Current Trends in Neurology
Vol. 11, 2017

Review

Dysfunctional neuronal synapses in multiple sclerosis

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ABSTRACT

Multiple sclerosis (MS), a debilitating neuroinflammatory disease of the human central nervous system, is typically considered as a white matter disease in which an auto-reactive immune system attacks components of the axonal myelin sheath to impair fast impulse transmission along myelinated axons in the brain. In the last few years, it has become clear that not only the white matter is affected in multiple sclerosis but also the grey matter and neuronal synapses, the key structures of neuronal communication. These synaptic changes occur early and independent of demyelination processes in the white matter. In this short review, we will summarize results that document an involvement of synapses in multiple sclerosis patients and in rodent models of multiple sclerosis. We discuss how inflammatory signalling in multiple sclerosis can influence synaptic transmission.

KEYWORDS: multiple sclerosis (MS), experimental autoimmune encephalomyelitis (EAE), synapse, synaptic communication, astrocytes, neuroinflammation, pro-inflammatory cytokines, microglia.

INTRODUCTION

Multiple sclerosis (MS) is a complex, multifaceted neuroinflammatory disease of the central nervous system (CNS) from which ≈2.5 million people suffers worldwide [1]. MS is typically considered as a white matter disease in which auto-reactive immune cells target components of the axonal myelin sheath in the white matter [2]. Recent evidence obtained from human MS patients as well as from rodent models of MS also point to an involvement of the grey matter and of synapses, the key structures for neuronal communication. These latter findings might initially appear surprising at the first sight. But they might not be this surprising based on the increasingly appreciated close functional connection between the immune system and neuronal synapses. This close connection has been uncovered particularly in the past few years and is relevant for modulating synaptic signalling in the healthy brain but also for signalling malfunctions in the diseased brain. In multiple sclerosis, neuroinflammatory signals are massively elevated and can negatively affect neuronal synapses and synaptic communication.

In the present review, we focus on MS-relevant issues such as how neuroinflammation and neuroinflammatory mediators influence synaptic transmission. In section 1, we summarize topic-relevant aspects on neuronal communication at chemical synapses, the key structures of synaptic communication in the CNS. In sections 2 and 3, we introduce brain glial cells (astrocytes, microglia) as major sources of pro-inflammatory cytokines that can influence synaptic transmission. Next, we will present some recently discovered links between the immune system and neuronal synapses (section 4) and discuss an emerging view, how the close interaction between the immune system and

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neuronal synapses influence synapse function not only in the healthy brain but also under the neuroinflammatory conditions of multiple sclerosis (section 5).

1. Synapses: versatile and adjustable communication nano-machines

Synapses are the central communication devices in the human nervous system. At chemical synapses, a presynaptic terminal communicates with a postsynaptic compartment that is separated by a thin extracellular synaptic cleft. Synaptic communication in the presynaptic terminals occurs *via* fusion (exocytosis) of neurotransmitter-containing synaptic vesicles with the presynaptic plasma membrane in a SNARE protein-dependent manner [3-8]. Fusion of synaptic vesicles occurs at the active zone, a protein-rich, electron-dense area of the presynaptic plasma membrane at which the vesicle fusion machinery tightly interacts with voltage-gated Cav-channels [3, 9]. Ca^{2+}-entry through voltage-gated Cav-channels triggers the rapid, stimulus-synchronous vesicle fusion by activating the Ca^{2+}-sensor synaptotagmin [8]. After exocytosis, fused synaptic vesicle components (proteins and lipids) are recycled *via* different modes of endocytosis [10, 11]. Following the release of neurotransmitter and its binding to postsynaptic neurotransmitter receptors, neurotransmitter action is terminated by different mechanisms. At glutamatergic synapses, glutamate is taken up by glutamate transporters (GluT) present in the plasma membrane of the presynaptic terminal [12-15] or by glutamate transporters present in the synapse-associated glial cells [16, 17].

The synaptic cleft consists of a dense array of synaptic adhesion proteins and specialized extracellular matrix components that align pre- and postsynaptic events [18-21]. Of particular importance is the synaptic adhesion complex consisting of presynaptic neurexins and postsynaptic neuroligins [18, 22, 23]. Dysfunctions of this central neurexin-neuroligin synaptic adhesion axis lead to cognitive disturbances and neuropsychiatric diseases [18]. The expression of neurexin/neuroligin is altered in multiple sclerosis patients (see below) and also the composition of the synaptic extracellular matrix appears to be relevant for MS [24-26]. At the postsynaptic site, neurotransmitter receptors are immobilized by the postsynaptic density (PSD), a dense protein network beneath the postsynaptic plasma membrane in which neurotransmitter receptors and synaptic adhesion proteins are interconnected with the postsynaptic cytoskeleton [27-30]. This postsynaptic network is important for postsynaptic plasticity [31-33, 30].

Chemical synapses are not static but highly dynamic nano-machines capable to adjust the strength and efficacy of synaptic communication. This dynamic behavior of synapses, coined "synaptic plasticity", is considered as the basis of learning and memory [34] and comprises several mechanisms. The so called "HEBB"-ian synaptic plasticity enables the CNS to operate on the basis of previous experience (i.e. to "learn"). The strength of an individual synapse that is frequently used within a distinct synaptic circuit is enhanced. Vice versa, the power of less frequently used synapses will be decreased. "HEBB"-ian synaptic plasticity includes short-term and long-term dynamic changes (short-term-, long-term-potentiation/ depression; [35, 31, 33]). Depending on the synaptic system, synaptic plasticity can be mediated either by pre- or postsynaptic mechanisms. Presynaptic mechanisms of synaptic plasticity control synaptic vesicle release probability, e.g. by modifying active zone components/Cav-channel number and/or opening properties and/or strength of presynaptic Ca^{2+} signalling [3, 4, 36, 37]. Postsynaptic mechanisms involve neurotransmitter receptor trafficking and surface expression [31, 38, 33]. NMDA- and AMPA-type of glutamate receptors play a central role in this process [39, 40, 33, 41-44].

Thus, Hebbian synaptic plasticity leads to the re-inforcement of strong, frequently used individual synapses and to a down-regulation of weak, less active individual synapses (positive feedback loops). In order to prevent over-activation/saturation of active synapses and complete dampening/ silencing of less active synapses, negative-feedback mechanisms are implemented that lead to compensatory adjustments of synaptic signalling and re-setting of the synaptic signalling range. These synaptic re-adjustment systems are collectively referred to as "Homeostatic Synaptic Plasticity" ("HSP") [45-49]. HSP maintains synaptic activity in a functional range and prevents unresponsiveness

of synaptic networks [45, 48]. At a molecular level, many key-players (e.g. number and surface availability of neurotransmitter receptors) are common for both Hebbian plasticity as well as for homeostatic synaptic plasticity [48, 44, 50]. Homeostatic synaptic plasticity (HSP) operates on a slower timescale than Hebbian synaptic plasticity and is regulated by pro-inflammatory cytokines TNFα and IL-1β [51, 45, 48, 44].

