

## The Glia Connection of the Glutamate/Glutamine Shuttle

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**Abstract: Problem statement:** Glia cells outnumber neurons but their role in synaptic transmission is still matter of debate. The recycling of Glutamate, the main excitatory neurotransmitter, carried out by the glutamate/glutamine shuttle, requires the involvement of glia, suggesting their involvement in neurotransmission. **Approach:** This review focuses on novel functions of glia proteins involved in this cycle. **Results:** An activity-dependent interaction of glial glutamate transporters, the Na<sup>+</sup>/K<sup>+</sup> ATPase, the glutamine and glucose transporters might support glutamatergic neurotransmission. **Conclusion:** Glia cells that surround glutamatergic contacts, respond to synaptic activity and modify accordingly, the amount and function of the proteins involved in their interaction with neurons thus assuring a synaptic transmission.

**Key words:** Glia cells, glutamate/glutamine shuttle, glutamate transporters, glutamine transporters, glia/neuronal coupling

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### INTRODUCTION

Regarded as passive elements, the functions of glia cells are nowadays re-evaluated. The description and characterization of neurotransmitter receptors expressed in their plasma membranes, attracted the attention of a number of researchers which over the years have contributed to the study of glia physiology in the context of neurotransmission (Parpura and Verkhratsky, 2012). The concept of the tripartite synapse: pre-synapsis, post-synapsis and glial cells, often referred as non-existent, has its better example in glutamatergic as well as gabaergic synapses, the reason is simple, the turnover of both of these transmitters require the synthesis of the neutral amino acid glutamine by glutamine synthetase, a glial enzyme (Albrecht *et al.*, 2010). A review of the most recent findings concerning the so-called glutamate/glutamine shuttle that provide strong support the concept of the tripartite synapse follows.

**Glial cells:** The contribution of neurons to brain function has been widely evaluated and actually gave birth to The Neurosciences. Nevertheless, glia cells outnumber neurons approximately by a factor of ten. In the Central Nervous System (CNS) different types of glial cells regulate aspects like architecture, function and plasticity. Glia cells are divided into two main

types: microglia and macroglia. The three main functional classes of macroglial cells in the CNS are: Ependymoglia, myelinating glia and astrocytes. Ependymoglia includes radial glia from the retina and the cerebellum (Müller and Bergmann cells). Myelin forming cells include oligodendroglia in the CNS and Schwann cells in the peripheral nervous system. Astrocytes have an important role in brain development and function (Perea and Araque, 2010). For example, astrocytes release heparin sulphate proteoglycans and by these means promote the formation of excitatory synapses (Allen *et al.*, 2012). Therefore it is clear that these cells are fundamental for neuronal survival and have been usually associated with support and replenishment of metabolic substrates. Despite of this, recent findings have called the attention to the involvement of glia in synaptic transactions throughout the CNS (Eroglu and Barres, 2010). Astrocytes, through a battery of neurotransmitter receptors and transporters present in their plasma membrane, are capable to release neuroactive molecules (glutamate, D-serine, ATP, glutamine, GABA,) that bind to pre and postsynaptic receptors. Additionally, classical transmitters evoke a transient increase in [Ca<sup>2+</sup>] intracellular levels in cultured astrocytes, or in brain slices, displaying a rough form of excitability, although astrocytes are considered as non-excitabile cells, since

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they are not capable to generate action potentials (Perea and Araque, 2010). These and other studies led to the proposal of the so-called “tripartite synapse” in which the astrocyte listens to synaptic activity and provides a feedback modulation of the strength of the synaptic connection (Haydon and Carmignoto, 2006). The synaptic control of the astrocyte  $\text{Ca}^{2+}$  signal is based in spatially restricted areas called “microdomains” of the astrocytic processes (Grosche *et al.*, 1999). Ultrastructural studies have shown the presence of small synaptic-like vesicles located in close proximity to synapses, apposed either to presynaptic and postsynaptic elements that are thought to contain the mentioned neuroactive substances (Jourdain *et al.*, 2007). Glutamate was one of the first neuroactive molecules known to be released by astrocytes that exert an effect on neural excitability.

