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Molecular signals of plasticity at the tetrapartite synapse

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Abstract

The emergence of astroglia as an important participant of the synaptic machinery has led to the 'tripartite synapse' hypothesis. Recent findings suggest that synaptic signaling also involves the surrounding extracellular matrix (ECM). The ECM can incorporate and store molecular traces of both neuronal and glial activities. It can also modulate function of local receptors or ion channels and send diffuse molecular signals using products of its use-dependent proteolytic cleavage. Recent experimental findings implicate the ECM in mechanisms of synaptic plasticity and glial remodeling, thus lending support to the 'tetrapartite synapse' concept. This inclusive view might help to understand better the mechanisms underlying signal integration and novel forms of long-term homeostatic regulation in the brain.

Introduction

Chemical synapses are elemental units of information processing in the brain. By implication, signal transfer between presynaptic and postsynaptic cells has been considered as a bipartite mechanism. Over the last decade, however, the emergence of astrocytes as an important local player has led to the concept of the tripartite synapse [1]. Recent findings suggest that all parts of the tripartite synapse interact, either directly or through soluble signaling molecules, with the extracellular matrix (ECM) [2–5]. ECM structures are formed in an activity-dependent manner and incorporate molecular signatures of both glial and synaptic elements. In turn, ECM molecules modulate activities of pre- and postsynaptic receptors and ion channels. The ECM can respond to network activity either by incorporating secreted molecules and shed extracellular domains of transmembrane molecules, or by freeing products of its activity-dependent proteolytic cleavage as signaling messengers [6]. These observations have suggested that the ECM is a fourth essential element of what could be termed as the 'synaptic quadriga' [7] or the 'tetrapartite synapse' [8]. Theoretically, including the ECM as a fourth player increases the number of interaction pathways in a synapse from 6 to 12 (Figure 1). Here we briefly review the underlying mechanisms, focusing on interactions beyond the classical pre–postsynaptic exchange, namely on signals between neurons, astroglia and the ECM.

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Presynaptic signals to glia and ECM

The bulk of information in the brain is processed via excitatory glutamatergic synapses. Once released, glutamate activates receptors inside the synaptic cleft but it can also reach some high-affinity receptors outside the cleft [9–11]. The excess of glutamate is rapidly buffered by high-affinity transporters [12–14] expressed in abundance by the surrounding astroglia [15,16]. Glial transporters EAAT1–EAAT2 account for >90% of brain glutamate uptake [17], and astrocytic protrusions can closely approach the synaptic cleft [18–20] altogether occupying 10–30% of the neuropil [21]. The uptake keeps the ambient glutamate concentration low, at ~25 n_M in quiescent tissue [22]. Clearly, buffering and uptake of released glutamate is a major channel of signal exchange between synaptic terminals and glia.

Astrocytes *in situ* also express glutamate receptors, including Ca^{2+} permeable AMPA receptors (AMPARs), NMDA receptors (NMDARs), and group I metabotropic glutamate receptors [23–27], as reviewed in detail recently [28,29]. Because the same astrocytes also express high-affinity glutamate transporters, successful actions of glutamate seem to require spatial colocalization of receptors and release sites (or otherwise suppression of local glutamate uptake). Indeed, AMPAR-mediated currents in Bergmann glia have been related to neuronal ectopic release sites occurring in front of the target receptors [30]. Alternatively, glutamatergic signal transfer between neurons and glia may actually occur through the transporter-dependent activation of astrocytic Na^+/Ca^{2+} exchanger leading to Ca^{2+} entry [31]. The inhibitory neurotransmitter GABA could activate metabotropic $GABA_B$ receptors in astrocytes resulting in Ca^{2+} rises which trigger release of glutamate [32] or ATP [33,34]. Unlike glutamatergic signals, this mode of diffuse communication is less restricted by high-affinity uptake: indeed, discharges of individual interneurons *in situ* could generate long-lasting, long-range extracellular GABA transients [35,36].

Presynaptic activity also controls the ECM. For instance, axonal terminals release the proteinase neurotrypsin [37], which cleaves the heparan sulfate proteoglycan agrin at central synapses [38••]. Earlier studies identified agrin as a major ECM player in the development and maintenance of the neuromuscular junction [39]. Neurotrypsin cleaves agrin at two homologous, highly conserved sites, releasing a 90-kDa (agrin-90) and a 22-kDa (agrin-22) fragment. The latter triggers the formation of dendritic filopodia after induction of NMDAR-dependent plasticity [38••]. Interestingly, agrin cleavage requires not only neurotrypsin exocytosis, but also activation of the postsynaptic neuron, suggesting a coincidence detection mechanism triggering structural plasticity in a Hebbian manner (Figure 2a).