Initially, the Malenka group discovered that TNFα is important for AMPA- and GABA-receptor trafficking in the synapse [52, 53, 51, 48]. AMPA- and GABA-receptor trafficking is regulated by TNFα in an antagonistic manner. TNFα increases postsynaptic AMPA receptor surface expression [52, 53, 51]. Interestingly, TNFα promotes surface expression of the GluR2 subunit-lacking and thus Ca^{2+}-permeable AMPA receptors [54, 53, 48]. The Ca^{2+}-permeability of the glutamate receptors is a particularly important aspect for excitotoxic effects in the case of overstimulation that can occur during neuroinflammatory diseases such as multiple sclerosis (see below). In contrast to glutamatergic AMPA receptors, TNFα promotes dynamin-dependent endocytosis of inhibitory GABA receptors and thus leads to a decrease in GABA receptor surface expression [53, 55]. These TNFα effects are mediated by neuronal TNFR1 receptors [53, 56]. IL-1β is also involved in the down-regulation of synaptic GABA receptors *via* distinct intracellular neuronal signalling pathways [57-60, 55, 61, 62]. Pro-inflammatory cytokines have also been shown to be important for memory formation in freely moving animals [63].

In multiple sclerosis, the levels of pro-inflammatory cytokines TNFα and IL-1β are massively increased and negatively impact synapse functions (see below). Pro-inflammatory cytokines are secreted mainly by glia cells, astrocytes and particularly microglia cells, that both establish close contacts with synapses.

2. Astrocytes: modulators of synaptic functions within the "tripartite" synapse

Astrocytes are centrally involved in synaptic neuroinflammatory pathology in multiple sclerosis. Astrocytes occupy distinct, spatially tiled areas (territories) in the CNS and communicate with each other *via* gap junctional networks [56]. Processes of astrocytes establish close perisynaptic contacts with neuronal synapses [56, 64-66]. In the mouse brain cortex, a single astrocyte can ensheath ≈100,000 synapses [67]. The expression "tripartite" synapse, i.e. presynapse, postsynapse and synapse-associated astrocyte, was coined to better appreciate the active roles of astrocytes in synaptic functions [68, 56, 69, 70]. These synapse-associated perisynaptic processes of astrocytes are important for several aspects of synaptic function [64, 56, 70]. These roles include, but are not restricted to, uptake of neurotransmitters (glutamate) that escaped from the synaptic cleft [71]. By this way, neuronal and glial glutamate uptake mechanisms collaborate to shape synaptic signalling and to prevent excitatory synaptic over-stimulation as well as spreading to neighboring synapses [68, 67, 71-73]. This glial uptake function is accomplished either by brain astrocytes or specialized radial astroglia cells, e.g. Bergmann glia cells in the cerebellum or Müller glia cells in the retina [16, 65]. Astrocytes possess different types of glutamate receptors to sense glutamate release by the presynaptic terminal and are regulated by synaptic activity [74-77, 69]. *Via* activation of glutamatergic cell surface receptors on astrocytes, released glutamate stimulates its uptake *via* glial glutamate transporters [78]. Dysfunctions of glutamate homeostasis and of glutamate uptake are important part of the synaptic pathology in multiple sclerosis (see below).

Astrocytes not only sense synaptic activity *via* various cell surface receptors (e.g. GluA-, GABA-B-, P2Y-, NMDA-, mGluR5-receptors) but also release various mediators ("gliotransmitters": glutamate, D-serine, ATP/adenosine) that modulate synaptic function [79, 80, 56, 70, 81]. Astrocytes release gliotransmitters in response to different stimuli, including increased levels of extracellular glutamate and TNFα ([52, 56] but see [82]). Astrocytes establish contacts and intensively communicate with microglia cells. This interaction provides important cues for the further differentiation of astrocytes into distinct sub-types, i.e. either into a beneficial, homeostatic and activity-maintaining/-restoring sub-type, or alternatively, into a neurotoxic subtype whose

activity is detrimental to the CNS [83-85]. These astrocyte-microglia interactions are highly relevant for neuroinflammatory synaptic changes in multiple sclerosis (see below).

Astrocytes serve a plethora of homeostatic functions for the CNS beyond those exerted directly at the synapse [86, 87]. These extrasynaptic functions of astrocytes (e.g. the control of the blood-brain-barrier) are not considered here. Also at synapses, astrocytes exert further additional functions that might be relevant for synaptopathies in multiple sclerosis. Astrocytes secrete various synaptogenic factors (e.g. thrombospondin, glypican, hevin, SPARC) that are important for synapse formation and maturation during development [88-90, 56, 91-94]. Astrocyte-secreted extracellular thrombospondins bind to the α2δ1 subunit of voltage-gated Cav-channels that could be critical for maintaining proper presynaptic functioning [88, 95, 96]. Astrocytes secrete into the synaptic cleft the glycoprotein hevin that bridges presynaptic neurexin1α and postsynaptic neuroligin1B [91]. Astrocyte-secreted glypicans increase the surface expression of postsynaptic AMPA receptors [97, 98]. Astrocytes secrete trophic factors (e.g. BDNF) that regulate complement protein C1q expression in the associated neurons [99]. This aspect is relevant for synapse elimination during development and might possibly be relevant for synapse loss in multiple sclerosis (see below). Also the composition of adhesion proteins at the synaptic cleft is modulated by the activity of astroglia cells [100, 98]. By means of their equipment with a specific set of cell surface receptors, astrocytes are also involved in the elimination of silenced or dysfunctional synapses [101, 56].

3. Microglia: CNS-resident immune cells with newly identified roles at the synapse in health and disease

Microglia (≈10% of total CNS brain cells) are brain-resident immune cells. Similar to astrocytes, microglia cells perform a multitude of functions in the injured and/or diseased brain but also in the healthy brain [102, 71, 103, 104]. In the injured brain, the so called “activated” microglia cells (with an amoeboid shape) migrate to sites of lesions and act as macrophages/scavengers that remove dead cells/debris [71]. ATP released from damaged or dead cells acts as a strong attracting and activation signal for microglia [105, 104]. In the healthy brain, microglia cells typically display a highly ramified morphology with many processes. These ramified microglia cells were initially considered as “resting”, i.e. inactive. But novel technologies, particularly live imaging approaches demonstrated that these “resting” microglia are in contrast highly active. Ramified microglia cells continuously scan and monitor the extracellular environment of the CNS via various cell surface receptors enriched on the highly motile cell processes [102, 71, 104]. By this, microglia cells respond and react to various extracellular signals in the healthy brain to maintain brain homeostasis under normal conditions [71, 104]. The signals detected by microglia are diverse at a molecular and functional level and include released neurotransmitters, ATP, neuronal activity or inactivity [105-109, 71, 104]. Complement proteins (e.g. complement proteins C1, C3) represent other signals that microglia can detect via cell surface complement receptors [110, 111, 56, 86, 104]. During development, complement proteins tag excess, inactive or dysfunctional synapses and mark these transient synapses for subsequent elimination by microglia. This function of microglia cells is called “synapse stripping” and is necessary for the development and refinement of functional neuronal circuits [110, 111, 71]. Various “danger”/“damage” signals [112] lead to rapid activation of microglia cells that subsequently secrete large amounts of biologically highly active cytokines [71, 113, 104]. Microglia cells are the major source of the pro-inflammatory cytokines IL-1β and TNFα [82, 71] although astrocytes were reported to also secrete TNFα [52, 56]. Pro-inflammatory cytokines IL-1β and TNFα mediate homeostatic synaptic functions in the healthy brain, as summarized above. Recently, previously unidentified roles have been discovered for microglia and microglia-derived signalling molecules. Live-imaging analyses revealed that microglia directly interact with synapses in an activity-dependent manner [105-107, 111, 114, 115]. This activity-dependent interaction is involved on one hand in developmental synapse pruning and neurodegenerative diseases but on the other hand in the refinement of neuronal circuits

