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BRAIN RESEARCH REVIEWS

Review

Contributions of astrocytes to synapse formation and maturation — Potential functions of the perisynaptic extracellular matrix

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ABSTRACT

The concept of the tripartite synapse proposes that in addition to the presynapse and the postsynaptic membrane closely apposed processes of astrocytes constitute an integral part of the synapse. Accordingly, astrocytes may influence synaptic activity by various ways. Thus glia- and neuron-derived neurotrophins, cytokines and metabolites influence neuronal survival, synaptic activity and plasticity. Beyond these facts, the past years have shown that astrocytes are required for synaptogenesis, the structural maintenance and proper functioning of synapses. In particular, astrocytes seem to play a key role in the organization of the brain's extracellular matrix (ECM) — most prominently the so-called perineuronal nets (PNNs), complex macromolecular assemblies of ECM components. Due to progress in cellular and molecular neurosciences, it has been possible to decipher the composition of ECM structures and to obtain insight into their function(s) and underlying mechanisms. It appears that PNN-related structures are involved in regulating the sprouting and pruning of synapses, which represents an important morphological correlate of synaptic plasticity in the adult nervous system. Perturbation assays and gene elimination by recombinant techniques have provided clear indications that astrocyte-derived ECM components, e.g. the tenascins and chondroitinsulfate proteoglycans (CSPGs) of the lectican family participate in these biological functions. The present review will discuss the glia-derived glycoproteins and CSPGs of the perisynaptic ECM, their neuronal and glial receptors, and in vitro assays to test their physiological functions in the framework of the synapse, the pivotal element of communication in the central nervous system.

Contents

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1. The concept of the tripartite synapse

The synapse as central information relay of the nervous system consists of the presynapse and the postsynapse separated by the synaptic cleft. It represents the central functional element of the nervous system. (Choquet and Triller, 2003; Garner et al., 2002; Sanes and Lichtman, 1999, 2001). This functional unit is formed during development of the nervous system and is subject to malleability in the adult nervous system (Araque et al., 2001). Until recently, our knowledge about the machinery involved in the assembly of the central nervous system (CNS) synapse was sparse. Clear evidence has accumulated that, similar to the peripheral nervous system, the CNS synapse is composed of three elements, namely the presynapse, the postsynaptic membrane and the nearby astrocyte and its processes that make intimate contact with the neuronal synaptic structures (Fig. 1) (Haydon, 2001; Sanes and Lichtman, 2001; Slezak and Pfrieger, 2003). Functional participation of astrocytes in stability and integrity of synapses had originally been inferred on the basis of morphological studies, for example the role of astroglia in the generation of the neuronal networks and the observation of astroglial processes in the proximity of CNS synapses by transmission electron microscopy (TEM) (Araque et al., 1999a,b). With the help of TEM, the phenomenon of synaptic stripping could be documented in the facial nucleus after peripheral lesion of the facial nerve, where astrocytes seal the neuronal cell bodies and withdraw afferent synapses (Scheiffele, 2003; Theodosis et al., 2008). Regulation of the proportion of neuronal surface covered by astrocytes has also been reported for hypothalamic nuclei, where the extent of astroglial-derived appositions varies with physiological parameters (Langle et al., 2002; Theodosis et al., 2008). The maintenance of plasticity in this brain region correlates with the expression of extracellular matrix (ECM) glycoproteins that are otherwise down-regulated in the CNS, namely tenascin-C, which is mainly expressed by astrocytes (Theodosis et al., 1997). Following this concept, co-culture experiments clearly indicated that astrocytes release molecules that are required to sustain the structural maturation as well as the functional activation of synapses (Beattie et al., 2002; Nagler et al., 2001; Pfrieger and Barres, 1997; Slezak and Pfrieger, 2003; Song et al., 2002; Ullian et al., 2001, 2004b). Some of these are released into the medium of astrocyte cultures and enriched in the high molecular weight fraction, displaying characteristic biochemical properties of

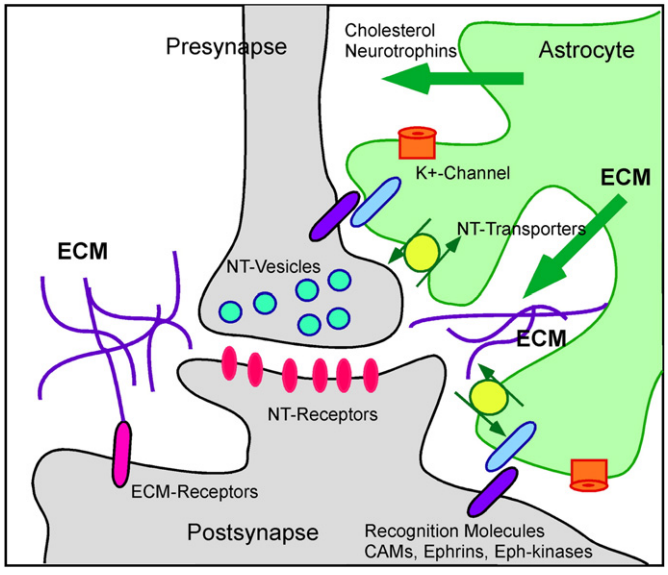

Fig. 1 – Concept of the tripartite synapse. The cartoon illustrates the concept of the tripartite synapse. Astrocyte processes are in close neighborhood of the pre- and postsynapse and interact with these functional elements in various multiple functional pathways. Thus, astrocytes release factors including ECM, cytokines and neurotransmitters (so-called gliotransmitters), metabolites such as cholesterol and interact with neurons via cell–cell and cell–ECM based adhesion mechanisms. For details see text.