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INVITED REVIEW

Astroglial amino acid-based transmitter receptors

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Abstract Amino acids appear in prebiotic period being one of the first organic molecules on Earth. For neurobiologists, it is of importance that AAs are not only representing building blocks of life, but are also the essential part of metabolism and cellular signaling. In the mammalian brain, the most common excitatory and inhibitory transmitters acting upon cellular plasmalemmal receptors are the amino acid glutamate and its derivative γ-aminobutyric acid, respectively. Other amino acids, i.e. aspartate, glycine, D-serine, and homocysteic acid, as well as the sulfonic acid taurine, are also active compounds involved in receptor-mediated brain signaling. Receptors for these amino acid-based transmitters are either ion channels, also referred to as ionotropic receptors, or metabotropic, i.e. seven transmembrane domain G-protein coupled receptors. In this mini-review, we focus our interest on amino acid-based transmitter receptors on neuroglia, astrocytes in particular.

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Introduction

Amino acids (AAs) appear in prebiotic period being one of the first organic molecules on Earth (Gutiérrez-Preciado et al. 2010). The discovery of the first AA was credited to Louis-Nicolas Vauquelin and Pierre Jean Robiquet, who in 1806 isolated it from the wild asparagus (Vauquelin and Robiquet 1806); subsequently this AA was named asparagine. Chemical evolution of amino acids might occur in the primordial soup on Earth itself (Miller 1953). Either additionally or alternatively, amino acids were introduced to our home planet by celestial bodies showering Earth, the bodies perhaps similar to a meteorite fragment of asteroid 2008 TC3 (Glavin et al. 2011). This intriguing dilemma on when, where and how prebiotic chemistry could occur is a subject of interest to theologists and planetary scientists alike. For neurobiologists and for the purpose of this mini-review, however, it is of importance that AAs are not only representing building blocks of life, i.e. proteins per se, but are also the essential part of metabolism and cellular signaling. In the mammalian brain, the most common excitatory and inhibitory transmitters acting upon cellular plasmalemmal receptors are the AA glutamate and its derivative γ-aminobutyric acid (GABA), respectively. Other AAs, i.e. aspartate, glycine, D-serine, and homocysteic acid (HCA), as well as the sulfonic acid taurine, are also active compounds involved in receptor-mediated brain signaling. In this mini-review, before we focus our interest on AA receptors on neuroglia, we provide primers on neuroglia and on synthesis of AA-based transmitters.

Primer on neuroglia and astrocytes

The nervous system is made of cellular networks composed of electrically excitable neurons and electrically non-excitable neuroglial cells (Verkhratsky et al. 2011). Signaling within these networks predominately utilizes chemical transmission which relies upon either direct diffusion of molecules between cells through gap junctions or regulated release and extracellular diffusion of signaling molecules to the target membranes, which results in activation of plasmalemmal receptors. The gap functional signaling is mainly employed in inter-glial communications because astrocytes are coupled into syncytia. The extracellular pathway is, however, central for signaling between neurons and between neurons and glia. Molecules accomplishing the extracellular chemical transmission are generally referred to as neurotransmitters which can mediate either homocellular (neurons to neurons or astrocytes to astrocytes) or heterocellular (neurons to astrocytes or astrocytes to neurons and other glial cells) communications. The central mechanism for regulated release of neurotransmitters is represented by Ca^{2+}-regulated exocytosis which in neurons appears mainly in presynaptic terminals although it can also occur extra-synaptically. Similarly, regulated exocytosis takes place in glial cells, although it is usually slower and spatially diffused.

