Invited review

The tripartite glutamatergic synapse

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ABSTRACT

Astroglial cells were long considered as structural and metabolic supporting cells are which do not directly participate in information processing in the brain. Discoveries of responsiveness of astrocytes to synaptically-released glutamate and their capability to release agonists of glutamate receptors awakened extensive studies of glia-neuron communications and led to the revolutionary changes in our understanding of brain cellular networks. Nowadays, astrocytes are widely acknowledged as inseparable element of glutamatergic synapses and role for glutamatergic astrocyte-neuron interactions in the brain computation is emerging.

Astroglial glutamate receptors, in particular of NMDA, mGluR3 and mGluR5 types, can activate a variety of molecular cascades leading astroglial-driven modulation of extracellular levels of glutamate and activity of neuronal glutamate receptors. Their preferential location to the astroglial perisynaptic processes facilitates interaction of astrocytes with individual excitatory synapses. Bi-directional glutamatergic communication between astrocytes and neurons underpins a complex, spatially-distributed modulation of synaptic signalling thus contributing to the enrichment of information processing by the neuronal networks.

Still, further research is needed to bridge the substantial gaps in our understanding of mechanisms and physiological relevance of astrocyte-neuron glutamatergic interactions, in particular ability of astrocytes directly activate neuronal glutamate receptors by releasing glutamate and, arguably, D-Serine. An emerging roles for aberrant changes in glutamatergic astroglial signalling, both neuroprotective and pathogenic, in neurological and neurodegenerative diseases also require further investigation.

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1. Introduction – Astroglia: from passive glue to active player

Glial cells have long been neglected as active participants in information processing in the brain, mainly due to initial lack of evidence for their electrical excitability. This view has been challenged when it has become evident that glial cells, especially astrocytes, can detect chemical transmitters released from neurons and respond by releasing their own extracellular signals, "gliotransmitters" (Cornell-Bell et al., 1990; Nedergaard, 1994; Parpura et al., 1994). The recognition of great importance of bi-directional communications between neurons and astrocytes gave rise to the concept of "tripartite synapse" which incorporates a presynaptic terminal, a postsynaptic spine, and an astrocytic processes (Halassa et al., 2007; Perez-Alvarez and Araque, 2013). Remarkably, it was the discovery of glutamate-evoked cytosolic Ca^{2+}-elevation in astrocytes and glial release of glutamate which awakened the extensive studies of glia-neuron communications (Cornell-Bell et al., 1990; Glaum et al., 1990; Parpura et al., 1994). Over last two decades, these studies led to the revolutionary changes in our understanding of brain cellular networks. (see Fig. 1)

Nowadays, it is widely acknowledged that glial cells are indispensable to mechanisms of brain plasticity, homeostasis and longevity (De Strooper and Karran, 2016; Soreq et al., 2017; Verkhratsky et al., 2019) and that astrocytes can play active roles in storage and processing of information (Adamsky et al., 2018; Savtchouk and Volterra, 2018; Singh and Abraham, 2017). In its early version, the "tripartite synapse" concept relied heavily on the idea of "fast gliotransmission" postulating that Ca^{2+}-dependent exocytosis of small molecular transmitters from astrocytes directly contributes to the excitatory synaptic transmission. This, unduly radical, notion was scrutinized (Agulhon et al., 2008; Hamilton and Attwell, 2010) and the other concepts of multi-partite cellular interactions in the brain, such as "astroglial cradle" and "glial metabolic hub", were proposed to extend and complement the "tripartite synapse" theory (Giaume et al., 2010; Halassa and Haydon, 2010; Verkhratsky and Nedergaard, 2014). The modern view on the tripartite synapse evolved to embrace non-vesicular release of gliotransmitters, slow and long-reaching modulation of neuronal activity and astrocyte-driven regulation of synaptic homeostasis (Araque et al., 2014; Caudal et al., 2020; Savtchouk and Volterra, 2018). Importantly, a multidirectional glutamatergic signalling remains instrumental for current models of glia-neuron interactions (Bazargani

and Attwell, 2016; Savtchouk and Volterra, 2018; Verkhratsky and Nedergaard, 2014). A primary focus of this review is to discuss the most important details of glutamatergic communications within "extended" tripartite synapse as well as recent evidence of its physiological importance.

2. Glutamate receptors in astroglia and neuron-to-glia signalling

All physiological functions of astrocytes, one way or another, rely on their ability to detect the activity of surrounding neuronal networks. By virtue of expression of diverse assortment of neurotransmitter receptors, astroglial cells can "listen" to fast synaptic transmission and respond by changes in their intracellular ion concentrations, in particular sodium and calcium. In this "receiving" part of tripartite synapse, a very important role belongs to different types of glutamate receptors.

2.1. mGluR receptors

One of the first receptors implicated in the detection of neurotransmitters by glial cells were metabotropic glutamatergic receptors, in particular of mGluR5 type (Cornell-Bell et al., 1990; Glaum et al., 1990). The evidence supporting prominent role for mGluRs spans from early

observations of significant contribution of intracellular Ca^{2+}-stores into glutamate-evoked Ca^{2+}-signalling in cultured astrocytes (Cornell-Bell et al., 1990) to the data demonstrating participation of group I/II mGluRs in the response of hippocampal astrocytes *in situ* to the activation of synaptic transmission by the train of stimuli (Porter and McCarthy, 1996) and even to the release of glutamate from individual synapses (Panatier et al., 2011). The functional evidence of participation of mGluRs in glial signalling were substantiated by the data on gene expression (Morel et al., 2014; Sun et al., 2013). The very interesting and important features of metabotropic glutamatergic Ca^{2+}-signalling in astrocytes are its spatial diversity, including the subcellular level (Arizono et al., 2014; Lavialle et al., 2011; Rusakov et al., 2014), and significant age-dependent alterations (Cai et al., 2000; Sun et al., 2013).

The mGluRs family consists of three groups based on the sequence homology and G-protein coupling, correspondingly mGluR1 and 5 (Group I), mGluR2 and 3 (Group II), and Group III including mGluRs 4, 6, 7, and 8. The main intracellular transduction cascade activated by group I mGluRs, coupled to Gq/G_{11}, is activation of phospholipase C, resulting in the generation of inositol 1,4,5-trisphosphate (IP3) and Ca^{2+} mobilization from intracellular stores (Niswender and Conn, 2010). This underlies an important role for the Group I mGluRs in the tripartite synapse signalling. The effects of group II and III mGluRs, coupled
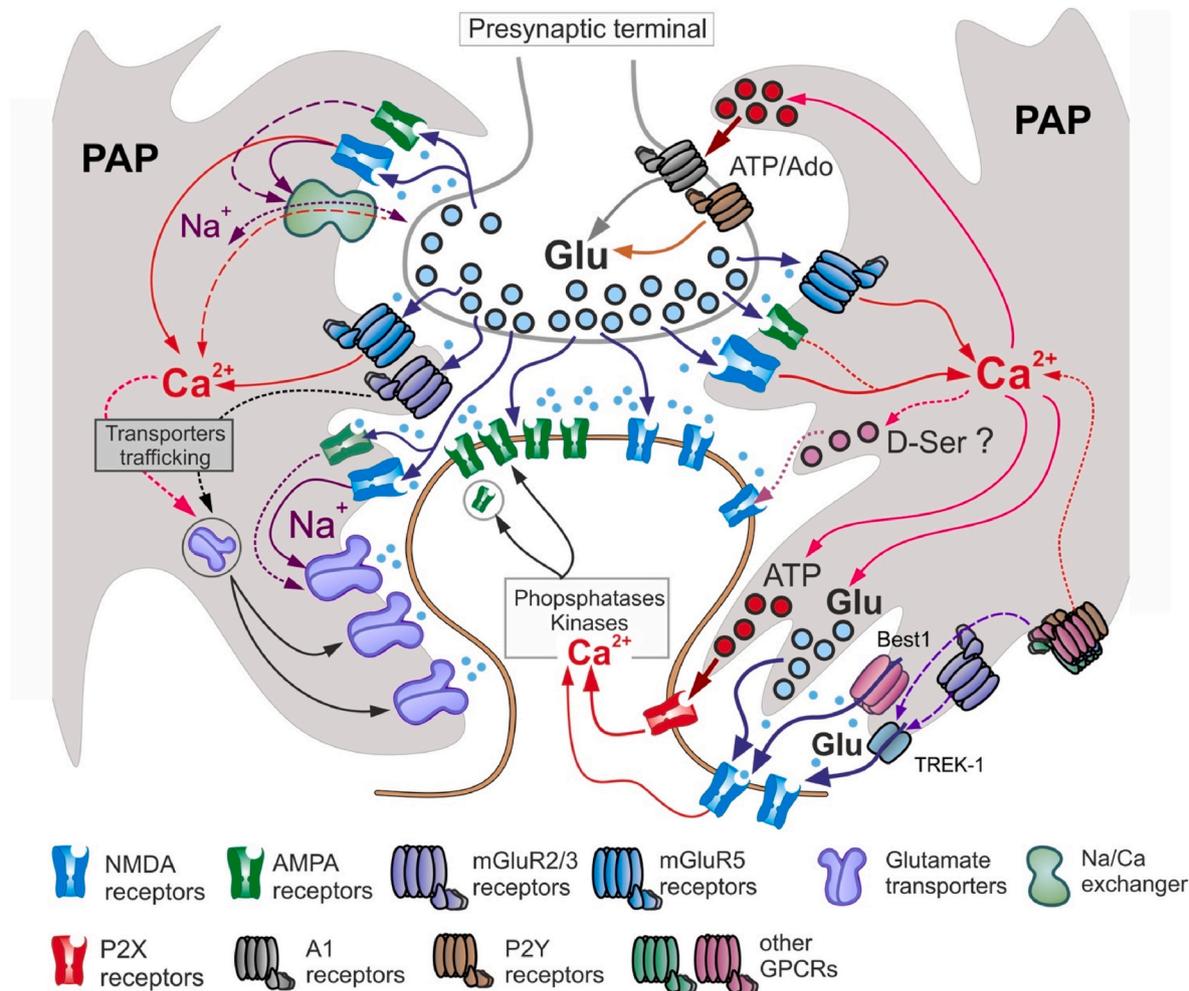
Fig. 1. The main pathways of glutamate-receptor mediated signalling within a tripartite synapse.
The NMDA and AMPA receptors located at the peri-synaptic astrocytic processes (PAP) provide the influx of Na^+ which modulates activity of EAAT glutamate transporters and Na/Ca exchanger (NCX). The NMDA, mGluR5 and, in some cases, AMPA receptors contribute to cytosolic Ca^{2+}-elevation in astrocytes which in turn modulates the trafficking and activity of glutamate transporters and motility of PAPs. These pathways can also be activated by astroglial mGluR2/3 receptors. Astroglial modulation of glutamate uptake and spillover affect the desensitization of post- and extrasynaptic NMDARs and functional isolation of excitatory synapses. The contribution of astroglial glutamate receptors into astroglial Ca^{2+}-elevation which triggers the release, among other transmitters, of the ATP, glutamate and, putatively, ᴅ-Serine. The astroglia-driven ATP and glutamate modulate the synaptic strength via several pre- and postsynaptic mechanisms.

predominantly to Gi/o proteins, are associated mainly with inhibition of adenylyl cyclase leading to regulation of ion channels and some other downstream signalling cascades, such as activation of MAPK and phosphatidyl inositol 3-kinase PI3 kinase (Niswender and Conn, 2010). Although the group II and III mGluRs are not supposed to be immediately involved in the Ca^{2+}-release from intracellular stores, their participation in the astroglial signalling has also been reported (Copeland et al., 2017; Lazutkaite et al., 2017).

Although gene expression studies revealed that all mGluR types could be found in astrocytes in the adult mammalian brain, at least at low levels, the most prominent subtypes of glial mGluRs are mGluR3 and mGluR5 (Durand et al., 2013; Panatier and Robitaille, 2016). Their abundant expression and functional roles in astrocytes have been reported in various brain areas (Cavaccini et al., 2020; D'Ascenzo et al., 2007; Durand et al., 2013; Sun et al., 2013; Umpierre et al., 2019), in particular thalamus, cortex, hippocampus, striatum and *nucleus accumbens* (Table 1).

Contrary to neurons, where functional roles for both members of group I have been demonstrated, mGluR5 receptors have predominant role in the metabotropic glutamatergic signalling in astrocytes. Numerous studies of astroglial glutamatergic signalling reported the significant contribution of mGluR5 receptors in the elevation of cytosolic Ca^{2+} (Panatier and Robitaille, 2016) (see also Table 1) as opposed to the typical lack of effects of the selective mGluR1 antagonists on astroglial functions (Honsek et al., 2012). Yet, there are some scattered data suggesting that mGluR1 receptors also can contribute into astroglial signalling in adult human patients and rodents (Aoki et al., 2019; Tang et al., 2015; Wang et al., 2006). Importantly, the level of expression mGluR1 in human astrocytes can increase dramatically in the pathological context (Aoki et al., 2019; Geurts et al., 2003; Sukigara et al., 2014).

Of the group II receptors, the mGluR3 type appears to be the most relevant for astroglial function (Durand et al., 2013), despite some recent data suggesting that mGluR2 receptor can also be involved in astroglial Ca^{2+}-signalling (Copeland et al., 2017). On the mRNA level, the preferential expression of mGluR3 in astrocytes, as compared to neurons and other types of glia, has been detected in the cerebral cortex (Zhang et al., 2014). Still, most of the experimental evidence of important roles for astroglial mGluR3 has been obtained in the pathological context, often in reactive astrocytes (Durand et al., 2013; Geurts et al., 2003; Planas-Fontanez et al., 2020), whereas reports of their participation in physiological glial signalling are scarce (Table 1). Regarding the tripartite synapse, an interesting feature of mGluR3 is their preferential localisation to the peripheral astrocytic processes where they can regulate astrocytic filopodia motility (Lavialle et al., 2011) and thereby affect uptake of neurotransmitters by astrocytes. The mGluR3-mediated regulation of glutamate uptake has been implicated in pathogenesis of many brain disorders (Peterson and Binder, 2020; Planas-Fontanez et al., 2020). Apart from regulation of surface expression and activity of GLT-1 glutamate transporter (Durand et al., 2013; Peterson and Binder, 2020; Umpierre et al., 2019), another role for astroglial mGluR3 is modulation of the release of glial-derived neurotrophic factor (GDNF), BDNF and TNF-β (Battaglia et al., 2015; Durand et al., 2013; Planas-Fontanez et al., 2020).

However, the physiological relevance of astroglial mGluRs, especially of the group I, has been hotly debated (Agulhon et al., 2008; Bazargani and Attwell, 2016; Savtchouk and Volterra, 2018). This debate, which is a part of more general discussion of physiological relevance of "tripartite synapse", has been fuelled by several factors. Firstly, early studies of neuron-to-glia signalling were focused mainly on the metabotropic Ca^{2+}-signalling in astrocytes and did not take into account a putative contribution of Ca^{2+}-influx via various transmembrane channels, such as NMDA and AMPA receptors (discussed below). So, after reports of the lack of effect of astroglia-specific knock-out of IP3 receptors on synaptic plasticity in hippocampus (Petravicz et al., 2008), the physiological role of IP3-mediated release of

Ca^{2+}-from intracellular stores in astrocytes, which includes mGluR5-mediated signalling, has been scrutinized (Agulhon et al., 2008; Bazargani and Attwell, 2016; Hamilton and Attwell, 2010). Secondly, the majority of the early studies of glia-neuron interactions was carried out, by obvious reasons, in the hippocampal CA1 area (Bezzi et al., 2004; Cornell-Bell et al., 1990; Halassa et al., 2007; Henneberger et al., 2010; Parpura et al., 1994; Porter and McCarthy, 1996), where expression of mGluR5 receptors in astrocytes undergoes a sharp age-dependent decline (Cai et al., 2000; Morel et al., 2014; Sun et al., 2013). Also, the surface expression of mGluR receptors in fine astrocytic processes can undergo dynamic local changes (Arizono et al., 2014; Lavialle et al., 2011), which makes the metabotropic astrocytic signalling highly sensitive to the physiological context and the way of activation (i.e. focal application of agonists, synaptic stimulation at different strength). For instance, the mGluR-mediated Ca^{2+}-response of cortical astrocytes to the *in vivo* whisker stimulation could be activated only at the moderate but not at the low or high stimulation frequencies (Wang et al., 2006). Although impact of these factors can explain most of the inconsistencies in the results of different groups, e.g. (Panatier et al., 2011; Sun et al., 2013; Wang et al., 2006), an unifying model of metabotropic glutamatergic signalling in astroglia is yet to be developed (Savtchouk and Volterra, 2018).

Nevertheless, the data obtained in the last decade in different brain regions strongly suggest that mGluR-mediated astroglial signalling is universally important for glia-driven modulation of synaptic function (Table 1). Furthermore, recent data highlighted the role for alterations, both positive and negative, in astroglial mGluR-signalling in pathology of many neurodegenerative disorders, such as epilepsy, stroke, amyotrophic lateral sclerosis (ALS), neuropathic pain and Alzheimer's disease (Durand et al., 2013; Kim et al., 2017; Planas-Fontanez et al., 2020; Umpierre et al., 2019).

2.2. NMDA receptors

Growing understanding that metabotropic Ca^{2+}-signalling alone cannot account for all complexity of astrocyte excitability and glia-neuron communications inspired an interest to the putative mechanisms of calcium influx from an extracellular space, such as ion exchangers or neurotransmitter-gated ion channels (Shigetomi et al., 2013; Volterra et al., 2014). The Ca^{2+}-permeable ionotropic glutamate receptors (iGluRs) seem to be a plausible candidate for alternative pathway of astrocyte activation since expression of various iGluRs virtually in all types of neuroglial was repeatedly detected (Brand-Schieber et al., 2004; Garcia-Barcina and Matute, 1996; Lee et al., 2010a; Rusnakova et al., 2013; Ziak et al., 1998). Although earlier studies reported the expression of GluN1 and GluN2 subunits in the cerebellar Bergmann glia and astrocytes of neocortex and amygdala (Conti et al., 1999; Farb et al., 1995; Luque and Richards, 1995; Schipke et al., 2001), participation of NMDA receptors in the astroglial signalling, for a long time, was deemed implausible due to the Mg^{2+}-block at negative membrane potentials characteristic of glial cells.

Several lines of evidence obtained in the last two decades helped to resolve this controversy. Initially, the small NMDA-induced transmembrane currents were observed in the Bergmann glia cells from mouse cerebellar slices (Muller et al., 1993); these currents were sensitive to ketamine but not to glycine and were not accompanied by the cytosolic Ca^{2+}-elevation. Later, the exposure of slice preparations was reported to induce the transmembrane currents and Ca^{2+}-transients in the astrocytes of neocortex (Schipke et al., 2001) and spinal cord (Ziak et al., 1998) and in the sub-population of hippocampal astrocytes (Porter and McCarthy, 1995). At the same time, astroglial NMDA responses in slice preparation were reported to be sensitive to inhibition of neuronal activity with tetrodotoxin and CNQX, arguing against direct activation of astrocytes (Porter and McCarthy, 1995; Schipke et al., 2001).

An unequivocal evidence of direct activation of astroglial NMDA responses was provided by recordings from individual astrocytes

Table 1

Contribution of glutamate receptors in signalling and physiological functions of brain astrocytes.

