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Review article

Cell adhesion and matricellular support by astrocytes of the tripartite synapse

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ABSTRACT

Astrocytes contribute to the formation, function, and plasticity of synapses. Their processes enwrap the neuronal components of the tripartite synapse, and due to this close interaction they are perfectly positioned to modulate neuronal communication. The interaction between astrocytes and synapses is facilitated by cell adhesion molecules and matricellular proteins, which have been implicated in the formation and functioning of tripartite synapses. The importance of such neuron-astrocyte integration at the synapse is underscored by the emerging role of astrocyte dysfunction in synaptic pathologies such as autism and schizophrenia. Here we review astrocyte-expressed cell adhesion molecules and matricellular molecules that play a role in integration of neurons and astrocytes within the tripartite synapse.

1. Introduction

Astrocytes are the main regulators of ion, water, nutrients, metabolites, and neurotransmitter homeostasis in the brain, and are actively involved in neural communication (Khakh and Sofroniew, 2015). They constitute a heterogeneous population of cells whose molecular, morphological and functional features differ across brain areas and species (Buosi et al., 2018; Freeman, 2010; John Lin et al., 2017; Matyash and Kettenmann, 2010; Oberheim et al., 2009). Astrocytes form spatially and functionally non-overlapping domains (Bushong et al., 2002; Reichenbach et al., 2010) through which they carry out their regulatory and homeostatic functions. In such a domain synapses closely interact with astrocyte processes. The number of synapses in direct contact with one astrocyte has been estimated to range from 20.000 to 100.000 in rodents and up to 2 million in humans (Oberheim et al., 2009). Astrocytes are connected through gap junctions that support intercellular communication (Pannasch and Rouach, 2013). Through such networks the astrocytes can spatially buffer potassium ions and potentially

Abbreviations: ACM, astrocyte-conditioned medium; AMIGO, adhesion molecule with IG-like domain; AMOG, A Molecule On Glia; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CAM, cell adhesion molecule; CASK, calcium/calmodulin-dependent serine protein kinase 3; CSPG, chondroitin sulfate proteoglycan; CNTN, contactin; CNS, central nervous system; CNTNAP, contactin-associated protein; Cx, connexin; DRG, dorsal root ganglion; EC, extracellular domain; ECM, extracellular matrix; EGF, epidermal growth factor; FGFR, fibroblast growth factor receptor; FN III, fibronectin III; GABAR, gamma-aminobutyric acid receptor; GLAST, glial glutamate transporter; GnRH, gonadotropin-releasing hormone; Gpc, glypican; GPI, glycosylphosphatidylinositol; HSPG, heparan sulfate proteoglycan; Ig SF, immunoglobulin superfamily; IP_3, inositol 1,4,5-trisphosphate; KD, knockdown; KO, knockout; LNS domain, laminin neurexin and sex hormone-binding globulin-like folding units; LRR, leucine-rich repeats; LRRTM4, leucine rich repeat transmembrane neuronal protein 4; LTD, long term depression; LTP, long term potentiation; mEPSC, miniature excitatory postsynaptic current; NCAM, neural cell adhesion molecule; NL, neuroligin; NMDAR, *N*-methyl-D-aspartate glutamate receptor; NMJ, neuromuscular junction; NP, pentraxin; Pcdh-γ, protocadherin γ; PDZ, Post synaptic density protein (PSD95) Drosophila disc large tumor suppressor (Dlg1) and zonula occludens-1 protein (zo-1); PSA, polysialic acid; PSD-95, postsynaptic density protein 95; PTRB, protein tyrosine phosphatase receptor-type-beta; RGC, retinal ganglion cell; RGD, arginyl-glycyl-aspartic acid; Sdc, syndecan; SPARC, secreted protein acidic and rich in cysteine; SynCAM, synaptic cell adhesion molecule; TGF, transforming growth factor; TN-C, tenascin-C; TSP, thrombospondin; VGCC, voltage-gated calcium channel; VWF, von Willebrand factor

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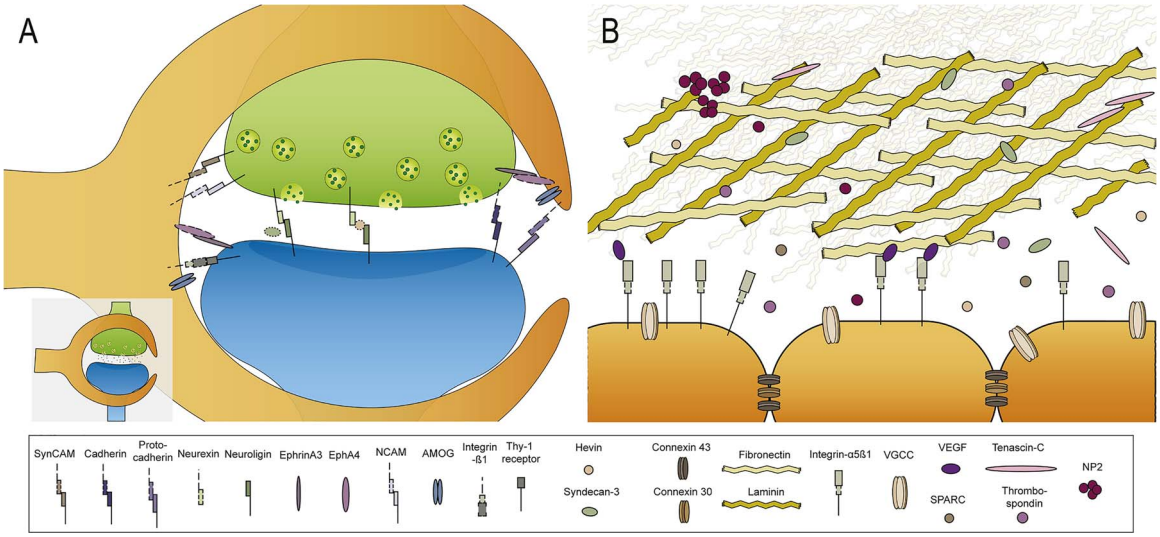

Fig. 1. (A) A schematic representation of a tripartite synapse, with a presynaptic neuron (green), a postsynaptic neuron (blue), and astrocyte processes (orange) surrounding the synaptic cleft. A selection of interactions between neuronal and/or astrocytic cell adhesion molecules (CAMs) are depicted. Dashed outer lines of CAMs indicate astrocytic localization; solid lines indicate neuronal localization. (B) A schematic representation of interactions between astrocytes (orange) and the ECM. Connexins allow for cellular communication within the astrocytic network. Astrocyte-secreted matricellular molecules are incorporated in the scaffold-like structures of the ECM.

coordinate neuronal activity (Chever et al., 2016). The regulation of the space between the synapse and the perisynaptic astrocyte processes (PAPs) determines the diffusion of signalling molecules, such as glutamate. This is of particular interest because it allows astrocytes to promote precision of neuronal activity in the synapse (Pannasch and Rouach, 2013) and synchronize synaptic inputs (Fellin et al., 2004; Rusakov and Kullmann, 1998). Astrocytic swelling decreases the volumetric fraction of the extracellular space, and this can affect neuronal excitability (Florence et al., 2012).

It is now recognized that astrocytic processes are an essential component of the synapse. These processes do not merely act as isolators of the synaptic cleft, but in fact actively modulate synaptic transmission. Astrocytes respond to neurotransmitters and can in turn release gliotransmitters, and thus act as an interactive partner in a tripartite synapse (Araque et al., 2014). The concept of the tripartite synapse was first described in the late nineties (Araque et al., 1999) and includes the classic pre- and postsynaptic neuronal structures as well as the PAPs (Fig. 1A). The degree of PAP coverage in synapses is highly plastic and varies widely across brain areas. For example, electron microscopy showed that PAP coverage of spines of the Purkinje cells (74%) in the cerebellum is more extensive than that of pyramidal cells (29%) in the visual cortex (Spacek, 1985). PAPs were present in 50% of synapses in a saturated reconstruction of the cortex (Kasthuri et al., 2015). In the hippocampus about 57% of synapses include PAPs (Ventura and Harris, 1999). Moreover, larger synapses with more synaptic vesicles are covered more extensively with PAPs than smaller synapses (Ventura and Harris, 1999). In line with this, chronic whisker stimulation in mice lead to an increase in such coverage of the bouton-spine interface of synapses in the barrel cortex (Genoud et al., 2006). Recruitment of PAPs by synaptic regions with high glutamate concentrations not only helps to protect against excitotoxicity, but may also promote more efficient gliotransmission (Araque et al., 2014; Genoud et al., 2006). These and other findings illustrate the plastic character of synapse coverage by astrocytic processes and how it is associated with experience- and activity-based mechanisms, including long term potentiation (LTP) (Bernardinelli et al., 2014; Butt, 2011; Heller and Rusakov, 2015; Henneberger et al., 2010; Krzisch et al., 2015; Lavialle et al., 2011). Especially in the hypothalamus the interaction between PAPs and neurons is very dynamic; the retraction of PAPs is rapid and reversible, and is regulated by dehydration and lactation (Panatier, 2009).

Induction of Ca^{2+} elevations in astrocyte populations leads to astrocyte-induced synaptic potentiation, but not all synapses in contact with activated astrocytes are potentiated (Perea and Araque, 2007). This supports the notion that astrocytic regulation of synaptic activity does not merely result from gliotransmitter spillover, although it should be noted that PAPs often do not encapsulate the synapse completely so that diffusion of neuroactive chemicals remains possible (Eroglu and Barres, 2010; Reichenbach et al., 2010). Diffusion is thus controlled directly by degree of PAP-coverage of synapses as well as indirectly by regulation of the volume of the extracellular space via astrocytic swelling. In addition, astrocytes can secrete a number of matricellular molecules that help form or interact with the extracellular matrix (ECM) inside the extracellular space (Faissner et al., 2010; Sykova and Vargova, 2008). The composition of the ECM is readily altered by astrocytic responses to the microenvironment (Fig. 1B) (Wiese et al., 2012). This forms another important mechanism by which astrocytes can modulate synapses both structurally and functionally.

The understanding of brain functioning has only recently shifted from a neurocentric view to a more integrative view, which recognizes an important role for astrocytes in neural information processing (Bashaw and Klein, 2010; Verkhratsky et al., 2016). Because of this, our knowledge of the mechanisms by which astrocytic molecules regulate synaptogenesis and functioning of tripartite synapses is just beginning to emerge (Araque et al., 2014; Diniz et al., 2012; Elmariah et al., 2005; Mauch et al., 2001; Stellwagen and Malenka, 2006). There is a suspected important role for proteins that mediate direct contact between astrocytes and synapses. Therefore, in this review we provide an overview of astrocyte-expressed cell adhesion molecules and astrocyte-expressed matricellular molecules and explore their role in the formation and functioning of tripartite synapses.

2. Astrocytic cell adhesion molecules are involved in synapse formation and function

Establishing the formation of synaptic structures and subsequent information transmission first requires the associated cells to be in close proximity to one another. Such a configuration is promoted by axon guidance molecules, which affect the actin-mediated cytoskeleton of growth cones to direct it towards dendrites in the nascent synapse (Bashaw and Klein, 2010; Dent et al., 2011; Missler et al., 2012; O'Donnell et al., 2009). A number of axon guidance molecules are

expressed by astrocytes, such as tenascin-C (Jones and Bouvier, 2014), ephrins (Filosa et al., 2009), and SynCAM (Frei and Stoeckli, 2014).

After alignment of axon and dendrites, cell adhesion molecules (CAMs) strengthen axo-dendritic contact and steer the subsequent molecular assembly of the newly formed synapse. CAMs support synapse formation in different ways, including axon guidance, alignment of pre- and postsynaptic sites through scaffolding mechanisms, providing adhesiveness in the synapse, and actin-induced cytoskeletal remodelling that fine-tunes differentiation of newly formed synapses (Siddiqui and Craig, 2011). After the initial stages of synapse formation, which include the establishment and assembly of the synapse, CAMs support functional specification of the synapse and synaptic plasticity (for an extensive review on CAM functions in the classic neuronal synapse, see (de Wit and Ghosh, 2016; Missler et al., 2012). The mechanisms by which CAMs can affect the structural plasticity of cells, as discussed extensively in this review, have implicated CAMs in various central nervous system (CNS) pathologies (Blanco-Suarez et al., 2016). Of particular interest in the current review are CAMs that are expressed by astrocytes as well as neurons (Dodla et al., 2010; Siddiqui and Craig, 2011; Togashi et al., 2009) and which potentially mediate cell adhesion mechanisms in bipartite and tripartite synapses in a similar fashion.

