



The trinity of Ca^{2+} sources for the exocytotic glutamate release from astrocytes

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ABSTRACT

Astrocytes can exocytotically release the transmitter glutamate. Increased cytosolic Ca^{2+} concentration is necessary and sufficient in this process. The source of Ca^{2+} for the Ca^{2+} -dependent exocytotic release of glutamate from astrocytes predominately comes from endoplasmic reticulum (ER) stores with contributions from both inositol 1,4,5-trisphosphate- and ryanodine/cafeine-sensitive stores. An additional source of Ca^{2+} comes from the extracellular space via store-operated Ca^{2+} entry due to the depletion of ER stores. Here transient receptor potential canonical type 1 containing channels permit entry of Ca^{2+} to the cytosol, which can then be transported by the store-specific Ca^{2+} -ATPase to (re)fill ER. Mitochondria can modulate cytosolic Ca^{2+} levels by affecting two aspects of the cytosolic Ca^{2+} kinetics in astrocytes. They play a role in immediate sequestration of Ca^{2+} during the cytosolic Ca^{2+} increase in stimulated astrocytes as a result of Ca^{2+} entry into the cytosol from ER stores and/or extracellular space. As cytosolic Ca^{2+} declines due to activity of pumps, such as the smooth ER Ca^{2+} -ATPase, free Ca^{2+} is slowly released by mitochondria into cytosol. Taken together, the trinity of Ca^{2+} sources, ER, extracellular space and mitochondria, can vary concentration of cytosolic Ca^{2+} which in turn can modulate Ca^{2+} -dependent vesicular glutamate release from astrocytes. An understanding of how these Ca^{2+} sources contribute to glutamate release in (patho)physiology of astrocytes will provide information on astrocytic functions in health and disease and may also open opportunities for medical intervention.

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A developing body of evidence implicates astrocytes as active participants in multi-directional signaling in the central nervous system (CNS) [reviewed in Haydon and Carmignoto, 2006; Theodosis et al., 2008]. Astrocytes communicate with neurons (Nedergaard, 1994; Parpura et al., 1994), endothelial cells of the cerebrovasculature (Zonta et al., 2003; Mulligan and MacVicar, 2004), and microglia (Davalos et al., 2005). They appear to be an integral part of neural communication throughout the CNS. For example, in the hippocampus, astrocytes integrate neuronal signals (Perea and Araque, 2005), potentiate transmitter release at single synapses (Perea and Araque, 2007), enhance long-term potentiation (Pascual et al., 2005), and synchronize neuronal activity (Fellin et al., 2004). In the thalamus, astrocytes have been shown to drive neuronal activity as a consequence of astrocytic intrinsic Ca^{2+} oscillations (Parri et al., 2001). In the supraoptic nucleus of the hypothalamus, morphological plasticity of astrocytes (Hatton, 2004) leading to differential synaptic coverage by astrocytic processes can modulate the activity of the output neurons (Panatier et al., 2006).

The abundance of astrocytes and their proximity to neurons enables their communication with neurons. Early studies indicated the numerical preponderance of glial cells in the CNS. For example, in layers I and IV of the rat cerebral cortex, glial cells consisting of astrocytes and oligodendrocytes, outnumbered neurons 3:1 (Bass et al., 1971). As more sophisticated tools for cell counting emerged, it appears, however, that the glia to neuron ratio in human cortex is ~1.65:1, while in rodent this ratio is about 0.3:1 (Nedergaard et al., 2003; Sherwood et al., 2006). Astrocytes occupy distinct domains within the CNS, only at the cells' peripheries do their processes overlap (Bushong et al., 2002; Ogata and Kosaka, 2002). Within their individual domains astrocytes have extensive morphological interactions with neurons. For example, in the cortex of adult mice, one astrocyte may contact 4–8 neurons and surround ~300–600 neuronal dendrites (Halassa et al., 2007). In the hippocampus, astrocytes are positioned to contact even more synapses. In adult rats, one astrocyte is estimated to contact ~140,000 synapses of CA1 pyramidal cells (Bushong et al., 2002). Classically, the intimate position of astrocytic processes around the neurons and the synapses has been solely attributed to glutamate uptake and regulation of extracellular K^+ by astrocytes. To provide these services, astrocytes possess excitatory amino acid transporters (EAAT's) (Huang and Bergles, 2004; Tzingounis and Wadiche, 2007; Yang and Rothstein, 2009) and K^+ inward rectifying (Kir)