in the healthy, postnatal brain. Neuronal activity has a strong impact on these synapse microglia interactions [106, 107]. In the cortex, microglial processes established fewer contacts with synapses if these were pharmacologically silenced or inactive. Microglia cells secrete trophic factors (e.g. brain-derived growth factor, BDNF and others) important for synapse formation and stabilization [114, 113] or neuronal survival [71, 116]. Furthermore, microglia interact and communicate with astrocytes and with the astrocytic syncytial network. This contact is important for the further signalling behavior of astrocytes. In response to interaction with microglia, astrocytes release various synapse-active components that either positively or negatively affect synaptic performance (e.g. [84, 81, 117, 104, 94]. The "normal" release of inflammatory cytokines modulates synapse functions without leading to inflammation [104]. Inflammatory over-activation of microglia, as it can occur in multiple sclerosis, leads to CNS dysfunction and synapse damage mainly due to the massively increased release of the pro-inflammatory cytokines, e.g. TNFα, IL-1β, that adversely affect synapse functions (see below). The close relation of microglia to both pre- and post-synaptic terminals as well as to the perisynaptic astrocytes has been referred to as "quad-partite" synapse to appreciate the importance and interplay of these cellular components for synaptic functions in health and disease [116].

4. Newly discovered crosstalks between neuronal synapses and the immune system and some shared molecules

Important new roles have been identified for the immune system in the development and maintenance of neuronal synaptic networks during CNS development. During early brain development, more synapses are initially formed than later needed to establish functional neuronal circuits [110, 118]. These transient superfluous synapses are removed during the maturation and refinement of neuronal networks. A series of impressive studies demonstrated that the classical complement system is crucially involved in removing excess, dysfunctional and hypoactive synapses during development of the CNS ("synaptic pruning"; [110, 119, 120, 104]. Supernumerary, non-needed synapses are tagged by complement proteins and are subsequently removed by microglia cells. Cell surface complement receptors of microglia cells recognize the complement-tagged synapses and eliminate them by phagocytosis [110, 119], by a similar mechanism as in other parts of the body [121, 122]. In the CNS, complement proteins are produced/secreted by glial cells (microglia and astrocytes) but also by neurons [119, 99, 123, 84]. Infiltrating, activated T-lymphocytes and a leaky blood-brain-barrier are further sources for complement proteins in the injured CNS, e.g. in MS [2, 124-127]. Interestingly, complement protein expression is strongly up-regulated in lesioned brain areas of MS patients [128-132]. Thus, complement-mediated synapse removal system might be also operating in synapse elimination in multiple sclerosis (see below). Complement protein expression in neurons is induced/up-regulated by astrocytes [110, 119]. The complement system is also up-regulated in severe neurodegenerative diseases and during aging [119, 133]. Interactions with synaptic proteins could be responsible for the localized enrichment of complement proteins at the synapse. Complement proteins (e.g. C1q) bind to synaptic proteins, e.g. to neuronal pentraxins [134, 110] a conserved family of pattern recognition molecules with a C-terminal homology to blood-borne pentraxins (including C-reactive protein (CRP), serum amyloid P component (SAP), PTX3 [48, 135, 136], and also to postsynaptic AMPA receptors [137-141]. Neuronal pentraxins are released by presynaptic terminals in response to glypican secretion from astrocytes to promote functional synapse formation [93]. Membrane-bound presynaptic neuronal pentraxins induce postsynaptic specializations at excitatory and inhibitory synapses [142].

Interestingly, a neuronal C1q-like/tumor necrosis factor (TNF) protein superfamily has been identified that includes various members, including the cerebellins, C1q-like proteins and also tumour necrosis factor, TNF (including TNFα) [143, 144]. Components of the C1q-like/TNF protein superfamily have been identified as important synapse organizers [145, 146, 18]. They are small proteins with a characteristic

domain structure secreted by the presynaptic nerve terminals [144]. These proteins bind both to the neurexin family of presynaptic adhesion proteins as well as to postsynaptic glutamate receptor subunits [145, 144, 147, 146, 18]. The dendritic adhesion-type G-protein-coupled receptor brain-specific angiogenesis inhibitor 3 (BAI3) is another interaction partner for C1q-like proteins [148, 144].

The major histocompatibility complex (MHC) class I represents an additional set of immune molecules important for synaptic pruning and synaptic rearrangement in the developing as well as in the mature CNS [149-154]. At the immunological synapse [155], MHC class I interacts with the T-cell receptor (TCR) complex of CD8-positive T-lymphocytes [151, 153]. MHC class I proteins are also expressed by neurons and interact with the presynaptic paired immunoglobulin-like receptor B, PirB [151, 153]. MHC class I expression in the brain is controlled by neuronal activity as well as by distinct patterns of cytokines and signalling cascades [156, 48, 157]. They are also involved in learning [158]. Similar to pro-inflammatory cytokines like TNFα, MHC class I proteins are important for synaptic scaling in the healthy brain [151, 153] as shown by the absence of the homeostatic up-scaling of synaptic transmission in tetrodotoxin-silenced neurons of MHC class I-deficient knockout mice [150].

5. Inflammatory synaptopathy, a new facet of multiple sclerosis

In recent years, neuronal synapses of the central nervous system emerged as potential targets in multiple sclerosis (MS). Synaptic alterations were observed both in multiple sclerosis patients as well as in mouse models of multiple sclerosis [60, 159, 160, 73]. Evidence for synaptic changes in multiple sclerosis (MS) in humans were obtained by clinical, morphological, biochemical, electrophysiological and imaging analyses of MS patients [161, 124, 159, 162, 60, 163, 160, 119]. Many MS patients have altered cognitive and/or emotional behavior which was interpreted as a consequence of synaptic dysfunction [161, 164, 165, 64, 73]. This view was supported by electrophysiological and imaging data from brains of MS patients [166, 167, 73]. Morphological (immunocytochemical and electron microscopic) data demonstrated reduction of synaptic markers and loss of synaptic structures [163]. Similarly, biochemical data from autopsy brains showed reduction in distinct synaptic proteins including the neurexin/neuroligin family of synaptic adhesion proteins [168]. Furthermore, various components of the complement system were found to be highly elevated in MS patients, particularly in cortical grey matter lesions [128-132]. Since the complement system is critical for synapse removal during development [110, 119], this system might be involved also in synapse loss/removal in MS.

The establishment of animal models of multiple sclerosis allowed the application of further analytical approaches in order to further corroborate the data from human patients and to get insights into the underlying molecular mechanisms at well defined conditions. A frequently used and well-validated animal model of MS is the experimental autoimmune encephalomyelitis (EAE) mouse model, in which the auto-immune disease is induced by immunization with an encephalitogenic peptide (MOG_{35-55}) from the myelin oligodendrocyte glycoprotein (MOG), a quantitative minor component of the myelin sheath in the central nervous system. After a defined period, the EAE mice develop characteristical clinical symptoms in a reproducible manner, starting at ≈10 days after initial immunization [169, 170].

