EPSP-Spike potentiation – which is a long-lasting enhancement of neuronal excitability without changes in synaptic transmission strength (Trompoukis et al., 2024). The dysregulation of β2-ARs in astrocytes is associated with many diseases i.e., multiple sclerosis, Parkinson's disease, and Alzheimer's disease (Dong et al., 2012).

Dopamine Receptors

The elevation of intracellular Ca^{2+} in response to dopamine has been observed in astrocytes across various brain regions (Jennings et al., 2017; Pitolo, 2022; Corkrum, 2020), and it can be elicited by all five dopamine receptor subtypes (DARs: D1-D5). Particularly strong DARs expression was found in pial astrocytes and cortical layer I (Oda & Funato, 2023). In the basal ganglia, both transcript and protein levels confirmed comprehensive astrocytic DAR expression (Miyazaki et al., 2004). The differential expression of D1-like and D2-like receptors, their distinct coupling mechanisms, and their regional specialization create sophisticated networks for dopamine-mediated circuit modulation. Notably, astrocytic D2 receptors comprise approximately one-third of all D2 receptor binding sites in several species, indicating a substantial contribution to dopaminergic signaling (Khan et al., 2001). Dopamine activation of astrocytic receptors elicits robust calcium responses across various brain regions, exhibiting regional specificity patterns (Pittolo et al., 2022). *In vivo* 2P recordings of spontaneous calcium fluctuations in astrocytes from the prefrontal and visual cortex showed that the patterns and dynamics differed between the regions. Also, in the visual cortex, astro-

cytes responded to locomotion, while prefrontal astrocytes did not, but they responded to aversive stimuli. Moreover, it was found that dopamine activates noradrenergic receptor α1-AR on prefrontal astrocytes. Pittolo et al. (2022) suggested that sustained prefrontal astrocyte response to dopamine may underlie the mechanism of sustained response of PFC neurons in working memory tasks, to which dopamine reward signaling and noradrenergic arousal signaling may contribute. The finding that dopamine can activate astrocytic noradrenergic receptors in the prefrontal cortex but not in the visual cortex suggests region-specific interactions within this neurotransmitter system (Pittolo et al., 2022). The finding by Khan et al. (2001) that D2Rs-rich astrocytic processes surround the subset of interneurons with low or undetectable D2 receptor expression represents a sophisticated regulatory mechanism within the "tripartite synapse", in which astrocytes actively participate alongside pre- and post-synaptic neuronal elements in synaptic transmission and modulation.

Astroglial DARs in Neuroplasticity

Increasing evidence suggests that astrocytic DARs play a role in neuroplasticity by modulating dopamine release. In the nucleus accumbens, astrocytes respond to synaptically released dopamine by elevating calcium, triggering ATP and adenosine release, and subsequently activating presynaptic adenosine receptors to depress excitatory synaptic transmission (Corkrum et al., 2020). This establishes a negative feedback mechanism for synaptic regulation in reward circuits, with behavioral relevance demonstrated through behavioral psychostimulant effects of amphetamine.

Further studies by Requie et al. (2022) on the reward system examined the plasticity of glutamatergic synapses on VTA dopaminergic neurons. The plasticity of glutamatergic synapses onto VTA dopamine neurons depends on calcium elevations in astrocytes, mediated by co-localized D2 and CB1 receptors. Selective *in vivo* astrocyte activation increases dopamine neuron burst firing and induces locomotor hyperactivity (Requie et al., 2022). The modulatory role of astrocytic dopamine receptors was also found in the cerebellum. Recent experiments by Li et al. (2023) have found that activation of D1 receptors on Bergmann glia (BG) affects synaptic transmission and plasticity in Purkinje cells (PCs), as depolarization of a single BG induces a significant increase in the frequency of sEPSCs recorded in an adjacent PC. Ca^{2}+ increases in BGs are associated with locomotion, and consequently, D1 receptor knockout in mice decreases locomotor activity.