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channels (Sontheimer et al., 1994; Kofuji and Newman, 2009), respectively. However, it is also at synapses where astrocytes have been shown to have modulatory effects on the activities of presynaptic and postsynaptic neurons by astrocytic ability to release a variety of transmitters using many different mechanisms [reviewed in Malarkey and Parpura, 2009]. This led to the concept of a functional tripartite synapse (Araque et al., 1999), a topic that has been recently reviewed elsewhere (Ni et al., 2007; Halassa and Haydon, 2009).

In this review we focus on the Ca^{2+} sources for the exocytotic release of the excitatory transmitter glutamate from astrocytes, which can readily occur under physiological conditions (Parpura and Haydon, 2000). We start with a historical brief on the Ca^{2+} -dependent glutamate release from astrocytes [reviewed in detail in Montana et al., 2004]. We then discuss the trinity of Ca^{2+} sources for this release: intracellular stores, extracellular space and mitochondria. An understanding of how these Ca^{2+} sources contribute to the glutamate release will provide information on glial functions in health and disease and may also introduce opportunities for medical intervention.

1. Ca^{2+} -dependent glutamate release in astrocytes: a historical brief

Astrocytes can couple their inherent intracellular Ca^{2+} excitability to the exocytotic release of transmitters including but not limited to glutamate (Parpura et al., 1994). Throughout this review we interchangeably use Ca^{2+} -dependent and exocytotic attributes of glutamate release from astrocytes. Excitation–secretion coupling in astrocytes involves the molecular machinery for vesicular fusion, including the core members of the soluble N-ethyl maleimide-sensitive fusion protein attachment protein receptor (SNARE) complex, as well as proteins responsible for packaging of glutamate inside vesicles, vacuolar-type proton ATPase and vesicular glutamate transporters [reviewed in Montana et al., 2006; Malarkey and Parpura, 2008].

Evidence for Ca^{2+} -dependent release of glutamate from astrocytes was originally demonstrated in experiments where the application of the Ca^{2+} ionophore ionomycin stimulated the release of glutamate from astrocytes in the presence of external free Ca^{2+} (2.4 mM). However, this ionophore failed to cause glutamate release when applied to astrocytes that were equilibrated in solution with low external free Ca^{2+} (24 nM), for 40–60 min, thus causing the depletion of internal Ca^{2+} stores and preventing the Ca^{2+} entry from the extracellular space (Parpura et al., 1994). These data indicate that Ca^{2+} is sufficient and necessary to cause glutamate release from astrocytes. Indeed, depleting internal Ca^{2+} stores by application of thapsigargin, a blocker of the sarco-endoplasmic reticulum Ca^{2+} -ATPase (SERCA), or buffering cytoplasmic Ca^{2+} with the membrane permeable Ca^{2+} chelator, 1,2-bis(o-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid acetoxymethyl ester (BAPTA-AM), resulted in reduction of glutamate release (Araque et al., 1998a; Bezzi et al., 1998; Innocenti et al., 2000; Hua et al., 2004; Montana et al., 2004). Furthermore, alternative stimuli that directly increased astrocytic intracellular Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$), such as mechanical stimulation (Parpura et al., 1994; Araque et al., 1998a, b; Hua et al., 2004; Montana et al., 2004), photostimulation (Parpura et al., 1994), and photolysis of Ca^{2+} cages (Araque et al., 1998b; Parpura and Haydon, 2000), all caused release of glutamate.

2. The trinity of Ca^{2+} sources

The source of Ca^{2+} for Ca^{2+} -dependent release of glutamate from astrocytes is tripartite, from (i) internal ER stores, (ii) extracellular space and (iii) mitochondria (Fig. 1).