Postsynaptic signals to glia and ECM

Quantitative electron microscopy suggests that astroglia occur more frequently on the postsynaptic side of some excitatory synapses [21]. Several types of retrograde messengers are released from postsynaptic neurons, including neurotransmitters, endocannabinoids, gasses, and peptides, as detailed in a recent review [40]. Similar to axonal releases, ectopic release of glutamate and GABA from postsynaptic dendrites could exert receptor actions in astrocytes (see above), but little is known about other signaling channels. Recent evidence suggests that cannabinoid CB1 receptors are expressed by brain astrocytes and could be activated by endocannabinoids which are released from nearby neurons [41] through a Ca^{2+} and depolarization dependent mechanism [42,43]. This activation triggers Ca^{2+} waves in astroglia [41], which in turn initiates glial release of glutamate [44,45•]. The subcellular distribution and properties of CB1 receptors in astrocytes should provide important clues regarding the downstream mechanisms involved.

Cell bodies and proximal dendrites of many central neurons are surrounded by the so-called perineuronal nets (PNNs), which are a specialized form of the ECM containing hyaluronan, chondroitin sulfate proteoglycans (CSPGs), tenascin-R and link proteins Crtl1 and Bral2 [3,46]. Expression patterns of ECM proteins and enzymes involved in the synthesis of hyaluronan (hyaluronan synthases 1–3) indicate that CSPG aggrecan, link proteins and hyaluronan are secreted or exported from the somatodendritic domain of the PNN-covered neurons [47]. Enzymatic removal of hyaluronan impairs formation of PNNs [48], whereas ablation of Crtl1 results in abnormal structure of PNNs [49].

Astroglial signals

Ca^{2+} signals in astrocytes could trigger release of glutamate [32,44,50], ATP [33,34,51], D-serine [52,53,54•], the pro-inflammatory cytokine tumor-necrosis factor α (TNFα), and other signaling molecules. Whether and how the underlying mechanisms differ, in terms of their Ca^{2+}-dependent molecular machinery and subcellular localization, remains intensely debated [29]. Presynaptic NMDARs and metabotropic glutamate receptors could be a target of glutamate released from astrocytes [44,45•] but further studies are required to understand how and where astrocytic glutamate can successfully compete with glutamate released by synapses. Indeed, a strategic juxtaposition of neuronal NMDARs and astroglial compartments featuring putative glutamate-containing vesicles has been identified [44].

ATP released from astrocytes [51] degrades in the extra-cellular space to adenosine which activates presynaptic A1 receptors inhibiting transmission in synaptic circuits [33,34]. This cascade may ultimately affect sleep [55] and prevent postsynaptic stabilization of LTP by interfering with actin polymerization [56](Figure 2c). In the retina, astrocytic ATP release activates A1 receptors coupled to K^+ channels in postsynaptic neurons, and the ensuing hyperpolarization decreases neuronal excitability [57]. In the neuromuscular junction, differential Ca^{2+} signals in Schwann cells either depress or potentiate neurotransmission through activation of, respectively, adenosine A1 or A2A receptors [58•]. Release of ATP from brainstem astrocytes, in response to either physiological pH changes or the stimuli optogenetically targeted to astrocytes, regulates neural circuits controlling breathing [59••].

Substantial evidence points to the release of the NMDAR coagonist D-serine from astroglia. Because D-serine is not buffered by transporters, it enables astrocytes to regulate remotely NMDAR activation in neurons [52,60,61]. Release of D-serine from astroglia is critical for induction of LTP in cultures [53] and explains a correlation between glial coverage of synapses and LTP in the supra-optic nucleus [61]. In acute brain slices, induction of NMDAR-dependent LTP requires synthesis and supply of D-serine by astrocytes [54•] (Figure 2b). Astrocytic release of TNFα helps to adjust synaptic strengths across the neural network, thus mediating a synaptic scaling phenomenon [62]. The underlying signaling cascade is initiated by a lack of transmitter release, which stimulates TNFα secretion from glia, which in turn upregulates postsynaptic expression of β3 containing integrins [63]. Since integrins are known to be major receptors to ECM molecules, the latter presumably enhances ECM signaling, with the net result being an increase in cell surface expression of postsynaptic AMPARs (Figure 2d).

In addition, astrocytes secrete ECM molecules, such as CSPG brevican and glycoprotein tenascin-C, and thrombospondins [4]. Brevican deficient mice show alterations in the expression of another ECM CSPG, neurocan, less prominent PNNs, and significant deficits in the maintenance of LTP [64]. Tenascin-C deficient mice also show impairment in LTP [65]. Examination of perisynaptic ECM composition in tenascin-C and brevican deficient mice could provide important clues regarding the interactions involved.