2.1. Neuron-astrocyte adhesion molecules in bi- and tripartite synapses

In the past, the role of a large number of CAMs has been studied in the classical bipartite synapse. The well-known adhesive qualities of some of these CAMs are achieved by rather varied mechanisms, affecting pre- or postsynaptic neuronal components in different ways. Furthermore, a number of CAMs have been traditionally associated with glia and neuron-glia interaction, although in some cases these were not immediately linked to tripartite synapses as they were identified prior to the introduction of the tripartite synapse concept (Araque et al., 1999). Various CAM families exist and many of them have been shown to provide adhesion between the neuronal components in bipartite synapses. CAMs share several extracellular domains, which often comprise multiple tandem repeats. These repeats allow for a greater interaction repertoire and probability and furthermore enable CAMs to provide mechanical stability in the synaptic cleft (Missler et al., 2012). For example, a large collection of CAMs are members of the immunoglobulin superfamily (IgSF). The extracellular portion of these proteins is composed of Ig-domains, which can form either homophilic or heterophilic complexes through interaction with other Ig-domains. Many of these IgCAMs also contain fibronectin III (FN-III) domains (Missler et al., 2012). IgCAMs have a broad repertoire of interaction: they can form complexes *in cis* as well as *in trans*. Several IgCAMs are now being studied with respect to their role in tripartite synapses. A number of CAMs that belong to other families have also been implicated in the tripartite synapse. The classifications of the molecules reviewed here are outlined in Table 1. Their expression ratios between astrocytes and neurons have been calculated based on Zhang et al., 2014b, and shows that CAMs can be highly expressed in astrocytes (Table 1). Below we review families of cell adhesion molecules that enable participation of astrocytes in synaptic functioning.

2.1.1. Neuroligins and neurexins

One family of CAMs that was previously primarily studied in the bipartite synapse is the neuroligin family. There are four homologs of these type I membrane proteins that are found on the postsynaptic neuronal membrane (Fig. 2a), where they induce synapse assembly primarily through interaction with presynaptic neurexins by binding to their extracellular LNS domain (Laminin, Neurexin and Sex hormone-binding globulin-like folding units (Missler et al., 2012). Neuroligin-1 (NL1) and neuroligin-2 (NL2) are expressed in excitatory and inhibitory synapses, respectively, whereas neuroligin-3 (NL3) expression is localized to both types of synapses (Budreck and Scheiffele, 2007). Note, however, that the synaptic specificity of NL members is mediated by postsynaptic proteins such as PSD-95 (Levinson et al., 2005), which are recruited by a PDZ-domain binding sequence in the cytoplasmic tail of neuroligins (Missler et al., 2012). Neuroligins are expressed by various glial cell types, including astrocytes, during embryonic development (Gilbert et al., 2001) and continue to be expressed in adulthood (Cahoy et al., 2008; Orre et al., 2014; Wang et al., 2012; Zhang et al., 2014b). The main interaction partners of neuroligins are neurexins. Three genes code for neurexins (Nrxns), but many isoforms exist due to extensive alternative splicing. A wide variety of these are likely to be found in the plasma membrane of neurons, astrocytes, and oligodendrocytes, based on RNA expression levels observed in different neural cell types (Zhang et al., 2014b). Neurexins are traditionally localized to the presynaptic site (Missler et al., 2012), but are also present on postsynaptic membranes (Choi et al., 2011b; Kattenstroth et al., 2004) and astrocytes (Cahoy et al., 2008). In astroglial cells, Nrxn1 and Nrxn2 mRNA is abundantly expressed (Orre et al., 2014). Expression of neurexin and neuroligin at the developing synapse is induced by bidirectional *in trans* neurexin-neuroligin signalling (Knight et al., 2011; Taniguchi et al., 2007). Furthermore, neuroligin-induced vesicle clustering is silenced by an *in cis* interaction between postsynaptic neurexins and neuroligins in hippocampal neuronal cultures (Taniguchi et al., 2007). In the developing retina, a similar inhibitory effect of postsynaptic neurexins on synapse formation occurs. Here, neurexins mediate glia contact-induced synapse formation on cultured retinal ganglion cells (RGCs) at embryonic day (E)17; dendritic neurexins were found to inhibit synaptogenesis, an effect that disappeared after PAPs established contact with these dendrites (Barker et al., 2008). This mechanism allows for an astrocyte-dendrite contact-mediated increase in synapse number. Thus, dendritic neurexins may enable astrocytes to control the ability of neurons to receive and form synaptic connections (Barker and Ullian, 2010; Taniguchi et al., 2007). These findings, together with the intricate expression mechanisms of neurexins and neuroligins (Knight et al., 2011), hint towards a complex mechanism of astrocyte-neurexin-neuroligin-mediated synaptogenesis. Neurexins and neuroligins may also promote synapse formation by interacting with other astrocytic synaptogenic molecules. For example, NL1 enhances thrombospondin-induced synaptogenesis in cultured hippocampal rat neurons (Xu et al., 2010). Additionally, neuroligins and neurexins in GABAergic neuromuscular junctions (NMJs) of the nematode *C. elegans* form a tripartite complex with MADD4 (punctin). This matricellular protein promotes clustering of neuroligin in the postsynaptic membrane in redundant fashion with Nrxn1 (Maro et al., 2015). Furthermore, since *Nrxn1*$^{-/-}$*:MADD4*$^{-/-}$ mutant animals reveal decreased synaptic activity (miPSCS) and synaptic density (Maro et al., 2015), astrocytic MADD4 secretion could facilitate postsynaptic maturation in the tripartite synapse. Another example of a mediator of neurexin-neuroligin complex formation was described by (Singh et al., 2016), who showed that a synapse-spanning complex of the non-interacting isoforms NL1B and Nrxn1α can be established through binding of both to astrocyte-secreted hevin (see also Section 4.1.5).

2.1.2. Integrins

Integrin receptors are composed of alpha and beta subunits, which are both type I transmembrane proteins (Tanigami et al., 2012). The different compositions of subunits are cell type specific and the subunits are differentially expressed by neurons and astrocytes (Arnaout et al., 2005; Clegg et al., 2003; Missler et al., 2012). Tanigami et al. (2012) has provided an overview of astroglial integrins that modulate astrocytic contact-dependent regulation of synapse formation, and proposed that in order to receive synaptic input neurons require physical contact with an astrocyte. For example, glial integrin-β1 establishes such neuron-astrocyte coupling and allows for neuronal protein kinase C activation to induce the formation of excitatory synapses (Hama et al., 2004). Astrocytic integrin-αVβ3 binds to neuronal Thy-1 receptors *in vitro* to establish astrocyte-neuron communication, which suppresses neurite outgrowth and causes the retraction of neuronal processes

Table 1
Astrocyte-expressed molecules that can regulate tripartite synapse formation and/or function.

Molecule family	Type	Molecule (entrez gene ID)	Expression		Interaction partners**	References
			Level*/#	Location**		
Neuroligin	Ig-domain family	1. Neuroligin 1 (Nlgn1)	4.48/11.2	*Post*[1,2]; *AP*[2]	TSP-1[1];	Xu et al., 2010[1];
		2. Neuroligin 3 (Nlgn3)	1.32/9.6	*Both*[1]; *AP*[2]	neurexins[1];	Missler et al., 2012; Knight et al., 2011;
					hevin[1,2];	Singh et al., 2016[1,2]
					MADD4[2]	Maro et al., 2015[2]
Neurexin	CAM	Neurexin 1 (Nrxn1)	2.19/13.5	*Pre*[1,2]; *post*[1,2]	Neuroligins[1];	Taniguchi et al., 2007[1];
					hevin[1,2];	Singh et al., 2016[1,2];
					MADD4[2]	Maro et al., 2015[1,2]
Integrin	IgCAM	1. Integrin-ß1 (Itgb1)	3.54/9.6	Pre; post; A	SPARC[1,2]	Jones et al., 2011[1,2];
		2. Integrin-αV (Itgav)	12.33/10.0	A[1,2]	Thy1-receptors[1];	Herrera-Molina et al., 2012[1]; Maldonado et al., 2017[1];
		3. Integrin-ß3 (Itgb3)	0.33/5.2	A[1]	TSP[1];	Yonezawa et al., 2010[1];
					TGF-ß;	Nishimura, 2009;
					Syndecan-4[1]	Avalos et al., 2009[1]
Cadherin	IgCAM	1. *N*-cadherin (Cdh2)	1.40/13.0	Both; A[1]; *AP*[1]	Other (proto)cadherins[1,2];	Yasuda et al., 2007[1,2]; Hirano and Takeichi, 2012
		2. γ-protocadherin (Pcdhg/Pcdhga9)	2.12/15.6	*Pre*[1,2]; *post*[1,2]; *PAP*[1,2]	GluA2[1,3]	Zhou et al., 2011[1]; Yamagata et al., 1999[3]; Saglietti et al., 2007[1]
		3. δ2-protocadherin (Pcdh8)	0.72/n.a.	Both[1,2]		
SynCAM	IgCAM	1. SynCAM 1 (Cadm1)	1.58/10.0	*Pre*[1,2]; *post*[1,2]; *AP*[1,2]	astrocytic ErbB4	Sandau et al., 2011[1,2]
		2. SynCAM 3 (Cadm3)	0.05/n.a.	*Pre; post*[1]; *AP*[2]	receptors[1,2]	
NCAM	IgCAM	NCAM1 (Ncam1)	2.54/12.2	*Pre*[2]; post; *AP*[2]	Polysialic acid[1];	Dityatev et al., 2004[1,2]
					FGFR2[1];	Christensen et al., 2006[1];
					AMPARs[2,3]	Vaithianathan et al., 2004[2,3]
					CSPGs and HSPGs[1];	Kulahin et al., 2005[1];
					NMDARs[1,2]	Dityatev et al., 2004[1,2]
Contactin	IgCAM	Contactin-1 (Cntn1)	0.04/10.1	*Pre*[1]	Cntnap1[1];	Labasque and Faivre-Sarrailh, 2010
					astrocytic versican[1];	Dours-Zimmermann et al., 2009[1];
					phosphacan[1];	Peles et al., 1995[1];
					tenascin-R[1];	Brummendorf et al., 1993[1]; Pesheva et al., 1993[1]; Zacharias et al., 2002[1]
					VGCCs[1]	Liu et al., 2001[1]
AMOG	Na/K pump	AMOG (Atp1b2)	6.54/13.7	*AP*[2]	Unknown	Antinocek and Schachner, 1988
					Na+/K+ ATPase α-subunits[1]	Schmalzing et al., 1992[1]; Tokhtaeva et al., 2012[1]
AMIGO	IgCAM/LRR	1. AMIGO1 (Amigo1)	0.54/9.7	*Pre*[1,2]; *post*; *A*[1,2]	Ampotherin[1];	Kuja-Panula et al., 2003[1]
		2.			Kv2.1 channels[1,2]	Peltola et al., 2011[1,2]; Zhao et al., 2014[2]
Eph/ephrin	Receptor tyrosine kinase	1. EphA4 receptor (Epha4)	0.14/8.13	*Post*[2,3]; **A**[1]	Other Eph/Esphrins[3]; Atrocytic D-serine[1,3];	Murai et al., 2003[3]; Qin et al., 2010[1];
						Zhuang et al., 2010[1,3];
		2. Ephrin-B3 (Efnb3)	0.13/n.a.	*Pre*[2]; post[1,2,3]; **AP**[1,2]	GLAST[2,3];	Carmona et al., 2009[2]; Filosa et al., 2009[2,3];
		3. Ephrin-A3 (Efna3)	0.05/n.a.	*PAP*[2,3]		
					NMDARs[1,2,3]	Filosa et al., 2009[2,3]; Nolt et al., 2011[1,2,3]
Connexin	Gap junction protein	1. Connexin 30 (Gjb6)	48.36/12.2	*A*[2]	Cytokines[1]	Froger et al., 2010[1]
		2. Connexin 43 (Gja1)	31.89/11.4	*A2*		
Thrombospondin	ECM	1. Thrombospondin 1 (Thbs1)	13.94/5.9	Post[2]; AP[1,2]; AS[1,2]	Fmr1[2];	Cheng et al., 2016[2];
					Synaptophysin[1,2]	Jayakumar et al., 2014[1,2];
		2. Thrombospondin 2 (Thbs2)	0.32/n.a.	PAP[1,2]	Integrin-β1[1];	Hennekinne et al., 2013[1]; DeFreitas et al., 1995[1]
					α2δ-1 receptor[1,2]	Eroglu et al., 2009[1,2]
					CAMs and ECM molecules[1];	Presser et al., 2011[1]; Risher and Eroglu, 2012;
					TGF-β1[1]	Risher and Eroglu, 2012; Wang et al., 2012[1]
Lectican/hyalectican	CSPG	Brevican (Bcan)	17.29/15.1	*Pre*[2]; AP[2]; **AS**[2]	Bral2[2];	Bekku et al., 2012[2];
					Tenascin-C	Midwood and Orend, 2009;
Neuregulin	CSPG	Neuroglycan-C (Cspg5)	5.64/15.8	*Both*[1,2]; AP[1,2]	Tenascin-C[1]	Schumacher et al., 1997[1,2]; Schumacher and Stube, 2003[1]