Serotonin Receptors

Astrocytes express multiple serotonin receptor subtypes (5-HTRs), each with distinct expression patterns and roles. All are G-protein-coupled receptors, and their stimulation activates cytosolic and nuclear signaling pathways, thereby altering cellular functions and gene expression.

The 5-HT1A receptor is found in approximately 60-80% of hippocampal astrocytes and shows particularly interesting age-dependent expression in the hippocampus and prefrontal cortex (Wu et al., 2024). They have neuroprotective effects by upregulating antioxidative molecules and promoting astrocyte proliferation (Miyazaki & Asanuma, 2016). The 5-HT2 receptor demonstrates moderate to high expression in astrocytes across multiple brain regions, including the medial prefrontal cortex and hippocampus (Zhang et al., 2010). These receptors are particularly important for calcium signaling and the IP3/DAG/PKC cascade, which directly influences synaptic plasticity mechanisms. Serotonin may affect cortical inhibition *via* 5-HT2A astrocytic receptors, which promote ATP release, thereby depolarizing inhibitory interneurons *via* purinergic receptors (Wotton et al., 2020). Consequently, increased activation of inhibitory interneurons leads to the release of GABA onto pyramidal neurons (Pacholko et al., 2020). The 5-HT4 receptor is expressed in approximately 33% of hippocampal astrocytes, where it couples to the Gα13-RhoA-ROCK signaling pathway to regulate cytoskeletal dynamics and synaptic transmission (Müller et al., 2021). These receptors form discrete clusters with a mean size of 136 ± 21 nm within individual astrocytes, suggesting specialized signaling microdomains.

The 5-HT5A receptors, localized on astrocyte cell bodies and processes, couple negatively to adenylyl cyclase and may regulate astrocyte physiology during reactive gliosis (Carson et al., 1996). The 5-HT6 receptor, uniquely expressed in the central nervous system, localizes to the primary cilia of neurons and astrocytes, with approximately 50% of receptors positioned near serotonergic axons (Dupuy et al., 2023).

Astroglial 5-HTRs in Neuroplasticity

Serotonin plays a crucial role in developmental synaptic plasticity in the CNS, with specific time windows during which serotonergic signaling is essential for normal plasticity. In young animals (P21), blocking 5-HT1A receptors in astrocytes facilitates LTD induction, while activation impairs it. Conversely, in adult animals (P60), 5-HT1A receptor blockade rescues impaired LTD. This age-dependent modu-

lation occurs through regulation of the excitatory/inhibitory balance, with 5-HT1A receptors primarily influencing GABAergic transmission frequency without affecting excitatory components (Wu et al., 2024). Astrocytic 5-HT1A receptors play a crucial role in fear memory extinction in mice, with conditional astrocytic knockdown impairing memory extinction (Wu et al., 2024). The 5-HT2A receptor pathway, signaling *via* IP3/DAG/PKC cascades, can facilitate LTD by promoting AMPA receptor internalization. The 5-HT4 receptor has been specifically implicated in hippocampal plasticity by regulating astrocytic morphology and synaptic function. Their activation triggers RhoA activity, leading to increased filamentous actin assembly and morphological changes, while simultaneously modulating presynaptic glutamate release at excitatory hippocampal synapses as evidenced by increased mEPSC frequency and reduced paired-pulse ratios (Müller et al., 2021).

Clinical relevance is demonstrated by the involvement of astrocytic serotonin receptors in depression, where fluoxetine specifically increases 5-HT2B receptor expression in astrocytes but not in neurons, thereby reversing the stress-induced decrease in 5-HT2B mRNA (Peng et al., 2014).