2.1. Inositol 1,4,5-trisphosphate (IP_3)- and ryanodine/cafeine-sensitive ER stores

The ER is the major source of intracellular Ca^{2+} , and it appears to be the main determinant of Ca^{2+} excitability in astrocytes (Verkhatsky, 2006; Deitmer et al., 2008). The concentration of free Ca^{2+} inside the ER ($[\text{Ca}^{2+}]_{\text{ER}}$) ranges from 100 to 800 μM (Burdakov et al., 2005), while the basal concentration of this ion in cytosol ($[\text{Ca}^{2+}]_{\text{cyt}}$) is ~ 100 nM. Ca^{2+} can be released from the ER through IP_3 receptors (IP_3R) and Ca^{2+} -induced Ca^{2+} release (CICR) by activation of caffeine/ryanodine-sensitive receptors (RyR) (Simpson et al., 1998). These two ER receptor/channel types may gate distinct Ca^{2+} stores (Golovina and Blaustein, 2000), although this notion has not been widely accepted [e.g., Hua et al., 2004; see below]. The $[\text{Ca}^{2+}]_{\text{ER}}$ can affect the sensitivity of the RyRs to cytosolic Ca^{2+} as well as the activity of the SERCA pumps (Burdakov et al., 2005). Thus, at the level of the ER, there is regulation of Ca^{2+} release and entry.

The initial, but indirect indication that ER stores play roles in Ca^{2+} -dependent release of glutamate from astrocytes came from experiments in which the neuropeptide bradykinin which caused cytosolic Ca^{2+} elevation in astrocytes also induced glutamate release from these glial cells (Parpura et al., 1994). Bradykinin binds to G-protein coupled plasma membrane receptors which activate the IP_3 pathway, and cause release of Ca^{2+} from the ER (Cholewinski et al., 1988; Stephens et al., 1993). In addition to bradykinin, other ligands including ATP can induce Ca^{2+} release from the ER (Peuchen et al., 1996) through the IP_3 pathway (Kastritsis et al., 1992). Indeed, ATP stimulation of purinergic 2 receptors caused an increase in astrocytic cytosolic Ca^{2+} which coincided with an increase in glutamate release from cultured astrocytes to the extracellular space (Jeremic et al., 2001). This ATP action was greatly reduced when astrocytes were pre-incubated with thapsigargin, implicating the role of ER stores in providing cytosolic Ca^{2+} for exocytotic glutamate release.

Hua et al. (2004) demonstrated that both IP_3 -sensitive and ryanodine/cafeine-sensitive stores play a role in Ca^{2+} -dependent mechanically induced glutamate release from astrocytes. The Ca^{2+} source for this exocytotic release is predominately from internal stores, as indicated by reduction of mechanically induced glutamate release in the presence of thapsigargin. To test whether IP_3 -sensitive internal stores mediate Ca^{2+} -dependent glutamate release from astrocytes, these cells were bathed in diphenylboric acid 2-aminoethyl ester (2-APB) solution, a cell-permeant IP_3R antagonist. This agent greatly reduced exocytotic glutamate release. Next, the role of ryanodine/cafeine-sensitive ER stores was assessed by incubating astrocytes with ryanodine, which at concentrations used (10 μM) blocked the release of Ca^{2+} from the ryanodine/cafeine-sensitive stores. Ryanodine also attenuated mechanically induced glutamate release. Furthermore, the sustained presence of caffeine that depleted ryanodine/cafeine stores, also reduced mechanically induced glutamate release. It should be noted, however, that the functionality of ryanodine receptors in astrocytes is still debated, since the lack of their activity in astrocytes *in situ* had been reported (Beck et al., 2004). Nonetheless, when astrocytes in culture were pre-treated with the combination of 2-APB with ryanodine or caffeine, there was no additive effect on reduction of mechanically induced glutamate release when compared to treatments with one pharmacological agent only. Since all pharmacological agents used in this study showed cytosolic Ca^{2+} changes that were in good agreement with glutamate release, these data suggested that exocytotic glutamate release requires the co-activation of both IP_3 - and ryanodine/cafeine-sensitive internal Ca^{2+} stores and that these stores are operating jointly (Fig. 1).

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