(*continued on next page*)

Table 1 (*continued*)

Molecule family	Type	Molecule (entrez gene ID)	Expression		Interaction partners**	References
			Level*/#	Location**		
Tenascin	CSPG	Tenascin-C (Tnc)	11.37/n.a.	*AS*[1]	CSPGs[1];	Schumacher and Stube, 2003[1]
					VDCCs[3];	Evers et al., 2002[3];
					Contactins[1];	Rigato et al., 2002[1]; Michele and Faissner, 2009[1];
					Integrins[1]	Andrews et al., 2009[1]; Midwood et al., 2011
SPARC	ECM	1. Hevin (Sparcl1)	23.77/16.8	AP[1,2]; AS[1,2]	SPARC[1,2];	Kucukdereli et al., 2011[1,2]; Blakely et al., 2015[1,2];
		2. SPARC (Sparc)	4.80/n.a.	Pre[1]; **A**[1,2]; *AS*[1,2]		
					Nxrn1α and NL1B[1,2]	Singh et al., 2016[1,2];
					integrin-ß$_3$[1,2]	Jones et al., 2011[1,2]
Syndecan	HSPG	1. Syndecan 2 (Sdc2)	3.13/11.0	*Both*[1,2]; *A*[1]	CASK[1,2];	Cohen et al., 1998[1]; Hsueh and Sheng, 1999[2]
		2. Syndecan 3 (Sdc3)	0.44/8.8	*Pre*[2]		
		3. Syndecan 4 (Sdc4)	26.34/8.6	*A*[2]	LRRTM4[1];	Siddiqui et al., 2013[1]
					EphB-receptors[1];	Ethell et al., 2001[1];
					integrins and	Fiore et al., 2014[1]; Kong et al., 2013[1]; Avalos et al., 2009[1];
					Thy1-receptors[1];	
					Fibronectin[1]	Midwood et al., 2004[1]; Huang et al., 2001[1]
Glypican	HSPG	1. Glypican 1 (Gpc1)	0.14/11.8	*A*[1], *AS*[1]	LRRTM4[1,2,3];	de Wit et al., 2013[1,2,3]; Siddiqui et al., 2013[1];
		2. Glypican 4 (Gpc4)	9.35/	Pre[1,2,3]; **A**[1,2,3]		
		3. Glypican 6 (Gpc6)	n.a.11.63/n.a.	**A**[1,2,3]	PTPσ[1];	Ko et al., 2015[1];
					GluA1[1,2,3];	Allen et al., 2012[1,2,3]; Sato et al., 2016[1]
					GluN1[1]	Sato et al., 2016[1]
Pentraxin	Pattern recognition receptors	1. Pentraxin 1 (Nptx1)	0.15/n.a.	*Both*[1]; AS[1]	TNF-α[1];	Basile et al., 1997[1]
		2. Pentraxin 2 (Nptx2)	1.54/n.a.	*Both*[1], AS[1]	C1q factor[1];	Nauta et al., 2003[1];
		3.			NPR[1,2]; GluA1-2[1];	Lee et al., 2017[1]
					GluA4[1,2];	Sia et al., 2007[1], Pelkey et al., 2015[2]; von Roemeling et al., 2014[1];
					lectin-binding factors in PNNs[1]	Chang et al., 2010[1]
Laminin	ECM	Laminin-ß2 (Lamb2)	21.50/10.8	*Pre*[1,2]; *AS*[1]	Thyroid hormone[1];	Martinez and Gomes, 2002[1]; Mendes-de-Aguiar et al., 2010[1];
					VGCCs[1,2];	Nishimune et al., 2004[1]; Carlson et al., 2010[2];
					integrin-ß1[1]	Gnanaguru et al., 2013[1]
Fibronectin	ECM	Fibronectin (Fn1)	3.36/n.a.	AS[1,2]	Syndecan-4[1]	Klass et al., 2000[1]; Midwood et al., 2004[1]
					TN−C[1];	Strekalova et al., 2002[1]; To and Midwood, 2011[1]; Ingham et al., 2004[1]
					VEGF[1];	Egervari, 2016[1];
					Integrins[1,2];	Bernard-Trifilo et al., 2005[1]; Stenzel et al., 2011[2]
					TSP[1]	Sottile and Hocking, 2002[1]

* Ratio of astrocyte:neuron mRNA expression levels, calculated based on data from Zhang et al. (2014a,b); # Log2 expression levels from microarray data of 10 weeks-old acutely isolated astrocytes form Orre et al. (2014), n.a. data not available, Log2 value of > 5 is above background.

** [1]: in vitro; [2]: ex vivo/in vivo; [3]: in acute brain slices; no indication: review. 'Pre': presynapse; 'Post': postsynapse; 'Both': pre- and postsynapse; 'A': astrocyte; '(P)APs': (perisynapstic) astrocytic processes; 'AS': astrocyte-secreted. Underscored: localization demonstrated at mRNA level; *italic*: localization demonstrated at protein level; **bold:** localization demonstrated at mRNA and protein level. No formatting: based on reviews or studies that showed location using functional assays but no localization experiments.

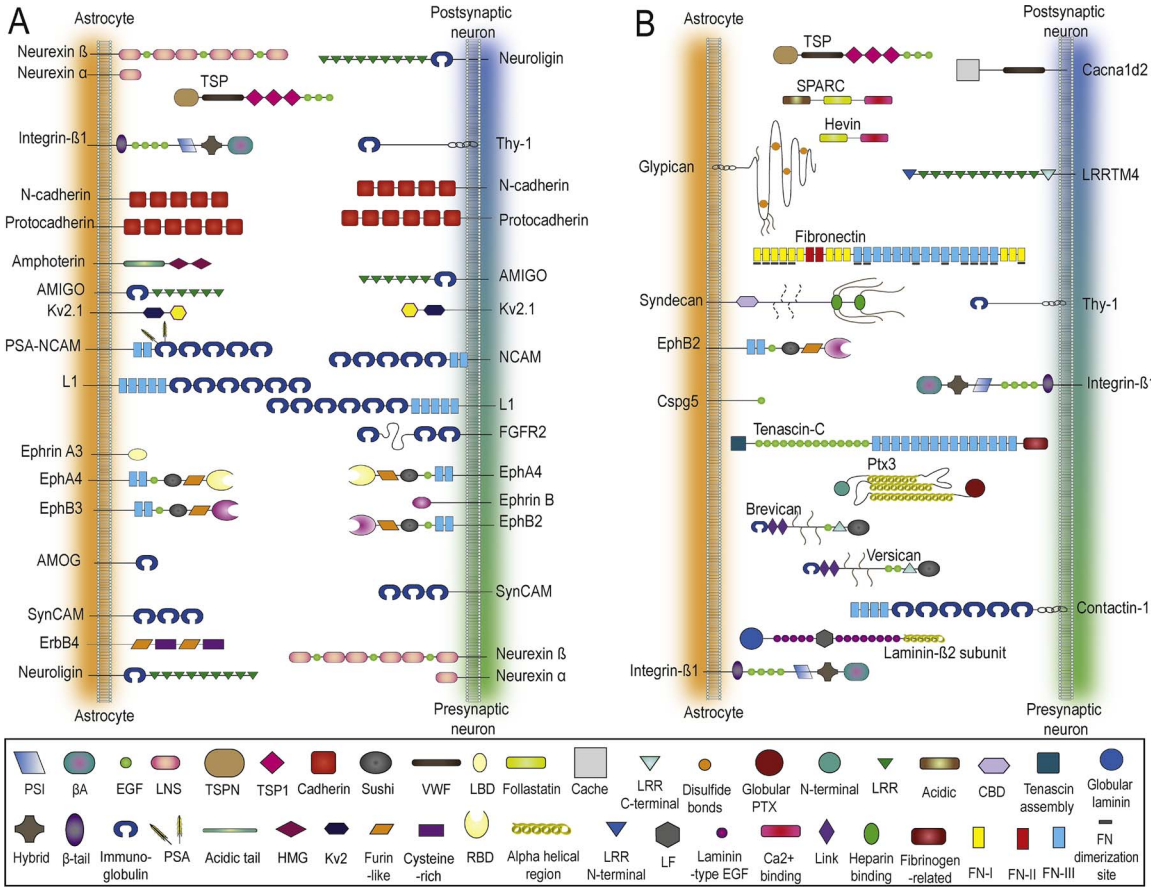

Fig. 2. (A) An overview of CAMs present in the astrocytic membrane (orange) and their interaction partners on the presynaptic (green bottom end) and/or postsynaptic neuron (blue, top). CAMs that are expressed on both pre- and postsynaptic membranes are located in the center. (B) An inventory of matricellular molecules expressed by astrocytes (orange) and the molecules they interact with located on presynaptic (green, bottom) and/or postsynaptic neuron (blue, top). Molecules that are expressed on both pre- and postsynaptic membranes are located in the center.

(Hermosilla et al., 2008; Herrera-Molina et al., 2012; Tanigami et al., 2012). Markedly, only *in trans* binding of astrocytic integrin-αVβ3 to neuronal Thy-1 receptors causes a retraction of neurites, whereas *cis* interactions of neuronal integrin-αVβ3 did not (Maldonado et al., 2017). Although integrin-αVβ3 is barely expressed by astrocytes of the postnatal or adult brain, it is upregulated after exposure to cytokines *in vitro* as well as after brain damage *in vivo*, which may indicate a role for the interaction with Thy-1 in inhibiting axonal regeneration (Hermosilla et al., 2008; Herrera-Molina et al., 2012). Integrins interact with many other astrocyte-expressed synaptogenic factors, such as ECM proteins (Arnaout et al., 2005; Dityatev and Rusakov, 2011; Jones et al., 2011; Myers et al., 2011; Risher and Eroglu, 2012) that can directly or indirectly support binding with neuronal adhesion molecules. For example, integrin-αVβ3 forms complexes with syndecan-4, which in turn interacts with neuronal Thy-1 receptors (Avalos et al., 2009; also see Section 4.1.7). It has to be noted that integrin-β3 expression has only been observed in a rat astrocyte cell line and that expression is very low in acutely isolated astrocytes (Orre et al., 2014; Zhang et al., 2014b); its role in astrocyte-synapse interactions *in vivo* is therefore still unclear. Integrin-α1β1 mediates type IV collagen-induced astrocytic TSP1 mRNA expression at focal adhesion sites and at astrocytic endfeet near blood vessels after cold injury in mice (Yonezawa et al., 2010). Other interaction partners of integrins include Transforming Growth Factors (TGFs) (Tanigami et al., 2012); for example integrin-αVβ8 and −αVβ6 signalling can lead to the uncaging of latent TGF-β by binding to RGD (arginyl-glycyl-aspartic acid) motifs of latency-associated proteins (Nishimura, 2009).

2.1.3. Cadherins and protocadherins

The cadherin superfamily is subdivided into classical cadherins, desmosomal cadherins and protocadherins (PCDHs). Its many members are expressed in the brain as well as in other organs. In the brain, a specific class of neural(N)-cadherins is expressed in astrocytes as well as neurons (Kanemaru et al., 2013; Orre et al., 2014; Tran et al., 2008; Zhang et al., 2014b). These cadherins comprise five cadherin repeats in their extracellular domain (EC1-5), of which the amino-terminal EC1 domain mediates adhesion *in trans*. N-cadherin functions at both pre- and postsynaptic sites, where it spans the synaptic cleft by forming predominantly homophilic bonds (Missler et al., 2012). Its expression inhibits neurite outgrowth of embryonic chick ciliary ganglia neurons grown on a cortical astrocyte monolayer (Tomaselli et al., 1988), a finding that is confirmed in mature rat hippocampal neurons (Saglietti et al., 2007). Binding of N-cadherin to GluA2 subunits of glutamate receptors in the synapse promotes spine morphogenesis and presynaptic maturation via the N-terminal domain of GluA2, and the recruitment of GluA2 at the synapse induces further N-cadherin accumulation in the synapse (Saglietti et al., 2007). N-cadherin is mainly involved in synapse maturation as opposed to synapse formation. A study using N-cadherin knockdown mice shows that the N-cadherin-GluA2 interaction is essential for receptor-dependent long-term depression (LTD) in the hippocampus (Zhou et al., 2011). In cultured rat cortical astrocytes, N-cadherin expression is regulated by ATP signalling and is upregulated after mimicked traumatic CNS injury (Tran et al., 2008). This was confirmed in an astrocyte-specific knockout mouse in which it was shown that an upregulation of astrocytic N-cadherin is required for proper astrogliosis and neuroprotection (Kanemaru et al., 2013).

