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Synaptic plasticity, astrocytes and morphological homeostasis

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Abstract

Recent discoveries suggest that astrocytes are an integral part of synaptic connections, as they sense and modulate synaptic activity. Moreover, there is evidence that astrocytes change the number of synaptic connections directly via synaptogenic signals or indirectly, by modifying the morphology of axons and dendrites. Here, we formulate the hypothesis that astrocytes mediate the morphological homeostasis of nerve cells, which is any adaptation of the morphology of a neuron to preserve its ability to respond to and generate synaptic activity during learning and memory-induced changes. We argue that astrocytes control neuronal morphology locally and across long-ranging assemblies of neurons and that on the other hand, astrocytes are part of the engram with plasticity-related changes affecting their morphology.

Keywords: Astrocytes; Neuroglia; Synaptic plasticity; Synaptogenesis; Learning; Memory; Engram; Calcium waves; Information processing

1. Introduction

One of the most intensely investigated topics in neuroscience are the cellular and molecular mechanisms of learning and memory. It is now largely accepted that the formation of long-term memory involves changes in the number and strength of synaptic connections between neurons (Bailey and Kandel, 1993; Greenough and Chang, 1988; Lamprecht and LeDoux, 2004). These changes are considered to be implemented solely by the neuronal network due to its ability to generate and process electrical signals. However, research within the last decade provokes the hypothesis that the neuronal network is not autonomous, but depends on the dialogue with a parallel network, which consists of astrocytes (Fig. 1). In a visionary article, Smith (1992) asked whether astrocytes participate in the generation and processing of information. The idea that astrocytes contribute to cognitive processes such as learning and memory is in line with an evolutionary increase in the glia-neuron index (Bass et al., 1971; Kuffler et al., 1984) and with differences in the organization and morphology of cortical astrocytes between primates and other mammals (Colombo and Reisin, 2004; Reisin and Colombo, 2002). Here, we propose that astrocytes are crucial elements for the homeostatic regulation of plasticity (Fig. 1). We suggest first that these cells regulate the number of synaptic connections between neurons to balance the level of activity in the whole network and second, that learning-induced structural changes in the astroglial network are part of memory traces. Comprehensive reviews on other aspects neuron–glia interactions can be found elsewhere (Araque et al., 1999; Bacci et al., 1999; Bezzi et al., 2001; Carmignoto, 2000; Castonguay et al., 2001; Hatton and Parpura, 2004; Haydon, 2001; Hertz et al., 2001; Kettenmann and Ransom, 2004; Laming et al., 2000; Slezak and Pfrieger, 2003; Ullian et al., 2004; Volterra et al., 2002).

2. The concept of morphological homeostasis

For many years, research on the mechanisms of learning and memory formation concentrated on changes in the

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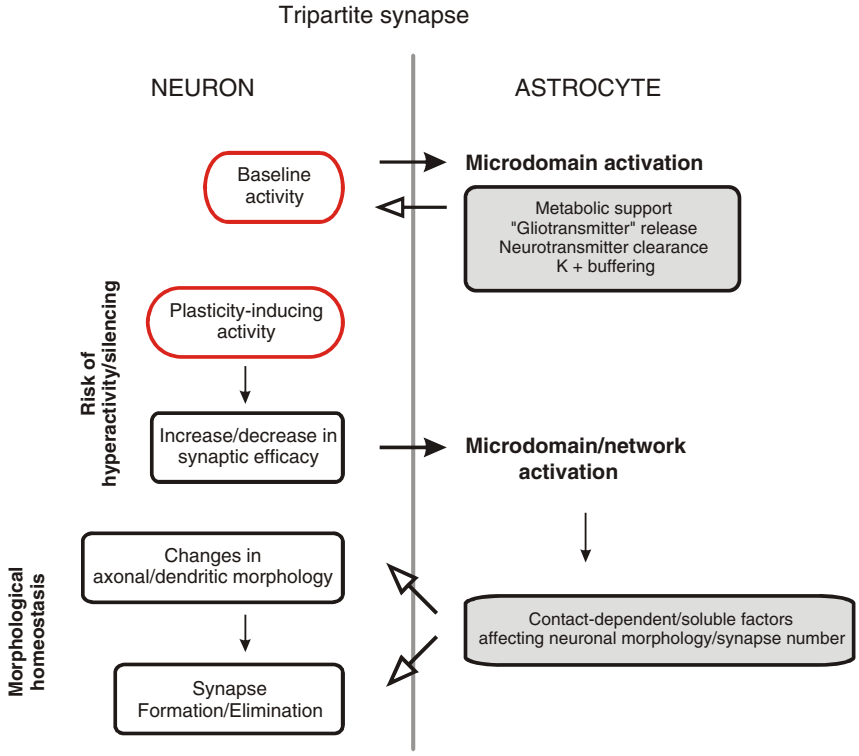