Somatostatin Receptors

Astrocytes express multiple somatostatin receptor (SSTRs) subtypes with distinct regional and developmental expression patterns. Transcriptional analysis has identified SSTR1, SSTR2, and SSTR4 receptor subtypes in cortical astrocytes, with SSTR2 being the most abundantly expressed subtype across most brain regions (Feindt et al., 1995; Schulz et al., 2000). Immunohistochemical studies reveal a strategic subcellular localization, with somatostatin receptors distributed on both astrocyte cell bodies and their fine processes, particularly in perisynaptic astrocytic processes that contact somatostatin-positive interneuron terminals (Viollet et al., 2008).

Astrocytic SSTRs are G-protein-coupled receptors that are primarily coupled to Gi/Go proteins, leading to inhibition of adenylyl cyclase and subsequent reduction in cAMP levels. However, recent research has revealed that the functional responses are considerably more complex than simple cAMP modulation. The work by Henriques et al. (2022) demonstrated that, while somatostatin contributes to astrocyte calcium responses in the visual cortex, these responses are primarily mediated through GABAB receptor activation

Table 1. Astro-glioreceptor systems comparison.

Neurotransmitter	Astrocytic Receptor Subtypes	Primary Signaling Mechanism	Impact on Neuronal Plasticity	Clinical Relevance
Glutamate	AMPA, NMDA, kainate, mGluR3/5	Ca^{2+} elevation *via* influx/IP3	LTP/LTD, structural plasticity	Alzheimer's disease, addiction, epilepsy, allodynia
GABA	GABAA, GABAB	Ca^{2+} elevation *via* depolarization/IP3	Oscillations, developmental plasticity, excitation-inhibition balance, goal-directed behaviors, working memory	Epilepsy, anxiety disorders
Acetylcholine	α4-nAChR, M1/M3-mAChR	Ca^{2+} elevation *via* influx/IP3, cAMP modulation	Memory gating, associative learning, fear conditioning, structural plasticity	Attention deficits, learning disorders, dementia
Noradrenaline	α1, β1/2	Ca^{2+} elevation, cAMP signaling, calcium wave propagation	Arousal, LTP induction, emotional memory recall, EPSP-potentiation	Depression, ADHD, Alzheimer's disease, Parkinson's disease
Dopamine	D1-D5	Ca^{2+} elevation, cAMP/PKA modulation	Reward-related plasticity, motor control	Addiction, Parkinson's disease
Serotonin	5-HT1A, 5-HT2A/C, 5-HT4	Ca^{2+} elevation/ IP3', cAMP modulation	Morphology, mood regulation, fear memory extinction, morphological plasticity	Depression, anxiety, developmental plasticity deficits
Somatostatin	SSTR1-5	Ca^{2+} elevation (GABAB-mediated), cAMP inhibition	Attention-related plasticity, interneuron coupling, State-dependent modulation, memory consolidation	Alzheimer's disease, epilepsy, cognitive decline
Opioids	Mu, delta, kappa	Ca^{2+} elevation, glutamate release, cAMP modulation	Reward learning, conditioned place preference	Addiction, chronic and neuropathic pain
Purines	P2X1-7, P2Y1/2/4/6/11-14, A1/A2A/A2B/A3	Ca^{2+} elevation *via* influx/IP3, cAMP modulation	LTP/LTD regulation, synaptic scaling, excitation-inhibition balance, heterosynaptic depression, developmental plasticity	Epilepsy, stroke, neurodegenerative diseases, neuropathic pain, cognitive dysfunction

rather than through direct SSTR signaling. This discovery reveals an essential principle of astrocyte-interneuron communication: somatostatin-positive interneurons co-release both GABA and somatostatin, creating a dual signaling system. In this system, GABA provides the primary drive to astrocytes through GABAB receptor-mediated calcium release from intracellular stores, while somatostatin provides modulatory fine-tuning of the astrocytic response. The somatostatin component appears to modulate the duration, amplitude, and spatial extent of GABAB-mediated calcium responses, creating a temporally sophisticated signaling mechanism.