A distinct family within the cadherin superfamily is that of the

protocadherins (Pcdhs), of which many family members are expressed in the CNS (Frank and Kemler, 2002). They are divided into genomically clustered and non-clustered members. γ-Protocadherins, a family of 22 neural cell adhesion proteins encoded by a single gene cluster (*Pcdh*-γ), are present in the tripartite synapse. The *Pcdh*-γ genes are expressed in both neurons and astrocytes, and γ-protocadherins are located in (peri)synaptic structures (Garrett and Weiner, 2009; Li et al., 2010; Phillips et al., 2003). Garrett and Weiner (2009) show that γ-protocadherins are localized on PAPs and that γ-protocadherins at neuron-astrocyte contacts are essential for synaptogenesis, although it could still occur in neurons co-cultured with Pcdh-γ-null astrocytes as long as the neurons express γ-protocadherins themselves. This synaptogenic effect is also present *in vivo*: transgenic mice with an astrocyte-specific restricted mutation of the *Pcdh*-γ gene cluster show delays in the formation of both inhibitory and excitatory synapses at E15-17 (Garrett and Weiner, 2009). A study that focused more specifically on Pcdh-γC5 showed a similar localization and role in (peri)synaptic neuron-astrocyte interactions (Li et al., 2010).

Non-clustered δ-protocadherins are also involved in synaptic functioning (Kim et al., 2011b; Redies et al., 2005). Of this subfamily, δ2-protocadherin Pcdh8 is expressed in astrocytes and neurons (Cahoy et al., 2008; Zhang et al., 2014b). Expression of the Pcdh8 rat homolog arcadlin is activity-dependent and localizes to synapses, where it induces endocytosis of N-cadherin and as a result inhibits spine remodelling (Yasuda et al., 2007). Interestingly, synaptic activity induces homophilic Pcdh8 *in trans* binding in a Ca^{2+}-dependent manner: application of Pcdh8 antibodies blocks LTP in rat hippocampal slices (Yamagata et al., 1999). If these qualities can be generalized to astrocytic Pcdh8, this would enable astrocytes to respond to synaptic activity by affecting synapse formation and plasticity, thus supporting an integrated function in the tripartite synapse. However, elucidating the existence of such mechanisms requires further study. Moreover, because homophilic protocadherin interactions are generally weaker than heterophilic (proto)cadherin interactions and homophilic classical cadherin interactions (Hirano and Takeichi, 2012; Kim et al., 2011b; Redies et al., 2005), it is currently unclear whether protocadherins can induce synapse formation independently through homophilic interactions or whether they play a supporting role in other mechanisms of synaptogenesis.

2.1.4. SynCAMs

Members of a small IgCAM-like family consisting of three proteins, the Synaptic CAMs (SynCAMs, or CADMs), have also been shown to be implicated in neuronal synapse formation, maturation, and plasticity (Doengi et al., 2016; Fowler et al., 2017; Robbins et al., 2010). SynCAMs have a regulatory effect on axo-dendritic contacts by forming presynaptic terminals on axonal growth cones to direct differentiation of nascent synapses into functional excitatory synapses (Giza et al., 2013; Stagi et al., 2010). Synapse size, number, and mEPSC size appear regulated in a redundant fashion by SynCAM1-3, forming a promoting factor for synapse size yet limitating to synapse number and mEPSC size (Fowler et al., 2017). The triple knockout animals used by Fowler et al. (2017) furthermore indicate that the *in vitro* effects on synaptic density and on the size of *trans*synaptic structures are brought about by SynCAMs located on the postsynaptic membrane. *In vivo* imaging experiments in young adult mice that show SynCAM1 overexpression promotes the maturation of newly formed spines, but does not support stability of pre-existing spines (Korber and Stein, 2016), corroborating on the postsynaptic targeting of SynCAM functioning. After synaptogenesis, neuronal SynCAMs promote maintenance of the synapse and regulate LTD (Robbins et al., 2010). Immunohistofluorescent labeling in postnatal day (P)28 mice was used to localize SynCAM1 to astrocytes, where it appears to mediate similar functions as neuronal SynCAMs (Sandau et al., 2011). This study used dominant negative SynCAM1 and ErbB4 mutations to show that astrocytic SynCAM1 promotes both glial and neuron-astrocyte adhesiveness in the hypothalamus. Adhesiveness was transiently enhanced through the physical association of SynCAM1 and ErbB4 receptors upon activation by the ErbB4 ligand neuregulin (Korber and Stein, 2016; Sandau et al., 2011). In addition, SynCAM3 mediates contact of axons with other axons, axonal shafts, and astrocytic processes (Kakunaga et al., 2005). Both the timing and site of SynCAM3 expression imply a role in the formation of PAPs (Kakunaga et al., 2005) and the inclusion of these astrocytic processes into nascent synapses.

2.1.5. NCAMs

The Neural CAM family of the IgSF consists of three IgCAMs: NCAM1, NCAM2 and NrCAM. An apparent player in the tripartite synapse is neural cell adhesion molecule 1 (NCAM1 or CD56, simply called NCAM here). NCAM is expressed in neurons as well as astrocytes (Mahler et al., 1997; Orre et al., 2014; Theodosis et al., 2008). NCAM mRNA expression is about three times higher in astrocytes than in neurons (Zhang et al., 2014b). Expression peaks during CNS development, but a highly polysialylated form (polysialic acid (PSA)-NCAM) remains high in plastic brain areas (Bonfanti and Theodosis, 2009; Kiss et al., 2001; Theodosis et al., 2008). In neurons, PSA-NCAM is primarily localized to the postsynaptic density, but is also present at presynaptic sites (Enriquez-Barreto et al., 2012; Kiss et al., 2001); in astrocytes, it is found in perisynaptic processes (Theodosis et al., 1999, 2004; Weber et al., 2006). In the hypothalamo-neurohypophysial system PSA-NCAM is a necessary permissive factor for oxytocin-induced morphological changes in astrocyte processes, which retract from neuronal somata and dendrites to allow for the formation of new synapses onto these neurons (Theodosis et al., 1999, 2004). Enzymatic removal of PSA in heterogenotypic cocultures of $NCAM^{-/-}$ and wildtype mouse hippocampal neurons showed that polysialylation of NCAM is required for the synaptogenic effects of NCAM (Dityatev et al., 2004). Interestingly, this effect was blocked by removal of heparan sulfate proteoglycans (HSPGs) as well as by addition of fibroblast growth factor receptor 2 (FGFR2) antagonists or NDMAR antagonists. This latter finding suggests a role of PSA-NCAM in synaptic plasticity and LTP, which has indeed been found (Dityatev et al., 2004). Homophilic PSA-NCAM binding may induce dimerization and auto-phosphorylation of FGFR2 tyrosine kinase domains (Christensen et al., 2006; Kiselyov, 2010). This activation of FGFR mediates NCAM-induced neurite outgrowth (Hansen et al., 2008) and induces a long-lasting memory improvement due to enhanced presynaptic functioning (Cambon et al., 2004). Additional interaction partners of NCAM include IgSF members which can bind to the five Ig-like domains and two fibronectin type-III domains in its extracellular domain (Bonfanti, 2006; Nielsen et al., 2010). NCAM may also regulate matricellular factors such as chondroitin and heparan sulfate glycoproteins by acting as a protease inhibitor (Kulahin et al., 2005). Interaction of NCAM and heparan sulfate chains affects NCAM homodimer formation, which is further modulated by the presence of PSA (Dityatev et al., 2004; Nielsen et al., 2010; Senkov et al., 2012). Although research on the adhesive effects of astrocytic NCAM specifically is lacking, the findings outlined above suggest a role of PSA-NCAM in establishing neuron-astrocyte interactions at the synapse (e.g. in an activity-dependent manner (Theodosis et al., 1999, 2004; Vaithianathan et al., 2004) and that this is modulated by various other factors in the synapse (Dityatev et al., 2004). The high PSA-NCAM expression in glial cells and plasticity-relevant brain structures may contribute to tripartite synapse functioning.

2.1.6. Contactins

Contactins form a six-membered subfamily of the IgSF that is distinguished by membrane anchoring through a GPI-link (Zuko et al., 2011, 2013). Particularly the best-studied members contactin-1 (Cntn1 aka F3/contactin) and contactin-2 (Cntn2, Tag1) have been implicated in axo-glial interactions. These interactions appear critical for the formation and maintenance of the nodal organization of the node of Ranvier (Labasque and Faivre-Sarrailh, 2010; Liu et al., 2001; Peles and

Salzer, 2000). In the juxtaparanode, axonal Cntn2/Tag1 forms heterodimeric complexes with contactin-associated protein 2 (Cntnap2, Caspr2), which clusters potassium channels, and has homophilic *in trans* interactions with glial Cntn2/Tag1 expressed on compact myelin. In the paranode, Cntn1 interacts *in cis* with Cntnap1 (Caspr1, Caspr) and *in trans* with neurofascin-155 (NF-155), an IgCAM located at myelin terminal loops. At the nodal gap, Cntn1 interacts *in cis* with NF-186 which clusters axonal sodium channels, and *in trans* with ECM proteins expressed by astrocytes (Labasque and Faivre-Sarrailh, 2010). These proteins include versican V2, secreted by the perinodal astrocyte, which assembles tenascin-R (TN-R) and phosphacan (Dours-Zimmermann et al., 2009). Phosphacan is a secreted chondroitin sulfate proteoglycan form of protein tyrosine phosphatase, receptor-type B (PTPRB). Cntn1 is able to bind to phosphacan/RPTPβ, the β1-subunit of voltage-gated sodium channels, NF186, and TN-R (Peles et al., 1995; Pesheva et al., 1993). RPTPβz and TN-R can mediate the potential of Cntn1 to interact with astrocytes. This interaction potential is employed, for instance, by GnRH-expressing neurons in the hypothalamus, which rely on plastic rearrangements of glia–GnRH neuron adhesiveness for the regulation of hormone secretion (Ojeda et al., 2008). Such functional protein–protein interactions can involve a number of other molecules, some of which are also expressed by astrocytes, like PTPRβ (Parent et al., 2007). It has been reported that Cntn1 also serves as receptor for TN-R, and that this interaction induces microprocesses along neurites and enlarged growth cones of tectal cells (Brummendorf et al., 1993; Zacharias et al., 2002). This interaction can be disturbed by competition of lecticans such as aggrecan, brevican and neurocan, resulting in the inhibition of the effects of TN-R on microprocess formation and growth cone size (Zacharias and Rauch, 2006). This suggests that astrocytes participate in the regulation of outgrowth of nerve terminals through Cntn1. Furthermore, Cntn1 has been implicated in the highly dynamic interactions between astrocytes in the neurohypophysis and nerve terminals of magnocellular neurons, and contributes to regulation of hormone secretion (Olive et al., 1995; Theodosis et al., 1994). Although expression databases indicate that astrocytes express most contactins (Lovatt et al., 2007; Orre et al., 2014; Zhang et al., 2014b) and a potential function in synaptic development has been indicated for Cntn4 (Big2), Cntn5 (NB1) and Cntn6 (NB2) (Zuko et al., 2011), a role in axo-astrocytic interactions has not yet been established for these members.