ECM signals

All members of the thrombospondin gene family trigger the formation of presynaptically active contacts *in vitro*, and double knockout mice deficient in thrombospondins 1 and 2 show reduced synaptic numbers [66]. This synaptogenic activity is mediated by the α2δ-1 Gabapentin receptor that is part of neuronal voltage-gated calcium channels (VGCCs) [67]. An extracellularly secreted protein, leucine-rich glioma-inactivated 1 (LGI1), has been found to interconnect presynaptic and postsynaptic complexes of proteins, including postsynaptic density proteins 95 and 93 and presynaptic K^+ channels [68••]. Signaling via the major ECM receptors integrins control synaptic trafficking of NMDA and glycine receptors [69,70•], and the activity of matrix metalloproteinase-9 can stimulate this pathway [69]. Furthermore, ECM structures are thought to restrict mobility of neurotransmitters and their postsynaptic receptors [5,71•].

Several ECM molecules, such as tenascin-C, laminin, fibronectin, retinoschisin and hyaluronan, modulate activity of postsynaptic L-type VGCCs (L-VGCCs) in various types of cells (reviewed by [6]). Genetic ablation of tenascin-C or removal of hyaluronan by hyaluronidase impaired LTP at CA3-CA1 synapses; these effects are occluded by L-VGCC blockade, whereas synaptic plasticity can be restored by pharmacological potentiation of L-VGCC activity [65,72•]. Removal of hyaluronan reduces spike-induced postsynaptic Ca^{2+} transients in hippocampal pyramidal neurons during induction of LTP, also impairing hippocampus-dependent contextual fear conditioning [72•]. The ECM-related upregulation of postsynaptic L-VGCC could be important for retrograde signaling via BDNF (Figure 2b) [73,74]. Another ECM glycoprotein, reelin, boosts the activity of NMDARs [75], while HNK-1 carbohydrate carried by tenascin-R inhibits postsynaptic $GABA_B$ receptors [76]. Signaling via post-synaptic integrins promotes polymerization of actin and hence consolidation of LTP [77](Figure 2c).

In the neuromuscular junction, laminin 11 concentrates in the synaptic cleft and prevents Schwann cell processes from entering it [78]. It is plausible to assume that accumulations of perisynaptic ECM molecules and associated cytokines in central synapses also help to stabilize interactions between presynaptic and postsynaptic cells by restraining invasion of astrocytic and micro-glial processes. Conversely, remodeling of ECM and changes in the expression of secreted factors might prompt invasive astroglial and microglial enwrapping of postsynaptic cells following a loss of afferent inputs, as observed in the human facial nucleus [79,80]. In hypothalamic nuclei, astrocytic coverage of neurons strongly depends on physiological condition, such as lactation or dehydration [81,82], and this type of plasticity correlates with local expression of tenascin-C [83]. Furthermore, deficiency in tenascin-C or tenascin-R, or enzymatic removal of hyaluronan or chondroitin sulfates leads to astrogliosis [84], highlighting an inhibitory influence of the ECM on astrocytes.

Outlook

We are only beginning to appreciate the many forms of functional and structural synaptic changes that rely on interactions with the ECM and the surrounding astroglia. The relationship between perisynaptic ECM and local astrocytic processes remains particularly poorly understood even though it may be essential for the formation and use-dependent modification of synaptic environment. By restraining glial processes and by counteracting the effects of glia-derived adenosine [56], the ECM may contribute to the stabilization of new synaptic configurations. It would seem reasonable to consider remodeling of the ECM and glial processes as an important element of synaptic plasticity, yet the hierarchy of their relationships remains largely unexplored. We suggest therefore that the concept of the tetrapartite synapse might help to understand better the mechanisms underlying information

processing in the brain. Indeed, astroglia have been thought to enable spatial integration of network activity, supporting conscious states [85,86]. Conversely, the mixed neuronal-glial origin of ECM suggests that it may contain memory traces of neural network activity and, in addition to the mechanisms discussed above, encompass novel forms of long-term homeostatic regulation.