Receptor	Cell type/location	Species age	Experimental evidence and main physiological effects	Reference:
mGluR1	Hippocampal CA1 astrocytes *in situ*	Adult Mice (6–8 wks)	Application of group I agonist DHPG evoked Ca^{2+}-response in the astrocytic processes which could not be reproduced by the selective mGluR5 agonist CHPG. mGluR1 receptors have modulatory action on the astrocytic Ca^{2+}-signalling evoked by synaptic stimulation	Tang et al. (2015)
mGluR1	Somatosensory cortex astrocytes *in vivo*	Adult Mice (6–8 wks)	The mGluR1 selective antagonist LY367385 partially reduced the astrocytic Ca^{2+}-response to the medium frequency whisker stimulation. The mGluR1 and mGluR5 bring approximately equal contributions into astrocytic response to sensory stimulation.	Wang et al. (2006)
mGluR2	Thalamic astrocytes *in situ*	Juvenile mice (P12-16)	Astrocytic cytosolic Ca^{2+}- transients were evoked by the group II agonist and were further potentiated by selective mGluR2 PAMs LY354740 and LY487379. The group II agonist-induced Ca^{2+}- responses were inhibited in the astrocytes of IP3R2-dificient mice. Astroglial mGluR2 were suggested to participate in the modulation of sensory processing in thalamic neurons.	Copeland et al. (2017)
mGluR3	Hippocampal and hypothalamic astrocytes in culture and *in vivo*	Juvenile rats Adult hamsters	Ultrastructural analysis and immunocytochemistry showed that mGluR3 are localized to the peripheral astrocyte processes; mGluR3 receptors mediate glutamate-induced filopodia motility in astrocytes.	Lavialle et al. (2011)
mGluR3	Spinal cord astrocytes in culture	Juvenile mice	The group II agonist enhanced release of GDNF from astrocytes in the wild-type but not in the mGluR3$^{-/-}$ mice.	Battaglia et al. (2015)
mGluR4	Hypothalamic tanycytes *in situ*	Adult mice	Significant reduction of amino-acid activated Ca^{2+}-response by mGluR4 antagonists, mGluR4 receptors participate amino acid sensing (umami taste perception).	Lazutkaite et al. (2017)
mGluR5	Hippocampal CA1 astrocytes *in situ*	Juvenile Mice (P13-16)	Large doses of MPEP (100 µM) dramatically reduced the amplitude of stimulation-evoked Ca^{2+} signalling in astrocytes. Amplitude of astrocyte Ca^{2+}signals was related to the number of activated synapses but did not correlate with the degree of potentiation of CA1 pyramidal cell synapses	Honsek et al. (2012)
mGluR5	Hippocampal CA1 astrocytes *in situ*	Adult Mice (6–8 wks)	The mGluR5 expression dramatically increased in the large population of stratum radiatum astrocytes in the kainic acid-induced epilepsy model. The astrocyte-specific KO of mGluR5 inhibited the DHPG-induced Ca^{2+}-transients; MPEP partially inhibited the astrocyte Ca^{2+}-response to synaptic stimulation. The astroglial mGluR5 receptors have positive modulatory effect on astrocytic uptake of glutamate during in *status epilepticus*.	Umpierre et al. (2019)
mGluR5	Striatal astrocytes *in situ*	Adult Mice (4–12 wks)	High-frequency stimulation of cortico-striatal synapses increased the frequency of Ca^{2+}-transients in the dorsolateral striatum astrocytes in mGluR5-dependent manner. The mGluR5-mediated Ca^{2+}-signalling activated the release of ATP/adenosine from astrocytes essential for the A1 receptor-mediated LTD in striatal synapses. The A1-dependent LTD was blocked by MPEP and intracellular perfusion of astrocytes with GDPβS.	Cavaccini et al. (2020)
mGluR5	Hippocampal CA1 astrocytes *in situ*	Juvenile rats (2–3 weeks)	The mGluR5 antagonist MPEP inhibited astrocytic Ca^{2+}-responses elicited by activation of individual synapses. Astroglial mGluR5 receptors caused downstream activation of presynaptic A2$_A$ receptors, presumably via triggering glial release of ATP/Adenosine.	Panatier et al. (2011)
mGluR5	Nucleus accumbens astrocytes *in situ*	Young mice (2–6 wks)	The strong mGluR5 immunoreactivity and DHPG-induced Ca^{2+}-signalling were observed in the GFAP-expressing astrocytes. The mGluR5 antagonist inhibited astrocytic Ca^{2+}-oscillations induced by the stimulation of cortical afferents. Activation of mGluR5 in the NA astrocytes caused Ca^{2+}-dependent release of glutamate leading to activation of extrasynaptic GluN2B receptors in the medium spiny neurons.	D'Ascenzo et al. (2007)
mGluR5	Somatosensory cortex astrocytes *in vivo*	Adult Mice (6–8 wks)	The mGluR5 antagonist MPEP partially reduced the astrocytic Ca^{2+}-response to the medium frequency whisker stimulation. The mGluR1 and mGluR5 bring approximately equal contributions into astrocytic response to sensory stimulation.	Wang et al. (2006)
NMDAR	Somatosensory cortex astrocytes *in situ*	Young, adult and old mice (2 weeks–2 years)	Application of NMDA and stimulation of cortical afferents evoked the transmembrane currents and Ca^{2+}-transients in the GFAP/EGFP-expressing astrocytes; astroglial signalling was inhibited by MK801, D-AP5 and GluN2C/D-specific antagonist. The glial NMDARs exhibit weak Mg^{2+}-block and bring significant contribution into astrocytic Ca^{2+}-signalling and release of gliotransmitters.	Lalo et al. (2006) (Lalo et al., 2011a; Palygin et al., 2011) Lalo et al. (2014)
NMDAR	Hippocampal CA1 astrocytes *in situ*	Young mice (2–3 weeks)	Application of NMDA induced depolarisation and Ca^{2+}-elevation in the sub-population of GFAP/EGFP-expressing astrocytes.	Serrano et al. (2008)
NMDAR	Hippocampal astrocytes in culture	Human	The expression of various GluN subunits has been detected at various levels. Application of glutamate induced Ca^{2+}-elevation which was inhibited by NMDAR antagonists MK801 and memantine.	Lee et al. (2010a)
NMDAR	Hippocampal CA1 astrocytes *in situ*	Juvenile rats (P14-21) and adult mice (4–8 wks)	Application of NMDA in the presence of TTX induced astrocyte membrane depolarisation which can be blocked by the intracellular infusion of MK-801 or deleting *GRIN1* in astrocytes. Astrocytic NMDARs trigger the Ca^{2+}elevation and release of gliotransmitters, presumably ATP/Ado, which regulate pre-synaptic strength.	Letellier et al. (2016)
NMDAR	Astrocytes of several brain regions	Adult EFGP/GluN2C-reporter mice	Enriched astrocytic expression of GluN2C subunit have been found in the cortex, striatum, hippocampus, substantia nigra and amygdala; functional expression of GluN2C-containing receptors in substantia nigra and cortical astrocytes has been confirmed using electrophysiology.	Ravikrishnan et al. (2018)
NMDAR	Somatosensory cortex astrocytes *in situ*	Young and adult mice *in situ*	Stimulation of glutamatergic afferents or glutamate application induced Na^+- and Ca^{2+}- in astrocytic processes, which were inhibited by D-AP5. The NMDAR-mediated signalling was observed in the neocortical but not in the	Ziemens et al. (2019)

Table 1 (*continued*)

Receptor	Cell type/location	Species age	Experimental evidence and main physiological effects	Reference:
			hippocampal astrocytes. NMDAR enhance the astroglial Ca^{2+}-signalling by altering the activity of sodium/calcium exchanger.	
AMPAR	Hippocampal CA1 astrocytes *in situ*	Juvenile mice	Application of glutamate and AMPA to acutely isolated astrocytes induced rapidly-desensitizing transmembrane currents which were potentiated by cyclothiazide. Moderate Ca^{2+} - permeability ($P_{ca}/P_{N\bar{a}}1$) of astrocytic AMPARs was observed.	Seifert and Steinhauser (1995)
AMPAR	Neocortical layer 2/3 astrocytes *in situ*	Young, adult and old mice	Application of glutamate to acute isolated astrocytes induced rapidly-desensitizing currents which were inhibited by NBQX. Stimulation of cortical afferents induced the transmembrane currents in astrocytes, which were potentiated by cyclothiazide and partially inhibited by NBQX or CNQX. Also, AMPA receptors mediated a fraction of the fast spontaneous currents in astrocytes. The amplitude of AMPAR-mediated currents in astrocytes was highest at 1 month and gradually declined with age.	(Lalo et al., 2006, 2011a)
AMPAR	Bergmann glia of cerebellum	Adult rats	Agonist application activated Ca^{2+}-permeable AMPA (GluA2-lacking) receptors leading to Ca^{2+} -elevation in the astrocytic processes. Entry of Ca^{2+} through the AMPA receptors located on Bergmann glia processes induces vesicular release of glutamate.	Cervetto et al. (2015)
AMPAR	Müller glial cells of retina *in vivo*	Larval zebrafish	Glutamate-induced electrical and Ca^{2+}- responses in MGCs were suppressed by the CNQX. The AMPA receptors mediate MGC Ca^{2+}-signalling during retinal waves induced by glutamate derived from bipolar cells; these waves are instrumental for the activity-dependent refinement of visual topographic maps.	Zhang et al. (2019)

isolated (with the aid of non-enzymatic vibro-dissociation technique) from cortices of GFAP/EGFP transgenic mice (Lalo et al., 2006; Palygin et al., 2011). These experiments also clearly demonstrated the significant shift of Mg^{2+}-block of glial NMDA receptors towards hyperpolarisation, with almost 100% of astrocytic NMDARs activated near the membrane potential of −80 mV (Lalo et al., 2006; Palygin et al., 2011). In parallel, the functional NMDA receptors, weakly sensitive to Mg^{2+}, were found in the oligodendrocytes, where their activity was associated with ischaemic brain injury (Karadottir et al., 2005; Micu et al., 2006; Salter and Fern, 2005) and regulation of glucose transport and axonal metabolism (Saab et al., 2016). These results highlighted the existence of functional glial NMDA receptors, active at negative membrane potential, as universal phenomenon potentially important for brain physiology and pathology (Lipton, 2006; Verkhratsky et al., 2020).

Glial NMDA receptors differ from the majority of neuronal NMDARs not only by the weaker Ma^{2+}-block but also by lower Ca^{2+}-permeability; the $P_{Ca}/P_{monovalent}$ ratio in cortical astrocytes is about 3 (Palygin et al., 2011), i.e. 3-4 times lower than in neurons. Conversely, astroglial NMDARs receptors exhibit much higher sensitivity to the memantine and GluNR2C/D subunit-selective antagonist UBP141 than neuronal receptors (Palygin et al., 2011). This peculiar combination of functional and pharmacological properties of glial NMDARs allowed to decipher their putative structure. The only feasible explanation of low sensitivity to Mg^{2+}-block and lower Ca^{2+}-permeability is incorporation of one or two GluN3 subunits (Henson et al., 2010). On another hand, dimeric GluN1/GluN3 receptors lack sensitivity to conventional NMDAR antagonists D-AP5 and MK-801 (Henson et al., 2010), which were shown to block the astroglial NMDA-mediated responses (Lalo et al., 2006; Porter and McCarthy, 1995; Schipke et al., 2001). Hence, the most feasible composition of glial NMDA receptor is the heterotetrameric assembly of two GluN1 subunits (required for trafficking to the membrane), one GluN2C or D subunit and one GluN3 subunit. This notion was corroborated by comparison of the functional properties of native NMDARs of cerebellar oligodendrocytes with recombinant doublet GluN1/GluN2C and triplet GluN1/GluN2C/GluN3A receptors (Burzomato et al., 2010) and further supported by the data on expression of GluN subunits in astrocytes. In particular, expression of GluN1, GluN2A, GluN2C, GluN2D, and GluN3A have been detected at mRNA levels in mice of different ages (Orre et al., 2014; Rusnakova et al., 2013; Zhang et al., 2014) and in cultured human astrocytes (Lee et al., 2010a). At protein level, a preferential localisation of GluN2C subunit to astrocytes rather than neurons have been recently found in the neocortex, hippocampus, and striatum (Ravikrishnan et al., 2018).

Histological and immunohistochemical studies of astroglial NMDARs

reported a preferential localisation of GluN subunits to the distal and perisynaptic processes (Conti et al., 1999; Farb et al., 1995; Hadzic et al., 2017; Ravikrishnan et al., 2018). Combined with the weak Mg^{2+}-block, this renders astrocytic NMDARs capable to respond to the glutamate released from synaptic terminals. Indeed, NMDAR-mediated transmembrane currents and Ca^{2+}- and Na^+-transients can be activated in the neocortical astrocytes by physiologically-attainable stimulation of cortical afferents (Lalo et al., 2011a; Palygin et al., 2010, 2011; Ziemens et al., 2019). The spontaneous miniature NMDAR-mediated currents, mostly likely activated by the vesicular glutamate release from individual synapses, were observed in the cortical astrocytes as well (Lalo et al., 2011a).

The level of expression of GluN subunits and NMDAR-mediated signalling in astroglia exhibit high regional diversity and strong age-dependence. Although expression of all seven GluN subunits has been detected in astrocytes of various brain regions, such as hippocampus, cerebellum, striatum and amygdala, the strongest and the most consistent evidence has been provided for the cortical astrocytes where the GluN1, GluN2C, 2D and GluN3A subunits appear to be the dominant ones (Hadzic et al., 2017; Lee et al., 2010a; Ravikrishnan et al., 2018; Zhang et al., 2014). Interestingly, the astroglial NMDAR-mediated signalling has not been observed in thalamus and basal ganglia which is consistent with reported lack of expression of GluN subunits in astrocytes of these regions (Ravikrishnan et al., 2018). On a functional level, the strong and consistent evidence of physiologically-relevant NMDAR-mediated astroglial signalling has been provided in the neocortex (Lalo et al., 2006, 2011a; Palygin et al., 2010; Schipke et al., 2001) whereas the functional role for NMDARs in the hippocampus remain controversial (Ziemens et al., 2019). Although earlier reports of NMDAR-mediated signals in sub-populations of hippocampal astrocytes (Porter and McCarthy, 1995; Serrano et al., 2008) were strongly supported by the later study demonstrating an instrumental role for the astrocytic NMDARs in regulation of presynaptic strength in the hippocampal neurons (Letellier et al., 2016), more recent research has not found a notable contribution of NMDA receptors in the Na^+-influx in CA1 astrocyte activated via stimulation of glutamatergic afferents or glutamate application (Ziemens et al., 2019).

The above discrepancy might be explained by the developmental regulation of surface expression of GluN subunits in hippocampal astrocytes with similar age-dependent pattern as for astroglial mGluR5 receptors (Sun et al., 2013) and astroglial NMDA receptors in the neocortex (Lalo et al., 2011a; Orre et al., 2014). In mouse neocortical astrocytes, the NMDAR-mediated signalling shows dramatic increase with CNS maturation, peaking in the adult animals (3–6 months) and

then gradually declines with aging (Lalo et al., 2011a); this dependence is in line with strong decrease in the GluN3A subunit expression in the old (15–18 months) reported by (Orre et al., 2014). Still, the age-dependence of NMDAR-mediated signalling in the hippocampal astrocytes and its functional relevance remain an open question.

It would appear reasonable to assume that physiological role of astroglial NMDA receptors is underpinned by their contribution into the cytosolic Ca^{2+}-elevation in astrocytes. This notion is strongly supported by the data obtained in the neocortical and sub-population of hippocampal astrocytes (Lalo et al., 2011a; Palygin et al., 2010; Schipke et al., 2001; Serrano et al., 2008; Ziemens et al., 2019). Moreover, Ca^{2+}- influx through NMDA receptors was reported to trigger the release of gliotransmitters (e.g. ATP) from neocortical astrocytes (Lalo et al., 2014). Besides the Ca^{2+}-influx, the Na^+-influx provided by the NMDA receptors can have a significant role in astroglial signalling (Lalo et al., 2011b; Verkhratsky et al., 2020). One can expect the activation of NMDA receptors to significantly increase the sodium concentration in astrocytic microdomains which in turn can cause considerable alterations in astroglial functions (Verkhratsky et al., 2020; Ziemens et al., 2019).

Firstly, the Na^+-influx via NMDA receptors can take part in astroglial Ca^{2+}-signalling by altering the activity of sodium/calcium exchanger (NCX) and thereby prolonging Ca^{2+}-transients (Ziemens et al., 2019) or leading to membrane depolarisation and activation of L-type voltage-gated Ca^{2+} channels (Letellier et al., 2016). The latter mechanism has been implicated in the NMDAR-dependent regulation of pre-synaptic strength by the hippocampal astrocyte (Letellier et al., 2016).

Furthermore, the Na^+-elevation provided by astroglial NMDA receptors can switch the flux via various transmembrane sodium-dependent transporters into reverse mode (Lalo et al., 2011b; Verkhratsky et al., 2020). In particular, the Na^+-triggered reversal of astroglial GABA and glycine transporters *in situ* has been reported in the neocortex and hippocampus (Eulenburg and Gomeza, 2010; Heja et al., 2012; Unichenko et al., 2013). At the same time, the astroglial Na^+-elevation can hardly reverse GLT1 and GLAST glutamate transporters under physiological conditions, since their thermodynamic equilibrium is strongly shifted towards uptake (Verkhratsky et al., 2020). Hence, Na^+-elevation mediated by astrocytic NMDA receptors can couple glutamatergic excitation with efflux of inhibitory neurotransmitters thereby mediating a negative feedback mechanism in glia-neuron networks. The elevation of intracellular Na^+ can affect the metabolic functions of astrocyte by stimulating the glutamine efflux via SNAT3 Na^+-dependent transporters (Todd et al., 2017) and activating astrocytic glucose uptake and lactate production (Chatton et al., 2016). There is also evidence that both the activity of NMDA receptors and Na^+-elevation are essential for the activity-dependent regulation of mitochondrial dynamics in astrocytes (Jackson et al., 2014; Stephen et al., 2015). This suggests a high potential importance of astroglial NMDARs for metabolic astrocyte-neuron cooperation.

Thus, astroglial NMDA receptors emerge as an important element of tripartite synapse whose physiological relevance is yet to be fully understood (Verkhratsky and Nedergaard, 2018; Verkhratsky et al., 2020).

2.3. Non-NMDA receptors

In earlier studies of astroglial iGluR-mediated signalling, the main emphasis was put on AMPA/KA receptors since they, in contrast to NMDARs, were expected to be active at physiological resting membrane potentials. Also, the GluA2-lacking AMPARs exhibiting a moderate Ca^{2+}- permeability (Traynelis et al., 2010) were suggested to contribute to the astroglial Ca^{2+}-signalling. The presence of AMPA/KA receptors in astroglial membrane, both at mRNA and functional level, has been well-documented *in vitro* and *in situ*. In particular, functional expression and physiological role for AMPARs was reported in the cerebellar Bergmann glia (Muller et al., 1992) and in the astrocytes of hippocampus (Jabs et al., 1994; Seifert and Steinhauser, 1995; Seifert et al., 1997), neocortex (Conti et al., 1994; Lalo et al., 2006, 2011a), spinal cord

(Brand-Schieber et al., 2004), thalamus (Hoft et al., 2014) and olfactory bulb (Droste et al., 2017). All four AMPA subunits (GluA1 – GluA4), as well as splice variants, have been reported to be expressed in astroglia, albeit in different combinations in different brain regions (Conti et al., 1994; Molders et al., 2018; Seifert et al., 1997). In the hippocampal and neocortical astrocytes, where expression of all four subunits was found, the abundance of GluA2 and GluA4 subunits was observed (Conti et al., 1994). The recent detailed study of heterogeneity of astrocytic AMPA receptors reported the predominance of GluA1/4 combination in cerebellum and GluA1/2 and GluA2/4 combination in hippocampus and neocortex (Molders et al., 2018). This closely agrees with the electrophysiological properties of AMPA-mediated signalling in these cells, i.e. linear I–V relationship and relatively low Ca^{2+} permeability (Seifert and Steinhauser, 1995). In contrast, the AMPA receptors found in Bergmann glia and periglomerular astrocytes of the olfactory bulb are devoid of GluA2 subunit and thereby exhibit moderate (P_{Ca}/P_{mono} ~1) Ca^{2+} permeability (Droste et al., 2017; Muller et al., 1992; Traynelis et al., 2010).

The most prominent evidence of physiological relevance of astroglial AMPA receptors was provided by several studies of Bergmann glia of cerebellum and Müller glia in retina (Muller et al., 1992; Saab et al., 2012; Zhang et al., 2019) where their functional importance is underlined by Ca^{2+}-permeability and slower desensitization of GluA1/A4 heteromeric structure (Molders et al., 2018). The putative downstream cellular effects caused by the Ca^{2+}-permeable astroglial AMPARs include release of gliotransmitters, e.g. glutamate and ATP (Cervetto et al., 2015; Hoogland et al., 2009), modulation of glial glutamate transporters (Zhang et al., 2019) and enhancement of motility and structural plasticity of glial peri-synaptic processes which in turn is crucial for function and sustainability of glutamatergic synapses in cerebellum (Iino et al., 2001; Saab et al., 2012).

