

Neurone-Glia Interactions

Besides neurons, astrocytes constitute the other main cell type in the brain, and for a long time were believed to act simply as extracellular K⁺ buffers and to provide structural support for neurons. With the development and refinement of single cell and population imaging techniques coupled with whole-cell recordings, the last 20 years have seen a marked increase in our knowledge of astrocytic properties and functions. Thus, astrocytes have been shown to have receptors for many synaptically released neurotransmitters such as glutamate, GABA, ATP and adenosine. A picture is also emerging of astrocytic morphological and physiological heterogeneity as well as specialisation of function within, and between brain areas, including the presence of different neurotransmitter receptors and responses to synaptic input. As astrocytes are not capable of generating Na⁺ action potentials, their basic form of excitation is a slowly rising, transient increase of intracellular Ca²⁺ concentration ([Ca²⁺]_i), which can be restricted to a single astrocyte or can take the form of a spontaneous or evoked network response, the so-called Ca²⁺ wave (Figs. 1 & 3).

The inter-astrocytic transmission of these responses is probably both via the intercellular transfer of substances (e.g. ATP) by the gap junctions that extensively link astrocytic networks or by the release of an astrocytic transmitter, i.e. gliotransmitter (GT) (mainly ATP and glutamate), that in turn activates appropriate receptors on neighbouring astrocytes. Indeed, some of the GTs are contained in astrocytic vesicles from where, at least under certain experimental conditions, they can be released following an increase in astrocytic [Ca²⁺]_i. These results and the possibility that astrocytes may release GTs via other mechanisms (e.g. anion channels, volume-activated channels, etc.) clearly provide the basis of complex signalling systems among astrocytes, and between astrocytes and neurons.

The newly realised functional attributes of astrocytes and their anatomical relationships with pre- and postsynaptic neurons have given rise to the concept of the 'tripartite synapse'. The working hypothesis of the tripartite synapse states that synaptically released neurotransmitter excites synapse-ensheathing astrocytes eliciting astrocytic [Ca²⁺]_i increases which triggers the release of a GT which then acts on the pre- or postsynaptic neurons. Depending on the GT identity and the receptor/effector mechanisms it activates, the resulting effect can be synaptic potentiation or depression. Also, in response to physiological stimuli astrocytes can vary their coverage of the synapse to modulate synaptic transmission.

The activation of neuronal receptors by a GT has a characteristic neuronal signature, with astrocytic glutamate release eliciting neuronal excitatory NMDA-mediated currents, termed Slow Inward Currents (SICs) (Figs. 1-3), and putative GABA release eliciting neuronal inhibitory GABA-mediated Slow Outward Currents (SOCs) (Fig. 4). These astrocytic-derived currents can be elicited in response to neuronal stimulation or can occur spontaneously, as originally described by our group in the thalamus, and later seen in many other brain regions.

In terms of function, astrocyte-derived SICs have powerful actions as they can synchronize the firing of small neuronal networks. The ability of thalamic astrocytes to release glutamate and GABA, and the pre- and postsynaptic location of receptors to these GTs in the thalamus indicate a potential for neuronal and synaptic modulation during normal brain function.

OUR RESEARCH

Our work has significantly contributed to an increased understanding of astrocytic function in health and epilepsy. In particular, our major findings in this field include:

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∅ identification of brain astrocytes as driver of neuronal excitation, and their underlying mechanism (Figs. 1-3) (Movie 1) (see publications 1, 5, 6 and 7, below)

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∅ characterization of an abnormal astrocytic GAT-1 function the underlying cause of an enhanced tonic GABA-A current in the thalamus of genetic absence epilepsy models

(see publication 3, below)

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∅ identification of afferent input-specificity in thalamic astrocytes (Movie 2)

(see publication 2, below)

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We are continuing to investigate i) the differential innervation of thalamic astrocytes by sensory and cortical afferents, ii) the properties of thalamic NG2-positive cells, and iii) the role of thalamic and cortical astrocytes in absence epilepsy.

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Details of our discoveries in this field can be found in the following publications:

1. Chen, L., Gould, T.M., Oddos, F., Crunelli, V. and Parri, H.R. (2010). MRP-dependent tonic glutamate controls spontaneous astrocyte-neuron signaling. *J. Neurosci.*, submitted.
2. Parri, H.R., Gould, T.M. and Crunelli, V. (2010). Input-specific activation of distinct glial cell subtypes in the somatosensory thalamus. *Eur J Neurosci*, under revision.
3. Cope, D.W., Fyson, S.J., Errington, A.C., Di Giovanni, G., Lörincz, M., Orbán, G., Gould, T.M., Carter, D.A. and Crunelli V. (2009). Enhanced tonic GABAergic inhibition is required for typical absence seizures. *Nature Medicine*, 15, 1392-1398.
4. Parri, H.R. and Crunelli, V. (2002) Astrocytes, spontaneity and the thalamus. *J. Physiol. (Paris)*, 96, 221-230.
5. Parri, H.R. and Crunelli, V. (2003) The role of Ca²⁺ in the generation of spontaneous astrocytic Ca²⁺ oscillations. *Neuroscience*, 120, 979-999.
6. Parri, H.R. and Crunelli, V. (2001). Pacemaker calcium oscillations in thalamic astrocytes in situ. *NeuroReport.*, 12, 3897-3900.
7. Parri, H.R., Gould, T.M. and Crunelli, V. (2001). Spontaneous astrocytic Ca²⁺ oscillations in situ driven NMDAR-mediated neuronal excitation. *Nature Neuroscience*, 4, 803-812.