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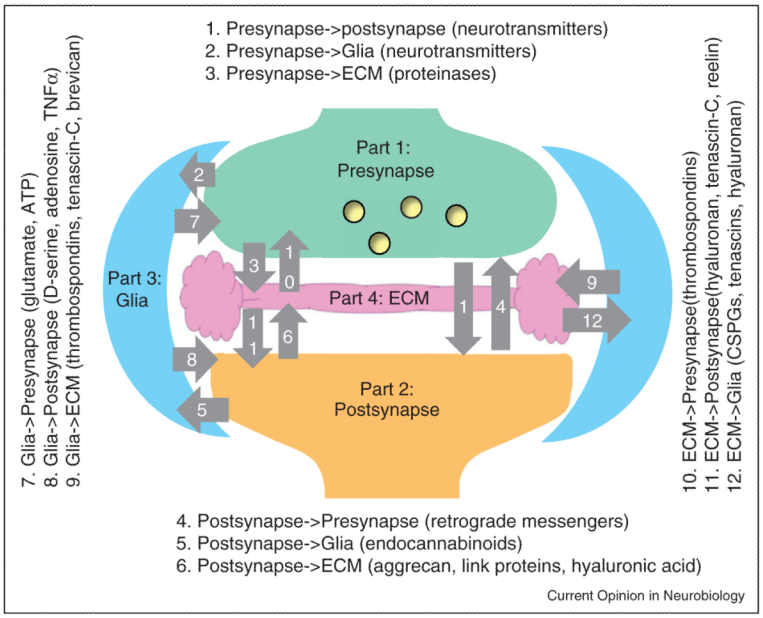

Figure 1.

The tetrapartite synapse and 12 possible signaling pathways among its four parts. Examples of signaling molecules are given in parentheses. *Abbreviations*: ATP, adenosine triphosphate; ECM, extracellular matrix; CSPGs, chondroitin sulfate proteoglycans; TNFα, tumor-necrosis factor α.

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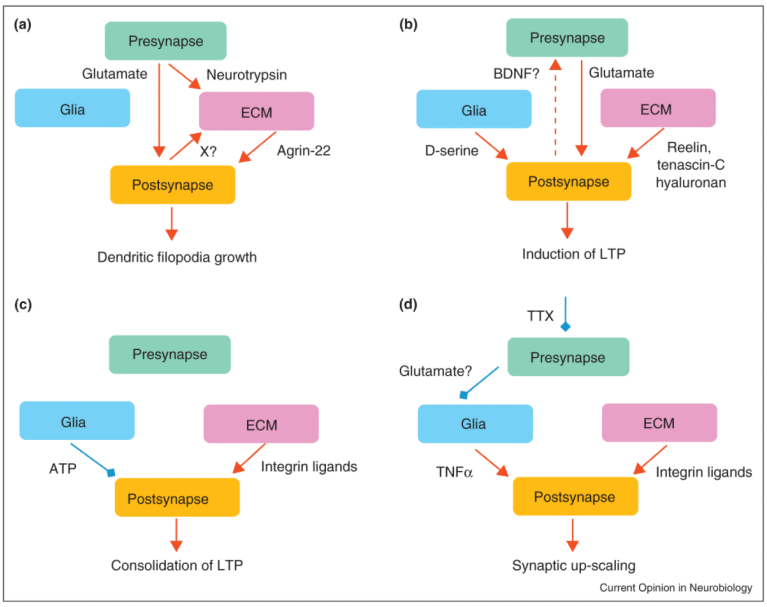

Figure 2.

Mechanisms of plasticity at the tetrapartite synapse: where the ECM and glia get involved. **(a)** Co-activation of presynaptic and postsynaptic cells results in release and activation of neurotrypsin. The product of agrin cleavage by neurotrypsin, agrin-22, induces formation of dendritic filopodia. **(b)** Release of D-serine from astroglia and positive modulation of NMDA receptors and L-type Ca^{2+} channels by ECM molecules reelin, tenascin-C and hyaluronan supports induction of LTP. Activation of postsynaptic L-type Ca^{2+} channels may lead to retrograde signaling and an increase in efficacy of presynaptic release. **(c)** Astroglia-derived ATP is converted into adenosine which, by acting via A1 receptors, can destabilize new synaptic configurations during a consolidation phase of LTP (first 30 min after induction of LTP). Integrin signaling in contrast promotes stabilization of new synaptic configurations promoting polymerization of actin. **(d)** Presynaptic inactivity leads to release of TNFα from astrocytes that upregulates expression of β3 integrins, which signal to inhibit endocytosis of AMPA receptors, and thus increases their cell surface expression at synapses.

Abbreviations: ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; CSPGs, chondroitin sulfate proteoglycans; ECM, extracellular matrix; LTP, long-term potentiation; TNFα, tumor-necrosis factorα; TTX, tetrodotoxin, a blocker of voltage-gated Na^+ channels; X?, unknown factor(s); ↑, stimulation; ↑ inhibition; – indirect evidence.