2.1.7. AMOG

A non-IgSF CAM also implicated in neuron-glia contact is A Molecule On Glia (AMOG). AMOG is predominantly expressed by CNS glial cells (Zhang et al., 2014b), including Bergmann glia and astrocytic processes (Boer et al., 2010; Gloor et al., 1990; Lecuona et al., 1996). As a homologue of the β-subunit of Na^+/K^+ ATPase (Gloor et al., 1990), it supports molecule transport through cell membranes in concert with the α-counterpart (Schmalzing et al., 1992). AMOG has additionally been shown to promote adhesion of different cell types, neuronal migration, and neurite outgrowth (Krupinski and Beitel, 2009; Togashi et al., 2009). The localization and function of AMOG in the synapse are largely unknown, but its expression at neuron-astrocyte contacts in the CNS (Togashi et al., 2009) indicates that AMOG may stimulate the initial formation of tripartite synapses. Its adhesive function has been illustrated by Ca^{2+}-independent mediation of neuron-astrocyte interactions by AMOG *in vitro* in the new born mouse cerebellum (Antonicek et al., 1987). In cultures, AMOG expression was found in Bergmann glia, but not in neurons. Addition of AMOG antibodies to such cultures decreased neuron-astrocyte adhesion by about 16%, but had no effect on adhesion between astrocytes (Antonicek et al., 1987). These findings indicate that AMOG-mediated neuron-astrocyte adhesion results from a heterophilic interaction between astrocytic AMOG and a yet to be identified interaction partner on the neuronal membrane (Antonicek and Schachner, 1988; Chen et al., 2012). The structural immunoglobulin-like fold in the C-terminal of all isoforms of Na^+/K^+ ATPase β-subunits (β1-3) (Bab-Dinitz et al., 2009) may enable interactions with other IgCAMs implicated in tripartite synapse adhesion (Antonicek and Schachner, 1988). However, due to differences in the exact make-up of the extracellular segments, AMOG can interact with different CAMs than the β1-subunits of Na^+/K^+ ATPase can. This may explain the neuron-glia adhesive characteristics unique to AMOG (Bab-Dinitz et al., 2009). In adherens junctions in epithelial tissue, β1-subunits have been shown to mediate association with the cytoskeleton via α1-subunits *in cis* and to contribute to the formation and stability of junctions through *trans*-dimerization (Vagin et al., 2012). Interestingly, AMOG assembles into a functional sodium pump together with an α1-subunit (Schmalzing et al., 1992; Tokhtaeva et al., 2012), indicating that the mechanisms responsible for AMOG adhesion and β1-subunit adhesion may be similar. These findings indicate that the AMOG-mediated adhesion may not only contribute to the stability in the tripartite synapse, but may also support its formation.

2.1.8. AMIGOs

The Adhesion Molecule with IG-like dOmain (AMIGO) family may comprise yet another group of transmembrane proteins in the tripartite synapse. This family consists of three homologs: AMIGO1-3. These transmembrane proteins share a similar configuration of their extracellular domains, which consists of a single Ig-like domain and six leucine-rich repeat (LRR) domains. Due to these similarities, the three members of the AMIGO family are able to form homo- and heterodimers (Kajander et al., 2011; Kuja-Panula et al., 2003). AMIGO1 is predominantly expressed in the CNS, whereas AMIGO2 and AMIGO3 are more widely distributed throughout the body (Kuja-Panula et al., 2003; Laeremans et al., 2013; Peltola et al., 2011; Rabenau et al., 2004). All AMIGOs are expressed by astrocytes and neurons (Ahmed et al., 2013; Chen et al., 2012; Zhang et al., 2014b). AMIGO is localized to axonal growth cones (Kuja-Panula et al., 2003). The axonal expression pattern is directed by the Ig-domain, since a truncated AMIGO mutant without the Ig-domain and full-length AMIGO are mainly expressed in dendrites (Chen et al., 2012). Expression is induced by amphoterin (HMGB1; AMIGO is also called Amphoterin-induced gene and ORF), a protein linked to neurite outgrowth (Rauvala and Rouhiainen, 2010), and dependent on neuronal activity in the case of AMIGO2 (Ono et al., 2003). This suggests a role in neural plasticity in the adult CNS. Effects on neurite outgrowth have also been found for AMIGO1 in rat hippocampal neuronal cultures (Chen et al., 2012; Kuja-Panula et al., 2003) and in cultured *Amigo3*$^{-/-}$ dorsal root ganglion (DRG) cells (Ahmed et al., 2013). The ability to form dimers *in trans* and the presence of its Ig-like domain have furthermore led to speculation on a role of AMIGO in cell–cell interactions and adhesion (Chen et al., 2012; Kajander et al., 2011; Rabenau et al., 2004; Zhao et al., 2014). No knockout studies targeting astrocytes have been conducted for any of the AMIGOs. Therefore, functional similarities between neuronal and astrocytic AMIGO remain speculative, yet conceivable. If they are indeed alike, this would suggest a comprehensive role of AMIGO in the tripartite synapse, as it could control bidirectional adhesion between glia cells and neurons (Chen et al., 2012) in an activity-dependent manner. The binding of AMIGO to Kv2.1 potassium channels (Peltola et al., 2011; Zhao et al., 2014) may additionally enable astrocytes to regulate neuronal excitability in the synapse.

2.1.9. The Eph system

The Eph system is a group of membrane-associated ligands and receptors that serve important and manifold functions in cell–cell communication. Although not strictly classified as CAMs, these proteins are involved in synaptic maturation of neuronal and astrocytic synaptic elements and are thus of relevance for the tripartite synapse. This system consists of a family of tyrosine kinase receptors (Eph receptors) and associated ligands (Ephrins) that are either transmembrane (class B) or GPI-linked (class A) membrane proteins (Filosa et al., 2009). The latter may occur in soluble form, since not all protein is fully anchored. Eph system signalling is bi-directional, since not only the Eph receptors

but also the membrane Ephrins confer signal transduction. Ephrins are implicated in axon guidance, synapse formation and maturation, and long-term synaptic plasticity (Klein, 2009). For example, binding of astrocytic ephrin-A3 to neuronal EphA4-receptors leads to postsynaptic maturation of excitatory synapses at P4–5 mice. This effect is dependent on Eph system-mediated contact between PAPs and dendritic spines, which induces a decrease in the number of dendritic filopodia (Nishida and Okabe, 2007). Thus, the limiting factor that astrocytic processes form to the arborisation of dendrites (Withers et al., 2017) and the stabilization of dendritic spines resulting from coverage by PAPs (Bernardinelli et al., 2014; Eroglu and Barres, 2010) might be established through ephrin signalling. The interaction of ephrin-A3 on PAPs with postsynaptic EphA4 contributes to spine morphology (Carmona et al., 2009; Murai et al., 2003) and also controls glial glutamate transporter (GLAST) levels in adult mice through post-transcriptional regulation (Carmona et al., 2009), affecting glutamate levels in the synaptic cleft and long-term plasticity (Filosa et al., 2009; Tanasic et al., 2016). Since EphA4 is also located perisynaptically on presynaptic specializations and on astrocytic membranes (Frugier et al., 2012; Tremblay et al., 2007), it may exert similar effects at presynaptic sites. Moreover, cross-over interactions between ligands and Eph receptors of the other class can also mediate neuron-glia interactions (Klein, 2009; Qin et al., 2010). In hippocampal slices of astrocyte-specific *EphB3* and *EphA4* KO mice, dendrite-excreted ephrin-B is required for the induction of D-serine release in astrocytes by activation of EphB3 as well as EphA4 receptors (Zhuang et al., 2010). In hippocampal and temporal neocortex tissue of epileptic rats and patients neuronal EphB3 and neuronal and astroglial ephrin-B3 upregulation, which is possibly related to the pathological synaptic network activity associated with epilepsy (Huang et al., 2016). In a mouse traumatic brain injury model both Ephrin-B1 and its receptor EphB2 are transiently upregulated in hippocampal reactive astrocytes 3 days post injury. Ephrin-B1 levels are downregulated again at 7 days post injury. The upregulation negatively impacted the number of excitatory glutamatergic presynaptic boutons that project onto CA1 hippocampal neurons (Nikolakopoulou et al., 2016). This can be due to astrocytic Ephrin-B1 inhibition of synapse formation by competing for EphB2-binding with neuronal Ephrin-B1, or alternatively, due to axon-repellent qualities of astrocytic Ephrin-B1 (Nikolakopoulou et al., 2016). Downregulation of astrocytic Ephrin-B2, but not astrocytic Ephrin-A3 or Ephrin-A4, was the potential culprit for impaired synapse formation in mouse Spinal Muscular Atrophy (SMA) astrocyte-neuron co-cultures (Zhou et al., 2016). Note that expression of its binding partner EphB2 is heterogeneous across brain areas; in the amygdala for example, no EphB2 is detected on astrocytes (Zhu et al., 2016). Interestingly, EphB-receptors can interact with NMDARs (Dalva et al., 2000) in an age-dependent manner (Nolt et al., 2011), underscoring the role of ephrins in synapse development and brain plasticity. Clearly, the complexity of interactions between the various astrocytic and neuronal ligands and receptors within the Eph system is vast, and allows for a remarkably flexible system in which astrocytes can control the synapse. The various mechanisms of action underlying these astrocyte-neuron interactions are yet to be fully uncovered (e.g. Amegandjin et al., 2016).

3. Astrocyte connections: gap junctions form glial networks

In addition to CAMs, astrocytes express molecules that support astrocytic interlinking in order to form a glial network. Astrocyte-astrocyte coupling is not only important for astrocytic communication but also mediates bidirectional signalling between astrocytes and other types of glial cells such as oligodendrocytes and microglia (Amaral et al., 2013; Ji et al., 2013; Pannasch et al., 2012; Pannasch and Rouach, 2013), as well as between astrocytes and neurons, as discussed next.

3.1. Connexins

To enable communication across their functional domains, astrocytes are connected by gap junctions. These are composed of hemichannels formed by connexins (Cxs), whose expression modifies and is modified by neuron-astrocyte contacts. During development, connexins mediate coupling of foetal hippocampal neurons and astrocytes (Rozental et al., 2001), bringing astroglial and neuronal structures of the tripartite synapse into close vicinity of one another. After the gestational period, physical contact with neurons is required for the induction of astrocytic Cx30 and upregulation of astrocytic Cx43 in neuron-astrocyte co-cultures (Koulakoff et al., 2008). Furthermore, connexin-mediated astrocyte–astrocyte coupling is affected by neuronal synaptic elements, and gap junction plasticity is responsive to neurotransmission. As a result of perturbed dopaminergic transmission, six-week old 6-hydroxydopamine lesioned rats showed an upregulation of astrocytic Cx43 and an increased synchronicity of the astrocytic network which was dependent on neuronal activity (Bosson et al., 2015). Moreover, an increase in the amount of bipartite synapses in lesioned animals versus control animals was mirrored in tripartite synapse numbers due to PAP relocalization towards neuronal synaptic structures, as determined by synaptophysin, PDZ-95, and phosphor-ezrin colocalization (Bosson et al., 2015). Ultrastructural data on the distribution of gap junctions and excitatory synapses in layer IV of the barrel cortex of adult mice also show a non-random integration of gap junctions and synapses: on average, the distance between a gap junction and an excitatory synapse is much smaller than the distance between two gap junctions or two synapses (Genoud et al., 2015). Cx30 and Cx43 are mainly expressed by astrocytes and have been shown to support transport of inositol 1,4,5-trisphosphate (IP_3) and various gliotransmitters (Nagy et al., 1999; Orellana and Stehberg, 2014; Pannasch and Rouach, 2013). In addition to a direct effect of gliotransmitters on synaptic activity, prevention of cytokine-induced activation of Cx43 hemichannels contributes to neuronal survival in excitotoxic circumstances(Froger et al., 2010), further illustrating a regulatory role of connexins on neuronal activity. Additional support for a role of Cxs on neurotransmission is observed in $Cx30^{-/-}$:$Cx43^{-/-}$ mice that display a distorted postsynaptic response to stimulation of Schaffer collaterals in the hippocampus. The retained postsynaptic activity results from disrupted regulatory functioning of astrocytes, as reflected by a decreased clearance of glutamate out of the synaptic cleft, increased levels of potassium in the cleft, alterations in gap junction structure, and altered swelling of astrocyte processes (Pannasch et al., 2011, 2012). Comparison of a *Cx43* single knockout mouse to a $Cx30^{-/-}$:$Cx43^{-/-}$ double mutant (Pannasch et al., 2014) allowed to distinguish between two distinct mechanisms of synaptic glutamate regulation by which Cx30 and Cx43 regulate synapse efficacy. Cx30 is implicated in astroglial coverage of the synapse and subsequent glutamate transport by astrocytes (Pannasch et al., 2014), whereas Cx43 regulates synaptic glutamate levels more directly by acting on the quantal size of presynaptic release of glutamate (Chever et al., 2014). In line with this, in vivo blockage of Cx43 hemichannels in the adult rat basolateral amygdala disrupts memory consolidation of auditory fear conditioning (Stehberg et al., 2012). The prevention of gliotransmission by blocking hemichannels has been proposed to lead to the disrupted neuronal functioning (Pannasch et al., 2011, 2012; Stehberg et al., 2012). Connexins are thus important in maintaining homeostasis of an extracellular milieu optimal for neurotransmission (Pannasch and Rouach, 2013). Together, these effects of connexins support the notion of astrocytes as a functional element in the synapse.