Astroglial SSTRs in Neuroplasticity

The functional significance becomes apparent when considering that somatostatin-positive interneurons are preferentially activated during specific behavioral states and learning paradigms. During periods of focused attention, sensory processing, and active learning, these interneurons exhibit increased activity, which, in turn, increases somatostatin release and astrocytic receptor activation. This creates state-dependent modulation of astrocyte function that could contribute to attention-related plasticity mechanisms and facilitate memory consolidation, thereby creating permissive conditions for plasticity induction and maintenance. Altered calcium dynamics influence the release of gliotransmitters, including D-serine, glutamate, and ATP, which are essential for various forms of synaptic plasticity. Alterations in somatostatin signaling are implicated in various neurological and psychiatric conditions, with corresponding changes in astrocytic receptor function. In Alzheimer's disease, somatostatin-positive interneurons are particularly vulnerable to degeneration, and somatostatin levels are significantly reduced in affected brain regions (Davies et al., 1980). This loss could disrupt normal astrocyte-interneuron communication, contributing to the synaptic dysfunction and cognitive decline observed in the disease. In epilepsy models, somatostatin receptor expression on astrocytes is altered, with some studies showing upregulation that may represent a compensatory response to increased interneuron activity and altered circuit dynamics (Viollet et al., 2008).

The functional significance of astrocytic SSTRs is amplified by their integration with other neurotransmitter receptor systems. The close coupling with GABAB receptors creates a co-detection system for inhibitory interneuron activity, while potential interactions with other Gi/Go-coupled receptors can create complex signaling networks within individual astrocytes. Somatostatin receptors on astrocytes represent a sophisticated mechanism for detecting and integrating inhibitory interneuron activity, particularly from somatostatin-positive GABAergic interneurons that serve as critical regulators of cortical circuit dynamics and plasticity.

Opioid Receptors

Astrocytes express mu, delta, and kappa opioid receptors (OPRs) across multiple brain regions, including the hippocampus, nucleus accumbens, periaqueductal gray, amygdala, and arcuate nucleus (Eriksson et al., 1992; Nam et al., 2019; Won et al., 2023). The delta-opioid receptor has been linked to the processing of neuropathic pain and analgesia in mice (Reiss et al., 2021) as well as neuroprotection through upregulation of glutamate transporters (EAAT1 and EAAT2) *via* the MEK-ERK-p38 pathway (Liang et al., 2014). Most functional studies, however, have focused on mu opioid receptors (MORs). Using the combination of calcium imaging and whole-cell patch clamp electrophysiology in the nucleus accumbens, Corkrum et al. 2019 showed that astrocytic MORs activation induces gliotransmitter glutamate release, which evokes slow inward currents in neurons through NMDA receptor activation, thereby establishing astrocyte-to-neuron opioid - glutamate signaling pathways (Woo et al., 2018; Corkrum et al., 2019). This astrocyte-released glutamate also activates presynaptic mGluR1 receptors, increasing release probability and potentiating synaptic transmission at Schaffer collateral-CA1 synapses.

Astroglial OPRs in Neuroplasticity

Behavioral studies demonstrate that astrocytic MORs activation is necessary for the acquisition of conditioned place preference, suggesting that enhanced synaptic transmission and plasticity contribute to the formation of reward-associated memory (Nam et al., 2019). However, the complexity of opioid receptor function is highlighted by findings that MORs knockdown produces normal morphine-induced place preference but stronger place aversion (Murianova et al., 2023).

Purine Receptors

Purinergic signaling may be the most ubiquitous mechanism of intercellular communication in the nervous system, mediating communication between neurons and glia. Purinergic receptors (PRs) are classified into two major families: P1 receptors, which are selec-

tive for adenosine, and P2 receptors, which primarily respond to ATP and ADP. Astrocytes express nucleotide receptors of both families on their surface, positioning them as key responders to purinergic signaling within neural circuits.