Neuroglia was described by Rudolf Virchow as a "substance… which lies between the proper nervous parts, holds them together and gives the whole its form in a greater or lesser degree" [(Virchow 1858); for more detailed account on the history of glia see (Kettenmann and Verkhratsky 2008; Verkhratsky 2006; Verkhratsky et al. 2011)]. This original concept of glia being a connective tissue was soon converted through the recognition of glial cells. These glial cells are generally classified into astrocytes (the term introduced by Michael von Lenhossek (Lenhossek 1895), oligodendrocytes, NG2 glia and microglia. Conceptually astrocytes are the main homeostatic cells of the central nervous system (CNS), oligodendrocytes and NG2 cells are responsible for myelination and hence define the connectome, whereas microglia is the main defensive cellular element of the nervous system.

Primer on synthesis of amino acid-based transmitters in the brain

Generally, the AA-based transmitters are synthesized within astrocytes as by-products of the tricarboxylic acid (TCA) cycle. Glutamate does not readily cross the blood–brain barrier and hence has to be synthesized in situ in the nervous tissue. In the brain, glutamate is synthesized in astrocytes and is subsequently distributed to neurons in the well characterized glutamine-glutamate cycle (Hertz et al. 1999). This compartmentalization of synthesis localization is due to differential expression of the mitochondrial enzyme pyruvate carboxylase needed for de novo synthesis of glutamate; neurons, unlike astrocytes, lack this enzyme [but see (Hassel and Brathe 2000)]. In astrocytes, glutamate is converted from the TCA intermediate, α-ketoglutarate, via transamination of another AA, mainly aspartate (Westergaard et al. 1996), albeit alanine (Westergaard et al. 1993) could also be used. Similarly, aspartate can be derived from the TCA cycle intermediate, oxaloacetate, by transamination of glutamate which is an important mechanism in the mitochondrial malate–aspartate shuttle (Lai et al. 1989). Aspartate can activate (although with less potency) ionotropic glutamate receptors (iGluRs).

The inhibitory neurotransmitter GABA is produced from glutamate by glutamic acid decarboxylase, an enzyme found in neurons but not in glia (Bak et al. 2006). D-Serine is converted from L-serine by serine racemase, an enzyme found in astrocytes (Wolosker et al. 1999) and neurons (Kartvelishvily et al. 2006; Rosenberg et al. 2010). D-Serine is a ligand (with greater potency that glycine) of the glycine modulatory binding site of the *N*-methyl-D-aspartic acid (NMDA) receptor (Mothet et al. 2000). Glycine is synthesized in the brain from serine by enzyme serine hydroxymethyltransferase in presence of pyridoxal phosphate as the cofactor. HCA is likely derived from methionine (McBean 2002) by a pathway that has not been well defined. HCA is an agonist for both NMDA receptors (Do et al. 1986; Cuenod et al. 1986) and metabotropic glutamate receptors (mGluRs) 1, 2, 4–6 and 8 (Kingston et al. 1998; Shi et al. 2003). Taurine is a naturally occurring 2-aminoethanesulfonic acid (thus not strictly an AA) derived from cysteine via an enzymatic pathway which may involve cooperation between astrocytes and neurons (Dominy et al. 2004); the neural cell subtypes localization of contributing enzymes is not clear in vivo. Taurine is an agonist to glycine and $GABA_A$ receptors, having higher affinities to glycine receptors.

Astroglial receptors for amino acid-based transmitters

Receptors for AA-based transmitters are either ion channels, also referred to as ionotropic receptors, or metabotropic, i.e. seven transmembrane domain G-protein coupled receptors (GPCRs). It is discovery of glial expression of neurotransmitter receptors at the beginning of 1980s (Bowman and Kimelberg 1984; Kettenmann et al. 1984a, b) that was fundamental for the development of the neurobiology of glia and the role of these cells in brain signaling, as reviewed elsewhere (Parpura and Verkhratsky 2012a, b; Verkhratsky et al. 2012; Zorec et al. 2012). In the

present article we provide a succinct overview of the main types of AA receptors expressed in astrocytes; some features of these receptors and their physiological effects are summarized in Table 1.