Physiological and pathological roles for AMPA receptors in other brain regions are yet to be established. The reported lack of Ca^{2+}-permeability of AMPA receptors expressed in hippocampal and cortical astrocytes argues against their direct contribution into cytosolic Ca^{2+}-elevation. Although participation of AMPA receptors in the physiologically relevant Ca^{2+} signalling in cortical astrocytes *in vivo* has been reported (Tran et al., 2018), it remains unclear whether this effect was related to direct Ca^{2+}-influx via AMPA receptors or their indirect effect on calcium homeostasis, e.g. via sodium/calcium exchanger. The non Ca^{2+}-permeable AMPA receptors have been shown to bring significant contribution into Na^+-mediated transmembrane currents in the thalamic, neocortical, and hippocampal astrocytes (Hoft et al., 2014; Lalo et al., 2011a; Seifert and Steinhauser, 1995). One might argue that Na^+-influx via channels of astroglial AMPA could contribute to the same signalling processes as influx via NMDARs discussed above. However, in comparison with glial NMDARs, overall increase in the cytosolic Na^+ provided by AMPA receptors would be much lower due to their faster desensitization and lower sensitivity to ambient glutamate. So, beyond the Bergmann glial cells, significance of glial AMPA receptors for physiological functions of tripartite synapse remains doubtful.

The pathological role for astroglial AMPA receptors also remains elusive, in contrast to oligodendrocytes and microglia (Ceprian and Fulton, 2019). There is only scarce evidence of a link between activity of astrocytic AMPA receptors and brain disorders (Ceprian and Fulton, 2019; Cervetto et al., 2016; Peters et al., 2009). In particular, the early data on the excitotoxicity mediated by glial AMPA receptors were obtained in cultured astrocytes in the presence of cyclothiazide blocking AMPAR desensitization (Ceprian and Fulton, 2019). Although increased functional expression of AMPA receptors has been detected in the mouse models of exocytotic brain injury and Alzheimer's disease (Cervetto et al., 2016; Peters et al., 2009), their causative role in brain insults is yet to be established.

As for the kainate (KA) receptors, the expression of GluK1-5 subunits in astrocytes was reported at the mRNA and protein levels in the white matter, hippocampus and spinal cord (Brand-Schieber et al., 2004;

Brand-Schieber and Werner, 2003; Das et al., 2012; Garcia-Barcina and Matute, 1996; Matschke et al., 2015) but their functional role remains elusive. Interestingly, high level of expression of GluK1–5 subunits has been detected in the reactive (but not in healthy) astrocytes in pathological context, both in rodents and human patients (Das et al., 2012; Li et al., 2009; Vargas et al., 2013). Still, it is unclear whether increased expression of GluK subunits is a cause or consequence of pathological state and whether these newly expressed kainate receptors exacerbate the excitotoxic damage of brain tissue (e.g. via Na^+-dependent down-regulation/reversion of glutamate uptake) or have some unknown neuroprotective role.

2.4. Functional significance of astroglial glutamate receptors

The morphology of astrocytes, in particular intimate contacts between their fine processes and synapses (Kim et al., 2017; Rusakov et al., 2014; Verkhratsky and Nedergaard, 2018), enables them to "listen" to various neurotransmitters released from synaptic terminals. Owing to the expression of various metabotropic and ionotropic glutamate receptors, astroglia can detect the activity of neighbouring excitatory synapses and respond by changing cytosolic concentrations of calcium and sodium. This underlies a special kind of ionic "excitability" which activates a plethora of downstream molecular cascades in astrocytes. The Ca^{2+}-mediated component of this excitability is traditionally viewed as a hallmark of astroglial physiological signalling (Bazargani and Attwell, 2016; Caudal et al., 2020; Savtchouk and Volterra, 2018; Verkhratsky and Nedergaard, 2018).

As detailed above, glutamate receptors can bring substantial contribution to the cytosolic calcium elevation in astrocytes. Although both mGluRs and iGluRs can work synergistically in the astroglial Ca^{2+} signalling, their relative contributions can vary to a large extent in different brain regions and different ages (Bazargani and Attwell, 2016; Panatier and Robitaille, 2016; Savtchouk and Volterra, 2018; Wang et al., 2006; Ziemens et al., 2019). In addition, ionotropic glutamate receptors can also provide an influx of Na^+ ions. Both calcium- and sodium-based responsiveness of astrocytes have physiological importance because these types of signalling can strongly affect structural plasticity and metabolic status of astrocytes and their bi-directional communication with nearby neurones (Caudal et al., 2020; Singh and Abraham, 2017; Verkhratsky and Nedergaard, 2018; Verkhratsky et al., 2020).

In principle, functional diversity of glutamatergic signalling in astroglia is governed by the repertoire of glutamate receptors they express and spatio-temporal profile of extracellular glutamate concentration. Astrocytes can be exposed to (i) fast local transients of glutamate released or spilled out from presynaptic neuronal terminals; (ii) fast vesicular and slow non-vesicular release of glutamate from glial cells and (iii) ambient glutamate present in the interstitial space which most likely originate from incomplete/reversed uptake (Moussawi et al., 2011; Rose et al., 2017). There are accumulating immunocytochemical and ultra-structural data of preferential expression of glutamate receptors in the fine astrocytic processes (Arizono et al., 2014; Hadzic et al., 2017; Lavialle et al., 2011; Ravikrishnan et al., 2018) which can make astrocytes responsive to all types of glutamate release. On a functional level, the responses of astrocytes to the synaptic release of glutamate activated by stimulation of individual axons *in situ* or sensory stimulation *in vivo* has been reported. The second, autocrine, pathway of astrocytic glutamatergic signalling might explain the existence of fast spontaneous TTX-independent AMPAR-mediated currents in cortical astrocytes (Lalo et al., 2011a) and delayed astrocytic responses to sensory stimulation (Tran et al., 2018). The tonic activation of astroglial glutamate receptors by ambient glutamate can also be viewed as an autocrine pathway since astrocytes play a dominant role in the glutamate uptake. Putative tonic activation of mGluR5s and NMDARs can contribute to the baseline level of cytosolic Ca^{2+} in astrocytes which has been shown to affect the amplitude of astrocytic Ca^{2+}-transients (King

et al., 2020). Still, the physiological role for autocrine glutamatergic signalling in astroglia needs further investigation.

So, a main factor underlying physiological importance of astroglial glutamate receptors is their ability to detect the excitatory synaptic activity which makes them instrumental for all types of glia-neuron communications. From a plethora of reported effects of astroglial mGluRs and iGluRs (Table 1), two major downstream mechanisms, common for many brain regions, emerge: (i) Ca^{2+}-dependent release of gliotransmitters and (ii) Ca^{2+}- and Na^+-mediated regulation of astroglial uptake of glutamate (and thereby glutamate/glutamine cycle). Both mechanisms can underlie a significant impact of astrocytes on glutamatergic signalling in neurons which is discussed below.

3. Astroglia-driven modulation of neuronal glutamatergic signalling

The glutamatergic glia-to-neuron communication within tripartite synapse can occur via two main pathways: regulation of glutamate uptake and metabolism by astrocytes and direct action of astrocyte-released gliotransmitters, first of all glutamate and D-Serine, on the postsynaptic glutamate receptors. While importance of former pathway is well-established and widely accepted, the physiological significance of the latter is hotly debated (Agulhon et al., 2008; Bazargani and Attwell, 2016; Papouin et al., 2017b; Petravicz et al., 2008; Savtchouk and Volterra, 2018). Still, there is growing evidence that both pathways can be of equal importance and work synergistically underlying role for astrocytes in brain functions (Araque et al., 2014; Caudal et al., 2020; Savtchouk and Volterra, 2018; Singh and Abraham, 2017; Verkhratsky and Nedergaard, 2018).

3.1. Astrocytes as key regulators of extracellular glutamate

Astroglial network is indispensable element of glutamatergic transmission in the brain which regulates the extracellular concentration and metabolism of glutamate (Peterson and Binder, 2020; Rose et al., 2017; Verkhratsky and Nedergaard, 2018). This fundamental role for astrocytes is underpinned by three main mechanisms: removal of glutamate from the synaptic cleft allowing to prevent of desensitization of synaptic AMPA receptors and NMDA receptor-mediated excitotoxicity, hampering the spill-out of glutamate by the perisynaptic astrocytic processes and thereby ensuring synaptic isolation and supplying neurons with glutamine, a precursor for glutamate and GABA (Moussawi et al., 2011; Rose et al., 2017; Verkhratsky and Nedergaard, 2014).

Astrocytes play a main role in clearance of extracellular glutamate by virtue of expression of high-affinity Na^+-dependent transporters EAAT1/SLC1A6 (or GLAST) and EAAT2/SLC1A2 (or GLT-1) (Peterson and Binder, 2020; Verkhratsky and Nedergaard, 2018). The EAAT1 exhibits high level of expression in the astroglial cells of cerebellum and retina, whereas EAAT2 shows a predominant expression in the astrocytes in the rest of the brain. Although the EAAT1 and EAAT2 can also be expressed in neurons, their highest density was found in the perisynaptic astroglial processes (Verkhratsky and Nedergaard, 2018). The astrocyte-specific knock-out of EAAT2 caused severe effects, including cortical tissue abnormalities and fatal seizures, demonstrating the key role for astrocytes in the glutamate uptake (Peterson and Binder, 2020; Rose et al., 2017; Verkhratsky and Nedergaard, 2018).

As a counterweight to EAAT-mediated uptake, astrocytes can also increase the extracellular glutamate concentration through the cysteine–glutamate exchanger or system Xc- (SLC7A11) (Moussawi et al., 2011) and, putatively, via vesicular and non-vesicular Ca^{2+}dependent release (discussed below in section 3.2). In contrast to the EAAT transporters, the highest density of astrocytic cysteine– glutamate exchangers is observed in extra-synaptic regions. The interplay between glial uptake and release leads to the heterogeneity in the baseline concentration of extracellular glutamate: glutamate is kept at low nanomolar levels in the synaptic cleft to prevent desensitization of AMPA receptors whereas the

extrasynaptic regions of neuronal membranes are exposed to low micromolar concentrations which enable tonic activation of extra-synaptic mGluR5 and NMDA receptors and modulation of synaptic plasticity (Moussawi et al., 2011; Rose et al., 2017; Valtcheva and Venance, 2019). There is a wide consensus across "glial" and "neuronal" research communities that astrocytes can regulate dynamics of gluta-mate concentration and, thereby, the amplitude and kinetics of gluta-matergic postsynaptic responses (Halassa and Haydon, 2010; Marcaggi and Attwell, 2004; Valtcheva and Venance, 2019; Verkhratsky and Nedergaard, 2014). Astroglial glutamate uptake has been demonstrated to decrease the amplitude and decay time of NMDAR-mediated EPSCs in hippocampus and cerebellum (Arnth-Jensen et al., 2002; Asztely et al., 1997; Otis et al., 1996; Overstreet et al., 1999). Although AMPA re-ceptors are deemed to be less sensitive to glutamate uptake due to their fast desensitization (Asztely et al., 1997; Marcaggi and Attwell, 2004; Sarantis et al., 1993), the effects of astroglial glutamate transporters on AMPAR-mediated EPSCs have also been reported in the *nucleus magno-cellularis* and cerebellum (Otis et al., 1996; Overstreet et al., 1999).

Capability of astrocytes to control the extracellular distribution of glutamate is complemented by their pivotal role in the glutamate-glutamine cycle (Araque et al., 2014; Marcaggi and Attwell, 2004; Schousboe et al., 2014). Astrocytes are indispensable for maintenance of glutamatergic transmission because they supply neurons with direct precursor of glutamate, glutamine. The latter cannot be synthesized in neurons since the key enzyme, glutamine synthetase, is expressed exclusively by astrocytes. Glutamate, taken into astrocytes by the EAAT transporters or synthesized *de novo* from glucose, is converted into glutamine by glutamine synthetase (Carmignoto and Haydon, 2012; Schousboe et al., 2014; Walls et al., 2015). After then, glutamine is transported to neurons through the coordinated system of sodium-coupled neutral amino acid transporters (SNATs). The export of glutamine from astrocytes is mediated by the SNAT3(SLC38A3) and SNAT5 (SLC38A5) proteins, whereas its import to neurons relies on SNAT1(SLC38A1), SNAT2 (SLC38A2) and SNAT4 (SLC38A4) trans-porters (Scalise et al., 2016; Walls et al., 2015). Combined, these biochemical mechanisms constitute the glutamate – glutamine shuttle which is crucial for sustainable glutamatergic synaptic signalling transmission (Edwards, 2007; Tani et al., 2014; Walls et al., 2015). Synthesis and release of glutamine by astrocytes can increase in response to the synaptic release of glutamate; this feedback mechanism relies on Na$^+$-dependence of glutamate and glutamine transporters and elevation of cytosolic Na$^+$ -level in the perisynaptic astroglial processes (Broer et al., 2004; Todd et al., 2017; Uwechue et al., 2012). The latter could be provided, most likely, by astroglial glutamate receptors (Rose et al., 2017; Tani et al., 2014; Verkhratsky et al., 2020; Ziemens et al., 2019).

Owing to high structural plasticity of perisynaptic astrocytic pro-cesses (Bellesi et al., 2015; Iino et al., 2001; Krzisch et al., 2015; Per-ez-Alvarez et al., 2014), astroglial modulation of glutamate spillover and functional isolation of synapses are dynamically regulated (Bellesi et al., 2015; Benediktsson et al., 2012; Moussawi et al., 2011; Rose et al., 2017; Valtcheva and Venance, 2019). This can underlie a specific form of astroglia-driven regulation of synaptic plasticity. In particular, the Ca^{2+}-impermeable AMPA receptors of Bergmann glial cells were re-ported to affect the potentiation of glutamatergic transmission in the cerebellum via regulation of motility of perisynaptic glial processes and removal of glutamate (Iino et al., 2001). Later, the similar mechanism, but activated by the metabotropic Ca^{2+}-signalling in astrocytes, has been implicated into astroglia-driven regulation of synaptic meta-plasticity in the hippocampus and somatosensory cortex (Perez-Alvarez et al., 2014). The important role for activity-dependent motility of astroglia processes and astroglial control of glutamate spillover has been confirmed again by the data showing that withdrawal of perisynaptic processes enhances extrasynaptic cross-talk during LTP induction (Henneberger et al., 2020).

On top of structural plasticity, the co-localisation of glutamate re-ceptors and transporters in the astroglial processes enables mGluRs and

NMDARs to modulate surface expression and activity of astroglial EAATs and SNATs (Lavialle et al., 2011; Peterson and Binder, 2020; Rose et al., 2017; Umpierre et al., 2019; Ziemens et al., 2019). Com-bined, the above pathways constitute an important feedback mechanism of activity-dependent regulation of tripartite synapse. The role for this feedback loop can be augmented in the pathological context. In partic-ular, it has been shown recently that expression of mGluR5 in astrocytes re-emerges in mouse models of temporal lobe epilepsy and selective knock-out of astrocytic mGluR5 downregulates the glutamate clearance (Umpierre et al., 2019). Impairment of astrocytic glutamate receptor -glutamate transporter regulatory cascade has been implicated in many neurodegenerative and neurological disorders (Kim et al., 2017; Per-ez-Alvarez and Araque, 2013; Peterson and Binder, 2020).

3.2. Release of glutamate and D-Serine from astrocytes and astrocyte-to-neuron glutamatergic signalling

A capability of astrocytes to release the glutamate and D-Serine was a cornerstone of many theories of glia-neuron interaction from early days of research and still is one of the hotly debated issues in the astroglial physiology. Arguably, vesicular exocytosis is the most frequently re-ported pathway of glutamate release from glial cells. Exocytosis is a universal and evolutionary conserved mechanism of molecular export by eukaryotic cells and astrocytes possess all necessary components, such as synaptic-like micro-vesicles, SNARE proteins and vesicular transporters, including VGLUT1–3 (Martineau et al., 2013; Montana et al., 2004; Sahlender et al., 2014; Savtchouk and Volterra, 2018). Microvesicles, containing glutamate or D-Serine, were found in astro-cytes of several brain areas and their activity-dependent fusion with astroglial plasma membrane was repeatedly reported (Bezzi et al., 2004; Marchaland et al., 2008; Martineau et al., 2013; Mothet et al., 2005; Santello et al., 2011). The large body of evidence showed that activation of astrocytes produced various effects on glutamatergic transmission *in situ* and *in vivo*, which were inhibited by selective, pharmacological or genetic, inhibition of astrocytic Ca^{2+}-signalling, SNARE proteins and vesicular glutamate transporters (Araque et al., 2014; Sahlender et al., 2014; Verkhratsky and Nedergaard, 2018). Yet, majority of reported astroglia-driven glutamatergic effects are indirect and typically include up- and down-regulation of evoked and spontaneous excitatory post-synaptic currents, increase in neuronal excitability and pre- and post-synaptic potentiation (Araque et al., 2014; Navarrete et al., 2013; Perea and Araque, 2007; Perez-Alvarez and Araque, 2013; Savtchouk and Volterra, 2018).

There are several confounding factors which undermine a putative physiological significance of "symmetrical" vesicular glutamatergic transmission from astrocytes to neurons. Due to the differences in the sub-type composition of SNARE proteins and functional organisation of exocytosis-triggering Ca^{2+}-microdomains (Sahlender et al., 2014; Verkhratsky and Nedergaard, 2018) (e.g. lack of clusters of Ca^{2+}-channels in astrocytes), exocytosis in astrocytes is slower than in neurons and can develop in a time scale of hundreds of milliseconds after the onset of Ca^{2+}-elevation (Marchaland et al., 2008; Sahlender et al., 2014; Santello et al., 2011). The number and spatial clustering of glutamate-containing vesicles is also different in astrocytes, lacking any kind of "active zones" where vesicles concentrate (Araque et al., 2014; Perez-Alvarez and Araque, 2013; Savtchouk and Volterra, 2018). Hence, in contrast to the synaptic release, the astroglial release of glutamate would be more broadly distributed in time and space, preferentially targeting extra-synaptic neuronal membrane (Araque et al., 2014; Sah-lender et al., 2014).

So, one might expect that activation of Ca^{2+}-signalling in astrocytes would elicit a distinct population of transient transmembrane currents in neurons which would generally resemble spontaneous miniature synaptic currents but exhibit a smaller amplitude and slower kinetics then mEPSCs of synaptic origin, similarly to the neuronal currents activated by the vesicular release of ATP (Lalo et al., 2014). Since

astroglial exocytosis would produce a smaller elevation of extracellular glutamate, very likely at the extra-synaptic location, glutamatergic currents of astroglial origin should be mediated mainly by the extra-synaptic NMDA receptors containing GluN2B subunits (Hamilton and Attwell, 2010; Sahlender et al., 2014). This hypothesis, however, was not entirely confirmed by the experimental observations.

Ability of astroglial Ca^{2+}-elevation to induce bursts of transient glutamatergic currents of small amplitude in neurons *in situ* has not been demonstrated so far. A feasible explanation for the lack of such observations could be a small amplitude of putative NMDAR-mediated currents activated by the release of individual vesicles from astrocytes, which would put them beyond the threshold of detection. Although individual events of astroglial exocytosis of glutamate could come undetected, it is conceivable that they can build up a baseline tone of NMDAR-activity in neurons which could explain at least some effects of astrocytes on synaptic plasticity (Araque et al., 2014; Savtchouk and Volterra, 2018). So far, the only example of transient glutamatergic neuronal responses to the activation of neighbouring astrocytes is provided by the GluN2B-mediated spontaneous slow inward currents (SICs) of very low frequencies (<2 min^{-1}), which were detected *in situ* in several brain regions (Araque et al., 2014; Fiacco and McCarthy, 2018; Sahlender et al., 2014; Savtchouk and Volterra, 2018).