4. Molecules in the extracellular matrix contribute to synapse formation and modulation

Astrocytes can also mediate synapse functioning by the secretion of matricellular proteins, which contribute to the body of proteins that

make up the ECM. The ECM provides mechanical, structural, and biochemical support to surrounding cells (Kim et al., 2011a; Lu et al., 2011; Tseng et al., 2012) and serves many functions in the synapse (Faissner et al., 2010). To underscore the importance of CNS ECM proteins in synaptic functioning, the term 'tetrapartite synapse' has been coined, which includes the ECM as the fourth element of the synaptic complex in addition to the tripartite synaptic components (Dityatev and Rusakov, 2011). By definition, the ECM can be considered an active element in the neural network only if it can transform its input into integrated output (Perea et al., 2014).

4.1. Astrocytic matricellular factors implicated in synapse functioning

In recent years, a number of molecules that constitute the ECM in the synapse have been identified to be expressed by astrocytes (Fig. 2b). Many of these molecules are proteoglycans, highly glycosylated proteins that form extracellular nets. Often these matricellular molecules are secreted by astrocytes into the ECM; others are GPI-linked or transmembrane proteins that enable cell-ECM interlinking. The following section summarizes current knowledge on the role of astrocytic molecules in the synaptic regulation by the ECM.

4.1.1. Thrombospondin

Thrombospondin (TSP) is an astrocyte-secreted ECM molecule that is important for synapse formation and plasticity. It is upregulated in astrocytes after stroke, where it aids in post-recovery synapse formation and axonal sprouting (Liauw et al., 2008). In cultured rat RGCs, TSP-depleted astrocyte-conditioned medium (ACM) reduces the number of postsynaptically silent excitatory synapses; an increase in pre- and postsynaptic puncta is accompanied by diminished co-localization, suggesting a role for TSP in aligning pre- and postsynaptic specializations (Bolton and Eroglu, 2009; Christopherson et al., 2005). The synaptic qualities of TSP are confirmed in a *Fmr1* KO mouse model of Fragile X Syndrome in which a potential astrocytic factor underliesthat displays the spine dysgenesis and altered synaptic functioning associated with Fragile X Syndrome (Cheng et al., 2016). *Fmr1* KO astrocytes interestingly showed decreased TSP protein levels, which co-occur with the disruption of dendritic spine development. A decrease in co-localized pre- and postsynaptic puncta furthermore indicated reduced synapse formation among hippocampal neurons co-cultured with *Fmr1* KO astrocytes. In line with a study by Christopherson et al. (2005), these synaptic defects are prevented by exposure to wild-type astrocytes or wild-type ACM, and rescued by application of exogenous TSP (Cheng et al., 2016). One way by which TSP regulates synaptogenesis is through binding of EGF-like TSP-2 domains to the VWF-A domain of postsynaptic $\alpha_2\delta$-1 receptors, subunits of L-type calcium channels (Eroglu et al., 2009). Although $\alpha_2\delta$-1 activity increases surface trafficking of Ca^{2+}-channels, studies on synaptogenic effects during overexpression of $\alpha_2\delta$-1 in the absence of TSP and pharmacological blockage of calcium channels (Eroglu et al., 2009) indicate that the synaptogenic effects of TSP-induced $\alpha_2\delta$-1 activation is not mediated by calcium channel trafficking. The exact molecular mechanism by which TSP-binding to calcium channel subunits results in synaptogenesis remains unclear, although the EGF-like domains of TSP have been proposed to be the synaptogenic element(Eroglu et al., 2009). Other interaction partners of TSPs are CAMs including neuroligin, ECM molecules, and TGF-β (Presser et al., 2011; Risher and Eroglu, 2012; Wang et al., 2012). In addition, *in vitro* and *in vivo* studies in rats have recently indicated a role for glial activity and TSP-1 in regulating synaptophysin levels (Jayakumar et al., 2014; Zhou et al., 2014). This latter effect of TSP is suggested by Jayakumar et al. (2014) to be mediated by integrin-α3β1, a receptor for TSP-1 known to stabilize synaptophysin (DeFreitas et al., 1995; Jayakumar et al., 2014). The integrin-β1-TSP interaction is also implicated in reducing excitability of synapses in mature spinal cord neuronal cultures; addition of TSP to these cultures lowers AMPA receptor stability in the synaptic membrane (Hennekinne et al., 2013). Interestingly, the same study shows that TSP simultaneously promotes glycine receptor accumulation. These effects of TSP on synaptic AMPA and glycine receptors disappear after application of anti-integrin β1 antibodies to the cultures. Integrin-β3 antibodies without TSP show effects similar to that of TSP on synaptic AMPA and glycine receptors accumulation. These results suggest that the TSP-integrin interactions are involved in inhibition/excitation regulation in the synapse (Hennekinne et al., 2013). Thus, the synaptogenic effects of TSP are established both directly as well as indirectly in concert with additional astrocytic factors to induce and regulate functionally active synapses.

4.1.2. Brevican

Brevican is a secreted member of the lectican/hyalectan family of hyaluronan-binding chondroitin sulfate proteoglycans (CSPGs; (Faissner et al., 2010)). Mediated by binding of homologous C-type lectin motifs in the C-terminal domain, brevican comprises a structural factor of the ECM together with tenascins and hyalurolan (Bekku et al., 2009). It is predominantly present in perineuronal nets (PNNs) of the adult CNS and is transiently expressed by neurons during development (Andrews et al., 2009; Faissner et al., 2010; Pyka et al., 2011). Neuron-secreted linker proteins such as Bral2 and Crtl1 are also important to the PNN structure; Bral2-deficient mice show mislocalization of brevican, leading to reduced stabilization of brevican at the PNN and subsequently in PNN stability. Interestingly, overall brevican protein levels remain similar to that of wild-type mice (Bekku et al., 2012). Brevican in the granule layer of the cerebellum is mainly produced by astrocytes that ensheath glomeruli, and inhibits *in vitro* neurite outgrowth of granule neurons (Dauth et al., 2016; Yamada et al., 1997). It is expressed throughout the adult rat brain (Dowell et al., 2009) but is particularly high in the cortex, hippocampus, spinal cord and the cerebellum (Dauth et al., 2016), the latter being confirmed in cerebellar primary cultures (Giamanco and Matthews, 2012) and *in vivo* (Carulli et al., 2006; Hubbard et al., 2015). Brevican furthermore supports the assembly of ECM elements to the nodes of Ranvier at axons in the CNS (Bekku et al., 2009). Co-cultured rat hippocampal neurons and astrocytes were used to study the synaptogenic function of CSPGs (Pyka et al., 2011): enzymatic digestion of CSPGs resulted in an increase in number of excitatory synapses but decreased synaptic strength, suggestive of an inhibitory role of CSPGs on plasticity. In agreement, a study in astrocyte-specific *ephrin-B2* KO mice shows that deletion of ephrin-B2 results in decreased astrogliosis, which was proposed to subsequently elicit inhibition of astrocytic secretion of CSPGs into the glial scar (Ren et al., 2013). Astrocytic ephrin-B may thus mediate the inhibitory effect of CSPGs on axonal re-growth after CNS injury. Upregulated brevican protein levels are indeed found on reactive astrocytes in lesioned entorhinal cortices of adult rats (Thon et al., 2000) as well as in mutant mice displaying Purkinje cell degeneration (Blosa et al., 2016). Along with the upregulation of other CSPGs, increased amounts of brevican protein in reactive astrocytes coincides with a decrease in co-localized synaptic puncta and neurite formation (Liddelow et al., 2017). Note however that while most CSPGs, like brevican, are found to inhibit synaptic plasticity (Harlow and Macklin, 2014), some may in fact promote such plasticity (Beller and Snow, 2014). A review on synaptogenic features of glia by (Allen, 2013) similarly suggests that the ECM forms a limiting factor in synaptic plasticity as a result of a stabilizing effect on neuronal synaptic AMPA receptors, as is seen in the TSP-mediated reduction of AMPA receptor accumulation in the synapse (Hennekinne et al., 2013). As one of the most ubiquitously expressed CSPG in the adult brain it is likely that brevican takes part in this regulatory effect on synaptic plasticity, although its function in the tripartite synapse as a singular molecule requires further research. For example, synaptic density is not altered in a brevican knockout mouse (Brakebusch et al., 2002), suggesting at least some functional redundancy among CSPGs within the PNN. Conversely, the Bral2-deficient mice discussed earlier that display decreased

brevican stabilization at the PNN also showed a reduced number of synapses in the deep cerebellar nuclei (Bekku et al., 2012). While this synaptogenic effect could be unique to the Bral2-brevican interaction, it exemplifies the need to better understand the various interactions of brevican within PNNs and their effects on synapses. It is also crucial to weed out synaptogenic differences amongst CSPGs, although this may prove challenging without careful and comprehensive manipulation of PNN content. PNNs in the adult rat brain seldom express brevican without aggrecan and/or Tenascin-R expression (Dauth et al., 2016). Moreover, PNN composition differs across brain regions, which possibly contributes to the regional variation in synaptic plasticity and neuroprotective qualities (Dauth et al., 2016).

4.1.3. Neuroglycan-C

Neuroglycan-C (Cspg5), a transmembrane chondroitin sulfate proteoglycan that is also classified as a neuregulin (Kinugasa et al., 2004), is expressed by astrocytes as well as neurons (Aono et al., 2004), albeit to a considerably lesser extent by the latter (Zhang et al., 2014b). Astrocytic expression is increased in the glial scar (Anderson et al., 2016), and studies on CALEB, the Neuroglycan-C homolog in chick and rodents, have localized it to astrocytic and axonal membranes in the developing CNS. These studies furthermore show that CALEB promotes neurite extension in rat RGC cultures at early postnatal stages (Inatani et al., 2000) and in cultured E6 chick tectal neurons (Schumacher et al., 1997). In the chick retina, CALEB expression and synapse formation coincide (Juttner and Rathjen, 2005; Schumacher and Stube, 2003), which together with its localization suggest it may be implicated in synaptogenesis (Juttner and Rathjen, 2005). Synapses in the superior colliculus of Neuroglycan-C-deficient mice display higher paired-pulse ratios, less depression during prolonged repetitive activation, a lower rate of spontaneous postsynaptic currents, and a lower release probability at early but not at mature postnatal stages (Juttner et al., 2005). The absence of Neuroglycan-C furthermore resulted in an impairment of presynaptic differentiation of GABAergic synapses (Juttner et al., 2013) in the mouse cerebellum. These findings indicate a role of Neuroglycan-C in maintaining normal release probability. However, it is not possible to differentiate between astrocytic and neuronal input to these effects of Neuroglycan-C, because a non-cell type specific knockout was used. Interestingly, Neuroglycan-C is converted to a truncated form in which the transmembrane protein exposes its EGF-like domain in response to neuronal depolarization, which was experimentally induced by elevated potassium chloride or agonists for AMPA receptor GluR subunits (Juttner and Rathjen, 2005). The EGF-like domain is implicated in spine formation and dendritic branching (Brandt et al., 2007), and together with the acidic amino acid domain it furthermore stimulates neuritogenic effects of Neuroglycan-C on E16 rat neocortical neurons *in vitro*, possibly at both the pre- and the postsynapse (Nakanishi et al., 2006). Future studies are needed to determine the molecular mechanism of this truncation and whether astrocytes express the factors necessary to induce such activity-dependent regulation of (pres)ynaptic functioning by Neuroglycan-C. It is currently also unknown whether Neuroglycan-C localizes on PAPs. However, immunostaining in adult rats has localized the protein to cortex and cerebellum neuropils (Aono et al., 2006), which are synapse-rich areas consisting of dendrites, unmyelinated axons, and glial processes. This suggests that astrocyte-expressed Neuroglycan-C may indeed be localized to PAPs and may be a potential factor in the formation of tripartite synapses. In addition to these direct effects on synaptic functioning, Neuroglycan-C has been shown in chicken to bind to fibrinogen-like domains of Tenascin-C (TN-C) via the acidic amino acid domain (Schumacher and Stube, 2003), thus supporting additional synaptogenic effects of the ECM.