P2 receptors are further divided into two subfamilies: P2X and P2Y receptors (del Puerto et al., 2013). P2X receptors, of which seven subtypes have been identified, are ligand-gated ion channels whose activation by ATP increases Na^+, K^+, and Ca^{2+} permeability, promoting rapid changes in membrane potential which may lead to release of excitatory amino acids or GABA (Illes, 2012). Notably, P2X1/5 receptors also mediate spontaneous "miniature" postsynaptic currents in astrocytes in cortical slices (Verkhratsky & Nedergaard, 2018).

P2Y receptors are metabotropic, G-protein-coupled receptors represented by eight subtypes. Typically, P2Y1, P2Y2, P2Y4, and P2Y6 are coupled to Gq proteins and activate phospholipase C, whereas P2Y12, P2Y13, and P2Y14 couple to Gi proteins, which results in the inhibition of adenylyl cyclases and the reduction of intracellular cAMP (del Puerto et al., 2013). This diversity in receptor subtypes and their downstream signaling pathways equips astrocytes with sophisticated tools to modulate neuronal function.

Stimulation of astrocytic P2Y receptors leads to PLC-dependent inositol triphosphate (InsP3) production and Ca^{2+} signals originating from InsP3-induced calcium release from endoplasmic reticulum storage. This triggers calcium waves, which in turn stimulate the release of glutamate, ATP, and other signaling molecules from astrocytes (Fields & Burnstock, 2006). ATP released from astrocytes *via* P2Y activation facilitates recruitment of synaptic neuronal P2X receptors into excitatory synapses, establishing a positive feedback mechanism that amplifies purinergic signaling at active synapses.

Activation of P2X neuronal receptors, on the other hand, leads to down-regulation of postsynaptic NMDA receptors. In this way, the synergistic action of glia- and neuron-derived ATP can modulate the efficacy of excitatory synapses and thereby play an important role in glia-neuron communication and synaptic plasticity (Lalo et al., 2016). In parallel, Pougnet et al. (2014) demonstrated that postsynaptic P2X receptors may be activated by ATP released from astrocytes and function to downregulate synaptic AMPA receptors in hippocampal neurons. This regulation of both NMDA and AMPA receptors by astrocyte-derived ATP highlights the central role of purinergic signaling in controlling excitatory synaptic strength and provides a mechanism for rapid, activity-dependent adjustment of synaptic efficacy.

Beyond excitatory synapses, purinergic signaling also profoundly affects inhibitory neurotransmission. Bowser and Khakh (2004) demonstrated that exogenous application of ATP to hippocampal stratum radiatum increased astrocyte intracellular Ca^{2+} levels and depolarized calbindin- and calretinin-positive GABAergic interneurons, leading to action potential firing and enhanced synaptic inhibition onto the postsynaptic targets of interneurons. The effect of ATP on interneurons was mediated by astrocytic P2Y1 receptors, leading to increased synaptic inhibition in hippocampal circuits. This mechanism provides astrocytes with the capability to bidirectionally regulate the excitation-inhibition balance, a fundamental property of neural circuit function.

Astroglial PRs in Neurolasticity

Purinergic astrocytic signaling plays pivotal roles in both LTP and LTD, the cellular correlates of learning and memory (Pasqual et al., 2005; Chen et al., 2013).

Vignoli and colleagues (2016) demonstrated that long-term memory retention requires synaptic glia for proBDNF uptake and recycling, with extracellular ATP activating P2X and P2Y receptors to regulate endocytic brain-derived neurotrophic factor (BDNF) secretion in cultured astrocytes. This connection between purinergic signaling and BDNF dynamics provides a molecular link between glial activity, synaptic plasticity, and memory consolidation. The role of P2Y receptors, however, extends beyond acute synaptic modulation to encompass long-term developmental processes. These receptors are considered to be involved in bidirectional neuronal-astroglial communication, exerting long-term effects on proliferation, differentiation, migration, and apoptosis (Neary & Zimmermann, 2009; Burnstock et al., 2011), which highlights the fundamental importance of purinergic signaling in shaping neural circuit architecture during brain maturation.