The onset of synaptic changes in the EAE rodent model occurred early before the onset of clinical symptoms and independent of demyelination arguing that the synaptic changes are not secondary to demyelination but independent events [60, 162, 160, 73]. Synaptic alterations at a functional level include a dysbalance between excitatory glutamatergic and inhibitory GABAergic neurotransmssion [171, 58-60, 162, 73]. In the EAE model of multiple sclerosis, excitatory glutamatergic synaptic signalling is strongly enhanced, whereas inhibitory GABAergic signalling is decreased [171, 58-60, 162, 73]. Several mechanisms are causing this imbalance between excitatory and inhibitory synaptic signalling. The pro-inflammatory cytokines TNFα and IL-1β

play a major role in the generation of this synaptic imbalance. In the healthy brain, the pro-inflammatory cytokines are released at relatively low levels by microglia. As described above, these physiological levels of TNFα and IL-1β perform important homeostatic functions at the synapse. In multiple sclerosis (MS), an excessively stimulated signalling of the pro-inflammatory cytokines TNFα/IL-1β is a main contributor to the synaptic pathology. In MS/EAE, these cytokines are massively released by activated microglia, infiltrating macrophages and astroglia [172, 171, 173, 174, 60, 73]. Also activated T-lymphocytes, that infiltrate the CNS through a leaky blood-brain barrier in MS, secrete pro-inflammatory cytokines and contribute to the strongly elevated levels of these cytokines in the CNS [60]. The massively increased levels of TNFα/IL-1β in MS/EAE [173, 60, 73], lead to an increased surface expression of Ca^{2+}-permeable AMPA receptors, that lack the GluR2 subunit, a decreased surface expression of GABA receptors and thus to the observed strong imbalance between excitatory and inhibitory synaptic signalling [175, 171, 59]. This overall strong activation of glutamatergic excitatory neurotransmission with its consequences, also for signalling within the multi-partite synapse, can lead to excitotoxic neuronal cell death and synapse loss in MS/EAE [60]. High concentrations of TNFα not only increase synaptic AMPA receptor expression but also non-synaptic AMPA receptor expression that further contributes to inflammation-induced glutamate excitotoxicity [175-177, 173]. Additionally, the massively enhanced secretion of pro-inflammatory TNFα and IL-1β during neuro-inflammation in MS [171, 59, 73] down-regulates glutamate transporter (GluT), i.e GLAST/EAAT1, in astrocytes and radial glia cells (Bergmann glia of the cerebellum) promoting a diminished clearance of glutamate from the synaptic cleft [178, 171, 59, 60, 73].

Interestingly, modulation of IL-1β signalling *via* recombinant IL-1β antagonists improved the clinical score and ameliorated inflammation-dependent synaptic alterations in the EAE model of multiple sclerosis [59]. Similar alterations were observed in different brain regions, i.e. cerebellum, striatum and hippocampus [171, 59, 179-181] arguing for a general role of neuroinflammation-induced synaptopathy in MS/EAE.

Astrocytes sense extracellular TNFα *via* cell surface TNFR1 receptors for TNFα [174, 165]. In response to release of high, pathological levels of TNFα in MS/EAE, astrocytes secrete glutamate [182, 174] that in turn stimulates presynaptic glutamate release e.g. in the entorhinal cortex/ dentate gyrus synapse *via* presynaptic NMDA receptors [75, 174]. Disturbances of this astroglia-to-synapse, TNFα-dependent signalling in the hippocampus were made responsible for memory deficits observed in the early pre-clinical phase in the EAE mouse model of multiple sclerosis [174].

Interestingly, a recently approved drug for the treatment of multiple sclerosis (fingolimod, FTY720) was shown to affect formation of the SNARE complex, the essential protein complex needed for vesicle fusion [183]. Though this effect of fingolimod/FTY720 on synaptic SNARE complex formation could be indirect, it further points to a previously less considered link between MS and synaptic functions.

CONCLUSION AND OUTLOOK

Synaptic functions in the central nervous system are strongly affected by inflammatory mediators. This finding is important for various CNS synaptic pathologies. These pathologies include inflammatory diseases such as multiple sclerosis that was in the focus of the current review, but also other CNS pathologies. Other CNS synaptic pathologies strongly influenced by inflammatory signalling include neurodegenerative diseases such as Alzheimer's disease [184, 119] and also less severe CNS alterations, e.g. mood disorders [185]. Even "normal" aging in humans is associated with changes in inflammatory mediators [133]. In these cases, neuroinflammatory mediators appear as a double-edged weapon [186]. On one hand, neuroinflammatory signals are beneficial at low concentrations at which they exert important regulatory functions at the synapse in the healthy brain. In case of over-activation, excessively generated levels of neuroinflammatory signals damage synapses. In case of multiple sclerosis, high levels of pro-inflammatory cytokines lead to a dysbalance of excitatory and inhibitory synaptic signalling, synapse damage and synapse loss,

neuronal excitotoxiticy and finally cell death/ neurodegeneration. The emerging tight connection between the immune system and synaptic communication and its dysregulation in various CNS pathologies can be expected to provide exciting new insights on CNS function and dysfunction.

ACKNOWLEDGEMENTS

Work of the authors was supported by the German Research Community DFG (FOR2289; Schm797/7-1). We thank Dr. Jutta Schmitz-Kraemer for critically reading the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ABBREVIATIONS

MS, multiple sclerosis; EAE, experimental autoimmune encephalo-myelitis; NMDA, N-methyl-D-aspartate; AMPA, α-amino-3-hydroxy-5-methyl-isoxazoleproprionic acid; GABA, γ-aminobutyric acid; MHC, major histocompatibility complex; IL-1β, interleukin-1beta; TNFα, tumor necrosis factor alpha; TNFR, TNF receptor; P2Y receptors, family of G protein-coupled purinergic receptors; GluA, ionotropic AMPA receptor subunit; mGluR, metabotropic glutamate receptor; SPARC, secreted protein acidic and rich in cysteine; BDNF, brain-derived neurotrophic factor.