Fig. 1. Diagram illustrating the concept of morphological homeostasis. Under baseline conditions, astrocytes maintain and modulate synaptic function. Activity-dependent synaptic plasticity changes the synaptic input to a neuron, which then may cause hyperactivity or silencing. In response to this, astrocytes induce local and distant compensatory changes in the number of synapses directly or by changing axonal and dendritic morphology to reset neuronal activity.

efficiency of individual synapses. The most frequently postulated mechanism for synaptic plasticity is based on Hebb's rule, which states that strengthening of a connection between two neurons occurs, if both cells are simultaneously and repeatedly active (Hebb, 1949). To avoid an intrinsic positive feedback that follows from Hebb's rule, theoreticians postulated compensatory mechanisms to adjust the total synaptic input of a neuron to local changes in efficacy (Fregnac, 1995; Viana Di Prisco, 1984; von der Malsburg, 1973). However, such mechanisms have only recently been described in real neurons. One of them is multiplicative synaptic scaling, a phenomenon that was discovered first in cultured cortical neurons (Turrigiano et al., 1998) and then described in cortical slices (Desai et al., 2002). In this process, which proceeds within hours to days, the strengths of all synaptic inputs to a given neuron are scaled up or down by a multiplicative factor to preserve the relative intersynaptic differences in efficacy and to keep the firing rate of the neuron in an optimal range. Without such compensatory scaling, an increase in synaptic efficiency would saturate the firing rate of neurons and, in consequence, ablate their ability to respond to changing stimulation patterns, whereas a decrease in synaptic strength could lower the probability for reaching the threshold for action potential initiation and silence neurons (Feldman, 2002; Fregnac, 1998; Turrigiano, 1999). The discovery of synaptic scaling raises the question whether the mechanisms that balance the overall activity of a neuron also comprise structural or morphological changes. This may involve the formation of new and elimination of existing connections and changes in the morphology of axons and dendrites. It is known that the shape of dendrites influences the firing rates of neurons (Duijnhouwer et al., 2001; Mainen and Sejnowski, 1996; Nasuto et al., 2001) and their ability for coincidence detection (Schaefer et al., 2003). This implies that neuronal morphology is under some form of homeostatic control. In fact, Greenough and co-workers have shown that learning-induced changes in synapse number are subject to homeostatic control: Synapse formation in rats housed in a complex environment, an experimental paradigm to test learning-induced changes (van Praag et al., 2000), was accompanied by a proportional increase in dendritic length thus keeping synaptic density constant (Jones and Greenough, 2002; Wallace et al., 1992). We will further refer to mechanisms that maintain the ability of a neuron to sense and generate meaningful outputs during plasticity-induced changes as "morphological homeostasis" (Fig. 1). Although it is conceivable that morphological homeostasis is implemented exclusively by neuron-intrinsic properties, we will argue that glial cells, namely astrocytes, play a significant role in this process.

3. Evidence for astrocyte-mediated morphological homeostasis

If astrocytes contribute to morphological homeostasis, they must be in close proximity to synapses and be able