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LATERAL REGULATION OF SYNAPTIC TRANSMISSION BY ASTROCYTES

A. COVELO AND A. ARAQUE *

Department of Neuroscience, University of Minnesota, Minneapolis, USA

Abstract—Fifteen years ago the concept of the ''tripartite synapse'' was proposed to conceptualize the functional view that astrocytes are integral elements of synapses. The signaling exchange between astrocytes and neurons within the tripartite synapse results in the synaptic regulation of synaptic transmission and plasticity through an autocrine form of communication. However, recent evidence indicates that the astrocyte synaptic regulation is not restricted to the active tripartite synapse but can be manifested through astrocyte signaling at synapses relatively distant from active synapses, a process termed lateral astrocyte synaptic regulation. This phenomenon resembles the classical heterosynaptic modulation but is mechanistically different because it involves astrocytes and its properties critically depend on the morphological and functional features of astrocytes. Therefore, the functional concept of the tripartite synapse as a fundamental unit must be expanded to include the interaction between tripartite synapses. Through lateral synaptic regulation, astrocytes serve as an active processing bridge for synaptic interaction and crosstalk between synapses with no direct neuronal connectivity, supporting the idea that neural network function results from the coordinated activity of astrocytes and neurons.

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Key words: astrocytes, synaptic transmission, gliotransmission, astrocyte–neuron interaction.

INTRODUCTION

Astrocytes were historically recognized as non-neuronal elements playing important roles in neuronal and synaptic function, providing metabolic and trophic support and maintaining the homeostatic conditions for the proper function of neurons and synapses through the regulation of extracellular levels of ions and neurotransmitters. Besides these supportive and homeostatic roles, evidence obtained in the last two decades has revealed that astrocytes may directly be involved in the regulation of neuronal and synaptic function, by responding to neurotransmitters released from synaptic terminals and by releasing gliotransmitters that can impact neurons and synapses controlling neuronal activity and animal behavior (Araque et al., 2001, 2014; Nedergaard et al., 2003; Volterra and Meldolesi, 2005; Haydon and Carmignoto, 2006; Theodosis et al., 2008; Perea et al., 2009, 2014; Parpura and Zorec, 2010).

Based on this bidirectional exchange of signaling between astrocytes and neuronal synaptic elements, 15 years ago the concept of tripartite synapse was devised (Araque et al., 1999). This idea, which represented a novel concept in synaptic physiology, proposed that astrocytes are functional integral parts of the synapses that they enwrap, and they can respond to and, in turn, regulate synaptic activity. This exchange of signals between astrocytes and neurons within the synapse results in the homosynaptic regulation of synaptic transmission and plasticity by astrocytes through a form of autocrine signaling that may serve as a feedback mechanism.

However, this synaptic regulation by astrocytes is not necessarily restricted to the active synapse and the surrounding astrocytes. Considering the morphological and functional properties of the astrocytes, such as the controlled spatial extension of the astrocyte calcium signal (Grosche et al., 1999; Perea and Araque, 2005; Di Castro et al., 2011; Panatier et al., 2011), the intercellular communication between astrocytes (Giaume and McCarthy, 1996; Rouach et al., 2008; Giaume et al., 2010), and the extensive cellular branching that allows a single astrocyte to be in contact with thousands of synapses (Bushong et al., 2002; Halassa et al., 2007), more complex spatial regulatory processes performed by astrocytes can be envisaged. For example, stimulation of an astrocyte by the activity of certain synapses could lead to the heterosynaptic regulation of other synapses through a form of paracrine signaling between tripartite synapses that may serve as a feedback or feedforward mechanism based on an indirect synaptic crosstalk (Fig. 1).

The astrocyte calcium signal is known to be triggered in specific subcellular compartments or microdomains by neurotransmitters released from synaptic terminals (Grosche et al., 1999; Perea and Araque, 2005; Di Castro et al., 2011; Panatier et al., 2011). From these microdomains the calcium signal can spread under different conditions to adjacent regions within the process, to

*Corresponding author. Address: Department of Neuroscience, University of Minnesota, 6-145 Jackson Hall, 321 Church St SE, Minneapolis, MN 55455, USA. Te.: +1-(+612)-624-0901.
E-mail address: araque@umn.edu (A. Araque).
Abbreviations: eCB, endocannabinoid; tLTD, timing-dependent depression; LTP, long-term potentiation.