REFERENCES

1. Dendrou, C. A., Fugger, L. and Friese, M. A. 2015, Nat. Rev. Immunol., 15, 545.
2. Frohman, E. M., Racke, M. K. and Raine, C. S. 2006, N. Engl. J. Med., 354, 942.
3. Südhof, T. C. 2012, Neuron, 75, 11.
4. Südhof, T. C. 2012, Cold Spring Harb. Perspect. Biol., 4, a011353.
5. Südhof, T. C. 2013, Neuron, 80, 675.
6. Südhof, T. C. 2014, Angew. Chem. Int. Ed. Engl., 53, 12696.
7. Jahn, R. and Fasshauer, D. 2012, Nature, 490, 201.
8. Rizo, J. and Xu, J. 2015, Annu. Rev. Biophys., 44, 339.
9. Ackermann, F., Waites, C. L. and Garner, C. C. 2015, EMBO Rep., 16, 923.
10. Wu, L. G., Hamid, E., Shin, W. and Chiang, H. C. 2014, Annu. Rev. Physiol., 76, 301.
11. Watanabe, S. 2015, Science, 350, 46.
12. Palmer, M. J., Taschenberger, H., Hull, C., Tremere, L. and von Gersdorff, H. 2003, J. Neurosci., 23, 4831.
13. Hasegawa, J., Ohara, T., Tanaka, K. and Tachibana, M. 2006, Neuron, 50, 63.
14. Furness, D. N., Dehnes, Y., Akhtar, A. Q., Rossi, D. J., Hamann, M., Grutle, N. J., Gundersen, V., Holmseth, S., Lehre, K. P., Ullensvang, K., Wojewodzuc, M., Zhou, Y., Attwell, D. and Danbolt, N. C. 2008, Neurosci., 157, 80.
15. Rimmele, T. S. and Rosenberg, P. A. 2016, Neurochem. Int., 98, 19.
16. Reichenbach, A. and Bringmann, A. 2013, Glia, 61, 651.
17. Murphy-Royal, C., Dupuis, J., Groc, L. and Oliet, S. H. R. 2017, J. Neurosci. Res., 95, 2140.
18. Südhof, T. C. 2017, Cell, 171, 745.
19. Mauger, O. and Scheiffele, P. 2017, Curr. Opin. Neurobiol., 45, 162.
20. Rudenko, G. 2017, Neural Plast., 2017, 6526151.
21. Biederer, T., Kaeser, P. S. and Blanpied, T. A. 2017, Neuron, 96, 680.
22. Reissner, C., Runkel, F. and Missler, M. 2013, Genome Biol., 14, 213.
23. Tang, A. H., Chen, H., Li, T. P., Metzbower, S. R., Mac Gillavry, H. D. and Blanpied, T. A. 2016, Nature, 536, 210.
24. Momčilović, M., Starnenković, V., Jovanović, M., Andjus, P. R., Jakovčevski, I., Schachner, M. and Miljković, D. 2017, J. Neuroimmunol., 302, 1.
25. Heikkinen, A., Pihlajaniemi, T., Faissner, A. and Yuzaki, M. 2014, Prog. Brain Res., 214, 29.
26. Senkov, O., Andjus, P., Radenovic, L., Soriano, E. and Dityatev, A. 2014, Prog. Brain Res., 214, 53.
27. Kim, E. and Sheng, M. 2009, Curr. Biol., 19, R723.
28. Bayes, A. and Grant, S. G. 2009, Nat. Rev. Neurosci., 10, 635.
29. Bayes, A., van de Lagemaat, L. N., Collins, M. O., Croning, M. D., Whittle, I. R., Choudhary, J. S. and Grant, S. G. 2011, Nat. Neurosci., 14, 19.

30. Sheng, M. and Kim, E. 2011, Cold Spring Harb. Perspect. Biol., 3(12), pii a005678.
31. Citri, A. and Malenka, R. C. 2008, Neuropsychopharm., 33, 18.
32. Feng, W. and Zhang, M. 2009, Nat. Rev. Neurosci., 10, 87.
33. Granger, A. J. and Nicoll, R. A. 2014, Philos. Trans. R. Soc. Lond. B Biol. Sci., 369(1633), 20130136.
34. Nabavi, S., Fox, R., Proulx, C. D., Lin, Y., Tsien, R. Y. and Malinow, R. 2014, Nature, 511, 348.
35. Malenka, R. C. and Bear, M. F. 2004, Neuron, 44, 5.
36. Michel, K., Müller, J. A., Oprisoreanu, A. M. and Schoch, S. 2015, Exp. Cell Res., 335, 157.
37. Petzoldt, A. G., Lutzkendorf, J. and Sigrist, S. J. 2016, Curr. Opin. Neurobiol., 39, 69.
38. Kessels, H. W. and Malinow, R. 2009, Neuron, 61, 340.
39. Makino, H. and Malinow, R. 2011, Neuron, 72, 1001.
40. Lüscher, C. and Malenka, R. C. 2012, Cold Spring Harb. Perspect. Biol., 4(6), pii a005710.
41. Huganir, R. L. and Nicoll, R. A. 2013, Neuron, 80, 704.
42. Chater, T. E. and Goda, Y. 2014, Front. Cell. Neurosci., 8, 401.
43. Herring, B. E. and Nicoll, R. A. 2016, Annu. Rev. Physiol., 78, 351.
44. Lisman, J. 2017, Philos. Trans. R. Soc. Lond. B Biol. Sci., 372(1715), pii 20160260.
45. Turrigiano, G. 2012, Cold Spring Harb. Perspect. Biol., 4(1), a005736.
46. Vitureira, N., Letellier, M. and Goda, Y. 2012, Curr. Opin. Neurobiol., 22, 516.
47. Vitureira, N. and Goda, Y. 2013, J. Cell Biol., 203, 175.
48. Pribiag, H. and Stellwagen, D. 2014, Neuropharm., 78, 13.
49. Fernandes, D. and Carvalho, A. L. 2016, J. Neurochem., 139, 973.
50. Yee, A. X., Hsu, Y. T. and Chen, L. 2017, Philos. Trans. R. Soc. Lond. B Biol. Sci., 372(1715), pii: 20160155.
51. Stellwagen, D. and Malenka, R. C. 2006, Nature, 440, 1054.
52. Beattie, E. C., Stellwagen, D., Morishita, W., Bresnahan, J. C., Ha, B. K., von Zastrow, M., Beattie, M. S. and Malenka, R. C. 2002, Science, 295, 2282.
53. Stellwagen, D., Beattie, E. C., Seao, J. Y. and Malenka, R. C. 2005, J. Neurosci., 25, 3219.
54. Ogoshi, F., Yin, H. Z., Kuppumbatti, Y., Song, B., Amindari, S. and Weiss, J. H. 2005, Exp. Neurol., 193, 384.
55. Pribiag, H. and Stellwagen, D. 2013, J. Neurosci., 33, 15879.
56. Chung, W. S., Allen, N. J. and Eroglu, C. 2015, Cold Spring Harb. Perspect. Biol., 7(9), a020370.
57. Wang, D. S., Zurek, A. A., Lecker, I., Yu, J., Abramian, A. M., Avramescu, S., Davies, P. A., Moss, S. J., Lu, W. Y. and Orser, B. A. 2012, Cell Rep., 2, 488.
58. Mandolesi, G., Grasselli, G., Musella, A., Gentile, A., Musumeci, G., Sepman, H., Haji, N., Fresegna, D., Bernardi, G. and Centonze, D. 2012, Neurobiol. Dis., 46, 414.
59. Mandolesi, G., Musella, A., Gentile, A., Grasselli, G., Haji, N., Sepman, H., Fresegna, D., Bullitta, S., De Vito, F., Musumeci, G., Di Sanza, C., Strata, P. and Centonze, D. 2013, J. Neurosci., 33, 12105.
60. Mandolesi, G., Gentile, A., Musella, A., Fresegna, D., De Vito, F., Bullitta, S., Sepman, H., Marfia, G. A. and Centonze, D. 2015, Nat. Rev. Neurol., 11, 711.
61. Yan, X., Jiang, E. and Wenig, H. R. 2015, J. Neuroinflammation, 12, 222.
62. Roseti, C., van Vliet, E. A., Cifeli, P., Ruffolo, G., Baayen, J. C., Di Castro, M. A., Bertollini, C., Limatola, C., Aronica, E., Vezzani, A. and Palma, E. 2015, Neurobiol. Dis., 82, 311.
63. del Rey, A., Balschun, D., Wetzel, W., Randolf, A. and Besedovsky, H. O. 2013, Brain Behav. Immun., 33, 15.
64. Chung, W. S., Welsh, C. A., Barres, B. A. and Stevens, B. 2015, Nat. Neurosci., 18, 1539.
65. Farmer, W. T. and Murai, K. 2017, Front. Cell. Neurosci., 11, 300.

