Tripartite Synapses and Astrocytic Plasticity

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Introduction

Astrocytes are the most abundant glial cells in the central nervous system. They are formed by a soma and many processes that can envelope thousands of synapses. Although it is not an optimal marker, astrocytes are usually detected by its expression of glial fibrillary acidic protein (**GFAP**). In the past, astrocytes were considered to have only structural and metabolic functions.
This review focuses on the role of astrocytes as cells that can actively regulate synaptic activity and the changes that they suffer in certain conditions such as lactation.

Methods

Bibliographic search of reviews and original articles in databases as PubMed (NCBI) and Web of Knowledge using the following keywords: tripartite synapses, gliotransmission, astrocytic plasticity, glial plasticity. A selection was done depending on the date of publication and the relevance of the topic to the review.

Astrocytes can release gliotransmitters and modify synaptic activity

Ca^{2+}-mediated excitability

Astrocytes show an unusual form of excitability that is based on **intracellular calcium waves** after the activation of neurotransmitter receptors on their membrane. Spontaneous excitability has been shown in hippocampus.
These waves are restricted to areas of the processes from where they spread, called **microdomains**.

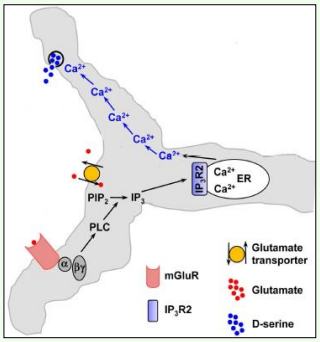


Figure 1. Ca^{2+}-mediated astrocytic excitability. Modified from Agulhon C et al. Front Pharmacol. 2012 Jan;3:139. Aug;20(4):466–73.

Gliotransmission

During the last years, many studies have shown that astrocytes are not passive cells in the synapses, but they have the ability of releasing transmitters (**gliotransmitters**). Most of them are stored in vesicles that are exocytosed in a Ca^{2+}-dependent manner. The most important ones are the following:

Glutamate	• Binds to NMDA receptors in hippocampus triggering its depolarization. • Binds to presynaptic metabotropic receptors and can potentiate or depress neurotransmitter release. • Heterosynaptic effects: bursts synchronization.
ATP	• Binds to presynaptic A1 receptors and causes synaptic depression. • Conversion to **adenosine** by ectonucleotidases.
D-serine	• Coactivator of NMDA receptors in hypothalamus, hippocampus and retina.

Tripartite synapses

The term *tripartite synapse* refers to the **exchange of information between neurons and astrocytes in the regulation of synapses.**

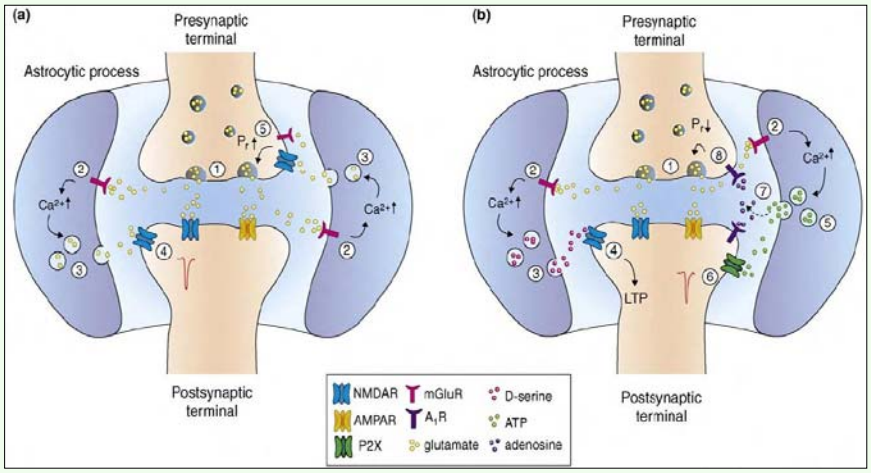


Figure 2. Tripartite synapse. **a)** Astrocyte release of glutamate. **b)** Astrocyte release of D-serine and ATP. From Paixão S, Klein R. Curr Opin Neurobiol. 2010 Aug;20(4):466–73.

Astrocytes present cellular plasticity

Astrocytic plasticity

Astrocytes are not static cells, but their **morphology and physiology can be modified** under certain conditions.