The biophysical properties of SICs, however, do not allow to unequivocally attribute them to the astroglial exocytosis (Fiacco and McCarthy, 2018; Perez-Alvarez and Araque, 2013; Verkhratsky and Nedergaard, 2018). Firstly, the NMDAR-mediated SICs exhibit much large amplitudes (typically >20–50 pA) and much slower rise and decay times (correspondingly 20–100 ms and 300–1000 ms) than what could be expected of currents elicited by individual synaptic-like vesicles. Rather, the currents of such magnitude and kinetics might be activated by release of a large multivesicular package, which seems not very likely in astrocytes accordingly to the morphological data (Fiacco and McCarthy, 2018; Hamilton and Attwell, 2010; Verkhratsky and Nedergaard, 2018). Secondly, the frequent failures and variable delays (in range of 1–20s) in the induction of SICs after astroglial Ca^{2+}elevation were observed. Finally, glutamatergic SICs might also by explained by indirect neuron-involving mechanism similar to the somatodendritic release of glutamate from Purkinje neurons (Duguid et al., 2007). So, the exact relation of SICs to the astroglial exocytosis is yet to be resolved; this could be done using similar approaches as in studies of astroglial ATP release (Lalo et al., 2014).

An alternative route for astroglial secretion of glutamate can be plasmalemmal ion channels. There is a large transmembrane concentration gradient of glutamate in astrocytes ([Glu]$_i$ ~0.3 mM, [Glu]$_O$ ~25 nM) and any pore large enough for glutamate to permeate would conduct its significant outflow. The most characterized ion channels capable to conduit glutamate include P2X7 receptors (in dilated state), connexins, volume-regulated and Ca^{2+}-dependent anion channels; all these channels have been reported to mediate the release of glutamate from astrocytes in different physiological context (Fellin et al., 2006; Hamilton and Attwell, 2010; Takano et al., 2005; Verkhratsky et al., 2014, 2016; Woo et al., 2012). Importantly, astrocytes can also release glutamate through the TREK-1 channels, directly activated by the interaction with G protein $\beta\gamma$-subunits (Woo et al., 2012). The kinetics of TREK-1 mediated outflux of glutamate are very close to those ones of glutamatergic SICs. This pathway of astroglial release can be triggered, potentially, by various metabotropic receptors including mGluRs. Glutamate release from astrocytes may also be mediated by the Ca^{2+}-dependent Bestrofin-1 chloride channels (Woo et al., 2012); this pathway was shown to activate the NMDA receptors in CA1 pyramidal neurons and modulate synaptic plasticity (Han et al., 2013; Park et al., 2015). The cooperation between astroglial exocytosis and channel-mediated release might explain many idiosyncrasies of glutamatergic glia-neuron interactions, yet this notion needs further investigation.

The issue of putative role for D-serine as gliotransmitter is even more complicated. It is widely accepted that D-serine acts as NMDA receptor co-agonists at excitatory synapses in many brain areas, including hippocampus, amygdala, hypothalamus and neocortex, and thereby is essential for the variety of cognitive functions. For more than two decades an important role of astrocytes as a powerful source of D-serine was widely accepted as a central dogma of glia-neuron communications. This view was based on extensive experimental data, including the presence of D-serine containing-vesicles in astrocytes (Martineau et al., 2013; Mothet et al., 2005; Schell et al., 1995), modulation of neuronal NMDARs induced by activation of astroglial Ca^{2+}-signalling and astroglial exocytosis and reliance of astroglia-driven modulation of synaptic plasticity on D-Serine (Halassa and Haydon, 2010; Henneberger et al., 2010; Panatier et al., 2006; Shigetomi et al., 2013). The role for impairment of astroglial release of D-Serine in cognitive deficits and neurodegenerative diseases has also been suggested (Araque et al., 2014; Halassa et al., 2007; Halassa and Haydon, 2010; Singh and Abraham, 2017).

However, this view has been recently scrutinized and an alternative model being suggested (Wolosker et al., 2016). This model states that, under physiological conditions, D-Serine is released predominantly by neurons and role for astrocytes in the D-serine mediated neuromodulation is confined to the supply of its obligatory precursor, L-serine, which cannot be synthesized in neurons. Once again, the question to what extent neurons and astrocytes act as sources of NMDA receptor co-agonists, and by what mechanisms co-agonists are released from either cell-type has become a topic of intense debate. The notion of predominant role of neurons in release of D-Serine originates mainly from the data suggesting a high level of expression of serine racemase (SRR) in neurons rather than astroglia. However, this contradicts to recent transcriptomic data showing relatively high level of *Srr* gene expression in cortical and hippocampal astrocytes (Chai et al., 2017). There are several other flaws in the "neuronal D-Serine" theory which have been thoroughly addressed by (Papouin et al., 2017b). One should note that even the studies, questioning astroglia-specific expression of serine racemase, do not deny an ability of astrocytes to accumulate D-serine and a reconciliating theory of cooperation between neuronal and glial release has been recently proposed (Ivanov and Mothet, 2019; Papouin et al., 2017b; Savtchouk and Volterra, 2018).

Whatever the intracellular D-Serine concentration is, the relative contribution of neurons and astrocytes into extracellular D-serine level will depend mainly on efficiency of neuronal *vs* glial mechanisms of release. Release of D-serine from astrocytes can occur via Ca^{2+}-dependent exocytosis, as suggested by work of (Sultan et al., 2015) where inhibition of vesicular release from astrocytes in transgenic models led to the impairment of D-Serine-mediated regulation of hippocampal synapses. Also, Ca^{2+}-dependent exocytosis of D-Serine has been implicated into astroglial response to the state of wakefulness and astroglial modulation of neuronal NMDA receptors (Papouin et al., 2017a). The SNARE-dependent exocytosis of D-Serine from neocortical astrocytes has also been supported by the direct measurements of its extracellular level with microelectrode biosensors (Lalo et al., 2018; Rasooli-Nejad et al., 2014). As an alternative pathway of Ca^{2+}-dependent D-Serine release, one might also suggest large conductance chloride channels (Woo et al., 2012). These channels have been shown to be permeable to glutamate (Woo et al., 2012) which has even larger molecular size than D-Serine.

So far, there is a lack direct evidence that neurons possess an efficient mechanism of release of D-serine (Papouin et al., 2017b). The Asc-1 transporter has been suggested to serve as main pathway of neuronal release (Wolosker et al., 2016). Compared to vesicular or channel-mediated release allowing the movement of multiple molecules, transporter, that releases a single molecule per single act of conformational change, is intrinsically slow. So, one could hardly expect the putative Asc-1 transporter-mediated release of D-Serine from neurons to be more efficient than Ca^{2+}-dependent release of D-Serine from astrocytes. This notion is supported by data showing the lack of D-Serine release from acutely isolated neocortical neurons (Lalo et al., 2018).

Still, despite an extensive experimental evidence of astrocyte-driven modulation of neuronal NMDA receptors, there is no definitive proof that astrocyte-derived glutamate and D-serine play crucial role in higher brain functions. It also remains elusive what mechanism, vesicular or channel-mediated, plays predominant role in the release of these glutamatergic agonists from astrocytes.

3.3. Modulation of glutamatergic synapses by other gliotransmitters

Beside the uptake and release of glutamate, the widely acknowledged function of astrocytes is a release of ATP, followed by its further conversion to adenosine. Astroglia-derived ATP has been implicated into propagation of glial Ca^{2+}-waves and the significant contribution of ATP and adenosine to the astroglia-driven modulation of neuronal activity and sleep homeostasis (Fields and Burnstock, 2006; Gourine et al., 2010; Halassa et al., 2007, 2009). The variety of molecular mechanisms of ATP release from astrocytes have been suggested, including exocytosis and concentration gradient-driven diffusion through the large conductance channels (Fields and Burnstock, 2006; Halassa et al., 2009; Lalo et al., 2011c). There is a large body of evidence that release of ATP from astrocytes may share common mechanisms of vesicular neurotransmitter release such as a dependence on the proton gradient and vesicular transporters, SNARE proteins and intracellular Ca^{2+}-elevation (Araque et al., 2014; Halassa et al., 2007; Hamilton and Attwell, 2010; Lalo et al., 2014; Zhang et al., 2007). As a source of Ca^{2+}-elevation, triggering the astroglial release of ATP, the glutamate and noradrenaline receptors have been widely reported (Boue-Grabot and Pankratov, 2017).

Neuronal receptors activated by astroglia-derived ATP and adenosine include correspondingly P2X/P2Y1 and A1/A2 receptors. These receptors activate several downstream cascades which converge to Ca^{2+}-dependent phosphorylation and regulation of trafficking of the post-synaptic NMDA and AMPA receptors (Boue-Grabot and Pankratov, 2017). In the framework of glutamatergic tripartite synapse, astroglia-derived ATP and adenosine were reported to cause bi-directional modulatory effects. While adenosine causes a suppression of glutamatergic EPSCs and EPSPs by presynaptic mechanisms (Martin et al., 2007; Pascual et al., 2005), the well-established effects of ATP include both enhancement (Gordon et al., 2005; Lalo et al., 2019; Lee et al., 2013) and down-scaling (Pougnet et al., 2016) of AMPAR-mediated signalling at postsynaptic *loci*. The former action occurs mainly via the P2X receptor-triggered PIK3-dependent insertion of AMPA receptors whereas the latter is underlined by the CaMKII-dependent internalization of AMPAR leading to a P2X receptor-dependent synaptic depression (Boue-Grabot and Pankratov, 2017; Pougnet et al., 2016). The P2 purinoreceptors can also cause an alteration of glutamatergic synapse plasticity by inhibiting NMDA function through the PSD-95/NMDAR complex (Lalo et al., 2016).

Another putative gliotransmitter, which has been recently implicated into regulation of glutamatergic synapses, is brain-derived neurotrophic factor (BDNF). The role for BDNF in the modulation of glutamatergic synaptic transmission and acute and homeostatic synaptic plasticity is well-established (Correa et al., 2012; Cowansage et al., 2010; Lu et al., 2013). There is growing evidence of capability of astrocytes to recycle (Vignoli et al., 2016) and release BDNF via Ca^{2+}-dependent (Stenovec et al., 2016) and mGluR3-dependent mechanisms (Durand et al., 2017). Astroglial release of BDNF has been recently reported to mediate the anti-aging effects of diet and exercise on the glutamatergic synapses in the neocortex (Lalo et al., 2020). This result is line with data linking the impairment of astroglial release of BDNF and age-related neurodegenerative disorders (Durand et al., 2017; Hong et al., 2016). There are also scattered data on modulation of glutamatergic synapses by the astroglia-released GABA (Kozlov et al., 2006; Lee et al., 2010b) or TNF-α (Stellwagen and Malenka, 2006).

In summary, astrocytes can strongly affect the glutamatergic synaptic signalling via multiple pathways, from which the most studied and best-established mechanism is the activity-dependent regulation of glutamate uptake. Despite a great effort made and numerous experimental results obtained, the detailed study of roles for astroglia-secreted transmitters, glutamate and D-Serine remains to be accomplished. Although the data on purinergic modulation of excitatory synapses are much less controversial, physiological relevance of this pathway is yet to be fully understood.

4. Physiological and pathological roles for glutamatergic glia-neuron interactions

Numerous morphological and functional data suggest that genesis and maturation of excitatory glutamatergic synapses occurs in the wake of astrogliogenesis (Eroglu and Barres, 2010; Miller and Gauthier, 2007) when neuronal developmental shift from massive synapse remodelling to more confined structural synaptic plasticity coincides with developmental shift in astroglial signalling somatic Ca^{2+}-oscillations to more localized Ca^{2+}- transients in astrocytic processes (Durkee and Araque, 2019; Khakh and Sofroniew, 2015; Verkhratsky and Nedergaard, 2014). During this events, astroglial perisynaptic sheath, which covers most excitatory synapses, is being formed and refined (Eroglu and Barres, 2010; Verkhratsky and Nedergaard, 2014). Across a lifetime, the astroglial coverage plays many essential roles in the homeostasis, maintenance, and plasticity of excitatory synapses (Rose et al., 2017; Valtcheva and Venance, 2019; Verkhratsky and Nedergaard, 2018). These roles rely on the activity of astroglial glutamate receptors and transporters. Age- and pathology-related alterations in glutamatergic communications within tripartite synapse can have both protective and pathogenic effects in the adult pathological brain (Halassa et al., 2007; Kim et al., 2017; Peterson and Binder, 2020; Verkhratsky et al., 2016).

4.1. Regulation of synaptic plasticity and cognitive functions

The most intensively studied and hotly debated, and yet mysterious, function of astrocytes in the brain is the regulation of synaptic plasticity and, therefore, direct contribution to the information processing. To a large extent, the notion of putative participation of astrocytes in cognitive functions, in particular learning and memory, has been based on their ability to respond to the synaptically released glutamate by regulating the extracellular glutamate and, thereby, the activity of synaptic glutamate receptors. Since crucial importance of neuronal NMDA and AMPA receptors for cognitive functions is universally recognized, the glutamatergic astrocyte-neuron interactions have been the centre of attention from early days of research into glial physiology (Araque et al., 2001; Halassa et al., 2007). Discovery of the glia-to-neuron transmission, in particular via release of glutamate and D-Serine (Bezzi et al., 2004; Montana et al., 2004; Panatier et al., 2006; Schell et al., 1995; Zhang et al., 2004), gave another impetus in search for significant role of astrocytes in the regulation of various types of synaptic plasticity.

A substantial experimental effort has been made to verify this notion in almost all region of the brain using a variety of techniques. The ability of astroglial uptake of glutamate and astrocyte-derived transmitters to modulate the strength of excitatory synaptic transmission and diversity in the mechanisms of this modulation is well-documented (Araque et al., 2014; Durkee and Araque, 2019; Halassa et al., 2007; Singh and Abraham, 2017; Verkhratsky and Nedergaard, 2014).

In particular, the activity-dependent regulation of astroglial morphology and glutamate uptake has been reported to regulated plasticity of glutamatergic synapses in the cerebellum (Iino et al., 2001), hippocampus (Arnth-Jensen et al., 2002; Marcaggi and Attwell, 2004; Moussawi et al., 2011) and somatosensory cortex (Perez-Alvarez et al., 2014) suggesting that control of NMDA receptor-dependent synaptic plasticity by astroglial glutamate could be a ubiquitous phenomenon in the brain (Valtcheva and Venance, 2019).

In the CA3-CA1 hippocampal excitatory synapses *in situ*, three seminal works reported different forms of synaptic plasticity which relied on

astrocytic Ca^{2+}-signalling and SNARE-dependent release of glutamate (Perea and Araque, 2007), ATP (Pascual et al., 2005) and D-Serine (Henneberger et al., 2010). While the former work reported the short-term potentiation dependent on the presynaptic mGluRs (Perea and Araque, 2007), two other studies were dealing with "classical" NMDAR-dependent LTP induced by tetanic stimulation of Schaffer collaterals. At the same time, astroglial release of glutamate was shown to mediate the spike-timing-dependent long-term depression (LTD) of glutamatergic transmission in the neocortical layer IV (Min and Nevian, 2012). Recently, Ca^{2+}-dependent release of ATP/adenosine from astrocytes has been reported to underlie the LTD in striatal synapses (Cavaccini et al., 2020).

These studies also have revealed an overwhelming complexity of astrocyte-neuron interactions, when release of even single gliotransmitter, e.g. glutamate, can exert opposing effects on synaptic transmission in the different spatial and physiological context (Durkee and Araque, 2019). The purinergic gliotransmitters were also shown to have bi-directional effects on glutamatergic synaptic transmission and NMDAR-dependent synaptic plasticity depression (Boue-Grabot and Pankratov, 2017; Pougnet et al., 2016). In addition, the presence of functionally different astroglial sub-populations associated to specific neuronal circuits and ability of astrocytes to release different gliotransmitters at different sub-cellular locations and in response to the different stimuli (Chai et al., 2017; Durkee and Araque, 2019; Perez-Alvarez and Araque, 2013; Rusakov et al., 2014) was suggested.

The extent of putative modulatory actions of astrocytes, both on individual glutamatergic synapses and large neuronal networks, appeared confusing and, in times, controversial (Agulhon et al., 2008; Hamilton and Attwell, 2010; Verkhratsky and Nedergaard, 2018). Moreover, some lines of evidence supporting importance of tripartite synapses in the synaptic plasticity and cognition, such as role for astroglial IP3-mediated Ca^{2+}-signalling and Ca^{2+}-dependent glial exocytosis of glutamate and D-Serine, were scrutinized (Agulhon et al., 2008; Fiacco and McCarthy, 2018; Petravicz et al., 2008; Wolosker et al., 2016). Also, it has been argued that many *ex vivo* studies study synaptic plasticity in brain slices of juvenile animals with immature astrocytes or use stimulation protocols which may compromise their metabolic and homeostatic functions leading to various artifacts in astrocyte-to-neuron signalling (Fiacco and McCarthy, 2018; Verkhratsky and Nedergaard, 2018). The initial wave of criticism (Agulhon et al., 2008; Hamilton and Attwell, 2010; Petravicz et al., 2008) was followed by a significant effort to reconcile available data and explain the apparent controversies (Bazargani and Attwell, 2016; Caudal et al., 2020; Durkee and Araque, 2019; Papouin et al., 2017b; Savtchouk and Volterra, 2018; Verkhratsky et al., 2020). Importantly, ability of astroglial glutamate receptors to monitor the activity of surrounding synapses and capability of astrocytes of activity-dependent regulation of glutamate uptake have never been opposed (Rose et al., 2017; Valtcheva and Venance, 2019; Verkhratsky and Nedergaard, 2018). Furthermore, these important functional features of astrocytes provide the basis for various models of astrocytes as integrators of neuronal information and regulators of synaptic homeostasis (Araque et al., 2014; Caudal et al., 2020; Durkee and Araque, 2019).

Apart from the modulation of short- and long-term synaptic plasticity, there is scattered evidence that process of learning is associated with structural and functional alterations with tripartite synapse. For instance, environmental enrichment has been shown to increase the astroglial synaptic coverage (Jones and Greenough, 1996; Rodriguez et al., 2013), which could lead to enhancement of glial uptake of glutamate, and to the enhancement of gliotransmitter release and astrocyte-driven modulation of excitatory synaptic transmission (Lalo et al., 2018, 2020). The astroglial exocytosis of ATP has been reported to down-regulate the NMDA receptors via PSD95 multiprotein complex (Lalo et al., 2016) and the impairment of this pathway was previously implicated into learning deficits (Migaud et al., 1998). Also, motor skill learning (Anderson et al., 1994) has been linked to the positive effect of hypertrophic astrocytes on synaptogenesis. Yet, these studies have not explored the causative role of astrocytes. So far, just a few studies have directly approached the role of glutamatergic tripartite synapse in learning and memory *in vivo* and some of these studies have brought controversial results (Caudal et al., 2020; Durkee and Araque, 2019; Fiacco and McCarthy, 2018; Verkhratsky and Nedergaard, 2018). So, direct participation of astroglial glutamate receptors and astroglia-driven glutamate in the complex cognitive functions or assistance to these functions via metabolic support remains an open question (Savtchouk and Volterra, 2018; Verkhratsky and Nedergaard, 2018). Further work, combining electrophysiological recordings in individual synapses and high-resolution fluorescent imaging in astrocytes expressing genetically-encoded Ca^{2+}- and cAMP-sensing proteins with behavioural studies and computer modelling, is needed to fully understand the relevance of tripartite synapse for cognitive function.

4.2. Roles in brain pathologies

It is widely accepted that impairment of astroglia-dependent glutamate homeostasis is a prerequisite for excitotoxic damage of brain tissue (Peterson and Binder, 2020; Planas-Fontanez et al., 2020). The aberrant glutamate uptake and excessive release from astrocytes have been repeatedly implicated in the pathogenicity of wide range of diseases, including ischemia, epilepsy, multiple sclerosis, Alzheimer's and Huntington diseases (Peters et al., 2009; Peterson and Binder, 2020; Verkhratsky et al., 2016). Due to key importance of glutamate uptake and glutamate/glutamine cycle for maintenance and plasticity of synaptic transmission (Edwards, 2007; Scalise et al., 2016; Schousboe et al., 2014; Valtcheva and Venance, 2019), their malfunction can lead to cognitive deficits. Indeed, downregulation of the expression and/or function of astroglial EAAT1, EAAT2 and SNAT transporters have been linked to epilepsy, ALS, schizophrenia, mood and anxiety disorders, Alzheimer's disease and addictive behaviour (Domingues et al., 2010; Lauriat and McInnes, 2007; Proper et al., 2002; Rothstein et al., 1995; Scofield, 2018; Verkhratsky and Parpura, 2016).