66. Chai, H., Diaz-Castro, B., Shigetomi, E., Monte, E., Octeau, C., Yu, X., Cohn, W., Rajendran, P. S., Vondriska, T. M. and Whitelegge, J. P. 2017, Neuron, 95, 531.
67. Halassa, M. M., Fellin, T., Takano, H., Dong, J. H. and Haydon, P. G. 2007, J. Neurosci., 27, 6473.
68. Halassa, M. M., Fellin, T. and Haydon, P. G. 2007, Trends Mol. Med., 13, 54.
69. Panatier, A. and Robitaille, R. 2016, Neurosci., 323, 29.
70. De Pitta, M., Brunel, N. and Volterra, A. 2016, Neurosci., 323, 43.
71. Kettenmann, H., Kirchhoff, F. and Verkhratsky, A. 2013, Neuron, 77, 10.
72. Danbolt, N. C., Furness, D. N. and Zhou, Y. 2016, Neurochem. Int., 98, 29.
73. Stampanoni Bassi, M., Mori, F., Buttari, F., Marfia, G. A., Sancesario, A., Centonze, D. and Iezzi, E. 2017, Clin. Neurophysiol., 128, 1148.
74. Matthias, K., Kirchhoff, F., Seifert, G., Huttmann, K., Matyash, M., Kettenmann, H. and Steinhäuser, C. 2003, J. Neurosci., 23, 1750.
75. Jourdain, P., Bergersen, L. H., Bhaukaurally, K., Bezzi, P., Santello, M., Domercq, M., Matute, C., Tonello, F., Gundersen, V. and Volterra, A. 2007, Nat. Neurosci., 10, 331.
76. Saab, A. S., Neumeyer, A., John, H. M., Cupido, A., Simek, A. A., Boele, H. J., Scheller, A., LeMeur, K., Götz, M., Monyer, H., Sprengel, R., Rubio, M. E., Deitmer, J. W., De Zeeuw, C. I. and Kirchhoff, F. 2012, Science, 337, 749.
77. Sun, W., McConnell, E., Pare, J. F., Xu, Q., Chen, M., Peng, W., Lovatt, D., Han, X., Smith, Y. and Nedergaard, M. 2013, Science, 339, 197.
78. López-Colomé, A. M., López, E., Mendez-Flores, O. G. and Ortega, A. 2016, Neurochem. Res., 41, 1797.
79. Halassa, M. M. and Haydon, P. G. 2010, Annu. Rev. Physiol., 72, 335.
80. Araque, A., Carmignoto, G., Haydon, P. G., Oliet, S. H., Robitaille, R. and Volterra, A. 2014, Neuron, 81, 728.
81. Schwarz, Y., Zhao, N., Kirchhoff, F. and Bruns, D. 2017, Nat. Neurosci., 20, 1529.
82. Pascual, O., Ben Achour, S., Rostaing, P., Triller, A. and Bessis, A. 2012, Proc. Natl. Acad. Sci. USA, 109, E197.
83. Khakh, B. S. and Sofroniew, M. V. 2015, Nat. Neurosci., 18, 942.
84. Liddelow, S. A., Guttenplan, K. A., Clarke, L. E., Bennett, F. C., Bohlen, C. J., Schirmer, L., Bennett, M. L., Münch, A. E., Chung, W. S., Peterson, T. C., Wilton, D. K., Frouin, A., Napier, B. A., Panicker, N., Kumar, M., Buckwalter, M. S., Rowitch, D. H., Dawson, V. L., Dawson, T. M., Stevens, B. and Barres, B. A. 2017, Nature, 541, 481.
85. Kabba, J. A., Xu, Y., Christian, H., Ruan, W., Chenai, K., Xiang, Y., Zhang, L., Saavedra, J. M. and Pang, T. 2017, Cell. Mol. Neurobiol., Epub: doi: 10.1007/s10571-017-0504-2.
86. Zuchero, J. B. and Barres, B. A. 2015, Development, 142, 3805.
87. Verkhratsky, A. and Nedergaard, M. 2016, Philos. Trans. R Soc. Lond. B Biol. Sci., 371(1700), pii: 20150428.
88. Eroglu, C., Allen, N. J., Susman, M. W., O'Rourke, N. A., Park, C. Y., Chakraborty, C., Mulinyawe, S. B., Annis, D. S., Huberman, A. D., Green, E. M., Lawler, J., Dolmetsch, R., Garcia, K. C., Smith, S. J., Luo, Z. D., Rosenthal, A., Mosher, D. F. and Barres, B. A. 2009, Cell, 139, 380.
89. Crawford, D. C., Jiang, X., Taylor, A. and Mennerick, S. 2012, J. Neurosci., 32, 13100.
90. Risher, W. C. and Eroglu, C. 2012, Matrix Biol., 31, 170.
91. Singh, S. K., Stogsdill, J. A., Pulimood, N. S., Dingsdale, H., Kim, Y. H., Pilaz, L. J., Kim, I. H., Manhaes, A. C., Rodrigues, W. S. Jr., Pamukcu, A., Enustun, E., Ertuz, Z., Scheiffele, P., Soderling, S. H., Silver, D. L., Ji, R. R., Medina, A. E. and Eroglu, C. 2016, Cell, 164, 183.
92. Song, I. and Dityatev, A. 2017, Brain Res. Bull., pii: S0361-9230(17)30135-1.
93. Farhy-Tselnicker, I., van Casteren, A. C. M., Lee, A., Chang, V. T., Aricescu, A. R. and Allen, N. J. 2017, Neuron, 96, 428.
94. Liddelow, S. A. and Barres, B. A. 2017, Immunity, 46, 957.