Glutamate receptors

Initial observation of GluR-mediated activation of glial cells was made in 1984. Electrophysiological recordings obtained from cultured astrocytes and oligodendrocytes showed that exposure of these cells to externally applied excitatory AAs, glutamate and aspartate, led to their depolarization (Bowman and Kimelberg 1984; Kettenmann et al. 1984a, b). The use of purified cell culture technique in these experiments was critical as it removes misinterpretations associated with indirect actions of AAs through neurons that would occur in situ. Subsequently, GluRs were identified in various astroglial cells throughout the brain (Condorelli et al. 1999; Seifert and Steinhauser 2001; Steinhäuser and Gallo 1996).

GluRs are either iGluRs, i.e. cationic ligand-gated channels or mGluRs, i.e. GPCRs. Ionotropic GluRs are represented by three families designated as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate and NMDA receptors, based on their distinct molecular structures and specific pharmacological properties.

AMPA receptors are represented by four types of subunits, designated GluA1-4 and encoded by distinct genes (Hollmann and Heinemann 1994; Wisden and Seeburg 1993). Topologically AMPA receptors are heterotetramers, often containing symmetric dimer(s). The AMPA receptors were the first GluR receptors identified in astroglia, and they represent the dominant iGluR type present in astrocytes. The functional properties of AMPA receptors are determined by their heterogeneous assembly from four receptor subunits with further diversity brought by alternative splicing and mRNA editing (Seeburg et al. 1998). AMPA receptors are functionally expressed in astroglial cells throughout the brain, including hippocampus, cerebellum, neocortex and retina (Gallo and Ghiani 2000; Seifert and Steinhauser 2001; Verkhratsky and Steinhauser 2000). The GluA2 subunit renders AMPA receptor impermeable to Ca^{2+} while fluxing Na^{+} and K^{+}.

Table 1 Aminoacid-based transmitter receptors in astroglial cells

Receptor type	Properties/Physiological effect	Localization in situ	References
Ionotropic receptors			
A. Glutamate receptors			
AMPA receptors	Na^{+}–K^{+} channels Na^{+}–K^{+}–Ca^{2+} channels Activation triggers cationic current and cell depolarization	Ubiquitous; grey matter in hippocampus, cortex, cerebellum, and white matter	(Gallo and Ghiani 2000; Steinhäuser and Gallo 1996; Seifert and Steinhauser 2001; Verkhratsky and Steinhauser 2000)
NMDA receptors	Na^{+}–K^{+}–Ca^{2+} channels Activation triggers inward Ca^{2+}/Na^{+} current, cell depolarization and substantial Ca^{2+} entry	Cortex, spinal cord	(Lalo et al. 2006; Ziak et al. 1998; Schipke et al. 2001; Conti et al. 1996)
B. $GABA_A$ receptors	Cl^{-} channel Activation triggers Cl^{-} efflux and cell depolarization	Ubiquitous; hippocampus, cortex, cerebellum, optic nerve, spinal cord, pituitary gland	(Pastor et al. 1995; Fraser et al. 1994; MacVicar et al. 1989; Muller et al. 1994; von Blankenfeld and Kettenmann 1991)
C. Glycine receptors	Cl^{-} channel Activation triggers Cl^{-} efflux and cell depolarization	Spinal cord	(Oertel et al. 2007; Kirchhoff et al. 1996)
Metabotropic receptors			
A. Glutamate receptors (mGluRs)	Group I (mGluRs 1,5) control PLC, $InsP_3$ production and Ca^{2+} release from the ER Group II (mGluRs 2,3) and Group III (mGluRs 4,6,7,8) control synthesis of cAMP	Ubiquitous; mGluR3 and mGluR5 are the most abundant	(Tamaru et al. 2001; Kirischuk et al. 1999)
B. $GABA_B$ receptors	Control PLC, $InsP_3$ production and likely Ca^{2+} release from the ER	Hippocampus	(Charles et al. 2003; Kang et al. 1998)