In response to immunological and biochemical challenges or brain injury, astrocytes can significantly alter their morphology and functions, becoming reactive astrocytes (Peterson and Binder, 2020; Planas-Fontanez et al., 2020; Verkhratsky and Parpura, 2016). Although effects caused by reactive astrocytes in neighbouring cells are complex and vary under different pathological situations, their neuroprotective action has been widely reported (Scalise et al., 2016; Walls et al., 2015). Regarding glutamatergic signalling and excitotoxicity, changes in the expression of mGluRs and iGluRs appear to be a typical reaction of astrocytes to various insults of central nervous system (Table 2). An important component of homeostatic response of astroglia, reported both in the model animals and human patients, is an increase in the expression and activity of mGluRs (Aronica et al., 2001; Geurts et al., 2003; Martorana et al., 2012; Planas-Fontanez et al., 2020; Umpierre et al., 2019). The neuroprotective effects caused by the activation of Group I and II receptors in reactive astrocytes include the enhancement of glutamate uptake (Battaglia et al., 2015; Peterson and Binder, 2020; Planas-Fontanez et al., 2020; Verkhratsky and Parpura, 2016) and release of glial neurotrophic factors, such as BDNF (Durand et al., 2017), glial-derived neurotrophic factor (Battaglia et al., 2015), and TGF-β (Planas-Fontanez et al., 2020; Spampinato et al., 2014). However, an excessive activation of mGluR5s followed by aberrant Ca^{2+}-signalling can also induce apoptosis in astrocytes (Martorana et al., 2012; Rossi et al., 2008) leading to detrimental consequences to neurons devoid of astroglial support. Although enhanced activity or overexpression mGluR5 receptors in the astrocytes were reported to contribute to the pathogenesis of epilepsy (Ding et al., 2007) and Fragile X Syndrome (Dolen and Bear, 2008), more recent data showed that overexpression of astrocytic mGluR5 could be induced by excessive neuronal activity as a compensatory mechanism (Umpierre et al., 2019). So, astroglial mGluRs can play both positive and negative roles in the defence mechanisms

Table 2
Roles for (astro)glial glutamate receptors in brain pathologies.

Receptor	Cell type/location	Species age	Disease/ pathological condition	Change in expression or activity	Effects and underlying mechanisms	Reference:
mGluR3	Hippocampal astrocytes in culture and *in situ*	Mouse AD model (PDAPP-J20)	Alzheimer's Disease	↓	The mGlu3R expression was reduced in hippocampal astrocytes from PDAPP-J20 mice. Selective activation of mGlu3R by LY379268 exerted neuroprotective effects in contrast to selective activation of mGluR2 which had neurotoxic effects. Neuroprotective activity of LY379268 was abolished in the wild-type neurons cultured with mGluR3-lacking astrocytes lacking mGlu3 receptors. Astrocytic mGlu3Rs mediate protection against Aβ neurotoxicity via the release of sAPPalpha and BDNF and activation of amyloid clearance from extracellular space by glia-mediated phagocytosis.	(Caraci et al., 2011; Durand et al., 2017)
mGluR3	Spinal cord astrocytes *in vivo* and in culture	ALS model mice (SOD1^{G93A}) mGluR3-KO mice	Amyotrophic Lateral Sclerosis	↑	Treatment of SOD1G93A mice with mGluR3 agonist LY379268 enhanced astrocytic expression of GLT-1 and release of GDNF. Effect of LY379268 was abolished in the mGluR3-KO mice.	Battaglia et al. (2015)
mGluR4	Cortical astrocytes *in situ* and in culture	MS model mice (EAE mice)	Multiple sclerosis Ischemia	↑	Stimulation of mGluR4 receptors reduced neuroinflammation in the EAE mice whereas knockout of mGluR4 exacerbated the EAE clinical symptoms. Astroglial mGluR4 receptors (contrary to microglia) mediate survival of oligodendrocytes under conditions of excitotoxicity and inflammation, most likely by activating the release of TGF-β.	(Besong et al., 2002; Spampinato et al., 2014)
mGluR5	Spinal cord astrocytes	ALS model mice (SOD1^{G93A})	Amyotrophic Lateral Sclerosis	↑↑	Upregulation of astrocytic mGluR5-mediated signalling led to degeneration of astrocytes, followed by impairment of glutamate uptake, excitotoxic damage and degeneration of neurons. Blocking mGluR5 *in vivo* slowed down the degeneration of astrocytes and delayed the onset of the disease.	(Rossi et al., 2008; Vergouts et al., 2018)
mGluR5	Hippocampal astrocytes	Adult mice (3–6 weeks)	Epilepsy	↑↑	The mGluR5-mediated Ca^{2+} signalling increased in astrocytes within 3 days during *status epilepticus* and contributed to cell death in the hippocampus. Selective loading of Ca^{2+}-chelators in astrocytes *ex vivo* after status epilepticus had neuroprotective action. Inhibition of mGluR5 *in vivo* (not cell-type specific) also produced neuroprotective effects.	Ding et al. (2007)
mGluR5	Hippocampal astrocytes	Adult mice (8–14 weeks)	Epilepsy	↑↑	The expression and activity of mGluR5 in astrocytes increased 3 days after the *status epilepticus*, most likely as a compensatory mechanism since mGluR5-expressing astrocytes exhibited enhanced glutamate uptake. Conditional knock-out of mGluR5 in astrocytes slowed down the glutamate clearance.	Umpierre et al. (2019)
NMDAR	Cortical astrocytes *in situ* and *in vivo*	Adult mice, model of focal cerebral ischemia	Ischemia	↑↑	Expression of GluN1, Glu2D and GluN3A subunits in astrocytes increased considerably after the focal ischemia. At the same time the glutamate-activated astrocytic Ca^{2+}-signalling decreased due to enhanced expression of GluN3A, suggesting a compensatory cell protective effect of alterations in NMDAR expression.	Dzamba et al. (2015)
NMDAR	Hippocampal astrocytes in culture	Mice	Alzheimer's Disease	↑↑	Chronic treatment with Aβ increased the expression of GluN2A and GluN2B NMDAR subunits in hippocampal astrocytes. However, changes in NMDAR expression had synaptoprotective effect, since pre-treatment of astrocytes with NMDAR antagonists MK-801 or CGP39551 exacerbate the Aβ-induced loss of PSD95 and synaptophysin. The synaptoprotective effect of was most mediated by astrocytic NMDAR-induced synthesis of nerve growth factor β (β-NGF).	Li et al. (2016)
AMPA (GluA1) AMPA (GluA2)	Spinal cord astrocytes	Adult rats	Ischemia	↑↑ ↓	The GluA1 subunit overexpression, accompanied by decreased GluA2 expression, was observed in the reactive astrocytes following experimental ischaemic spinal cord injury. The alterations in	(Hefferan et al., 2007; Oshiro et al., 2010)

Table 2 (*continued*)

Receptor	Cell type/location	Species age	Disease/ pathological condition	Change in expression or activity	Effects and underlying mechanisms	Reference:
AMPA (GluA2 subunit)	Spinal cord astrocytes	Mouse MS model (experimental autoimmune encephalomyelitis, EAE)	Multiple sclerosis	↓	expression of astrocytic AMPA receptors potentiated clinical signs of spasticity and rigidity, most likely via excitotoxic neuronal damage caused by secondary release of glutamate from astrocytes. Intrathecal or systemic treatment of animals with the selective AMPA receptor antagonist NGX424 ameliorated the ischemia-induced spasticity, very likely via inhibiting astrocytic Ca^{2+}-signalling. In reactive astrocytes, GluA2 subunit interacted with glyceraldehyde 3-phosphate dehydrogenase (GAPDH), enzyme of glycolysis metabolic pathway, recently implicated in initiation of apoptosis. Formation of GluA2-GADPH complex led to internalization of astrocytic AMPA receptors, causing deleterious effects on morphology and mitochondrial function of astrocytes, most likely via disrupting actin filament organisation and Ca^{2+}-dependent phosphorylation. Abnormal levels of GluA2-GADPH complex were associated with MS-related neurodegeneration both in the mouse models and human patients.	Lee et al. (2018)
KA (GluK2 subunit)	Cortical astrocytes in culture and *in vivo*	Adult mice	Mood disorders Excitotoxicity	↑	Overexpression and overactivation of astrocytic GluK2 receptors has been linked to Bipolar disorder and mood disorders. Most likely mechanism of GluK2-mediated excitotoxic cell damage is up-regulation of ERK phosphorylation. Chronic treatment of astrocytes, both in culture and *in vivo*, with the mood-stabilizing drugs (Li^+, carbamazepine or valproate) reduced the expression of GluK2 subunit and the glutamate-induced ERK phosphorylation.	Li et al. (2009)

against brain injuries and pharmacological manipulation of these receptors has been suggested as perspective therapeutic strategy, at least in some disease conditions (Planas-Fontanez et al., 2020; Verkhratsky et al., 2016).

Apart from the metabotropic glutamate receptors, response of astrocytes to brain pathologies also involves changes in expression of AMPA, KA and NMDA receptors (Cervetto et al., 2016; Hoogland et al., 2009; Peters et al., 2009; Rusnakova et al., 2013). Although potential contribution of Ca^{2+}-permeable astroglial AMPA and NMDA receptors to the aberrant elevation of cytosolic Ca^{2+} leading to apoptotic cell death and spreading of "vicious cycle" of excitotoxicity has been proposed (Ceprian and Fulton, 2019; Singh and Abraham, 2017; Verkhratsky and Parpura, 2016), their causative role in brain insults is yet to be verified. At the same time, changes in the expression and activity of astrocytic NMDARs and AMPARs were reported to have neuroprotective effects (Table 2) underlined by several mechanisms including down-regulation of astrocytic Ca^{2+}-signalling due to over-expression of GluN3A and GluA1 subunits (Dzamba et al., 2015; Hefferan et al., 2007), release of neurotrophic factors (Li et al., 2016) and modulation of glutamate uptake (Peterson and Binder, 2020; Rose et al., 2017; Verkhratsky and Nedergaard, 2018). Also, the Ca^{2+}-influx via NMDA receptors in the astrocytic endfeet have been implicated in the regulation of neurovascular coupling. This could underlie a potential role of astroglial NMDARs in diseases associated with impairment of brain metabolism, such as diabetes or vascular dementia. Still, the data on pathological connection of glial NMDAR receptors are scarce and related mainly to oligodendrocytes, which were shown to mediate white matter damage under ischaemic conditions (Karadottir et al., 2005; Salter and Fern, 2005).

In addition to modulation of structural plasticity of astrocytic processes and glutamate/glutamine cycle, astroglial mGluRs and NMDARs were shown to trigger the release of ATP (Cavaccini et al., 2020; Lalo et al., 2014; Letellier et al., 2016). The latter is widely acknowledged to serve as a "danger signal" in the brain; the important role for ATP-mediated signalling in various brain pathologies is universally recognized and extensively reviewed elsewhere, e.g. (Rodrigues et al., 2015; Verkhratsky et al., 2014). The putative role for ATP/Ado released by reactive astrocytes remains elusive. As for the astroglial-driven glutamate and D-Serine, their roles in brain diseases were frequently proposed in many thematic reviews (Halassa and Haydon, 2010; Planas-Fontanez et al., 2020; Singh and Abraham, 2017; Verkhratsky et al., 2016). Still, we think that detailed discussion of pathological implications of these gliotransmitters should be postponed until controversies about their physiological relevance are resolved.

4.3. Astrocytic glutamate receptors as perspective pharmacological targets

Involvement of glutamatergic signalling and glutamate homeostasis in variety of physiological functions and pathological processes underpins a great interest to development of therapeutic agents targeting glutamate receptors and transporters. The efficacy of mGluR and NMDAR ligands in treatment of various pathologies, such as depression, chronic pain, epilepsy, Parkinson's disease and drug addiction has been verified in numerous pre-clinical studies (Durand et al., 2013; Panatier and Robitaille, 2016; Peterson and Binder, 2020; Planas-Fontanez et al., 2020; Verkhratsky et al., 2014, 2016). Still, usage of glutamatergic compounds in clinical practice is hampered by various side-effects of different severity which originate from ubiquity of glutamate receptors and complexity of glutamatergic signalling in central and peripheral nervous systems (Durand et al., 2013; Niswender and Conn, 2010; Peterson and Binder, 2020; Planas-Fontanez et al., 2020). Most previous research and reported findings in the field were focused on neuronal glutamate receptors and contribution of astrocytes into complexity of glutamatergic interactions was underestimated. More recent data,

however, suggested that communications within the tripartite synapse could underlie both beneficial and adverse effects of modulators of glutamate transporters and receptors (Liu et al., 2017; Peterson and Binder, 2020; Planas-Fontanez et al., 2020; Verkhratsky et al., 2016). There is growing evidence that in many neurodegenerative diseases genetic and biochemical alterations in glial cells can precede or even cause pathological changes in neuronal function (Liu et al., 2017; Singh and Abraham, 2017; Soreq et al., 2017; Verkhratsky and Parpura, 2016). So, usage of astroglia-targeting compounds which could enhance homeostatic and neuroprotective function of astrocytes without negative side-effects on synaptic signalling has been widely suggested as a perspective therapeutic approach to brain dysfunction (Liu et al., 2017; Planas-Fontanez et al., 2020; Verkhratsky and Parpura, 2016; Verkhratsky et al., 2016).

Research in this area is still in its infancy and a main obstacle to overcome is entanglement of astrocytic and synaptic signalling mediated by metabotropic and ionotropic glutamate receptors (Table 3). Theoretically speaking, one might expect astrocyte-specific therapeutic effects of glutamate receptor ligands under certain, not mutually excluding, conditions: (i) preferential expression of certain types of mGluRs and/or iGluRs in reactive astrocytes in brain tissue affected by pathology, (ii) predominant role for astroglial glutamate receptors in physiological/pathological mechanisms involved and (iii) specific

action of drug on receptors selectively expressed by astrocytes. Interestingly, several works highlighted a stark contrast between specific neuroprotective action of astrocytic mGluR3 receptors and neurotoxic action of neuronal mGluR2 receptors (Caraci et al., 2011; Corti et al., 2007; Durand et al., 2013). This goes in line with preferential increase of mGluR3 expression in reactive astrocytes in the brain and spinal cord of rodent models and human patients in contrast to mGluR1, predominantly expressed in neurons, and mGluR5, represented both in neurons and glial cells (Aronica et al., 2001; Durand et al., 2013; Geurts et al., 2003; Planas-Fontanez et al., 2020). Thus, astroglial mGlu3R seems to be a perspective therapeutic target for treatment of neurodegenerative and psychiatric disorders (Battaglia et al., 2015; Planas-Fontanez et al., 2020). Selective activation of astroglial mGluR3 receptors by LY379268 and NAAG has been reported to exert neuroprotective effect against glutamate excitotoxicity and Aβ-induced neuro-degeneration (Battaglia et al., 2015; Caraci et al., 2011; Durand et al., 2013, 2017); LY379268 can also protect astrocytes against oxidative stress (Durand et al., 2013). In contrast to mGluR3, astrocytic mGluR5 receptors play mainly pro-pathogenic roles (Table 2) and administration of their specific antagonists, such as MPEP, exhibited neuroprotective effects in models of epilepsy and ALS (Peterson and Binder, 2020; Planas-Fontanez et al., 2020; Rossi et al., 2008). A suitability of mGluR5-ligands as astrocyte-targeting drugs is undermined, however, by their potential

Table 3
Perspective pharmacological agents modulating astroglial glutamatergic signalling.

Targeted Receptor	Drug	Action	EC50 or IC50	Astrocyte specificity	Notes	Reference
mGluR1	(S)-3,5-DHPG	Group I selective agonist	6–10 μM	No specificity	Does not discriminate between mGluR1 and mGluR5	Niswender and Conn (2010)
mGluR1	LY367385 LY 456236	mGluR1 selective antagonists	8.8 μM 143 nM	Weak specificity	In the pathological context, may preferentially affect astrocytes due to dramatic increase in mGluR1 expression	(Aoki et al., 2019; Niswender and Conn, 2010; Sukigara et al., 2014; Wang et al., 2006)
mGluR1	Ro 01-6128 Ro 67-7476	mGluR1 selective PAMs	104 nM 60 nM			
mGluR3	LY 379268	Group II selective agonist	4.5–5 nM	Moderate	Drug does not discriminate between mGluR2 and mGluR3. In the adult brain, mGluR2 is expressed predominantly in neurons, while mGluR3 expression is high in reactive astrocytes.	(Caraci et al., 2011; Corti et al., 2007; Durand et al., 2013; Geurts et al., 2003; Planas-Fontanez et al., 2020)
mGluR3	NAAG (N-acetyl-aspartyl-glutamate)	Endogenous agonist	10–50 μM	High	Affinity for mGluR3 is much higher than for other mGluRs, so action of NAAG may be highly specific for reactive astrocytes	Durand et al. (2013)
mGluR3	LY 541850 LY 395756	Antagonists for mGluR3 Agonists for mGluR2	~300 nM	High	One can expect opposing effects of these drugs in astrocytes and neurons	(Durand et al., 2013; Hanna et al., 2013; Niswender and Conn, 2010)
mGluR5	(S)-3,5-DHPG	Group I selective agonist	2–2.5 μM	No specificity	Does not discriminate between mGluR1 and mGluR5	Niswender and Conn (2010)
mGluR5	CDPPB VU 0360172 VU 0409551	mGluR5 highly selective PAM	10–20 nM 16 nM 260 nM	Weak	In the pathological context, may preferentially affect reactive astrocytes (as opposed to neurons) due to mGluR5 overexpression	(Aoki et al., 2019; Geurts et al., 2003; Niswender and Conn, 2010; Rossi et al., 2008; Umpierre et al., 2019; Vergouts et al., 2018)
mGluR5	MPEP MTEP	mGluR5 selective antagonists	36 nM 10 nM			
mGluR5	Fenobam	mGluR5 selective NAM	87 nM			
NMDAR NMDAR	UBP141 memantine	GluN2C/D subunit-specific antagonists	2.3 μM 2.2 μM	Moderate to High	These drugs affect astroglial receptors with much higher affinity than GluN2A/B-containing receptors (main neuronal NMDARs) Also, at therapeutic concentrations (0.1–0.5 μM), memantine would predominantly affect GluN2C/D-containing astrocytic NMDARs	(Kotermanski and Johnson, 2009; Palygin et al., 2011)
EAAT1/2	Riluzole	Positive modulator	~10 μM	Moderate	Enhances activity and upregulates gene expression membrane trafficking of astroglial Glu transporters. Also inhibits release of glutamate, uptake of GABA, voltage-gate Na-channels and TRPC5 channels. Toxic in high concentrations (>100 μM)	(Fumagalli et al., 2008; Liu et al., 2017; Peterson and Binder, 2020)

side-effects on synaptic transmission mediated by pre-synaptic mGluR5 receptors (Panatier and Robitaille, 2016; Planas-Fontanez et al., 2020).

Another interesting example of pharmacological specificity is provided by astrocytic NMDARs, which, due to their peculiar subunit composition, exhibit much higher sensitivity to GluNR2C/D subunit-selective antagonist UBP141 than neuronal receptors (Palygin et al., 2011). At physiological concentrations of extracellular Mg^{2+}, astrocytic NMDARs also show almost 7-fold higher affinity to the NMDAR antagonist memantine than neuronal GluN2A/B-containing receptors (Palygin et al., 2011). Hence, it is possible that inhibition of astrocytic NMDARs contributes to the therapeutic effects of memantine, especially at lower dosage. Potentially, astrocytic NMDAR can be highly sensitive to the GluN3 subunit-specific ligands. Yet, pharmacological properties and therapeutic effects of astroglial NMDAR remain largely unexplored.