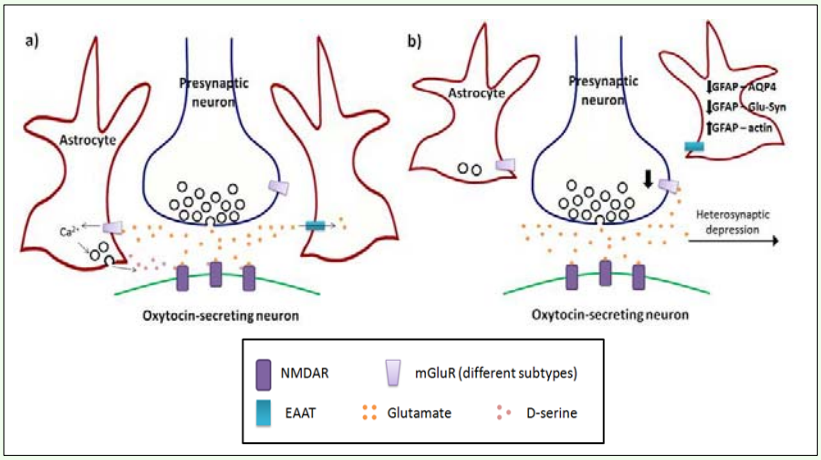


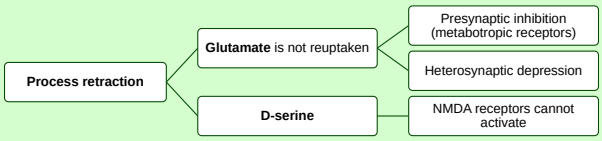
Figure 3. Tripartite synapse in supraoptic nucleus in normal conditions **(a)** and during suckling **(b)**. Changes in gliotransmission and the interaction of GFAP with other proteins can be observed.

Figure 4. Electron microscopy images of the rat supraoptic nucleus (SON) when it is not stimulated **(left)** and when it is stimulated during lactation **(right)**. From Theodosis DT, Poulain DA, Oliet SHR. Physiol Rev. 2008 Jul;88(3):983–1008.

Lactation: an example of plasticity

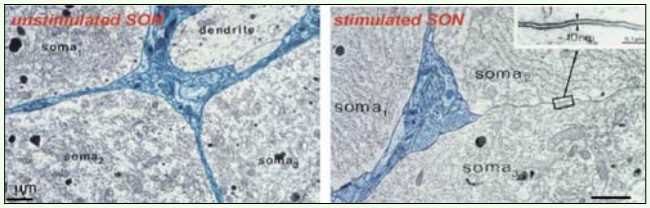
Oxytocin is a hormone released by magnocellular neurons in the supraoptic (SON) and paraventricular (PVN) nuclei in the hypothalamus. During lactation, oxytocin release is enhanced in order to promote the contraction of myoepithelial cells of the mammary gland and favor milk ejection.

For this purpose, it is important that oxytocin-secreting neurons have high activity and are synchronized. Astrocytes play an important role in this mechanism, as there is **process retraction**, which affects synaptic transmission. In general, neurons that are not involved in oxytocin release are inhibited; the ones that release oxytocin are highly stimulated and can reverse this inhibition.



Process retraction also allows the **juxtaposition of neurons** and therefore the formation of gap junctions, favoring neuronal synchronization.

Molecularly, GFAP levels are reduced as it depolymerizes or degradates, and also its interaction with other proteins such as aquaporin-4 (AQP4), glutamine synthetase or actin can be altered.



Conclusions

• Although it is still under debate, synapses seem to be tripartite, as it has been seen that astrocytes can release gliotransmitters and therefore be active partners in the regulation of synapses.
• Astrocytes present cellular plasticity, as their morphology and function can change under certain conditions, such as lactation, inducing changes in synaptic transmission.
• It is necessary that research in neuroscience focuses not only in neurons but also in astrocytes, which could be implicated in some neurological diseases.

References

(1) Agulhon C et al. Front Pharmacol. 2012 Jan;3:139. Aug;20(4):466–73.
(2) Paixão S, Klein R. Curr Opin Neurobiol. 2010 Aug;20(4):466–73.
(3) Wang Y-F, Hatton GI. J Neurosci. 2009 Feb 11;29(6):1743–54.
(4) Theodosis DT, Poulain DA, Oliet SHR. Physiol Rev. 2008 Jul;88(3):983–1008.