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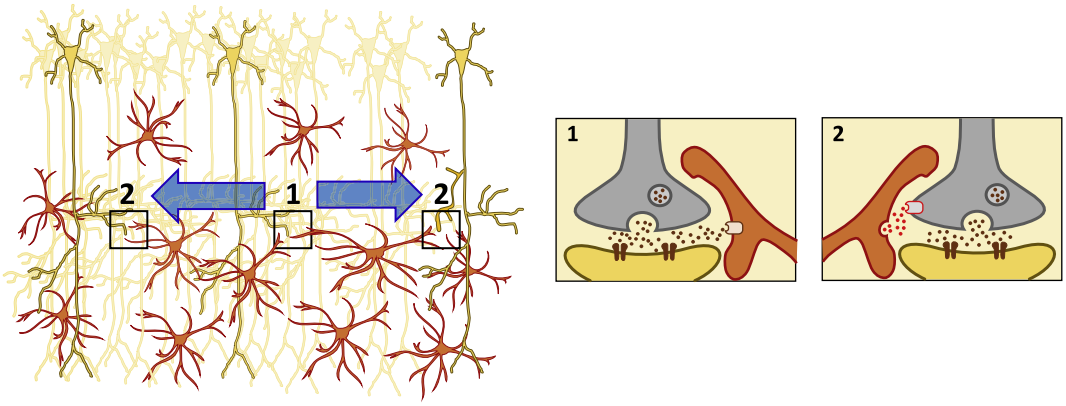

Fig. 1. Scheme showing the lateral astrocyte synaptic regulation. The neurotransmitter released during the activity of a synapse (1) stimulates the surrounding astrocytes (red). The evoked astrocyte calcium signal may extend intracellularly (and perhaps intercellularly) to stimulate the release of gliotransmitters in a distal astrocyte region, thus regulating synaptic transmission in relatively distant synapses (2), which would otherwise be unaffected by the activity of synapse 1.

different processes and eventually to the whole cell (for a recent detailed and comprehensive review on the properties of the astrocyte calcium signal, see Volterra et al., 2014). The spatial extension of the calcium signal is not a passive phenomenon, rather it seems to be a regulated process that depends on the neuronal activity and interaction of different synaptic inputs (Perea and Araque, 2005; Araque et al., 2014; Volterra et al., 2014). Therefore, beyond the passive diffusion of gliotransmitters, the spatial extension of the calcium signal evoked by the activity of single synapses, may impact other synapses within the astrocyte territory. The spatial extension of the calcium signal and, consequently, the astrocytic signal responsible for the synaptic modulation critically depends on the morphological characteristics of astrocytes. Indeed, astrocytic size, orientation, synaptic coverage and astrocyte/synapse ratio are expected to determine the extension of the regulatory signal, and differences of these parameters in different brain areas are expected to influence the functional properties of the lateral astrocyte synaptic regulation. In addition, since astrocytes are extensively connected through gap-junctions forming a syncytium, and perhaps a functional network (Rouach et al., 2008; Giaume et al., 2010), and can communicate with adjacent astrocytes, the calcium signal could even spread to larger distances from the original source point, leading to the regulation of even more distant synapses.

These ideas, originally hypothesized based on these considerations (Fellin and Carmignoto, 2004; Perea and Araque, 2005), have been recently supported by several experimental results demonstrating the regulation of transmission and plasticity in synapses relatively distant from active synapses through astrocyte signaling. This concept, termed lateral astrocyte synaptic regulation, refers to a phenomenon that resembles the classical heterosynaptic modulation and shares several properties with this process, but is mechanistically different. While canonical heterosynaptic modulation relies exclusively on neuronal activity, lateral astrocyte synaptic regulation involves specific signaling, such as gliotransmitters, astrocyte receptors, astrocyte calcium signal properties and intercellular communication between astrocytes. It also depends on the morphological characteristics of the astrocytes and the functional interaction with the neuronal synaptic elements.

In the following sections we will discuss key findings that have led to this novel view of the heterosynaptic regulation by astrocytes.

HIPPOCAMPAL HETEROSYNAPTIC DEPRESSION

Heterosynaptic depression of excitatory synaptic transmission is a well-known phenomenon consisting in the depression of transmission in inactive synapses induced by strong stimulation of different synaptic inputs into the same postsynaptic neuron. This process has been thought to serve as a contrast mechanism between synaptic inputs (Lynch et al., 1977). For example, in the hippocampus, a tetanizing stimulus in a subset of Schaffer collaterals elicits the depression of unstimulated synapses in the same CA1 pyramidal neuron. Complex signaling mechanisms involving the concerted activity of astrocytes and neurons have been shown to underlie this heterosynaptic depression. During strong stimulation of Schaffer collaterals, the glutamate released from the synaptic terminals not only activates CA1 pyramidal neurons but also inhibitory GABAergic interneurons. The release of the neurotransmitter GABA activates GABA-B receptors in astrocytes, which stimulate astrocyte calcium signaling and the release of the gliotransmitter ATP, which, after being extracellularly converted to adenosine, leads to the synaptic depression of adjacent unstimulated synapses (Zhang et al., 2003; Serrano et al., 2006; Andersson et al., 2007). These findings represent a clear example of how the activity of certain synapses (CA3-CA1 glutamatergic synapses and GABAergic synapses) may influence synaptic transmission in less active synapses through the necessary contribution of astrocyte signaling.