**Glial glutamate receptors:** Glutamate receptors have been classified in terms of their signalling strategy in ionotropic (iGluRs) and metabotropic (mGluRs) receptors. The iGluRs are ligand-gated ion channels that are activated by selective agonists: N-methyl-D-aspartate (NMDA),  $\alpha$ -Amino-3-hydroxy-5-Methylisoxazole-4-Propionate (AMPA) and Kainate (KA) each one of them was representing a family of homo or heterologomer receptors (Gasic and Heinemann, 1992). Metabotropic receptors are G-protein coupled receptors that are divided based on their primary structure into group I, group II and group III and are activated preferentially by quisqualate (Quis), 1-Amino-4, 5-Ciclopentane-trans-1, 3-Dicarboxylate (t-ACPD) and L-2-amino-phosphonobutanoate (L-AP-4) (Pin and Duvoisin, 1995). Glia cells of different brain structures express both types of receptors, of particular interest is to mention that these receptors have been extensively studied in glial cells that surround glutamatergic synapses like cerebellar Bergmann glia and retinal Müller glia cells (Bellamy, 2006). Bergmann glia cells display a glutamate-dependent continuous dialogue with Purkinje and granules cells, through  $\text{Ca}^{2+}$ -permeable AMPA receptors. A series of elegant experiments transducing the  $\text{Na}^{+}$ -determinant AMPA subunit, GluR2 into Bergmann glia cells, modifies its architecture and its physical contacts with Purkinje cells (Iino *et al.*, 2001). It also should be noted that neuronal stimulation elicits glutamate-dependent changes in glial membrane potential in a number of preparations and that these electrical responses are carried out not only by GluRs but also by the  $\text{Na}^{+}$ -dependent glutamate transporters (see below). In any event, glial GluRs, like their neuronal counterpart, are

linked to gene expression regulation both at the transcriptional as well as the translational level (Gallo and Ghiani, 2000; Rosas *et al.*, 2007). In this context, it is pertinent to emphasize that among the genes that are regulated by glial GluRs are the glutamate transporters. It is quite possible then that glutamate released activates neuronal and glial receptors, modifying gene expression patterns in both cell types and that among the target genes, those involved in glia/neuronal interactions are represented.

**Glial glutamate transporters:** Glial glutamate transporters are important for the removal of this neurotransmitter from the synaptic cleft. Five glutamate transporters have been characterized: the  $\text{Na}^{+}$ -dependent glutamate/aspartate transporter (GLAST/EAAT-1), the glutamate transporter 1 (Glt-1/EAAT-2), the excitatory amino acid carrier 1 (EAAC-1/EAAT3), the Excitatory Amino Acid Transporter 4 (EAAT-4) and the Excitatory Amino Acid Transporter 5 (EAAT-5) (Danbolt, 2001). GLAST and Glt-1 are expressed mainly in glia cells while the other three transporters are expressed in neurons. The importance of glial glutamate transporters in pathological scenarios has been deduced from the knock out studies, that demonstrated an elevation of glutamate extracellular levels, neurodegeneration and progressive paralysis (Rothstein *et al.*, 1996). The bulk of glutamate transport in the cerebellum is carried out by GLAST, whereas in the other brain areas it is accomplished by Glt-1. Therefore, glial glutamate transporters are key elements in the prevention of over-stimulation of glutamate receptors, a process that triggers neuroplastic changes and excitotoxic cascades in several pathological conditions (Trotti *et al.*, 2001). In this sense, it has been postulated that disruption of glial glutamate transport affects the time course, fidelity and modulation of excitatory transmission.

The mRNA levels of GLAST and Glt-1 have been investigated during development and in pure glial preparations. At the early stages of development both mRNAs are present in significant amounts, especially at the time of gliogenesis (mouse E15-E19). At birth, GLAST is present in abundance while Glt-1 is barely detectable. In fact, GLAST has been considered as a glia lineage marker (Kriegstein and Alvarez-Buylla, 2009). Glial glutamate transport is regulated in the short and the long term. Short-term regulation includes cell-surface expression and post translational modifications like phosphorylation, ubiquitination and/or acetylation that in one way or another modifying transporter expression at the plasma membrane (Robinson, 2006).

Long-term regulation includes transcriptional as well as translational control (Lopez-Bayghen and Ortega, 2011). Diverse stimulus are known to affect glial glutamate transporters function, among them glutamate is the most important. It has been shown that glutamate regulates GLAST at the short and long-term, in both cases the net result is a decrease in glutamate uptake activity, albeit the molecular mechanisms are different. In the short-term, glutamate decreases the amount of plasma membrane transporters by interfering with the traffic of the protein to and from the membrane. This is a transporter-dependent effect (Gonzalez and Ortega, 2000). In contrast, in the long-term glutamate, acting through its receptors, down regulates the transcription of the GLAST gene (Rosas *et al.*, 2007). It should be mentioned that this regulation takes place in the cerebellum, while an opposite effect has been recorded for long-term effects of glutamate in the cerebral cortex, where an increase in glast has been detected (Gegelashvilli *et al.*, 2000).