Aberrant purinergic signaling has been implicated in epilepsy, neurodegenerative diseases, and cognitive dysfunction (Nikolic et al., 2020), and the involvement of astrocytic purinergic receptors in pathological processes has become increasingly apparent. Activation of P2X and P2Y receptors induces astrogliosis in injured nerve tissue (Franke & Illes, 2014). Notably, astroglial expression of P2X7 receptors increases after brain injury of various etiologies (Verkhratsky & Nedergaard, 2018), suggesting that this receptor subtype may serve as a sensor for tissue damage and a trigger for reactive astrogliosis. As our understanding of these mechanisms deepens, it becomes increasingly clear that targeting astrocytic purinergic signaling may offer innovative therapeutic approaches for disorders of synaptic dysfunction and cognitive impairment.

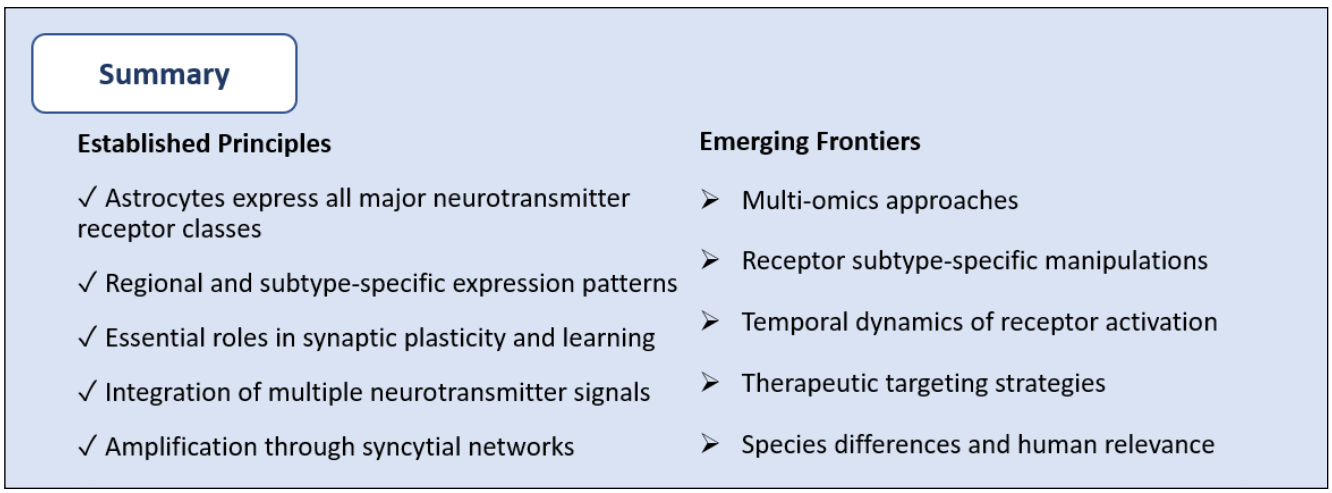

Fig 2. Astrocytic neurotransmitter receptors: Summary and prospects.