AMPA α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, *cAMP* adenosine 3′:5′ cyclic monophosphate, *GABA* γ-aminobutyric acid, *ER* endoplasmic reticulum, *$InsP_3$* inositol 1,4,5-trisphosphate, *mGluR* metabotropic glutamate receptor, *NMDA* *N*-methyl-D-aspartate, *PLC* phospholipase C

Interestingly, many glial cells do not express GluA2 and as a result astroglial AMPA receptors are often Ca^{2+} permeable (Burnashev 1998); the permeability ratio $P_{Ca}/P_{monovalent}$ for these receptors is about 1, and fractional Ca^{2+} currents in physiological conditions are tiny, reaching mere 4 %. Nonetheless, prolonged activation of Ca^{2+} permeable AMPA receptors with kainate can trigger intracellular Ca^{2+} signaling in astrocytes (Enkvist et al. 1989; Glaum et al. 1990; Muller et al. 1992; Porter and McCarthy 1995; Jabs et al. 1994).

The second type of iGluRs, the kainate receptor, is a homo- or hetero-tetramer, which contributing subunits, GluK1-5 (formerly known as GluR5-7 and KA1-2 subunits, respectively), are encoded by distinct genes (Lerma 2003; Reiner et al. 2012). All four subunits were identified in certain types of astroglial cells (e.g., in bovine corpus callosum or in rodent perivascular astrocytes) at either the mRNA or the protein level (Garcia-Barcina and Matute 1996; Brand-Schieber et al. 2004).

NMDA receptors, the third type of iGluRs, are hetero-tetramers composed of two obligatory GluN1 subunits, along with GluN2 and GluN3 subunits. There are: (a) eight variants of the GluN1 subunits due to alternative splicing of *GRIN1*(Stephenson 2006); (b) four distinct isoforms, A–D, of the GluN2 subunit (coded by *GRIN2A, GRIN2B, GRIN2C* and *GRIN2D*, respectively) expressed in vertebrates (Teng et al. 2010); and (c) two isoforms, A and B, of the GluN3 subunit (coded by *GRIN3A* and *GRIN3B,* respectively) (Pachernegg et al. 2012).

Astroglial expression of the NMDA receptors was denied for a long time as it was believed that NMDA receptors are neuron-specific. This belief had a solid foundation in properties of NMDA receptors. Namely, NMDA receptors due a Mg^{2+} flickery block (Mayer et al. 1984; Nowak et al. 1984; Ascher and Nowak 1988) are unavailable for activation at negative membrane potentials. This block can be relieved by cell depolarization to ~ -40 mV, which makes neuronal NMDA receptors excellent coincidence detectors. Glial cell membrane potential is characteristically set at about -80 mV; high densities of K^+ channels make substantial depolarization almost impossible. As a consequence it was generally believed that NMDA receptors in astrocytes cannot be operational and that the NMDA receptors are exclusively present in neurons, where they act as a molecular substrate for learning and memory through their established role in controlling synaptic plasticity (Malenka and Nicoll 1993).

Nonetheless, reports on astroglial NMDA receptor-mediated responses sporadically appeared in literature. Several groups had identified presumed NMDA receptor-mediated activation of cultured radial glial cells and astrocytes (Puro et al. 1996; Nishizaki et al. 1999; Lopez et al. 1997; Kondoh et al. 2001). Similarly, in situ preparations indicated that astroglia can respond to NMDA. For example, applications of exogenous NMDA to brain slices triggered electrical or intercellular Ca^{2+} responses in the cortical (Schipke et al. 2001), the spinal cord (Ziak et al. 1998), and in a sub-population of hippocampal astrocytes (Porter and McCarthy 1995; Steinhauser et al. 1994), as well as in cerebellar Bergmann glial cells (Muller et al. 1993). Furthermore, NMDA receptor mRNA and proteins were detected in cortical astrocytes (Schipke et al. 2001; Conti et al. 1996).