4.1.4. Tenascin-C

This interaction partner of Neuroglycan-C and other CSPGs, the astrocyte-secreted glycoprotein TN-C (Midwood and Orend, 2009), is another important constituent of the ECM. TN-C expression peaks during development and is poorly expressed in the adult brain, but it is again upregulated at neural injury sites (Jones and Bouvier, 2014). In cell-insert hippocampal co-cultures, TN-C is present on neuronal somata as well as on astrocytes (Pyka et al., 2011), where it modulates membrane channel-activity through L-type Ca^{2+}-channels (Evers et al., 2002; Jones and Bouvier, 2014). Indeed, TN-C can affect fibre outgrowth in cultured rat hippocampal neurons by regulating intracellular Ca^{2+}-levels (Michele and Faissner, 2009) as well as synaptic plasticity (Faissner et al., 2010). In line with this, deletion of a number of ECM genes in astrocytes, including TN-C and brevican, leads to reduced formation and stability of new synapses in cell-insert co-cultures of primary embryonic mouse hippocampal neurons and astrocytes (Geissler et al., 2013). TN-C may also affect plasticity at a structural level through interactions with IgCAMs. For example, TN-C may interact with integrins via its FN-III domain repeats (Andrews et al., 2009), regulating synaptic functioning through these interactions differentially depending on the integrin isoform (Andrews et al., 2009; Midwood et al., 2011). Neurite outgrowth is also induced by the FN-III domains of TN-C and is dependent on activation of neuronal Cntn1 receptors (Michele and Faissner, 2009). In support of this, contactin expression in hippocampal neurons *in vitro* concurs with the developmental period in which TN-C levels peak (Rigato et al., 2002). Together these effects of TN-C on synaptic adhesion and plasticity (Allen et al., 2012; Dityatev and Rusakov, 2011; Geissler et al., 2013; Jones and Bouvier, 2014; Pyka et al., 2011) indicate a role for TN-C in tripartite synaptic functioning. However, like brevican, TN-C needs to be studied in isolation of other ECM components before definite conclusions on its function can be made.

4.1.5. Hevin

The fifth element of the ECM that might be involved in tripartite synapse formation and function is hevin, a member of the secreted protein acidic and rich in cysteine (SPARC) family that is expressed both by neurons and by astrocytes. Hevin has been localized in PAPs (Buosi et al., 2018; Dowell et al., 2009; Jones et al., 2011; Kucukdereli et al., 2011; Lively et al., 2007) and although expression peaks during development, levels remain high during adulthood where it serves a synaptogenic function within the ECM (Jones and Bouvier, 2014; Lloyd-Burton and Roskams, 2012; Risher et al., 2014). Astrocytic secretion of hevin is increased after injuries such as transient focal ischemia (Lively et al., 2011) or controlled cortical impact (Furman et al., 2016). Hevin promotes the formation of excitatory synapses on RGCs in the superior colliculus in P14 hevin KO mice, in part by stimulating the maturation of presynaptic boutons. Like TSP (Christopherson et al., 2005), hevin-induced synaptogenesis results in ultrastructurally normal synapses that are postsynaptically silent (Kucukdereli et al., 2011). In the developing mouse thalamus, hevin also aids proper thalamocortical synaptogenesis and connectivity postsynaptically by promoting the maturation of dendritic spines and by inhibiting synapse formation onto dendritic shafts (Risher et al., 2014). Interestingly, this study did not observe a decrease in the number of tripartite synapses in hevin-deficient mice, suggesting the availability of hevin is no obligatory factor in establishing glia-neuron contacts at the synapse. Hevin is, however, required as a mediating interaction partner of the non-binding forms Nxrn1α and NL1B during synapse formation of excitatory thalamic axons on cortical dendrites in the developing visual cortex of P13-16 mice (Singh et al., 2016). This molecular complex was furthermore found to induce NMDA receptor-mediated plasticity at these synapses. In line with the hevin-induced presynaptic maturation (Kucukdereli et al., 2011), hevin bound to the complex employs the ability of Nxrn1α and NL1B to organize pre- and postsynaptic specializations, respectively (Singh et al., 2016).

4.1.6. SPARC

Like hevin, SPARC is a matricellular protein that is secreted by astrocytes and the founding member of the SPARC family (Blakely et al.,

2015; Buosi et al., 2018; Dowell et al., 2009; Mendis et al., 1995). Curiously, the synaptogenic effect of hevin appears to be counteracted by SPARC as *SPARC*-null mice display an increased synapse formation (Kucukdereli et al., 2011). The antagonistic role of SPARC on hevin-mediated synaptogenesis may take place via the SPARC-like homolog, because each member of the SPARC family contains an extracellular calcium binding E-F hand motif and a follistatin-like domain (Bradshaw, 2012). In a mouse model of multiple sclerosis, the retraction of postsynaptic densities from motor neuron cell bodies and proximal dendrites coincides with a decrease in hevin-to-SPARC mRNA and protein ratios in the spinal cord, as compared to naive conditions (Blakely et al., 2015). SPARC thus appears to act as an inhibitory counterbalance to the synaptogenic features of hevin. In agreement, peaks in SPARC expression during normal development are associated with pruning of axonal branches in cholinergic synapses. A comparison between peptides containing different regions of the SPARC protein shows that the C-terminal domain but not the follistatin-like domain is crucial for the inhibition of synaptogenesis by SPARC and SPARC-induced elimination of synapses (Lopez-Murcia et al., 2015). This finding was confirmed *in vivo* in the same study by showing motor deficits and a reduced number of NMJs in the tails of developing *X. tropicalis* tadpoles injected with the C-terminal domain-containing peptide. In contrast to hevin's positive effects on bouton formation, dendritic spine maturation, and structural maturation (Kucukdereli et al., 2011; Risher et al., 2014), SPARC prevents the maturation of presynaptic terminals, even in nanomolar concentrations (Albrecht et al., 2012). Other effects of astrocytic SPARC on maturation include an interaction with integrin-β_3 that reduces postsynaptic AMPA receptor levels at synapses (Jones et al., 2011). Although the exact mechanism of this interaction in neurons is not yet clear, a portion of the follistatin-like domain of SPARC has been shown to interact with integrin-β receptors on non-neuronal cells such as HEK293T cells (Jones et al., 2011). Since integrin-β_3 stabilizes GluR2 subunits at synaptic membranes (Cingolani et al., 2008), SPARC may thus indirectly regulate the excitatory strength of synapses. Interestingly, the SPARC release that is required for integrin-β_3-induced AMPA receptor regulation is dependent on neuronal glutamate release (Jones et al., 2011); astrocytic regulation of synaptic strength is thus partially regulated by preceding neuronal activity. This indicates a negative feedback loop mediated by SPARC, where neuronal activity ultimately leads to a decreased synaptic strength *via* astrocyte activation. Interactions of hevin and integrins are not thoroughly investigated but seem likely, as many ECM factors do interact with integrins (Myers et al., 2011). A mechanism of competitive equilibrium between hevin and SPARC functioning has been proposed to occur through the SPARC-like homolog (Kucukdereli et al., 2011). The opposing effects of astrocytic hevin and SPARC in the synapse point to an interdependent regulatory function of the two proteins (Blakely et al., 2015), and illustrate the complex and diverse interactions of astrocytic factors in the synapse.

4.1.7. Syndecans

Syndecans (Sdcs) are transmembrane proteins that function as co-receptors of G-protein coupled receptors. All four members in the syndecan family are expressed in the peripheral nervous sytem and the CNS (Lambaerts et al., 2009; Xian et al., 2010), and are expressed by astroglial cells in the newborn rodent cortex (Dowell et al., 2009; Mendes-de-Aguiar et al., 2008; Properzi et al., 2008). Sdc3 is expressed so abundantly in the CNS that it is also referred to as neural syndecan (N-syndecan). Sdc3 has been mostly localized to axons in the developing synapse (Reizes et al., 2008) and plays an inhibitory role in synaptic plasticity: Sdc3-deficient mice were shown to suffer from memory impairments due to saturation of LTP (Kaksonen et al., 2002). However, Sdc3 protein was not found on astrocytes of neonatal rats *in vitro* (Winkler et al., 2002) which may be due to the much lower astroglial Sdc3 mRNA expression than neuronal expression (Zhang et al., 2014b). However, it was found that astrocytic secretion of soluble factors, including Sdc3 and Sdc4, can be induced by thyroid hormone T3 (Dezonne et al., 2013). Interestingly, this study also observed that conditioned medium of astrocytes treated with T3 cannot fully mimic the effects of astrocyte-neuron co-cultures, thus indicating that cell–cell contact, possibly mediated by an astrocytic CAM, is required for neuron maturation and neurite outgrowth. In contrast to Sdc3, Sdc2 and Sdc4 are expressed at higher levels in astrocytes than in neurons (Zhang et al., 2014b). Sdc2 accumulates at hippocampal synapses where it alters the cytoskeleton through binding of CASK and induces maturation of neuronal dendritic spines (Cohen et al., 1998; Hsueh and Sheng, 1999; Lin et al., 2007). It also promotes F-actin reorganization to drive postsynaptic bouton formation (Lucido et al., 2009). Phosphorylation of Sdc2 at these synapses is mediated by EphB2 receptors (Ethell et al., 2001), suggesting that Sdc2 may promote dendritic spine maturation in synergy with ephrin-mediated spine maturation. Syndecans furthermore modulate integrin-based cell adhesion through interactions with various integrins (Choi et al., 2011a; Fiore et al., 2014; Morgan et al., 2007; Xian et al., 2010). For example, neuronal Thy-1 engages with astrocytic Sdc4 and integrin-αVβ3 in the rat (Kong et al., 2013) to promote the integrin-mediated coupling of neuron-astrocytes as discussed earlier (Avalos et al., 2009; Hermosilla et al., 2008). In this process, Sdc4 binds the heparin-binding domain of Thy-1 (Kong et al., 2013). Sdc4 also serves as a co-receptor in fibronectin-induced integrin signalling, but the effects on matrix-cell adhesion of Sdc4 compete with TN-C in binding to their shared binding site on the FN-III_{13} module of fibronectin (Huang et al., 2001; Midwood et al., 2004; Saito et al., 2007). Syndecan-fibronectin binding is enabled by the heparan sulfate and chondroitin sulfate chains in syndecan's extracellular domain (Choi et al., 2011a; Reizes et al., 2008), which also allow for interaction with other synaptogenic constituents of the ECM (Xian et al., 2010). Because syndecans dimerize through GxxxG motifs in their transmembrane domain (Kwon et al., 2015) and form heteromeric complexes with homologous transmembrane domains (Dews and Mackenzie, 2007), isoform-specific syndecan functions are potentially shared among members of the family. *In vivo* data on this issue is on demand. The various functions of syndecans in the synapse, in addition to their interaction with other astrocytic synaptogenic factors, make astrocyte-expressed syndecans promising players in the formation and maturation of the tripartite synapse.

4.1.8. Glypicans

Glypicans form a six-member family of heparin sulfate proteoglycans (HSPGs) that is widely expressed throughout the body (Song and Kim, 2013) and by astrocytes (Allen et al., 2012; Dowell et al., 2009; Liddelow et al., 2017; Xiong et al., 2016). In the brain, astrocytic glypican isoforms are differentially expressed by specific astrocyte subpopulations: Glypican-4 (gpc4) is predominantly expressed in the dentate gyrus of the hippocampus and is also observed in the neocortex (Ko et al., 2015; Xiong et al., 2016), while Glypican-6 (gpc6) expression is found in the cerebellum (Allen et al., 2012). This expression pattern may reverse during development or could be altered *in vitro*, since qPCR data on newborn mice tissue mirrors that of the P12 mice that Allen et al. (2012) used (Buosi et al., 2018). Glypican-1 protein is produced by neonatal rat midbrain astrocytes *in vitro* (Winkler et al., 2002) and its mRNA is expressed in the CA3 hippocampal region *in vivo* (Ko et al., 2015). Glypicans are sereted and constitute an ACM factor implicated in the development of functionally active glutamatergic synapses in RGCs (Allen et al., 2012). Astrocytic glypicans are sufficient yet not necessary for synapse formation, as synaptogenesis persists, albeit to a lesser extent, in RGCs treated with glypican-depleted ACM. Furthermore, *Gpc4* knockout mice display a decreased mEPSC amplitude in CA1 pyramidal neurons *in vivo*. This effect results from AMPA receptor GluA1 subunit regulation and clustering by downstream gpc4 signalling molecules (Allen et al., 2012). These include glypican-binding to LRRTM4, a postsynaptic transmembrane protein that regulates excitatory synapse development (Lauren et al., 2003; Linhoff et al., 2009). Binding to