Astrocytic glutamate transporters, which have been implicated in various pathologies linked to the neurotoxic effects of high concentration of glutamate (Ceprian and Fulton, 2019; Peterson and Binder, 2020; Singh and Abraham, 2017), also gain attention as perspective targets for glutamatergic therapeutic agents. Here, "astroglial specificity" of therapeutic action can arise from preferential expression of EAAT2 in astrocytes. The drugs up-regulating the expression of EAAT2, such as riluzole and ceftriaxone, showed beneficial effects, resulted from reduction of glutamate excitotoxicity, in animal models of Parkinson's Disease, ischemia, epilepsy, ALS and multiple sclerosis (Liu et al., 2017; Peterson and Binder, 2020; Planas-Fontanez et al., 2020). However, the therapeutic efficiency of riluzole and ceftriaxone in clinical trials of ALS and multiple sclerosis was not particularly high, which could be attributed to their side-effects on other signalling systems (De Angelis et al., 2020; Liu et al., 2017). The pre-clinical trials of ceftriaxone also revealed some adverse effects on synaptic plasticity and memory (Peterson and Binder, 2020). Relevance of these effects to the up-regulation of astroglial glutamate uptake is yet to be established.

Taken together, the available data on physiological and pathological aspects of glutamatergic tripartite synapse suggest good therapeutic perspectives for astrocyte-targeting drugs. However, further research, in particular in the cell type-specific KO mice and human astrocytes, is needed to harness this potential and translate data obtained in cell cultures and mouse models to clinical setting.

5. Summary

With discovery of multitude of effects exerted by synaptically-released glutamate on astrocytes and pathways of astroglial-driven modulation of extracellular levels of glutamate and activity of glutamate receptors, it becomes increasingly evident that astroglial element is inseparable from glutamatergic synapses. The role for glutamatergic astrocyte-neuron interactions in the brain computation is just starting to emerge. Although the mechanistic details and spatial dynamics of this interaction require further investigation, one can highlight two features common for many brain regions: (i) astrocytes often act as integrators of synaptic and metabolic signals and (ii) astrocytic perisynaptic processes can receive input from neurons and respond by rapid morphological alterations which in turn affect function of individual glutamatergic synapses. Astroglial glutamate receptors are instrumental for the integrative role of astrocytes due to their capability to regulate activity and surface expression of glutamate and glutamine transporters. Their preferential location to the astrocytic perisynaptic processes can facilitate an intimate interaction of astrocytes with a single synapse. Combination of the diffuse and localized communications between astrocytes and glutamatergic synapses enables spatially distributed and diverse modulation of neuronal firing thus contributing to the enrichment of information processing. Still, further experimental and theoretical work is needed to bridge the substantial gaps in our understanding of computational function of tripartite synapses and its relevance for cognitive functions.

An importance of the astroglial element for the homeostatic and

pathological alterations in the tripartite glutamatergic synapse is less controversial. A growing interest to the pathological aspects of glutamatergic astrocyte-neuron communications is based on the well-documented pivotal role for the glutamate uptake in the mechanisms of excitotoxicity and more recent data on alterations in the functional expression of glutamate receptors in reactive astrocytes. Yet, despite substantial descriptive work implicating the astroglial glutamate receptors and transporters in various neurological and neurodegenerative diseases, it is still unclear whether aging- and pathology-related changes in glutamatergic astroglial signalling has a neuroprotective or pathogenic role. Hopefully, recent advances in the optogenetic techniques and astrocyte-specific transgenic animals will help to answer this question and fully uncover therapeutic potential of astroglial glutamate receptors.

References

Adamsky, A., Kol, A., Kreisel, T., Doron, A., Ozeri-Engelhard, N., Melcer, T., Refaeli, R., Horn, H., Regev, L., Groysman, M., London, M., Goshen, I., 2018. Astrocytic activation generates de novo neuronal potentiation and memory enhancement. Cell 174, 59–71 e14.

Agulhon, C., Petravicz, J., McMullen, A.B., Sweger, E.J., Minton, S.K., Taves, S.R., Casper, K.B., Fiacco, T.A., McCarthy, K.D., 2008. What is the role of astrocyte calcium in neurophysiology? Neuron 59, 932–946.

Anderson, B.J., Li, X., Alcantara, A.A., Isaacs, K.R., Black, J.E., Greenough, W.T., 1994. Glial hypertrophy is associated with synaptogenesis following motor-skill learning, but not with angiogenesis following exercise. Glia 11, 73–80.

Aoki, Y., Hanai, S., Sukigara, S., Otsuki, T., Saito, T., Nakagawa, E., Kaido, T., Kaneko, Y., Takahashi, A., Ikegaya, N., Iwasaki, M., Sugai, K., Sasaki, M., Goto, Y., Oka, A., Itoh, M., 2019. Altered expression of astrocyte-related receptors and channels correlates with epileptogenesis in hippocampal sclerosis. Pediatr. Dev. Pathol. 22, 532–539.

Araque, A., Carmignoto, G., Haydon, P.G., 2001. Dynamic signaling between astrocytes and neurons. Annu. Rev. Physiol. 63, 795–813.

Araque, A., Carmignoto, G., Haydon, P.G., Oliet, S.H., Robitaille, R., Volterra, A., 2014. Gliotransmitters travel in time and space. Neuron 81, 728–739.

Arizono, M., Bannai, H., Mikoshiba, K., 2014. Imaging mGluR5 dynamics in astrocytes using quantum dots. Curr Protoc Neurosci 66, 2 21 21–22 21 18.

Arnth-Jensen, N., Jabaudon, D., Scanziani, M., 2002. Cooperation between independent hippocampal synapses is controlled by glutamate uptake. Nat. Neurosci. 5, 325–331.

Aronica, E., Catania, M.V., Geurts, J., Yankaya, B., Troost, D., 2001. Immunohistochemical localization of group I and II metabotropic glutamate receptors in control and amyotrophic lateral sclerosis human spinal cord: upregulation in reactive astrocytes. Neuroscience 105, 509–520.

Asztely, F., Erdemli, G., Kullmann, D.M., 1997. Extrasynaptic glutamate spillover in the hippocampus: dependence on temperature and the role of active glutamate uptake. Neuron 18, 281–293.

Battaglia, G., Riozzi, B., Bucci, D., Di Menna, L., Molinaro, G., Pallottino, S., Nicoletti, F., Bruno, V., 2015. Activation of mGlu3 metabotropic glutamate receptors enhances GDNF and GLT-1 formation in the spinal cord and rescues motor neurons in the SOD-1 mouse model of amyotrophic lateral sclerosis. Neurobiol. Dis. 74, 126–136.

Bazargani, N., Attwell, D., 2016. Astrocyte calcium signaling: the third wave. Nat. Neurosci. 19, 182–189.

Bellesi, M., de Vivo, L., Tononi, G., Cirelli, C., 2015. Effects of sleep and wake on astrocytes: clues from molecular and ultrastructural studies. BMC Biol. 13, 66.

Benediktsson, A.M., Marrs, G.S., Tu, J.C., Worley, P.F., Rothstein, J.D., Bergles, D.E., Dailey, M.E., 2012. Neuronal activity regulates glutamate transporter dynamics in developing astrocytes. Glia 60, 175–188.

Besong, G., Battaglia, G., D'Onofrio, M., Di Marco, R., Ngomba, R.T., Storto, M., Castiglione, M., Mangano, K., Busceti, C.L., Nicoletti, F.R., Bacon, K., Tusche, M., Valenti, O., Conn, P.J., Bruno, V., Nicoletti, F., 2002. Activation of group III metabotropic glutamate receptors inhibits the production of RANTES in glial cell cultures. J. Neurosci. 22, 5403–5411.

Bezzi, P., Gundersen, V., Galbete, J.L., Seifert, G., Steinhauser, C., Pilati, E., Volterra, A., 2004. Astrocytes contain a vesicular compartment that is competent for regulated exocytosis of glutamate. Nat. Neurosci. 7, 613–620.

Boue-Grabot, E., Pankratov, Y., 2017. Modulation of central synapses by astrocyte-released ATP and postsynaptic P2X receptors. Neural Plast. 2017, 9454275.

Brand-Schieber, E., Lowery, S.L., Werner, P., 2004. Select ionotropic glutamate AMPA/ kainate receptors are expressed at the astrocyte-vessel interface. Brain Res. 1007, 178–182.

Brand-Schieber, E., Werner, P., 2003. AMPA/kainate receptors in mouse spinal cord cell-specific display of receptor subunits by oligodendrocytes and astrocytes and at the nodes of Ranvier. Glia 42, 12–24.

Broer, A., Deitmer, J.W., Broer, S., 2004. Astroglial glutamine transport by system N is upregulated by glutamate. Glia 48, 298–310.

Burzomato, V., Frugier, G., Perez-Otano, I., Kittler, J.T., Attwell, D., 2010. The receptor subunits generating NMDA receptor mediated currents in oligodendrocytes. J. Physiol. 588, 3403–3414.

Cai, Z., Schools, G.P., Kimelberg, H.K., 2000. Metabotropic glutamate receptors in acutely isolated hippocampal astrocytes: developmental changes of mGluR5 mRNA and functional expression. Glia 29, 70–80.

Caraci, F., Molinaro, G., Battaglia, G., Giuffrida, M.L., Riozzi, B., Traficante, A., Bruno, V., Cannella, M., Merlo, S., Wang, X., Heinz, B.A., Nisenbaum, E.S., Britton, T. C., Drago, F., Sortino, M.A., Copani, A., Nicoletti, F., 2011. Targeting group II metabotropic glutamate (mGlu) receptors for the treatment of psychosis associated with Alzheimer's disease: selective activation of mGlu2 receptors amplifies beta-amyloid toxicity in cultured neurons, whereas dual activation of mGlu2 and mGlu3 receptors is neuroprotective. Mol. Pharmacol. 79, 618–626.

Carmignoto, G., Haydon, P.G., 2012. Astrocyte calcium signaling and epilepsy. Glia 60, 1227–1233.

Caudal, L.C., Gobbo, D., Scheller, A., Kirchhoff, F., 2020. The paradox of astroglial Ca(2 +) signals at the interface of excitation and inhibition. Front. Cell. Neurosci. 14, 609947.

Cavaccini, A., Durkee, C., Kofuji, P., Tonini, R., Araque, A., 2020. Astrocyte signaling gates long-term depression at corticostriatal synapses of the direct pathway. J. Neurosci. 40, 5757–5768.

Ceprian, M., Fulton, D., 2019. Glial cell AMPA receptors in nervous system health, injury and disease. Int. J. Mol. Sci. 20.

Cervetto, C., Frattaroli, D., Venturini, A., Passalacqua, M., Nobile, M., Alloisio, S., Tacchetti, C., Maura, G., Agnati, L.F., Marcoli, M., 2015. Calcium-permeable AMPA receptors trigger vesicular glutamate release from Bergmann gliosomes. Neuropharmacology 99, 396–407.

Cervetto, C., Vergani, L., Passalacqua, M., Ragazzoni, M., Venturini, A., Cecconi, F., Berretta, N., Mercuri, N., D'Amelio, M., Maura, G., Mariottini, P., Voci, A., Marcoli, M., Cervelli, M., 2016. Astrocyte-dependent vulnerability to excitotoxicity in spermine oxidase-overexpressing mouse. NeuroMolecular Med. 18, 50–68.

Chai, H., Diaz-Castro, B., Shigetomi, E., Monte, E., Octeau, J.C., Yu, X., Cohn, W., Rajendran, P.S., Vondriska, T.M., Whitelegge, J.P., Coppola, G., Khakh, B.S., 2017. Neural circuit-specialized astrocytes: transcriptomic, proteomic, morphological, and functional evidence. Neuron 95, 531–549 e539.

Chatton, J.Y., Magistretti, P.J., Barros, L.F., 2016. Sodium signaling and astrocyte energy metabolism. Glia 64, 1667–1676.

Conti, F., Barbaresi, P., Melone, M., Ducati, A., 1999. Neuronal and glial localization of NR1 and NR2A/B subunits of the NMDA receptor in the human cerebral cortex. Cerebr. Cortex 9, 110–120.

Conti, F., Minelli, A., Brecha, N.C., 1994. Cellular localization and laminar distribution of AMPA glutamate receptor subunits mRNAs and proteins in the rat cerebral cortex. J. Comp. Neurol. 350, 241–259.

Copeland, C.S., Wall, T.M., Sims, R.E., Neale, S.A., Nisenbaum, E., Parri, H.R., Salt, T.E., 2017. Astrocytes modulate thalamic sensory processing via mGlu2 receptor activation. Neuropharmacology 121, 100–110.

Cornell-Bell, A.H., Finkbeiner, S.M., Cooper, M.S., Smith, S.J., 1990. Glutamate induces calcium waves in cultured astrocytes: long-range glial signaling. Science 247, 470–473.

Correa, S.A., Hunter, C.J., Palygin, O., Wauters, S.C., Martin, K.J., McKenzie, C., McKelvey, K., Morris, R.G., Pankratov, Y., Arthur, J.S., Frenguelli, B.G., 2012. MSK1 regulates homeostatic and experience-dependent synaptic plasticity. J. Neurosci. 32, 13039–13051.

Corti, C., Battaglia, G., Molinaro, G., Riozzi, B., Pittaluga, A., Corsi, M., Mugnaini, M., Nicoletti, F., Bruno, V., 2007. The use of knock-out mice unravels distinct roles for mGlu2 and mGlu3 metabotropic glutamate receptors in mechanisms of neurodegeneration/neuroprotection. J. Neurosci. 27, 8297–8308.

Cowansage, K.K., LeDoux, J.E., Monfils, M.H., 2010. Brain-derived neurotrophic factor: a dynamic gatekeeper of neural plasticity. Curr. Mol. Pharmacol. 3, 12–29.

D'Ascenzo, M., Fellin, T., Terunuma, M., Revilla-Sanchez, R., Meaney, D.F., Auberson, Y. P., Moss, S.J., Haydon, P.G., 2007. mGluR5 stimulates gliotransmission in the nucleus accumbens. Proc. Natl. Acad. Sci. U. S. A. 104, 1995–2000.

Das, A., Wallace, G.C.t., Holmes, C., McDowell, M.L., Smith, J.A., Marshall, J.D., Bonilha, L., Edwards, J.C., Glazier, S.S., Ray, S.K., Banik, N.L., 2012. Hippocampal tissue of patients with refractory temporal lobe epilepsy is associated with astrocyte activation, inflammation, and altered expression of channels and receptors. Neuroscience 220, 237–246.

De Angelis, F., Connick, P., Parker, R.A., Plantone, D., Doshi, A., John, N., Stutters, J., MacManus, D., Prados, F., Marshall, I., Solanky, B., Samson, R.S., Barkhof, F., Ourselin, S., Braisher, M., Ross, M., Cranswick, G., Pavitt, S.H., Gnanapavan, S., Giovannoni, G., Wheeler-Kingshott, C., Hawkins, C., Sharrack, B., Bastow, R., Weir, C.J., Stallard, N., Chandran, S., Chataway, J., 2020. Amiloride, Fluoxetine or Riluzole to Reduce Brain Volume Loss in Secondary Progressive Multiple Sclerosis: the MS. SMART four-arm RCT, Southampton (UK).

De Strooper, B., Karran, E., 2016. The cellular phase of alzheimer's disease. Cell 164, 603–615.

Ding, S., Fellin, T., Zhu, Y., Lee, S.Y., Auberson, Y.P., Meaney, D.F., Coulter, D.A., Carmignoto, G., Haydon, P.G., 2007. Enhanced astrocytic Ca2+ signals contribute to neuronal excitotoxicity after status epilepticus. J. Neurosci. 27, 10674–10684.

Dolen, G., Bear, M.F., 2008. Role for metabotropic glutamate receptor 5 (mGluR5) in the pathogenesis of fragile X syndrome. J. Physiol. 586, 1503–1508.

Domingues, A.M., Taylor, M., Fern, R., 2010. Glia as transmitter sources and sensors in health and disease. Neurochem. Int. 57, 359–366.

Droste, D., Seifert, G., Seddar, L., Jadtke, O., Steinhauser, C., Lohr, C., 2017. Ca(2+)-permeable AMPA receptors in mouse olfactory bulb astrocytes. Sci. Rep. 7, 44817.

Duguid, I.C., Pankratov, Y., Moss, G.W., Smart, T.G., 2007. Somatodendritic release of glutamate regulates synaptic inhibition in cerebellar Purkinje cells via autocrine mGluR1 activation. J. Neurosci. 27, 12464–12474.

Durand, D., Carniglia, L., Caruso, C., Lasaga, M., 2013. mGlu3 receptor and astrocytes: partners in neuroprotection. Neuropharmacology 66, 1–11.

Durand, D., Carniglia, L., Turati, J., Ramirez, D., Saba, J., Caruso, C., Lasaga, M., 2017. Amyloid-beta neurotoxicity and clearance are both regulated by glial group II metabotropic glutamate receptors. Neuropharmacology 123, 274–286.

Durkee, C.A., Araque, A., 2019. Diversity and specificity of astrocyte-neuron communication. Neuroscience 396, 73–78.

Dzamba, D., Honsa, P., Valny, M., Kriska, J., Valihrach, L., Novosadova, V., Kubista, M., Anderova, M., 2015. Quantitative analysis of glutamate receptors in glial cells from the cortex of GFAP/EGFP mice following ischemic injury: focus on NMDA receptors. Cell. Mol. Neurobiol. 35, 1187–1202.

Edwards, R.H., 2007. The neurotransmitter cycle and quantal size. Neuron 55, 835–858.

Eroglu, C., Barres, B.A., 2010. Regulation of synaptic connectivity by glia. Nature 468, 223–231.

Eulenburg, V., Gomeza, J., 2010. Neurotransmitter transporters expressed in glial cells as regulators of synapse function. Brain Res. Rev. 63, 103–112.

Farb, C.R., Aoki, C., Ledoux, J.E., 1995. Differential localization of NMDA and AMPA receptor subunits in the lateral and basal nuclei of the amygdala: a light and electron microscopic study. J. Comp. Neurol. 362, 86–108.

Fellin, T., Pozzan, T., Carmignoto, G., 2006. Purinergic receptors mediate two distinct glutamate release pathways in hippocampal astrocytes. J. Biol. Chem. 281, 4274–4284.

Fiacco, T.A., McCarthy, K.D., 2018. Multiple lines of evidence indicate that gliotransmission does not occur under physiological conditions. J. Neurosci. 38, 3–13.

Fields, R.D., Burnstock, G., 2006. Purinergic signalling in neuron-glia interactions. Nat. Rev. Neurosci. 7, 423–436.

Fumagalli, E., Funicello, M., Rauen, T., Gobbi, M., Mennini, T., 2008. Riluzole enhances the activity of glutamate transporters GLAST, GLT1 and EAAC1. Eur. J. Pharmacol. 578, 171–176.

Garcia-Barcina, J.M., Matute, C., 1996. Expression of kainate-selective glutamate receptor subunits in glial cells of the adult bovine white matter. Eur. J. Neurosci. 8, 2379–2387.

Geurts, J.J., Wolswijk, G., Bo, L., van der Valk, P., Polman, C.H., Troost, D., Aronica, E., 2003. Altered expression patterns of group I and II metabotropic glutamate receptors in multiple sclerosis. Brain 126, 1755–1766.

Giaume, C., Koulakoff, A., Roux, L., Holcman, D., Rouach, N., 2010. Astroglial networks: a step further in neuroglial and gliovascular interactions. Nat. Rev. Neurosci. 11, 87–99.

Glaum, S.R., Holzwarth, J.A., Miller, R.J., 1990. Glutamate receptors activate Ca2+ mobilization and Ca2+ influx into astrocytes. Proc. Natl. Acad. Sci. U. S. A. 87, 3454–3458.

Gordon, G.R., Baimoukhametova, D.V., Hewitt, S.A., Rajapaksha, W.R., Fisher, T.E., Bains, J.S., 2005. Norepinephrine triggers release of glial ATP to increase postsynaptic efficacy. Nat. Neurosci. 8, 1078–1086.