Recently, the role of transporters as signalling entities has began to emerge and glial glutamate transporters are no exception. A transporter dependent increase in p42/44 mitogen kinase activity and in activity of the Mammalian Target of Rapamycin (MTOR) has also been reported (Martinez-Lozada *et al.*, 2011). Furthermore, a signalling complex containing GLAST and the Na<sup>+</sup>/K<sup>+</sup> ATPase has also been described (Gegelashvilli *et al.*, 2007; Rose *et al.*, 2009).

**Glial glutamine transporters:** Glutamine is the most abundant amino acid in plasma and in the brain extracellular space (Hamberger and Nystrom, 1984). It is the main precursor of glutamate and GABA (Hamberger *et al.*, 1979; Paulsen *et al.*, 1988). Glutamine uptake activity in the brain presents a particular challenge since it is substrate of multiple transporter proteins that also move other neutral amino acids (Barker and Ellory, 1990). The molecular and functional properties of the various amino acid transport systems are characterized by their overlapping substrate specificities, generally low substrate affinities and widespread cellular distribution (Collarini and Oxender, 1987; Broer and Brookes, 2001). The solute carrier families in mammalian cells are the solute carriers SLC1, SLC7 and SLC38 (Hediger *et al.*, 2004; Kanai and Hediger, 2004). SLC1 are Na<sup>+</sup> dependent neutral amino acid exchange proteins that prefer the substrates alanine, serine and cysteine and therefore are known as the ASC family. Two members ASCT1 and ASCT2 comprise this family and function as exchangers capable to uptake or release amino acids (Christensen *et al.*, 1967). ASCT1 is the most

abundant isoform in the brain, despite of this; glutamine is a poor substrate for this transporter (Zerangue and Kavanaugh, 1996). In contrast, ASCT2 transports glutamine and is expressed in mainly in primary cultures of rat astrocytes but also at lower levels in adult and embryonic brain (Broer *et al.*, 1999). The evidence for a neuronal ASCT2 activity is weak (Su *et al.*, 1997) although recent data demonstrates ASCT2 immunoreactivity in cerebellar Purkinje cell bodies and dendrites (Giddon *et al.*, 2009).

SLC7 is a Na<sup>+</sup> independent transporter and its preference for leucine, gave rise to its cognate name as System L. This family was originally described in kidney tubule cells and includes the heterodimeric transporters LAT1 and LAT2. A low-affinity, high-capacity glutamine uptake activity was described by this system in astrocytes and neurons (Nagaraja and Brookes, 1996; Su *et al.*, 1997). Functional studies suggest a minor role for system L-mediated glutamine transport in astrocytes, contributing with approximately 10% of the total uptake (Broer and Brookes, 2001; Sidoryk-Wegrzynowicz *et al.*, 2011).

The SCL38 family corresponds to a Na<sup>+</sup>-dependent neutral amino acid transporters that are divided in two different systems, known as system A and system N, based on the ability of the former to transport alanine and the capacity of the latter to transport amino acids with Nitrogen in its R group. Both systems respond to hormonal regulation and their function and expression are associated with volume regulation, nutrition and metabolism (Rennie *et al.*, 1998; Haussinger, 1990). System A members include Sodium-Dependent Neutral Amino acid Transporter 1 (SNAT1); SNAT2 and SNAT4, all of them transport small zwitterionic amino acids and are pH sensitive (Albers *et al.*, 2001; Chaudhry *et al.*, 2002). SNAT1 protein expression is confined to the brain, retina, placenta and heart. Within the CNS, SNAT1 its expression is restricted to neurons (Mackenzie *et al.*, 2003; Mackenzie and Erickson, 2004) as does that of SNAT2, both transporters are particularly associated to glutamatergic neurons (Gonzalez-Gonzalez *et al.*, 2005; Melone *et al.*, 2006). In contrast, SNAT4 is expressed in perivenous hepatocytes (Gu *et al.*, 2003), glutamine is not the preferred substrate and it also transports cationic amino acids independent of Na<sup>+</sup> (Sugawara *et al.*, 2000).

System N has two isoforms: SNAT3 and SNAT5, both coupled to Na<sup>+</sup> and H<sup>+</sup> gradients. These transporters are extremely important since these proteins are glutamine carriers capable to mediate glutamine influx and efflux (Baird *et al.*, 2004; Broer *et al.*, 2002; Boulland *et al.*, 2003). It is not surprising that

its expression in the brain is largely confined to astrocytes (Chaudhry *et al.*, 1999; Boulland *et al.*, 2003).

