Calcium Signaling in Astrocytes

Internal Calcium Increases in Astrocytes: Channels and Receptors:

Astrocytes have many channels and receptors that allow for increases in internal calcium concentration. The first evidence of this kind of channel came from MacVicar in 1994, who showed that cultured astrocytes express voltage-gated calcium channels (VGCCs) (Hatton 298). The presence of VGCCs in the hippocampus in situ, however, has been controversial. Gap junction coupling and the fine processes where VGCCs are likely to be make these channels difficult to detect in situ, and it is difficult to say if their lack of detection is because of these features or because VGCCs are not expressed in mature astrocytes (Achour et al. 2010). Carriero et al. in 1988 found no evidence for the presence of VGCCs in situ, but there also has been evidence from Fraser et al. in 1995 in favor of the presence of VGCCs in hippocampus (Hatton 298). The most likely option is that which Akopian et al. found in 1996, that is, that VGCCs are expressed in immature astrocytes and that calcium releases are not detectable in adult astrocytes.

The primary source of calcium increases in hippocampal astrocytes has been attributed to release from internal calcium stores. The phospholipase C pathway, activated by Gq GPCRs, breaks down PIP2 into DAG and IP3 (inositol triphosphate), which can activate the IP3 receptor on the endoplasmic reticulum to release calcium (Hatton 298-299). The two major types of Gq GPCRs in astrocytes are P2Y purinergic receptors and metabotropic glutamate receptors, type 3 and 5 (mGluR3 and mGluR5) (Achour et al. 2010). There is an additional, smaller calcium compartment in the endoplasmic reticulum, activated by the natriuretic receptor, specialty type 3 (RyRs). This compartment is not linked to purinergic or glutamatergic signaling. Mitochondria also have a role in calcium buffering through calcium uptake and storage. (Hatton 298-99).

The phospholipase C pathway is also linked to transient receptor potential channels (TRPCs), which are a kind of non-selective calcium channel. The activation of Gq GPCRs and subsequent depletion of internal calcium stores can activate these channels either through a second messenger released by the depletion of calcium from the internal stores or by binding of IP3 itself. The other product of the phospholipase C pathway (PLC) – DAG – also can open these channels in order to allow calcium to enter. Blocking these channels (TRPC in particular) in cultured astrocytes led to reduced calcium signaling and reduced glutamate release (Achour et al. 2010). These results lend support to the hypothesis that astrocyte calcium signaling leads to glutamatergic signaling, and the presence of these channels and their link to the PLC pathway would complicate the picture of the Gq GPCR-IP3 pathway leading to internal calcium release as the main mechanism of calcium signaling. It has also been found that TRPCs can activate store operated calcium entry in the absence of PLC activation (Achour et al. 2010).

Though the phospholipase C/IP3 pathway is considered the major pathway for calcium increases in astrocytes, there are a number of other ways for calcium to come into the cells. Bergmann glia express calcium-permeable AMPA receptors – these receptors have no GluR2 subunit (Hatton 298). Other astrocytes in other other brain regions also express calcium-permeable AMPARs, but these have been found only in complex, that is, immature astrocytes. Astrocytes can also have NMDA receptors, which are also permeable to calcium. Unlike the calcium-permeable AMPARs, NMDARs seem to be expressed in adult astrocytes as well as immature ones and are found in the hippocampus (Achour et al. 2010). The inhibitory neurotransmitter GABA can also increase calcium inside astrocytes through both GABA and GABAB receptors. Because of the high internal chloride concentration in astrocytes, GABA receptor activation can cause enough depolarization to open VGCCs. Kang et al. in 1998 showed that this mechanism can potentiate inhibitory transmission in the hippocampus. ATP can also increase intracellular calcium through the metabolotropic PSY-type receptor and perhaps the ionotropic P2X receptor (Hatton 299-300). The evidence for the existence of P2X receptors in situ has been absent, despite the evidence for P2X receptors in vitro (Achour et al. 2010). Araque et al. showed in 2002 that there were also acetylcholine-mediated calcium currents in astrocytes by stimulation of the stratum oriens/lacunosum. Calcium currents have also been shown to be mediated in some cases by non-selective, nonspecific acetylcholine channels, and histamine channels in hippocampus and cerebellum, perhaps an important part of the glial role in inflammation (Hatton 298-99).

Astrocytic calcium waves have been shown in slices as well as in vitro (Hatton 302-303). Calcium waves are evoked by mechanical stimulation of a glial cell. Proposed mechanisms for propagation of calcium waves. IP3, generated by the active phospholipase C pathway, would diffuse to nearby glia, release calcium from their internal stores. The release of ATP, which can cause further generation of IP3 and release of ATP of nearby cells, could explain longer signaling. (From Haydon, 2001)

Calcium waves and oscillations:

The ability to study calcium transients in astrocytes was greatly aided by several technological advances: patch-clamping, caged compounds, fluorescent dyes, and confocal microscopy that allowed for calcium imaging and manipulations of intracellular calcium concentrations (Haydon 2001). These techniques allowed researchers to identify two types of calcium waves (see Cornell-Bell et al.): oscillations in calcium concentration and propagating calcium waves. The calcium waves were proposed to be a kind of long-distance signal as they can travels hundreds of micrometers, possibly signaling to hundreds of cells. These waves travel at 10-20 micrometers/second, an order of magnitude slower than neuronal signaling. The waves are often associated with waves of ATP or glutamate increases in the extracellular space. The ATP release seems to be independent of calcium and can propagate in the absence of calcium. The glutamate release appears to be calcium dependent: it only occurs with calcium waves and is blocked by SNARE-complex toxins. There are two proposed mechanisms for the propagation of these waves: gap junction coupling or the release of ATP from an upstream astrocyte that could then activate calcium signaling in downstream astrocytes. Astrocytic calcium waves have been shown in slices as well as in vitro (Hatton 302-303).

a. Calcium waves evoked by mechanical stimulation of a glial cell. b. Proposed mechanisms for propagation of calcium waves. IP3, generated by the active phospholipase C pathway, would diffuse to nearby glia, release calcium from their internal stores. The release of ATP, which can cause further generation of IP3 and release of ATP of nearby cells, could explain longer signaling. (From Haydon, 2001)
Most of the calcium imaging performed on astrocytes cannot resolve calcium transients in small astrocytic compartments very well, so little is known about the role of these micro- (or even nano-) domains. In 1999 Grosche et al. found that there can be calcium elevations in these domains that do not spread to the rest of the astrocyte, so it is very possible that these compartments are a kind of functional unit that may have a yet unknown effect on the synapse (Achour et al. 2010).

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