Gourine, A.V., Kasymov, V., Marina, N., Tang, F., Figueiredo, M.F., Lane, S., Teschemacher, A.G., Spyer, K.M., Deisseroth, K., Kasparov, S., 2010. Astrocytes control breathing through pH-dependent release of ATP. Science 329, 571–575.

Hadzic, M., Jack, A., Wahle, P., 2017. Ionotropic glutamate receptors: which ones, when, and where in the mammalian neocortex. J. Comp. Neurol. 525, 976–1033.

Halassa, M.M., Fellin, T., Haydon, P.G., 2007. The tripartite synapse: roles for gliotransmission in health and disease. Trends Mol. Med. 13, 54–63.

Halassa, M.M., Florian, C., Fellin, T., Munoz, J.R., Lee, S.Y., Abel, T., Haydon, P.G., Frank, M.G., 2009. Astrocytic modulation of sleep homeostasis and cognitive consequences of sleep loss. Neuron 61, 213–219.

Halassa, M.M., Haydon, P.G., 2010. Integrated brain circuits: astrocytic networks modulate neuronal activity and behavior. Annu. Rev. Physiol. 72, 335–355.

Hamilton, N.B., Attwell, D., 2010. Do astrocytes really exocytose neurotransmitters? Nat. Rev. Neurosci. 11, 227–238.

Han, K.S., Woo, J., Park, H., Yoon, B.J., Choi, S., Lee, C.J., 2013. Channel-mediated astrocytic glutamate release via Bestrophin-1 targets synaptic NMDARs. Mol. Brain 6, 4.

Hanna, L., Ceolin, L., Lucas, S., Monn, J., Johnson, B., Collingridge, G., Bortolotto, Z., Lodge, D., 2013. Differentiating the roles of mGlu2 and mGlu3 receptors using LY541850, an mGlu2 agonist/mGlu3 antagonist. Neuropharmacology 66, 114–121.

Hefferan, M.P., Kucharova, K., Kinjo, K., Kakinohana, O., Sekerkova, G., Nakamura, S., Fuchigami, T., Tomori, Z., Yaksh, T.L., Kurtz, N., Marsala, M., 2007. Spinal astrocyte glutamate receptor 1 overexpression after ischemic insult facilitates behavioral signs of spasticity and rigidity. J. Neurosci. 27, 11179–11191.

Heja, L., Nyitrai, G., Kekesi, O., Dobolyi, A., Szabo, P., Fiath, R., Ulbert, I., Pal-Szenthe, B., Palkovits, M., Kardos, J., 2012. Astrocytes convert network excitation to tonic inhibition of neurons. BMC Biol. 10, 26.

Henneberger, C., Bard, L., Panatier, A., Reynolds, J.P., Kopach, O., Medvedev, N.I., Minge, D., Herde, M.K., Anders, S., Kraev, I., Heller, J.P., Rama, S., Zheng, K., Jensen, T.P., Sanchez-Romero, I., Jackson, C.J., Janovjak, H., Ottersen, O.P., Nagelhus, E.A., Oliet, S.H.R., Stewart, M.G., Nagerl, U.V., Rusakov, D.A., 2020. LTP induction boosts glutamate spillover by driving withdrawal of perisynaptic astroglia. Neuron 108, 919–936 e911.

Henneberger, C., Papouin, T., Oliet, S.H., Rusakov, D.A., 2010. Long-term potentiation depends on release of D-serine from astrocytes. Nature 463, 232–236.

Henson, M.A., Roberts, A.C., Perez-Otano, I., Philpot, B.D., 2010. Influence of the NR3A subunit on NMDA receptor functions. Prog. Neurobiol. 91, 23–37.

Hoft, S., Griemsmann, S., Seifert, G., Steinhauser, C., 2014. Heterogeneity in expression of functional ionotropic glutamate and GABA receptors in astrocytes across brain regions: insights from the thalamus. Philos. Trans. R. Soc. Lond. B Biol. Sci. 369, 20130602.

Hong, Y., Zhao, T., Li, X.J., Li, S., 2016. Mutant huntingtin impairs BDNF release from astrocytes by disrupting conversion of rab3a-GTP into rab3a-GDP. J. Neurosci. 36, 8790–8801.

Honsek, S.D., Walz, C., Kafitz, K.W., Rose, C.R., 2012. Astrocyte calcium signals at Schaffer collateral to CA1 pyramidal cell synapses correlate with the number of activated synapses but not with synaptic strength. Hippocampus 22, 29–42.

Hoogland, T.M., Kuhn, B., Gobel, W., Huang, W., Nakai, J., Helmchen, F., Flint, J., Wang, S.S., 2009. Radially expanding transglial calcium waves in the intact cerebellum. Proc. Natl. Acad. Sci. U. S. A. 106, 3496–3501.

Iino, M., Goto, K., Kakegawa, W., Okado, H., Sudo, M., Ishiuchi, S., Miwa, A., Takayasu, Y., Saito, I., Tsuzuki, K., Ozawa, S., 2001. Glia-synapse interaction through Ca2+-permeable AMPA receptors in Bergmann glia. Science 292, 926–929.

Ivanov, A.D., Mothet, J.P., 2019. The plastic d-serine signaling pathway: sliding from neurons to glia and vice-versa. Neurosci. Lett. 689, 21–25.

Jabs, R., Kirchhoff, F., Kettenmann, H., Steinhauser, C., 1994. Kainate activates Ca(2+)-permeable glutamate receptors and blocks voltage-gated K+ currents in glial cells of mouse hippocampal slices. Pflügers Archiv 426, 310–319.

Jackson, J.G., O'Donnell, J.C., Takano, H., Coulter, D.A., Robinson, M.B., 2014. Neuronal activity and glutamate uptake decrease mitochondrial mobility in astrocytes and position mitochondria near glutamate transporters. J. Neurosci. 34, 1613–1624.

Jones, T.A., Greenough, W.T., 1996. Ultrastructural evidence for increased contact between astrocytes and synapses in rats reared in a complex environment. Neurobiol. Learn. Mem. 65, 48–56.

Karadottir, R., Cavelier, P., Bergersen, L.H., Attwell, D., 2005. NMDA receptors are expressed in oligodendrocytes and activated in ischaemia. Nature 438, 1162–1166.

Khakh, B.S., Sofroniew, M.V., 2015. Diversity of astrocyte functions and phenotypes in neural circuits. Nat. Neurosci. 18, 942–952.

Kim, S.K., Nabekura, J., Koizumi, S., 2017. Astrocyte-mediated synapse remodeling in the pathological brain. Glia 65, 1719–1727.

King, C.M., Bohmbach, K., Minge, D., Delekate, A., Zheng, K., Reynolds, J., Rakers, C., Zeug, A., Petzold, G.C., Rusakov, D.A., Henneberger, C., 2020. Local resting Ca(2+) controls the scale of astroglial Ca(2+) signals. Cell Rep. 30, 3466–3477 e3464.

Kotermanski, S.E., Johnson, J.W., 2009. Mg2+ imparts NMDA receptor subtype selectivity to the Alzheimer's drug memantine. J. Neurosci. 29, 2774–2779.

Kozlov, A.S., Angulo, M.C., Audinat, E., Charpak, S., 2006. Target cell-specific modulation of neuronal activity by astrocytes. Proc. Natl. Acad. Sci. U. S. A. 103, 10058–10063.

Krzisch, M., Temprana, S.G., Mongiat, L.A., Armida, J., Schmutz, V., Virtanen, M.A., Kocher-Braissant, J., Kraftsik, R., Vutskits, L., Conzelmann, K.K., Bergami, M., Gage, F.H., Schinder, A.F., Toni, N., 2015. Pre-existing astrocytes form functional perisynaptic processes on neurons generated in the adult hippocampus. Brain Struct. Funct. 220, 2027–2042.

Lalo, U., Bogdanov, A., Moss, G.W., Pankratov, Y., 2020. Astroglia-derived BDNF and MSK-1 mediate experience- and diet-dependent synaptic plasticity. Brain Sci. 10.

Lalo, U., Bogdanov, A., Pankratov, Y., 2018. Diversity of astroglial effects on aging- and experience-related cortical metaplasticity. Front. Mol. Neurosci. 11, 239.

Lalo, U., Bogdanov, A., Pankratov, Y., 2019. Age- and experience-related plasticity of ATP-mediated signaling in the neocortex. Front. Cell. Neurosci. 13, 242.

Lalo, U., Palygin, O., North, R.A., Verkhratsky, A., Pankratov, Y., 2011a. Age-dependent remodelling of ionotropic signalling in cortical astroglia. Aging Cell 10, 392–402.

Lalo, U., Palygin, O., Rasooli-Nejad, S., Andrew, J., Haydon, P.G., Pankratov, Y., 2014. Exocytosis of ATP from astrocytes modulates phasic and tonic inhibition in the neocortex. PLoS Biol. 12, e1001747.

Lalo, U., Palygin, O., Verkhratsky, A., Grant, S.G., Pankratov, Y., 2016. ATP from synaptic terminals and astrocytes regulates NMDA receptors and synaptic plasticity through PSD-95 multi-protein complex. Sci. Rep. 6, 33609.

Lalo, U., Pankratov, Y., Kirchhoff, F., North, R.A., Verkhratsky, A., 2006. NMDA receptors mediate neuron-to-glia signaling in mouse cortical astrocytes. J. Neurosci. 26, 2673–2683.

Lalo, U., Pankratov, Y., Parpura, V., Verkhratsky, A., 2011b. Ionotropic receptors in neuronal-astroglial signalling: what is the role of "excitable" molecules in non-excitable cells. Biochim. Biophys. Acta 1813, 992–1002.

Lalo, U., Verkhratsky, A., Pankratov, Y., 2011c. Ionotropic ATP receptors in neuronal-glial communication. Semin. Cell Dev. Biol. 22, 220–228.

Lauriat, T.L., McInnes, L.A., 2007. EAAT2 regulation and splicing: relevance to psychiatric and neurological disorders. Mol. Psychiatr. 12, 1065–1078.

Lavialle, M., Aumann, G., Anlauf, E., Prols, F., Arpin, M., Derouiche, A., 2011. Structural plasticity of perisynaptic astrocyte processes involves ezrin and metabotropic glutamate receptors. Proc. Natl. Acad. Sci. U. S. A. 108, 12915–12919.

Lazutkaite, G., Solda, A., Lossow, K., Meyerhof, W., Dale, N., 2017. Amino acid sensing in hypothalamic tanycytes via umami taste receptors. Mol Metab 6, 1480–1492.

Lee, F.H.F., Zhang, H., Jiang, A., Zai, C.C., Liu, F., 2018. Specific alterations in astrocyte properties via the GluA2-GAPDH complex associated with multiple sclerosis. Sci. Rep. 8, 12856.

Lee, H.U., Yamazaki, Y., Tanaka, K.F., Furuya, K., Sokabe, M., Hida, H., Takao, K., Miyakawa, T., Fujii, S., Ikenaka, K., 2013. Increased astrocytic ATP release results in enhanced excitability of the hippocampus. Glia 61, 210–224.

Lee, M.C., Ting, K.K., Adams, S., Brew, B.J., Chung, R., Guillemin, G.J., 2010a. Characterisation of the expression of NMDA receptors in human astrocytes. PloS One 5, e14123.

Lee, S., Yoon, B.E., Berglund, K., Oh, S.J., Park, H., Shin, H.S., Augustine, G.J., Lee, C.J., 2010b. Channel-mediated tonic GABA release from glia. Science 330, 790–796.

Letellier, M., Park, Y.K., Chater, T.E., Chipman, P.H., Gautam, S.G., Oshima-Takago, T., Goda, Y., 2016. Astrocytes regulate heterogeneity of presynaptic strengths in hippocampal networks. Proc. Natl. Acad. Sci. U. S. A. 113, E2685–E2694.

Li, B., Zhang, S., Li, M., Zhang, H., Hertz, L., Peng, L., 2009. Down-regulation of GluK2 kainate receptor expression by chronic treatment with mood-stabilizing anti-convulsants or lithium in cultured astrocytes and brain, but not in neurons. Neuropharmacology 57, 375–385.

Li, Y., Chang, L., Song, Y., Gao, X., Roselli, F., Liu, J., Zhou, W., Fang, Y., Ling, W., Li, H., Almeida, O.F., Wu, Y., 2016. Astrocytic GluN2A and GluN2B oppose the synaptotoxic effects of amyloid-beta 1-40 in hippocampal cells. J Alzheimers Dis 54, 135–148.

Lipton, S.A., 2006. NMDA receptors, glial cells, and clinical medicine. Neuron 50, 9–11.

Liu, B., Teschemacher, A.G., Kasparov, S., 2017. Astroglia as a cellular target for neuroprotection and treatment of neuro-psychiatric disorders. Glia 65, 1205–1226.

Lu, B., Nagappan, G., Guan, X., Nathan, P.J., Wren, P., 2013. BDNF-based synaptic repair as a disease-modifying strategy for neurodegenerative diseases. Nat. Rev. Neurosci. 14, 401–416.

Luque, J.M., Richards, J.G., 1995. Expression of NMDA 2B receptor subunit mRNA in Bergmann glia. Glia 13, 228–232.

Marcaggi, P., Attwell, D., 2004. Role of glial amino acid transporters in synaptic transmission and brain energetics. Glia 47, 217–225.

Marchaland, J., Cali, C., Voglmaier, S.M., Li, H., Regazzi, R., Edwards, R.H., Bezzi, P., 2008. Fast subplasma membrane Ca2+ transients control exo-endocytosis of synaptic-like microvesicles in astrocytes. J. Neurosci. 28, 9122–9132.

Martin, E.D., Fernandez, M., Perea, G., Pascual, O., Haydon, P.G., Araque, A., Cena, V., 2007. Adenosine released by astrocytes contributes to hypoxia-induced modulation of synaptic transmission. Glia 55, 36–45.

Martineau, M., Shi, T., Puyal, J., Knolhoff, A.M., Dulong, J., Gasnier, B., Klingauf, J., Sweedler, J.V., Jahn, R., Mothet, J.P., 2013. Storage and uptake of D-serine into astrocytic synaptic-like vesicles specify gliotransmission. J. Neurosci. 33, 3413–3423.

Martorana, F., Brambilla, L., Valori, C.F., Bergamaschi, C., Roncoroni, C., Aronica, E., Volterra, A., Bezzi, P., Rossi, D., 2012. The BH4 domain of Bcl-X(L) rescues astrocyte degeneration in amyotrophic lateral sclerosis by modulating intracellular calcium signals. Hum. Mol. Genet. 21, 826–840.

Matschke, V., Theiss, C., Hollmann, M., Schulze-Bahr, E., Lang, F., Seebohm, G., Strutz-Seebohm, N., 2015. NDRG2 phosphorylation provides negative feedback for SGK1-dependent regulation of a kainate receptor in astrocytes. Front. Cell. Neurosci. 9, 387.

Micu, I., Jiang, Q., Coderre, E., Ridsdale, A., Zhang, L., Woulfe, J., Yin, X., Trapp, B.D., McRory, J.E., Rehak, R., Zamponi, G.W., Wang, W., Stys, P.K., 2006. NMDA receptors mediate calcium accumulation in myelin during chemical ischaemia. Nature 439, 988–992.

Migaud, M., Charlesworth, P., Dempster, M., Webster, L.C., Watabe, A.M., Makhinson, M., He, Y., Ramsay, M.F., Morris, R.G., Morrison, J.H., O'Dell, T.J., Grant, S.G., 1998. Enhanced long-term potentiation and impaired learning in mice with mutant postsynaptic density-95 protein. Nature 396, 433–439.

Miller, F.D., Gauthier, A.S., 2007. Timing is everything: making neurons versus glia in the developing cortex. Neuron 54, 357–369.

Min, R., Nevian, T., 2012. Astrocyte signaling controls spike timing-dependent depression at neocortical synapses. Nat. Neurosci. 15, 746–753.

Molders, A., Koch, A., Menke, R., Klocker, N., 2018. Heterogeneity of the astrocytic AMPA-receptor transcriptome. Glia 66, 2604–2616.

Montana, V., Ni, Y., Sunjara, V., Hua, X., Parpura, V., 2004. Vesicular glutamate transporter-dependent glutamate release from astrocytes. J. Neurosci. 24, 2633–2642.

Morel, L., Higashimori, H., Tolman, M., Yang, Y., 2014. VGluT1+ neuronal glutamatergic signaling regulates postnatal developmental maturation of cortical protoplasmic astroglia. J. Neurosci. 34, 10950–10962.

Mothet, J.P., Pollegioni, L., Ouanounou, G., Martineau, M., Fossier, P., Baux, G., 2005. Glutamate receptor activation triggers a calcium-dependent and SNARE protein-dependent release of the gliotransmitter D-serine. Proc. Natl. Acad. Sci. U. S. A. 102, 5606–5611.

Moussawi, K., Riegel, A., Nair, S., Kalivas, P.W., 2011. Extracellular glutamate: functional compartments operate in different concentration ranges. Front. Syst. Neurosci. 5, 94.

Muller, T., Grosche, J., Ohlemeyer, C., Kettenmann, H., 1993. NMDA-activated currents in Bergmann glial cells. Neuroreport 4, 671–674.

Muller, T., Moller, T., Berger, T., Schnitzer, J., Kettenmann, H., 1992. Calcium entry through kainate receptors and resulting potassium-channel blockade in Bergmann glial cells. Science 256, 1563–1566.

Navarrete, M., Perea, G., Maglio, L., Pastor, J., Garcia de Sola, R., Araque, A., 2013. Astrocyte calcium signal and gliotransmission in human brain tissue. Cerebr. Cortex 23, 1240–1246.

Nedergaard, M., 1994. Direct signaling from astrocytes to neurons in cultures of mammalian brain cells. Science 263, 1768–1771.

Niswender, C.M., Conn, P.J., 2010. Metabotropic glutamate receptors: physiology, pharmacology, and disease. Annu. Rev. Pharmacol. Toxicol. 50, 295–322.

Orre, M., Kamphuis, W., Osborn, L.M., Melief, J., Kooijman, L., Huitinga, I., Klooster, J., Bossers, K., Hol, E.M., 2014. Acute isolation and transcriptome characterization of cortical astrocytes and microglia from young and aged mice. Neurobiol. Aging 35, 1–14.

Oshiro, M., Hefferan, M.P., Kakinohana, O., Lukacova, N., Sugahara, K., Yaksh, T.L., Marsala, M., 2010. Suppression of stretch reflex activity after spinal or systemic treatment with AMPA receptor antagonist NGX424 in rats with developed baclofen tolerance. Br. J. Pharmacol. 161, 976–985.

Otis, T.S., Wu, Y.C., Trussell, L.O., 1996. Delayed clearance of transmitter and the role of glutamate transporters at synapses with multiple release sites. J. Neurosci. 16, 1634–1644.

Overstreet, L.S., Kinney, G.A., Liu, Y.B., Billups, D., Slater, N.T., 1999. Glutamate transporters contribute to the time course of synaptic transmission in cerebellar granule cells. J. Neurosci. 19, 9663–9673.

Palygin, O., Lalo, U., Pankratov, Y., 2011. Distinct pharmacological and functional properties of NMDA receptors in mouse cortical astrocytes. Br. J. Pharmacol. 163, 1755–1766.

Palygin, O., Lalo, U., Verkhratsky, A., Pankratov, Y., 2010. Ionotropic NMDA and P2X1/5 receptors mediate synaptically induced Ca2+ signalling in cortical astrocytes. Cell Calcium 48, 225–231.

Panatier, A., Robitaille, R., 2016. Astrocytic mGluR5 and the tripartite synapse. Neuroscience 323, 29–34.

Panatier, A., Theodosis, D.T., Mothet, J.P., Touquet, B., Pollegioni, L., Poulain, D.A., Oliet, S.H., 2006. Glia-derived D-serine controls NMDA receptor activity and synaptic memory. Cell 125, 775–784.

Panatier, A., Vallee, J., Haber, M., Murai, K.K., Lacaille, J.C., Robitaille, R., 2011. Astrocytes are endogenous regulators of basal transmission at central synapses. Cell 146, 785–798.