95. Dolphin, A. C. 2016, J. Physiol., 594, 5369.
96. Tong, X. J., López-Soto, E. J., Li, L., Liu, H., Nedelcu, D., Lipscombe, D., Hu, Z. and Kaplan, J. M. 2017, Neuron, 95, 326.
97. Allen, N. J., Bennett, M. L., Foo, L. C., Wang, G. X., Chakraborty, C., Smith, S. J. and Barres, B. A. 2012, Nature, 486, 410.
98. Allen, N. J. 2014, Annu. Rev. Cell Dev. Biol., 30, 439.
99. Bialas, A. R. and Stevens, B. 2013, Nat. Neurosci., 16, 1773.
100. Thalhammer, A. and Cingolani, L. A. 2014, Neuropharm., 78, 23.
101. Chung, W. S., Clarke, L. E., Wang, G. X., Stafford, B. K., Sher, A., Chakrabarty, C., Joung, J., Foo, L. C., Thompson, A., Chen, C., Smith, S. J. and Barres, B. A. 2013, Nature, 504, 394.
102. Nimmerjahn, A., Kirchhoff, F. and Helmchen, F. 2005, Science, 308, 1314.
103. Bilimoria, P. M. and Stevens, B. 2015, Brain Res., 1617, 7.
104. Salter, M. W. and Stevens, B. 2017, Nat. Med., 23, 1018.
105. Davalos, D., Grutzender, J., Yang, G., Kim, J. V., Zuo, Y., Jung, S., Littman, D. R., Dustin, M. L. and Gan, W. B. 2005, Nat. Neurosci., 8, 752.
106. Wake, H., Moorhouse, A. J., Jinno, S., Kohsaka, S. and Nabekura, J. 2009, J. Neurosci., 29, 3974.
107. Tremblay, M. E., Lowery, R. L. and Majewska, A. K. 2010, PLoS Biol., 8, e1000527.
108. Fontainhas, A. M., Wang, M., Liang, K. J., Chen, S., Mettu, P., Darmani, M., Fariss, R. N., Li, W. and Wong, W. T. 2011, PLoS One, 6(1), e15973.
109. Li, Y., Du, X. F., Liu, C. S., Wen, Z. L. and Du, J. L. 2012, Dev. Cell, 23, 1189.
110. Stevens, B., Allen, N. J., Vazquez, L. E., Howell, G. R., Christopherson, K. S., Nouri, N., Micheva, K. D., Mehalov, A. K., Huberman, A. D., Stafford, B., Sher, A., Litke, A. M., Lambris, J. D., Smith, S. J., John, S. W. and Barres, B. A. 2007, Cell, 131, 1164.
111. Schafer, D. P., Lehrman, E. K., Kautzmann, A. G., Koama, R., Mardinly, A. R., Yamasaki, R., Ransohoff, R. M., Greenberg, M. E., Barres, B. A. and Stevens, B. 2012, Neuron, 74, 691.
112. Schaefer, L. 2014, J. Biol. Chem., 289, 35237.
113. Masuda, T. and Prinz, M. 2016, ACS Chem. Neurosci., 7, 428.
114. Wang, X., Zhao, L., Zhang, J., Fariss, R. N., Ma, W., Kretschmer, F., Wang, M., Qian, H. H., Badea, T. C., Diamond, J. S., Gan, W. B., Roger, J. E. and Wong, W. T. 2016, J. Neurosci., 36, 2827.
115. Hong, S. and Stevens, B. 2016, Dev. Cell., 38, 126.
116. Schafer, D. P., Lehrman, E. K. and Stevens, B. 2013, Glia, 61, 24.
117. Burda, J. E. and Sofroniew, M. V. 2017, Cell Res., 27, 726.
118. Huberman, A. D., Feller, M. B. and Chapman, B. 2008, Annu. Rev. Neurosci., 31, 479.
119. Stephan, A. H., Barres, B. A. and Stevens, B. 2012, Annu. Rev. Neurosci., 35, 369.
120. Martinelli, D. C., Chew, K. S., Rohlmann, A., Lum, M. Y., Ressl, S., Hattar, S., Brunger, A. T., Missler, M. and Südhof, T. C. 2016, Neuron, 91, 1034.
121. Carlucci, F., Ishaque, A., Ling, G. S., Szajna, M., Sandison, A., Donatien, P., Cook, H. T. and Botto, M. 2016, J. Immunol., 196, 1488.
122. Thielens, N. M., Tedesco, F., Bohlson, S. S., Gaboriaud, C. and Tenner, A. J. 2017, Mol. Immunol., 89, 73.
123. Fonseca, M. I., Chu, S. H., Hernandez, M. X., Fang, M. J., Modarresi, L., Selvan, P., MacGregor, G. R. and Tenner, A. J. 2017, J. Neuroinflammation, 14, 48.
124. Friese, M. A., Schattling, B. and Fugger, L. 2014, Nat. Rev. Neurol., 10, 225.
125. Arbore, G., Kemper, C. and Kolev, M. 2017, Mol. Immunol., 89, 2.
126. Liszewski, M. K., Elvington, M., Kulkarni, H. S. and Atkinson, J. P. 2017, Mol. Immunol., 84, 2.
127. Spencer, J. I., Bell, J. S. and DeLuca, G. C. 2017, J. Neurol. Neurosurg. Psychiatry, pii: jnnp-2017-316011. doi: 10.1136/jnnp-2017-316011.

128. Ingram, G., Hakobryan, S., Robertson, N. P. and Morgan, B. P. 2009, Clin. Exp. Immunol., 155, 128.
129. Michailidou, I., Willems, J. G., Kooi, E. J., van Eden, C., Gold, S. M., Geurts, J. J., Baas, F., Huitinga, I. and Ramaglia, V. 2015, Ann. Neurol., 77, 1007.
130. Michailidou, I., Naessens, D. M., Hametner, S., Guldenaar, W., Kooi, E. J., Geurts, J. J., Baas, F., Lassmann, H. and Ramaglia, V. 2017, Glia, 65, 264.
131. Watkins, L. M., Neal, J. W., Loveless, S., Michailidou, I., Ramaglia, V., Rees, M. I., Reynolds, R., Robertson, N. P., Morgan, B. P. and Howell, O. W. 2016, J. Neuroinflammation, 13, 161.
132. Lindblom, R. P. 2016, Clin. Immunol., 166-167, 89.
133. Stephan, A. H., Madison, D. V., Mateos, J. M., Fraser, D. A., Lovelett, E. A., Coutellier, L., Kim, L., Tsai, H. H., Huang, E. J., Rowitch, D. H., Berns, D. S., Tenner, A. J., Shamloo, M. and Barres, B. A. 2013, J. Neurosci., 33, 13460.
134. Nauta, A. J., Bottazzi, B., Mantovani, A., Salvatori, G., Kishore, U., Schwaeble, W. J., Gingras, A. R., Tzima, S., Vivanco, F., Egido, J., Tijsma, O., Hack, E. C., Daha, M. R. and Roos, A. 2003, Eur. J. Immunol., 33, 465.
135. Fornai, F., Carrizzo, A., Ferrucci, M., Damato, A., Biagioni, F., Gaglione, A., Puca, A. A. and Vecchione, C. 2015, Int. J. Biochem. Cell Biol., 69, 70.
136. Bottazzi, B., Inforzato, A., Messa, M., Barbagallo, M., Magrini, E., Garlanda, C. and Mantovani, A. 2016, J. Hepatol., 64, 1416.
137. O'Brien, R. J., Xu, D., Petralia, R. S., Steward, O., Huganir, R. L. and Worley, P. 1999, Neuron, 23, 309.
138. Sia, G. M., Belque, J., Rumbaugh, G., Cho, R. and Worley, P. F. 2007, Neuron, 55, 87.
139. Chang, M. C., Park, J. M., Pelkey, K. A., Grabenstatter, H. L., Xu, D., Linden, D. J., Sutula, T. P., McBain, C. J. and Worley, P. F. 2010, Nat. Neurosci., 13, 1090.
140. Koch, S. M. and Ullian, E. M. 2010, J. Neurosci., 30, 5404.
141. Figueiro-Silva, J., Gruart, A., Clayton, K. B., Podlesniy, P., Abad, M. A., Gasull, X., Delgado-Garcia, J. M. and Trullas, R. 2015, J. Neurosci., 35, 5504.
142. Lee, S. J., Wie, M., Zhang, C., Maxeiner, S., Pak, C., Calado Botelho, S., Trotter, J., Sterky, F. H. and Südhof, T. C. 2017, J. Neurosci., 37, 1062.
143. Kishore, U., Gaboriaud, C., Waters, P., Shrive, A. K., Greenbough, T. J., Reid, K. B. M., Sim, R. B. and Arlaud, G. J. 2004, Trends Immunol., 25, 551.
144. Ressl, S. B. K., Vivona, S., Martinelli, D. C., Südhof, T. C. and Brunger, A. T. 2015, Structure, 23, 688.
145. Yuzaki, M. 2017, Curr. Opin. Neurobiol., 45, 9.
146. Matsuda, K. 2017, Neurosci. Res., 116, 46.
147. Cheng, S., Seven, A. B., Wang, J., Skiniotis, G. and Özkan, E. 2016, Structure, 24, 2163.
148. Bolliger, M. F., Martinelli, D. C. and Südhof, T. C. 2011, Proc. Natl. Acad. Sci. USA, 108, 2534.
149. Huh, G. S., Boulanger, L. M., Du, H., Riquelme, P. A., Brotz, T. M. and Shatz, C. J. 2000, Science, 290, 2155.
150. Goddard, C. A., Butts, D. A. and Shatz, C. J. 2007, Proc. Natl. Acad. Sci. USA, 104, 6828.
151. Shatz, C. J. 2009, Neuron, 64, 40.
152. Needleman, L. A., Liu, X. B., El-Sabeawy, F., Jones, E. G. and McAllister, A. K. 2010, Proc. Natl. Acad. Sci. USA, 107, 16999.
153. Elmer, B. M. and McAllister, A. K. 2012, Trends Neurosci., 35, 660.
154. Lee, H., Brott, B. K., Kirkby, L. A., Adelson, J. D., Cheng, S., Feller, M. B., Datwani, A. and Shatz, C. J. 2014, Nature, 509, 195.
155. Dustin, M. L. 2012, J. Clin. Invest., 122, 1149.
156. Dixon-Salazar, T. J., Fourgeaud, L., Tyler, C. M., Poole, J. R., Park, J. J. and Boulanger, L. M. 2014, J. Neurosci., 34, 11844.
157. Lv, D., Shen, Y., Peng, Y., Liu, J., Miao, F. and Zhang, J. 2015, PLoS One, 10(8), e0135223.

