Brain circuitry outside the synaptic cleft

Dmitri A. Rusakov1 and Alexander E. Dityatev2

1 UCL Institute of Neurology, University College London, Queen Square, London WC1N 3BG, UK
2 Molecular Neuroplasticity Group, German Center for Neurodegenerative Diseases (DZNE), D-39120 Magdeburg, Germany

A growing body of experimental evidence suggests that astroglia, and possibly microglia, play an important part in regulating synaptic networking of the brain. It has also emerged that extracellular matrix (ECM) structures that enwrap synaptic connections can generate molecular signals affecting both neuronal and glial activity. Thus it appears that the mechanism of information processing in the brain, which has hitherto been associated almost exclusively with neural circuits, could also involve informative signal exchange outside the synaptic cleft. In this Theme Issue, research teams including leading experts on astroglia–neuron communication and on ECM signalling report their recent findings, share their views and discuss future conceptual advances in the field. Potential implications for drug development and new therapeutic targets with regard to some common neurological conditions are discussed throughout the issue.

In their review, Navarrete et al. [1] discuss the emerging roles of the endocannabinoid signalling system, in particular type 1 cannabinoid receptors, in controlling intracellular calcium elevations and subsequent release of glutamate by astroglia, with an ensuing regulatory action on local synapses. Losi et al. [2] overview and analyse current experimental evidence for the adaptive physiological roles played by GABAergic signalling between inhibitory interneurons and astrocytes in the brain. Morawski et al. [3] present their recent evidence that tenascin-R promotes assembly of the perineuronal nets through the clustering of aggrecan and demonstrate that it is possible to compensate a genetic deficiency in an ECM molecule by pharmacological intervention. In another experimental research paper, Korotchenko et al. [4] report that the enzymatic removal of heparan sulfates—carried by a number of extracellular matrix (ECM) molecules—induces homeostatic synaptic plasticity and epileptiform network activity. A research study by Klueva et al. [5] proposes that α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor mobility on aspiny neurons, in contrast to pyramidal cells, depends on intracellular Ca2+ signalling rather than on the local ECM. An experimental report by Anders et al. [6] uses advanced imaging techniques to reveal three-dimensional features of astrocyte gap-junction coupling in the hippocampus, with a discussion of potential physiological implications. In their review, Hines & Haydon [7] discuss in some depth the versatile physiological roles of astroglia-originated adenosine, from its regulatory actions at synapses to its complex modulatory network effects impacting on respiration, the sleep–wake cycle, and potentially the neurophysiological basis of some common psychiatric disorders. Hirase et al. [8] review a growing body of experimental data suggesting that during states of attention the volume transmission of neuromodulators could be a mechanism to activate astrocytic G protein-coupled receptors and thus switch cortical circuits to a ‘plastic’ mode. Panatier et al. [9] in their article explain the concept and implementation of super-resolution stimulated emission depletion microscopy, focusing on its potential for deciphering morpho-functional interactions between astrocytes and synaptic connections. A comprehensive review by Xavier et al. [10] focuses on the fine-tuning of neural connectivity enabled by the microglia-assisted shaping of the cellular and synaptic architecture. Papouin & Oliet [11] review recent experimental findings and theoretical concepts related to the subcellular organization, subunit composition and endogenous control of extrasynaptic N-methyl-D-aspartate receptors. A research article by Rasooli-Nejad et al. [12] focuses on the causal relationship between cannabinoid CB1...
receptors, astroglial Ca\(^{2+}\) signals, and the regulatory effects on synaptic plasticity in the neocortex, suggesting an important role of glial exocytosis for the underlying mechanism. Gottipati et al. [13] review and discuss the use of chemically functionalized carbon nanotubes in controlling morphology and function of astrocytes, with their potential future applications as neural prostheses. Experimental findings reported by Gould et al. [14] focus on the gamma-aminobutyric acid B (GABA\(_B\)) receptor-mediated activation of astrocytes by gamma-hydroxybutyric acid (GHB), which may have important implications for our understanding of the addictive and pro-epileptic actions of GHB. A research article by Chever et al. [15] reports that connexin 43, a key component of astroglia gap-junction coupling, regulates astrocyte cell volume and also affects synaptic glutamate release in the hippocampus, thus making an important contribution to the control of synaptic efficacy. Savtchenko & Rusakov [16] in their research article use extensive models of realistic networks of hippocampal neurons to explore the potential impact of volume-transmitted, astroglia-like molecular signals on rhythm generation in brain circuits. A review by Sahlender et al. [17] discusses cellular mechanisms that could explain the diversity of physiological Ca\(^{2+}\) signals in astroglia and their respective adaptive roles in generating distinct modes of molecular signals that target functional neural connections. Valenzuela et al. [18] in their experimental study report that major ECM components, including chondroitin sulfate proteoglycans such as brevicin, undergo substantial reorganization upon induction of homeostatic neural plasticity, thus potentially facilitating structural remodelling of synapses. A research report by Höft et al. [19] provides a detailed comparative analysis of AMPA and GABA receptor expression in astroglia in the murine ventrobasal thalamus and other brain regions, providing evidence for substantial functional heterogeneity of astrocytes across the brain. Medvedev et al. [20] in their study employ quantitative three-dimensional electron microscopy to find that ultrathin astroglial protrusions tend to provide more substantial coverage to excitatory synapses formed on thin, as opposed to large (mushroom-type), dendritic spines. A review by Vargova & Sykova [21] discusses the role of ECM and astroglia in extrasynaptic volume transmission and its potential implications for a better understanding of pathological functional states, brain disease diagnosis, drug delivery and treatment. Verkhratski & Nedergaard [22] in their review put forward and discuss a concept proposing that astrocytic persynaptic processes act as an ‘astroglial cradle’ that is essential for synaptogenesis, maturation, isolation and maintenance of synapses across the CNS.

References