CONCLUSIONS

The comprehensive analysis of astrocytic neurotransmitter receptors reveals their importance as mediators of neuron-glia communication and regulators of neuroplasticity. Recent evidence suggests that astrocytes can simultaneously detect multiple neurotransmitter signals and integrate them into coherent, context-appropriate responses. Glioreceptors serve multiple critical functions: they enable detection and integration of neuronal activity, trigger calcium signaling cascades that regulate gliotransmitter release, and modulate astrocytic morphology to influence tripartite synaptic structure. The evidence demonstrates that astrocytic neurotransmitter receptors play a crucial role in plasticity through several key mechanisms. They regulate the release of essential co-agonists, such as D-serine, required for NMDA receptor-dependent synaptic plasticity. They also control the motility of astrocytic processes, influencing synaptic structure, the release of gliotransmitters that directly modulate synaptic transmission, and the induction of plasticity. The functional significance of astrocytic glioreceptors extends beyond individual receptor systems to encompass complex interactions between multiple neurotransmitter pathways. Mounting evidence indicates that these pathways do not operate uniformly across all astrocytes or brain regions, but rather exhibit sophisticated patterns of co-expression, segregation, and regional dominance that reflect the specialized functional demands of different neural circuits. At the single-cell level, astrocytes can co-express multiple neurotransmitter receptor systems, enabling them to integrate diverse neuronal signals. Recent work has demonstrated functional interactions between different receptor pathways within the same astrocyte. For example, dopamine has been shown to activate α1-ADRs on prefrontal cortex astrocytes, revealing cross-talk between dopaminergic and noradrenergic systems (Pittolo et al., 2022). Notably, this interaction is region-specific, occurring in the prefrontal cortex but not in the visual cortex, suggesting that pathway convergence patterns are tailored to local circuit requirements. In the VTA, astrocytes express both D2 and CB1 cannabinoid receptors in close proximity, with their coordinated activation regulating the plasticity of glutamatergic synapses onto dopamine neurons (Requie et al., 2022). These examples illustrate how astrocytes function as coincidence detectors, integrating multiple neuromodulatory signals to fine-tune circuit function.

The regional and subtype-specific expression patterns revealed by single-cell transcriptomic analyses suggest functional specialization within astrocyte populations (Hennes et al., 2025), and recent transcriptomic studies have identified distinct subpopulations with differential receptor expression profiles (Batiuk et al., 2020). Regional specialization is particularly evident in neuromodulatory systems (Muller et al., 2021; Gao et al., 2024), but it is also evident in the GABAB receptor (Mederos et al., 2021) and the NR2C NMDAR subtype, which shows layer-specific expression in the hippocampus (Chipman et al., 2021). Layer-specific differences in mGluR expression and AMPA receptor subunit composition suggest that glutamatergic pathways are differentially tuned across cortical layers to match local synaptic architecture (Morel et al., 2014; Batiuk et al., 2020). The regional segregation of astrocytic glioreceptor expression patterns may have profound implications for neural circuit function, since it may create an anatomically segregated signaling domain. However,

the observation of enrichment of glutamatergic *versus* GABAergic receptor-associated genes in different cortical astrocyte subtypes occupying partially overlapping spatial territories suggests that pathway segregation occurs within intermingled subpopulations rather than at strict regional boundaries (Batiuk et al., 2020).

Despite lower receptor density than neurons, astrocytes' unique structural properties amplify their functional impact. Individual astrocytes contact hundreds of thousands of synapses and form electrically coupled networks, enabling small numbers of activated astrocytes to coordinate plasticity across extensive neural circuits. The astro-glioreceptor landscape thus reveals a sophisticated organization in which multiple neurotransmitter pathways converge on individual astrocytes while simultaneously showing regional specialization. Rather than all pathways operating uniformly across all astrocytes, evidence supports a model of regional tuning in which certain receptor systems dominate in specific brain regions, reflecting local circuit demands. This is complemented by pathway interactions within individual cells that enable integration of multiple signals. The spatial segregation of molecularly distinct astrocyte subtypes with characteristic receptor expression profiles adds another layer of complexity, allowing for local microdomains with specialized responsiveness to neuronal activity. This positions astrocytic neurotransmitter receptors as significant modulators of neuroplasticity and active participants in learning, memory, and the modification of neuronal circuits. Understanding these patterns of pathway interaction, segregation, and regional dominance will be essential for developing targeted therapeutic interventions that can modulate specific circuits while minimizing off-target effects. Future research employing genetic approaches and advanced spatial transcriptomics will be crucial for mapping the functional architecture of astro-lioreceptor systems across the brain.

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