**Glutamate/glutamine shuttle:** Glutamine is required as a precursor for other amino acids, protein synthesis and metabolism processes. Particularly, glutamine has an important role in kidney ammoniogenesis (Wadoux and Welbourne, 1975), driving the urea cycle in the liver nitrogen metabolism (Haussinger, 1990) and in the glutamate/glutamine cycle in the brain (Rothstein and Tabakoff, 1984). This shuttle provides an interesting model to understand the cooperative function of different transporters that interact in synaptic transmission and the release of neurotransmitters. In glutamatergic synapses, the Vesicular Glutamate Transporters (VGLUT) (Takamori *et al.*, 2000) located in the presynaptic neuron; charge the synaptic vesicles with the glutamate produced by the hydrolysis of glutamine by Glutaminase. Synaptic vesicles contain large amounts of glutamate and release it by exocytosis to the synaptic cleft, where it interacts with glutamatergic receptors and transporters. Glutamate is cleared from the synaptic space by the glial glutamate transporters (GLAST and Glt-1) (Schousboe, 1981) where Glutamine Synthetase (GS) converts it to glutamine. Glia cells, using system N transporters (SNAT3 and SNAT5) mediate the efflux of glutamine to the extracellular milieu (Chaudhry *et al.*, 2002), to be taken up by neurons by system A transporters (SNAT1 and SNAT2) (Varoqui *et al.*, 2000) completing the cycle (Daikhin and Yudkoff, 2000).

It should be note, however that neurons do not depend exclusively on the astrocytic shuttle cycle for the replenishment of glutamate. The glutamate uptake via EAAC1/EAAT3 transporter and the glutamate synthesis from the tricarboxylic cycle, are two potential glutamatergic sources involved in the neuron replenishment of glutamate (Hertz *et al.*, 2000; Broer and Brookes, 2001). The dysfunctionality of any of the steps in the cycle is associated with a variety of neurological disorders and conditions (Cruz and Cerdan, 1999).

**A tripartite synapse: The Glia connection:** Glutamatergic synapses are unique structures in which the actual contribution of glial cells to neurotransmission has been reported (Iino *et al.*, 2001; Lopez-Bayghen *et al.*, 2007; Uwechue *et al.*, 2012). It is tempting to speculate that once the presynaptic terminal is stimulated and glutamate released, the amino acid is taken up avidly by the glial glutamate transporters (either GLAST in cerebellum or Glt-1 in most of the other brain structures) resulting in a net Na<sup>+</sup> influx.

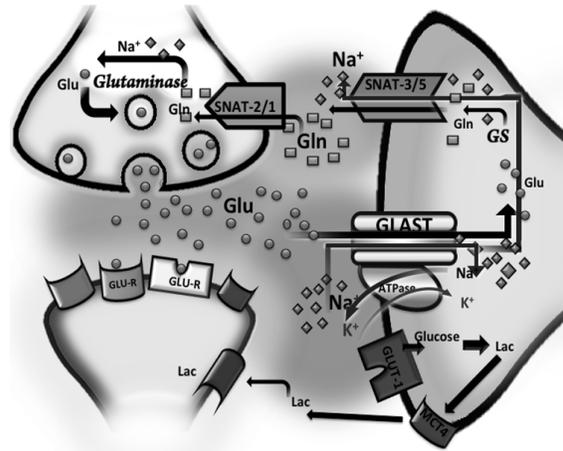


Fig. 1: Summary of the molecular transactions involved in the glia/neuronal interactions upon glutamatergic stimulation. Glutamate released from the presynaptic terminal reaches postsynaptic and glial glutamate receptors and transporters (see text for details). Abbreviations: GluRs, glutamate receptors, GLAST, Na<sup>+</sup>-dependent glutamate/aspartate transporter. Glt-1, glutamate transporter 1. GS, glutamine synthetase, Lac, lactate, MCT-4, monocarboxylate transporter 4. SNAT, sodium-dependant neutral amino acid transporter

Increased intracellular Na<sup>+</sup> triggers glucose uptake (Maekawa *et al.*, 2006) and glutamine release (Uwechue *et al.*, 2012) to be finally pumped out through that transporter-associated Na<sup>+</sup>/K<sup>+</sup>ATPase (Rose *et al.*, 2009). A sustained glutamatergic activity would envisage a reduction in ATP levels, which would shut down transiently protein synthesis (Barrera *et al.*, 2010). The properties thus far described for the glial proteins involved in this hypothesis support this elegant and exquisite coupling. A schematic diagram of our interpretation of the role of glial cells in the tripartite synapse is depicted in Fig. 1.

## CONCLUSION

Glial cells participate actively in the formation and function of glutamatergic synapses. The glial protein repertoire is constantly responding to synaptic activity and therefore these cells should be considered as an integral part of the synapses.

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