Papouin, T., Dunphy, J.M., Tolman, M., Dineley, K.T., Haydon, P.G., 2017a. Septal cholinergic neuromodulation tunes the astrocyte-dependent gating of hippocampal NMDA receptors to wakefulness. Neuron 94, 840–854 e847.

Papouin, T., Henneberger, C., Rusakov, D.A., Oliet, S.H.R., 2017b. Astroglial versus neuronal D-serine: fact checking. Trends Neurosci. 40 (9), 517–520.

Park, H., Han, K.S., Seo, J., Lee, J., Dravid, S.M., Woo, J., Chun, H., Cho, S., Bae, J.Y., An, H., Koh, W., Yoon, B.E., Berlinguer-Palmini, R., Mannaioni, G., Traynelis, S.F., Bae, Y.C., Choi, S.Y., Lee, C.J., 2015. Channel-mediated astrocytic glutamate modulates hippocampal synaptic plasticity by activating postsynaptic NMDA receptors. Mol Brain 8, 7.

Parpura, V., Basarsky, T.A., Liu, F., Jeftinija, K., Jeftinija, S., Haydon, P.G., 1994. Glutamate-mediated astrocyte-neuron signalling. Nature 369, 744–747.

Pascual, O., Casper, K.B., Kubera, C., Zhang, J., Revilla-Sanchez, R., Sul, J.Y., Takano, H., Moss, S.J., McCarthy, K., Haydon, P.G., 2005. Astrocytic purinergic signaling coordinates synaptic networks. Science 310, 113–116.

Perea, G., Araque, A., 2007. Astrocytes potentiate transmitter release at single hippocampal synapses. Science 317, 1083–1086.

Perez-Alvarez, A., Araque, A., 2013. Astrocyte-neuron interaction at tripartite synapses. Curr Drug Targets 14, 1220–1224.

Perez-Alvarez, A., Navarrete, M., Covelo, A., Martin, E.D., Araque, A., 2014. Structural and functional plasticity of astrocyte processes and dendritic spine interactions. J Neurosci 34, 12738–12744.

Peters, O., Schipke, C.G, Philipps, A., Haas, B., Pannasch, U., Wang, L.P., Benedetti, B., Kingston, A.E., Kettenmann, H., 2009. Astrocyte function is modified by Alzheimer's disease-like pathology in aged mice. J Alzheimers Dis 18, 177–189.

Peterson, A.R., Binder, D.K., 2020. Astrocyte glutamate uptake and signaling as novel targets for antiepileptogenic therapy. Front Neurol 11, 1006.

Petravicz, J., Fiacco, T.A., McCarthy, K.D., 2008. Loss of IP3 receptor-dependent Ca2+ increases in hippocampal astrocytes does not affect baseline CA1 pyramidal neuron synaptic activity. J Neurosci 28, 4967–4973.

Planas-Fontanez, T.M., Dreyfus, C.F., Saitta, K.S., 2020. Reactive astrocytes as therapeutic targets for brain degenerative diseases: roles played by metabotropic glutamate receptors. Neurochem Res 45, 541–550.

Porter, J.T., McCarthy, K.D., 1995. GFAP-positive hippocampal astrocytes in situ respond to glutamatergic neuroligands with increases in [Ca2+]i. Glia 13, 101–112.

Porter, J.T., McCarthy, K.D., 1996. Hippocampal astrocytes in situ respond to glutamate released from synaptic terminals. J Neurosci 16, 5073–5081.

Pougnet, J.T., Compans, B., Martinez, A., Choquet, D., Hosy, E., Boue-Grabot, E., 2016. P2X-mediated AMPA receptor internalization and synaptic depression is controlled by two CaMKII phosphorylation sites on GluA1 in hippocampal neurons. Sci Rep 6, 31836.

Proper, E.A., Hoogland, G., Kappen, S.M., Jansen, G.H., Rensen, M.G., Schrama, L.H., van Veelen, C.W., van Rijen, P.C., van Nieuwenhuizen, O., Gispen, W.H., de Graan, P.N., 2002. Distribution of glutamate transporters in the hippocampus of patients with pharmaco-resistant temporal lobe epilepsy. Brain 125, 32–43.

Rasooli-Nejad, S., Palygin, O., Lalo, U., Pankratov, Y., 2014. Cannabinoid receptors contribute to astroglial Ca(2)(+)-signalling and control of synaptic plasticity in the neocortex. Philos Trans R Soc Lond B Biol Sci 369, 20140077.

Ravikrishnan, A., Gandhi, P.J., Shelkar, G.P., Liu, J., Pavuluri, R., Dravid, S.M., 2018. Region-specific expression of NMDA receptor GluN2C subunit in parvalbumin-positive neurons and astrocytes: analysis of GluN2C expression using a novel reporter model. Neuroscience 380, 49–62.

Rodrigues, R.J., Tome, A.R., Cunha, R.A., 2015. ATP as a multi-target danger signal in the brain. Front Neurosci 9, 148.

Rodriguez, J.J., Terzieva, S., Olabarria, M., Lanza, R.G., Verkhratsky, A., 2013. Enriched environment and physical activity reverse astrogliodegeneration in the hippocampus of AD transgenic mice. Cell Death Dis 4, e678.

Rose, C.R., Felix, L., Zeug, A., Dietrich, D., Reiner, A., Henneberger, C., 2017. Astroglial glutamate signaling and uptake in the Hippocampus. Front Mol Neurosci 10, 451.

Rossi, D., Brambilla, L., Valori, C.F., Roncoroni, C., Crugnola, A., Yokota, T., Bredesen, D. E., Volterra, A., 2008. Focal degeneration of astrocytes in amyotrophic lateral sclerosis. Cell Death Differ 15, 1691–1700.

Rothstein, J.D., Van Kammen, M., Levey, A.I., Martin, L.J., Kuncl, R.W., 1995. Selective loss of glial glutamate transporter GLT-1 in amyotrophic lateral sclerosis. Ann Neurol 38, 73–84.

Rusakov, D.A., Bard, L., Stewart, M.G., Henneberger, C., 2014. Diversity of astroglial functions alludes to subcellular specialisation. Trends Neurosci 37, 228–242.

Rusnakova, V., Honsa, P., Dzamba, D., Stahlberg, A., Kubista, M., Anderova, M., 2013. Heterogeneity of astrocytes: from development to injury - single cell gene expression. PLoS One 8, e69734.

Saab, A.S., Neumeyer, A., Jahn, H.M., Cupido, A., Simek, A.A., Boele, H.J., Scheller, A., Le Meur, K., Gotz, M., Monyer, H., Sprengel, R., Rubio, M.E., Deitmer, J.W., De Zeeuw, C.I., Kirchhoff, F., 2012. Bergmann glial AMPA receptors are required for fine motor coordination. Science 337, 749–753.

Saab, A.S., Tzvetavona, I.D., Trevisiol, A., Baltan, S., Dibaj, P., Kusch, K., Mobius, W., Goetze, B., Jahn, H.M., Huang, W., Steffens, H., Schomburg, E.D., Perez-Samartin, A., Perez-Cerda, F., Bakhtiari, D., Matute, C., Lowel, S., Griesinger, C., Hirrlinger, J., Kirchhoff, F., Nave, K.A., 2016. Oligodendroglial NMDA receptors regulate glucose import and axonal energy metabolism. Neuron 91, 119–132.

Sahlender, D.A., Savtchouk, I., Volterra, A., 2014. What do we know about gliotransmitter release from astrocytes? Philos Trans R Soc Lond B Biol Sci 369, 20130592.

Salter, M.G., Fern, R., 2005. NMDA receptors are expressed in developing oligodendrocyte processes and mediate injury. Nature 438, 1167–1171.

Santello, M., Bezzi, P., Volterra, A., 2011. TNFalpha controls glutamatergic gliotransmission in the hippocampal dentate gyrus. Neuron 69, 988–1001.

Sarantis, M., Ballerini, L., Miller, B., Silver, R.A., Edwards, M., Attwell, D., 1993. Glutamate uptake from the synaptic cleft does not shape the decay of the non-NMDA component of the synaptic current. Neuron 11, 541–549.

Savtchouk, I., Volterra, A., 2018. Gliotransmission: beyond black-and-white. J Neurosci 38, 14–25.

Scalise, M., Pochini, L., Galluccio, M., Indiveri, C., 2016. Glutamine transport. From energy supply to sensing and beyond. Biochim Biophys Acta 1857, 1147–1157.

Schell, M.J., Molliver, M.E., Snyder, S.H., 1995. D-serine, an endogenous synaptic modulator: localization to astrocytes and glutamate-stimulated release. Proc Natl Acad Sci U S A 92, 3948–3952.

Schipke, C.G., Ohlemeyer, C., Matyash, M., Nolte, C., Kettenmann, H., Kirchhoff, F., 2001. Astrocytes of the mouse neocortex express functional N-methyl-D-aspartate receptors. Faseb J 15, 1270–1272.

Schousboe, A., Scafidi, S., Bak, L.K., Waagepetersen, H.S., McKenna, M.C., 2014. Glutamate metabolism in the brain focusing on astrocytes. Adv Neurobiol 11, 13–30.

Scofield, M.D., 2018. Exploring the role of astroglial glutamate release and association with synapses in neuronal function and behavior. Biol Psychiatry 84, 778–786.

Seifert, G., Steinhauser, C., 1995. Glial cells in the mouse hippocampus express AMPA receptors with an intermediate Ca2+ permeability. Eur J Neurosci 7, 1872–1881.

Seifert, G., Zhou, M., Steinhauser, C., 1997. Analysis of AMPA receptor properties during postnatal development of mouse hippocampal astrocytes. J Neurophysiol 78, 2916–2923.

Serrano, A., Robitaille, R., Lacaille, J.C., 2008. Differential NMDA-dependent activation of glial cells in mouse hippocampus. Glia 56, 1648–1663.

Shigetomi, E., Jackson-Weaver, O., Huckstepp, R.T., O'Dell, T.J., Khakh, B.S., 2013. TRPA1 channels are regulators of astrocyte basal calcium levels and long-term potentiation via constitutive D-serine release. J Neurosci 33, 10143–10153.

Singh, A., Abraham, W.C., 2017. Astrocytes and synaptic plasticity in health and disease. Exp Brain Res 235, 1645–1655.

Soreq, L., Consortium, U.K.B.E., North American Brain Expression, C., Rose, J., Soreq, E., Hardy, J., Trabzuni, D., Cookson, M.R., Smith, C., Ryten, M., Patani, R., Ule, J., 2017. Major shifts in glial regional identity are a transcriptional hallmark of human brain aging. Cell Rep 18, 557–570.

Spampinato, S.F., Merlo, S., Chisari, M., Nicoletti, F., Sortino, M.A., 2014. Glial metabotropic glutamate receptor-4 increases maturation and survival of oligodendrocytes. Front Cell Neurosci 8, 462.

Stellwagen, D., Malenka, R.C., 2006. Synaptic scaling mediated by glial TNF-alpha. Nature 440, 1054–1059.

Stenovec, M., Lasic, E., Bozic, M., Bobnar, S.T., Stout Jr., R.F., Grubisic, V., Parpura, V., Zorec, R., 2016. Ketamine inhibits ATP-evoked exocytotic release of brain-derived neurotrophic factor from vesicles in cultured rat astrocytes. Mol Neurobiol 53, 6882–6896.

Stephen, T.L., Higgs, N.F., Sheehan, D.F., Al Awabdh, S., Lopez-Domenech, G., Arancibia-Carcamo, I.L., Kittler, J.T., 2015. Miro 1 regulates activity-driven positioning of mitochondria within astrocytic processes apposed to synapses to regulate intracellular calcium signaling. J Neurosci 35, 15996–16011.

Sukigara, S., Dai, H., Nabatame, S., Otsuki, T., Hanai, S., Honda, R., Saito, T., Nakagawa, E., Kaido, T., Sato, N., Kaneko, Y., Takahashi, A., Sugai, K., Saito, Y., Sasaki, M., Goto, Y., Koizumi, S., Itoh, M., 2014. Expression of astrocyte-related receptors in cortical dysplasia with intractable epilepsy. J Neuropathol Exp Neurol 73, 798–806.

Sultan, S., Li, L., Moss, J., Petrelli, F., Casse, F., Gebara, E., Lopatar, J., Pfrieger, F.W., Bezzi, P., Bischofberger, J., Toni, N., 2015. Synaptic integration of adult-born hippocampal neurons is locally controlled by astrocytes. Neuron 88, 957–972.

Sun, W., McConnell, E., Pare, J.F., Xu, Q., Chen, M., Peng, W., Lovatt, D., Han, X., Smith, Y., Nedergaard, M., 2013. Glutamate-dependent neuroglial calcium signaling differs between young and adult brain. Science 339, 197–200.

Takano, T., Kang, J., Jaiswal, J.K., Simon, S.M., Lin, J.H., Yu, Y., Li, Y., Yang, J., Dienel, G., Zielke, H.R., Nedergaard, M., 2005. Receptor-mediated glutamate release from volume sensitive channels in astrocytes. Proc Natl Acad Sci U S A 102, 16466–16471.

Tang, W., Szokol, K., Jensen, V., Enger, R., Trivedi, C.A., Hvalby, O., Helm, P.J., Looger, L.L., Sprengel, R., Nagelhus, E.A., 2015. Stimulation-evoked Ca2+ signals in astrocytic processes at hippocampal CA3-CA1 synapses of adult mice are modulated by glutamate and ATP. J Neurosci 35, 3016–3021.

Tani, H., Dulla, C.G., Farzampour, Z., Taylor-Weiner, A., Huguenard, J.R., Reimer, R.J., 2014. A local glutamate-glutamine cycle sustains synaptic excitatory transmitter release. Neuron 81, 888–900.

Todd, A.C., Marx, M.C., Hulme, S.R., Broer, S., Billups, B., 2017. SNAT3-mediated glutamine transport in perisynaptic astrocytes in situ is regulated by intracellular sodium. Glia 65, 900–916.

Tran, C.H.T., Peringod, G., Gordon, G.R., 2018. Astrocytes integrate behavioral state and vascular signals during functional hyperemia. Neuron 100, 1133–1148 e1133.

Traynelis, S.F., Wollmuth, L.P., McBain, C.J., Menniti, F.S., Vance, K.M., Ogden, K.K., Hansen, K.B., Yuan, H., Myers, S.J., Dingledine, R., 2010. Glutamate receptor ion channels: structure, regulation, and function. Pharmacol Rev 62, 405–496.

Umpierre, A.D., West, P.J., White, J.A., Wilcox, K.S., 2019. Conditional knock-out of mGluR5 from astrocytes during epilepsy development impairs high-frequency glutamate uptake. J Neurosci 39, 727–742.

Unichenko, P., Dvorzhak, A., Kirischuk, S., 2013. Transporter-mediated replacement of extracellular glutamate for GABA in the developing murine neocortex. Eur J Neurosci 38, 3580–3588.

Uwechue, N.M., Marx, M.C., Chevy, Q., Billups, B., 2012. Activation of glutamate transport evokes rapid glutamine release from perisynaptic astrocytes. J Physiol 590, 2317–2331.

Valtcheva, S., Venance, L., 2019. Control of long-term plasticity by glutamate transporters. Front Synaptic Neurosci 11, 10.

Vargas, J.R., Takahashi, D.K., Thomson, K.E., Wilcox, K.S., 2013. The expression of kainate receptor subunits in hippocampal astrocytes after experimentally induced status epilepticus. J Neuropathol Exp Neurol 72, 919–932.

Vergouts, M., Doyen, P.J., Peeters, M., Opsomer, R., Hermans, E., 2018. Constitutive downregulation protein kinase C epsilon in hSOD1(G93A) astrocytes influences mGluR5 signaling and the regulation of glutamate uptake. Glia 66, 749–761.

Verkhratsky, A., Nedergaard, M., 2014. Astroglial cradle in the life of the synapse. Philos Trans R Soc Lond B Biol Sci 369.

Verkhratsky, A., Nedergaard, M., 2018. Physiology of astroglia. Physiol Rev 98, 239–389.

Verkhratsky, A., Parpura, V., 2016. Astrogliopathology in neurological, neurodevelopmental and psychiatric disorders. Neurobiol Dis 85, 254–261.

Verkhratsky, A., Rodrigues, J.J., Pivoriunas, A., Zorec, R., Semyanov, A., 2019. Astroglial atrophy in Alzheimer's disease. Pflugers Arch.

Verkhratsky, A., Rodriguez, J.J., Parpura, V., 2014. Neuroglia in ageing and disease. Cell Tissue Res 357, 493–503.

Verkhratsky, A., Steardo, L., Parpura, V., Montana, V., 2016. Translational potential of astrocytes in brain disorders. Prog Neurobiol 144, 188–205.

Verkhratsky, A., Untiet, V., Rose, C.R., 2020. Ionic signalling in astroglia beyond calcium. J Physiol 598, 1655–1670.

Vignoli, B., Battistini, G., Melani, R., Blum, R., Santi, S., Berardi, N., Canossa, M., 2016. Peri-synaptic glia recycles brain-derived neurotrophic factor for LTP stabilization and memory retention. Neuron 92, 873–887.

Volterra, A., Liaudet, N., Savtchouk, I., 2014. Astrocyte Ca(2)(+) signalling: an unexpected complexity. Nat Rev Neurosci 15, 327–335.

Walls, A.B., Waagepetersen, H.S., Bak, L.K., Schousboe, A., Sonnewald, U., 2015. The glutamine-glutamate/GABA cycle: function, regional differences in glutamate and GABA production and effects of interference with GABA metabolism. Neurochem Res 40, 402–409.

Wang, X., Lou, N., Xu, Q., Tian, G.F., Peng, W.G., Han, X., Kang, J., Takano, T., Nedergaard, M., 2006. Astrocytic Ca2+ signaling evoked by sensory stimulation in vivo. Nat Neurosci 9, 816–823.

Wolosker, H., Balu, D.T., Coyle, J.T., 2016. The rise and fall of the d-serine-mediated gliotransmission hypothesis. Trends Neurosci 39, 712–721.

Woo, D.H., Han, K.S., Shim, J.W., Yoon, B.E., Kim, E., Bae, J.Y., Oh, S.J., Hwang, E.M., Marmorstein, A.D., Bae, Y.C., Park, J.Y., Lee, C.J., 2012. TREK-1 and Best 1 channels mediate fast and slow glutamate release in astrocytes upon GPCR activation. Cell 151, 25–40.

Zhang, Q., Pangrsic, T., Kreft, M., Krzan, M., Li, N., Sul, J.Y., Halassa, M., Van Bockstaele, E., Zorec, R., Haydon, P.G., 2004. Fusion-related release of glutamate from astrocytes. J Biol Chem 279, 12724–12733.

Zhang, R.W., Du, W.J., Prober, D.A., Du, J.L., 2019. Muller glial cells participate in retinal waves via glutamate transporters and AMPA receptors. Cell Rep 27, 2871–2880 e2872.

Zhang, Y., Chen, K., Sloan, S.A., Bennett, M.L., Scholze, A.R., O'Keeffe, S., Phatnani, H.P., Guarnieri, P., Caneda, C., Ruderisch, N., Deng, S., Liddelow, S.A., Zhang, C., Daneman, R., Maniatis, T., Barres, B.A., Wu, J.Q., 2014. An RNA-sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the cerebral cortex. J Neurosci 34, 11929–11947.

Zhang, Z., Chen, G., Zhou, W., Song, A., Xu, T., Luo, Q., Wang, W., Gu, X.S., Duan, S., 2007. Regulated ATP release from astrocytes through lysosome exocytosis. Nat Cell Biol 9, 945–953.

Ziak, D., Chvatal, A., Sykova, E., 1998. Glutamate-, kainate- and NMDA-evoked membrane currents in identified glial cells in rat spinal cord slice. Physiol Res 47, 365–375.

Ziemens, D., Oschmann, F., Gerkau, N.J., Rose, C.R., 2019. Heterogeneity of activity-induced sodium transients between astrocytes of the mouse Hippocampus and neocortex: mechanisms and consequences. J Neurosci 39, 2620–2634.