Only recently, however, astroglial expression of functional NMDA receptors was confirmed in experiments on cortical astrocytes isolated from genetically modified mice, in which astrocytes expressed green fluorescent protein (Lalo et al. 2006). Such a model allows unambiguous identification of astrocytes. Individual acutely isolated astrocytes, obtained by non-enzymatic vibro-dissection procedure, were whole-cell voltage-clamped and exposed to NMDA or glutamate. NMDA caused astrocytic currents that were sensitive to glycine and NMDA receptor antagonists MK-801 and D-2-amino-phosphonopentanoic acid (D-AP5) (Lalo et al. 2006); the antagonists also significantly reduced astrocytic currents triggered by application of glutamate. When green fluorescent protein expressing astrocytes were voltage-clamped in slices, the NMDA-mediated postsynaptic currents activated by electrical stimulation of neuronal afferents were recorded (Lalo et al. 2006). Thus, cortical astrocytes express functional NMDA receptors. The degree to which this is a uniform property of astrocytes in different brain regions requires further examination.

It turned out that astroglial NMDA receptors show fundamentally different properties from neuronal NMDA receptors. They had a very weak sensitivity to Mg^{2+} block as both NMDA-activated currents in isolated cells and synaptically activated NMDA currents in astrocytes in cortical slices were recorded at resting membrane potentials (-80 mV) in the presence of a physiological concentration (1 mM) of extracellular Mg^{2+} and were unaffected by elevated levels (up to 4–10 mM) of this cation (Lalo et al. 2006). Mg^{2+} block was only evident at membrane potentials more negative (<-100 mV) than the resting potential of astrocytes (Palygin et al. 2011). It is also noteworthy that astrocytic NMDA receptors have Ca^{2+} permeability ($P_{Ca}/P_{monovalent} \sim 3$) sufficient to generate cytosolic Ca^{2+} signals (Palygin et al. 2010). Incidentally, NMDA-induced currents and intracellular Ca^{2+} responses were also recorded from oligodendrocytes (Karadottir et al. 2005; Micu et al. 2006; Salter and Fern 2005), where they also showed weak Mg^{2+} block. The molecular basis for low Mg^{2+} sensitivity, which seems to be a conserved property of glial NMDA receptors, remains unexplained. It may result from a specific expression of

GluN3 subunits, found in oligodendrocytes (Burzomato et al. 2010), but up to date not in astrocytes. Alternatively, an unidentified post-translational modification of GluN subunits comprising NMDA receptors in astrocytes could underlie this phenomenon.

Physiological and pathological potential of astroglial NMDA receptors is yet to be fully explored. Nonetheless, astrocytic NMDA receptors appeared to cluster in a close proximity to the presynaptic glutamatergic terminals, as evidenced by the occurrence of spontaneous "miniature" excitatory postsynaptic currents in astrocytes (Lalo et al. 2006, 2011a, b), confirming physiological function of these receptors in neuron-astrocyte signaling.

MGluRs are classical seven transmembrane domain receptors, GPCRs, encompassing eight genetically distinct members, mGluR1-8 (Ferraguti and Shigemoto 2006; Nakanishi 1994), classified into three functionally different groups. The group I includes mGluR1 and mGluR5, which are coupled to phospholipase C (PLC) and synthesis of 1,4,5-inositol-trisphosphate ($InsP_3$) and diacylglycerol (DAG). Group II (mGluRs 2 and 3) and group III (mGluRs 4, 6, 7 and 8) downstream signaling occurs via adenylate cyclase. Astrocytes abundantly express mGluRs 3 and 5 that were in situ identified in their processes (Aronica et al. 2000; Petralia et al. 1996; Tamaru et al. 2001). Activation of mGluR5 triggers cytosolic Ca^{2+} signaling through stimulation of $InsP_3$-induced Ca^{2+} release from the endoplasmic reticulum Ca^{2+} store; in Bergmann glial cells, the mGluR5 represents the main route for Ca^{2+} signal generation following stimulation with glutamate, as the Ca^{2+} entry through AMPA receptors is rather limited due to rapid desensitization (Kirischuk et al. 1999). While other types of mGluRs are also present in astrocytes throughout the brain, they are less characterized.