158. Nelson, P. A., Sage, J. R., Wood, S. C., Davenport, C. M., Anagnostaras, S. G. and Boulanger, L. M. 2013, Learn. Mem., 20, 505.
159. Calabrese, M., Magliozzi, R., Ciccarelli, O., Geurts, J. J., Reynolds, R. and Martin, R. 2015, Nat. Rev. Neurosci., 16, 147.
160. Friese, M. A. 2016, Brain, 139, 2.
161. Yirmiya, R. and Goshen, I. 2011, Brain Behav. Immun., 25, 181.
162. Di Filippo, M., de Iure, A., Durante, V., Gaetani, L., Mancini, A., Sarchielli, P. and Calabrese, P. 2015, Brain Res., 1621, 205.
163. Jürgens, T., Jafari, M., Kreutzfeldt, M., Bahn, E., Brück, W., Kerschensteiner, M. and Merkler, D. 2016, Brain, 139, 39.
164. Acharjee, S., Nayani, N., Tsutsui, M., Hill, M. N., Ousman, S. S. and Pittman, Q. J. 2013, Brain Behav. Immun., 33, 164.
165. Osso, L. A. and Chan, J. R. 2015, Cell, 163, 1574.
166. Shi, J., Baxter, L. C. and Kuniyoshi, S. M. 2014, Cogn. Behav. Neurol., 27, 1.
167. DeLuca, G. C., Yates, R. L., Beale, H. and Morrow, S. A. 2015, Brain Pathol., 25, 79.
168. Dutta, R., Chang, A., Doud, M. K., Kidd, G. J., Ribaudo, M. V., Young, E. A., Fox, R. J., Staugaitis, S. M. and Trapp, B. D. 2011, Ann. Neurol., 69, 445.
169. Mix, E., Meyer-Rienecker, H., Hartung, H. P. and Zettl, U. K. 2010, Prog. Neurobiol., 92, 386.
170. Robinson, A. P., Harp, C. T., Noronha, A. and Miller, S. D. 2014, Handb. Clin. Neurol., 122, 173.
171. Centonze, D., Muzio, L., Rossi, S., Cavasinni, F., De Chiara, V., Bergami, A., Musella, A., D'Amelio, M., Cavallucci, V., Martorana, A., Bergamaschi, A., Cencioni, M. T., Diamantini, A., Butti, E., Comi, G., Bernardi, G., Cecomi, F., Battistini, L., Furlan, R. and Martino, G. 2009, J. Neurosci., 29, 3442.
172. McCoy, M. K. and Tansey, M. G. 2008, J. Neuroinflammation, 5, 45.
173. Probert, L. 2015, Neurosci., 302, 2.
174. Habbas, S., Santello, M., Becker, D., Stubbe, H., Zappia, G., Liaudet, N., Klaus, F. R., Kollias, G., Fontana, A., Pryce, C. R., Suter, T. and Volterra, A. 2015, Cell, 163, 1730.
175. Leonoudakis, D., Zhao, P. and Beattie, E. C. 2008, J. Neurosci., 28, 2119.
176. Ferguson, A. R., Christensen, R. N., Gensel, J. C., Miller, B. A., Sun, F., Beattie, E. C., Bresnahan, J. C. and Beattie, M. S. 2008, J. Neurosci., 28, 11391.
177. Santello, M. and Volterra, A. 2012, Trends Neurosci., 35, 638.
178. Prow, N. A. and Irani, D. N. 2008, J. Neurochem., 105, 1276.
179. Rossi, S., Muzio, L., De Chiara, V., Grasselli, G., Musella, A., Musumeci, G., Mandolesi, G., De Ceglia, R., Maida, S., Biffi, E., Pedrocchi, A., Menegon, A., Bernardi, G., Furlan, R., Martino, G. and Centonze, D. 2011, Brain Behav. Immun., 25, 947.
180. Rossi, S., Furlan, R., De Chiara, V., Motta, C., Studer, V., Mori, F., Musella, A., Bergami, A., Muzio, L., Bernardi, G., Battistini, L., Martino, G. and Centonze, D. 2012, Ann. Neurol., 71, 76.
181. Nisticò, R. Mango, D., Mandolesi, G., Piccinin, S., Berretta, N., Pignatelli, M., Feligioni, M., Musella, A., Gentile, A., Mori, F., Bernardi, G., Nicoletti, F., Mercuri, N. B. and Centonze, D. 2013, PLoS One, 8, e54666.
182. Santello, M., Bezzi, P. and Volterra, A. 2011, Neuron, 69, 988.
183. Darios, F. D., Jorgacevski, J., Flasker, A., Zorec, R., Garcia-Martinez, V., Villanueva, J., Gutierrez, L. M., Leese, C., Bal, M., Nosyreva, E., Kavalali, E. T. and Davletov, B. 2017, Sci. Rep., 7, 5958.
184. Selkoe, D. J. 2002, Science, 298, 789.
185. Pfau, M. L., Menard, C. and Russo, S. J. 2017, Annu. Rev. Pharmacol. Toxicol., Epub: doi: 10.1146/annurev-pharmtox-010617-052823.
186. Sochocka, M., Diniz, B. S. and Leszek, J. 2017, Mol. Neurobiol., 54, 8071.