GABA receptors

The ionotropic GABA receptors belong to the superfamily of pentameric Cys-loop receptors (Lester et al. 2004) and are denoted as $GABA_A$ type. They are present in many types of astrocytes in culture and in situ (Fraser et al. 1994; Verkhratsky and Steinhauser 2000). Using slice preparation, GABA-mediated currents were identified throughout the brain including hippocampus, cerebellum, pituitary gland, optic nerve, retina and spinal cord (Verkhratsky and Steinhauser 2000). Astroglial $GABA_A$ receptors are heteropentameric Cl^- channels, with biophysical and pharmacological properties similar to those of neuronal receptors, with a notable exception of benzodiazepine inverse agonists potentiating GABA responses in cultured astrocytes (Backus et al. 1988; Bormann and Kettenmann 1988). However, in terms of their effect on membrane potential, glial $GABA_A$ receptors are remarkably different from $GABA_A$ receptors in mature neurons, as GABA-induced activation invariably produces depolarization of astrocytes, otherwise seen only in immature neurons. Namely, astrocytes have relatively high intracellular Cl^- concentration when compared to mature neurons ($\sim$35 mM vs. $\sim$3–5 mM), which is maintained by the activity of the astrocytic plasma membrane $Na^+/K^+/2Cl^-$ co-transporter and Cl^-/HCO_3^- exchanger (Kettenmann 1990; Kimelberg 1990). Consequently, the equilibrium potential for Cl^- in astrocytes and oligodendrocytes is ~ -40 mV, while in neurons this is ~ -65 mV. Naturally, activation of $GABA_A$ receptors in glial cells, which resting potential is ~ -80 mV, triggers efflux of Cl^- ions and cell depolarization (MacVicar et al. 1989; von Blankenfeld and Kettenmann 1991). Although the physiological significance of astroglial $GABA_A$ receptors remains elusive, it is tempting to speculate that these receptors may be involved in neuronal-glial cross-talk at synaptic level. For instance, Bergmann glial cells $GABA_A$ receptors are clustered in membranes enwrapping inhibitory synapses (Riquelme et al. 2002), which would allow glia to sense GABA-ergic synaptic transmission.

There is some evidence for astroglial expression of metabotropic $GABA_B$ receptors. For example, all the three $GABA_B$ receptor subtypes ($GABA_{B1a}$, $GABA_{B1b}$ and $GABA_{B2}$) were detected in astroglial processes in CA1 area of hippocampus (Charles et al. 2003). Presumed $GABA_B$-mediated Ca^{2+} signals originating from intracellular stores were detected in cultured astrocytes (Nilsson et al. 1993) and in astrocytes in hippocampal slices (Kang et al. 1998).

Glycine receptors

Glycine receptors are Cl^--selective homo- or hetero-pentameric channels that belong to superfamily of Cys-loop receptors (Lester et al. 2004). They are expressed in astrocytes from spinal cord, where their activation triggers Cl^- efflux (Kirchhoff et al. 1996), and cell depolarization, very similarly to $GABA_A$-mediated responses. Astrocytes from spinal cord express an unusual $\beta\Delta 7$ subunit, encoded by exon 7 of the *Glrb* gene (Oertel et al. 2007). Expression of this subunit does not affect the channel properties and its functional significance, while physiological role of glial glycine receptors remains unknown.

Concluding remarks

Several AAs have been chosen by the evolution to be the ubiquitous extracellular signaling molecules. In the CNS these AAs represented by excitatory transmitter glutamate, inhibitory transmitters GABA and glycine, and modulatory

transmitters D-serine and taurine are secreted from neurons and neuroglia, thus being central for information processing in neural networks. The AA-based transmitters act through activation of several families of receptors differentially expressed in neurons and neuroglia.

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