LRRTM4 is mediated by glypican heparin sulfate chains (de Wit et al., 2013; Siddiqui et al., 2013). Knockdown of LRRTM4 in mice leads to a decrease in mEPSCs frequency at 7-14 days in vitro (de Wit et al., 2013), which is likely regulated by synaptic AMPA receptor content (Schwenk et al., 2012; Siddiqui et al., 2013), and in a decrease in dendritic spine density. In addition, a decrease in mEPSC amplitude occurs in 6 to 7 weeks old *LRRTM4*$^{-/-}$ mice (Siddiqui et al., 2013). As opposed to the *Gpc4*$^{-/-}$ mice (Allen et al., 2012), this effect is observed in dentate gyrus granule neurons, but not CA1 pyramidal neurons (Siddiqui et al., 2013). This is in agreement with the cellular expression pattern of the knockout targets: LRRMT4 is preferentially expressed in the dentate gyrus whereas HSPG expression is more widespread (Song and Kim, 2013). At the presynapse, heparin sulfate chains of proteolytically cleaved gpc4 interact *in cis* with Ig domains on PTPσ, a receptor protein tyrosine phosphatase family member (Ko et al., 2015). This organizes the presynapse through interaction with postsynaptic proteins, including LRRTM4. The co-receptor function of PTPσ for gpc4-LRRTM4 binding is crucial for the synaptogenic effects of LRRTM4: in heterologous synapse-formation assays using lentiviral knockdowns of PTPσ or gpc4 it was shown that removal of either two diminished LRRTM4-induced presynaptic differentiation and that their reexpression rescued these effects. Interestingly, the PTPσ knockdown also results in a decreased mEPSC frequency and amplitude in cultured hippocampal neurons (Ko et al., 2015). PTPσ could thus be another downstream factor of gpc4 signalling implicated in the synaptic GluA1 subunit regulation and clustering found by Allen et al. (2012). These data indicate a role for astrocytic glypican in recruiting and stabilizing synaptic AMPA receptors, which makes postsynaptically silent synapses receptive to neurotransmitters; that is, it 'unsilences' them (Kerchner and Nicoll, 2008). Interestingly, application of gpc6 to the medium of human induced pluripotent stem cells during neuronal differentiation also leads to an increase in the amount of NMDA receptors on the membrane (Sato et al., 2016). This effect was mediated by upregulation of GluN1, an NMDA receptor subunit, whereas surface levels of GluA1 had increased markedly less. Accordingly, calcium imaging of these stem cell-derived neurons showed no functional synaptic activity (Sato et al., 2016). Although deviations between species and differences in neuronal maturation, regional identity, and other additional ACM factors present in the culture should be taken into account when comparing the above mentioned studies, it is clear that more work on the various glypican isoforms is needed to clarify their possibly differential roles in synaptic functioning.

4.1.9. Pentraxins

Additional molecules implicated in synaptic unsilencing are pentraxins. This family of extracellular soluble pattern recognition receptors includes three secreted isoforms that may be implicated in tripartite synapse functioning: neuronal pentraxin 1 (NP1), neuronal pentraxin 2 (NP2 or Neuronal Activity Regulated Pentraxin, NARP), and long pentraxin 3 (PTX3) (Jeon et al., 2010; Yin et al., 2009). Pentraxins and their receptor (NPR) are expressed by neurons as well as astrocytes (Elbaz et al., 2015; Jeon et al., 2010; Stahlberg et al., 2011; Wang et al., 2012; Yin et al., 2009) and their upregulation is sensitive to certain pro-inflammatory factors. For example, Tumor Necrosis Factor-α signalling may induce expression of PTX3 as well as NARP through their shared transcription factor NFκB (Basile et al., 1997; Daigo et al., 2014). Furthermore, *in vitro* upregulation of NP1 mRNA levels occurs in astrocytes but not in neurons following application of valproic acid (Wang et al., 2012), an anti-convulsant drug with pro-inflammatory characteristics (Dambach et al., 2014). After its early peak in expression around P7 in mice (Bjartmar et al., 2006), NP1 continues to contribute to synaptic plasticity by forming a complex with NP2 linked by N-terminal mediated disulfide bonds (Xu et al., 2003). NP1 and NP2 recruit AMPA receptor clusters in nascent synapses in the developing mouse visual system, mediating synaptic unsilencing during a defined early developmental period only (Koch and Ullian, 2010). AMPA receptor recruitment by pentraxins is mediated by the preferential binding of NP1 and NP2 to the N-terminal X domain of GluR4 subunits (Sia et al., 2007; von Roemeling et al., 2014). Indeed, GluA4 is drastically reduced at synaptic membranes in an *NP2*$^{-/-}$*:NPR*$^{-/-}$ knockout mouse (Pelkey et al., 2015). NP1 or NP2 can additionally bind to the N-terminal domains of GluA1 and GluA2 subunits when in a heteropentameric configuration with NPR at the membrane (Kirkpatrick et al., 2000). A reduction of NPR protein in cultured hippocampal neurons after knockdown leads to lower levels of surface GluA1 and to a drecrease in inhibitory and excitatory postsynaptic specialization markers, suggesting a role of NPR and pentraxins in organizing and establishing *trans*synaptic complexes (Lee et al., 2017). Lee et al. (2017) propose that the disproportionately large effects at the synapse caused by a relatively small decrease in NPR protein result from a regulatory role of NPR on the levels of secreted pentraxins, clustering them at the presynaptic membrane. The function of secreted pentraxins would therefore also be hindered by NPR knockdown. This notion is partially corroborated by the finding that in NPR knockdown mice indeed NP2 levels are decreased, although those of NP1 are not; however NPR overexpression did result in an increase of both NP1 and NP2 (Lee et al., 2017). Interestingly, pentraxins interact with the C-terminal globular head domain of C1q factor, a protein of the classical complement system (Nauta et al., 2003; Stevens et al., 2007), potentially linking synapse scaling cascades to synaptic activity-regulated proteins like NP2 (Koch and Ullian, 2010; Yuzaki, 2010). NP2 activity has indeed been associated with scaling of synapses, but the required accumulation of NP2 at excitatory interneuron synapses appears to be dependent on the proximity of PNNs in the ECM. NP2 accumulation might be established by signalling of lectin-binding factors in PNNs, although this process may involve more complex pathways than the direct binding of NP2 to such factors (Chang et al., 2010). While it is clear that pentraxins are important activity-dependent and developmental factors in synaptic plasticity, further similarities in neuronal and astrocytic pentraxin functioning within the synapse remain to be determined.

4.1.10. Laminins

Laminins constitute a family of developmentally secreted glycoproteins that form heterotrimers composed of α, β, and γ chains (Durbeej, 2010). All laminins appear to play a role in synaptic stabilization, although different isoforms are found in different kinds of synapses, including NMJs, and hippocampal and photoreceptor synapses (Egles et al., 2007). Laminins promote neurite outgrowth, dendrite and axon outgrowth, and alignment and maturation of pre- and postsynaptic elements (Dansie and Ethell, 2011; Fusaoka-Nishioka et al., 2011; Guizzetti et al., 2008; Nishimune et al., 2004, 2008; Patton et al., 2001). Astrocytes produce laminins (Dansie and Ethell, 2011; Liesi et al., 1983, 2001; Lovatt et al., 2007), and some effects of laminin have been shown to emanate specifically from their secretion by astrocytes. For example, laminins have been identified as components of ACM that promote dendritic spine proliferation in mouse Purkinje cell cultures (Seil, 1998, 2014). *In vitro* work on cerebellar astrocytes showed that astrocytic expression of laminin in the rat is induced by thyroid hormone which in concert with epidermal growth factors allows for neurite outgrowth (Martinez and Gomes, 2002; Mendes-de-Aguiar et al., 2010). In studies focusing on synaptogenic effects of a neuronal laminin-β2 knockout in the mouse NMJ, it was found that the processes of terminal Schwann cells entered synaptic clefts and disrupted neurotransmission (Noakes et al., 1995; Patton et al., 1998). Laminin-β2 also binds and clusters voltage-gated Ca^{2+} channels (VGCCs), which induces maturation of presynaptic structures that are important for successful neurotransmission (Carlson et al., 2010; Nishimune, 2012). Disruption of the laminin-VGCC interaction was found to impair quantal neurotransmitter release in mice (Chand et al., 2015; Knight et al., 2003). Binding of laminin-β2 chains to VGCCs furthermore provides a presynaptic anchor for a synapse-spanning scaffold that attaches to

postsynaptic integrin-β1 receptors in NMJs (Darabid et al., 2014). Interestingly, astrocytes in a laminated layer of the retina show laminin-β2 and -γ3 chain-induced expression of integrin-β1 and extension of astrocytic processes *in vitro* (Gnanaguru et al., 2013). These findings together indicate that laminins are involved in a bidirectional neuron-glia communication that regulates maturation and functionality of the synapse. As of yet, most research on laminin has focused on NMJs and (terminal) Schwann cells, a synapse model that extrapolates sufficiently well to central synapses (Egles et al., 2007), although the NMJ model has been implicated in a broader synaptic organisation as well (Johnson-Venkatesh and Umemori, 2010). However, it is of interest to determine whether the current knowledge on astrocyte-expressed synaptic laminins can indeed be extrapolated to the synapses of the CNS.

4.1.11. Fibronectin

Another matricellular factor that plays a role in adhesion and synaptic functioning during development and injury is fibronectin. Following injury in the CNS, especially astroglial fibronection expression is relatively rapidly upregulated in an activity-dependent manner (Hoffman et al., 1998). In the CNS, the soluble form of this glycoprotein is primarily produced and secreted by astrocytes (Niquet et al., 1994; Stoffels et al., 2013; Zhang et al., 2014b). Fibronectin production by cortical primary mouse astrocytes is dependent on PKA signalling activity induced by lysophospholipid acid, a signalling molecule released by post-mitotic neurons (Spohr et al., 2014). Secreted fibronectin disulfide-bonded dimers are assembled into multimeric insoluble fibrils at the cell surface, which form an important contribution to the mechanical structure of the ECM. For example, astrocyte-secreted VEGF, a growth factor critical for the survival and remodelling of the brain vasculature, is immobilized at fibronectin-rich fibrils at cell-matrix adhesion sites *via* integrin-β1 (Egervari, 2016). The active distribution of VEGF by astrocytes to a cell-surface bound state in complex with fibronectin could stabilize maturing fibrils by decreasing integrin-β1 turnover at cell-matrix adhesions (Egervari, 2016). Integrin-fibronectin interactions are furthermore important for crucial fibronectin functions: the conversion of fibronectin dimers into insoluble matrix fibrils is induced by integrin-α5β1 receptors on the cell surface (King et al., 2001; Schwarzbauer and DeSimone, 2011). This synaptogenic integrin has been localized to astrocytes and, to a lesser degree, to hippocampal neurons (Webb et al., 2007; Zhang et al., 2014b). After fibrillogenesis fibronectin continues to be a ligand to various types of neuron- and astrocyte-expressed integrin receptors, and clusters them on the cell membrane (Pankov and Yamada, 2002). Such clustering of integrin receptors is facilitated by an RGD motif in the FN III_{10} module that functions as a recognition site for a number of integrins, including α5β1 and αv-containing isoforms, at least *in vitro* (Bernard-Trifilo et al., 2005; Pankov and Yamada, 2002; Stenzel et al., 2011). Fibronectin-bound integrin isoforms differ in their fibrillogenic ability, α5β1 being the most potent (Leiss et al., 2008). Furthermore, fibronectin-induced integrin receptor clustering facilitates adhesion to the astrocytic matrix in order to enable cell migration (Milner et al., 1999; Stenzel et al., 2011). Interestingly, blocking the fibronectin RGD sequence prevents synaptic plasticity processes such as LTP in rats (Chun et al., 2001; McGeachie et al., 2011). The disruption of LTP appeared to be due to an integrin-mediated effect of fibronectin on synaptic NMDA receptor functioning (Bernard-Trifilo et al., 2005; Shi and Ethell, 2006). In addition to plasticity in the synapse, fibronectin also provides mechanical support for cell adhesion by binding many different CAMs through Ig-like folds in the FN-III modules of its extracellular domain (Steward et al., 2002). The FN-III domain additionally facilitates synaptic functioning by binding to other ECM elements, such as TN-C, syndecans, TSP, and heparin (Ingham et al., 2004; Jones and Bouvier, 2014; Klass et al., 2000; Schwarzbauer and DeSimone, 2011; Sottile and Hocking, 2002; Strekalova et al., 2002; To and Midwood, 2011).

5. Concluding remarks

Numerous recent findings on the effects of astrocyte-derived CAMs and matricellular factors in the synapse have revealed that astrocytes are an essential third synaptic element. This function of astroglial cells has been increasingly investigated in the last decade, which has resulted in the identification of many molecules that are implicated in the formation, maturation, maintenance, and function of the tripartite synapse. Here we have provided an overview of recent findings centred around astrocyte-expressed cell adhesion- and matricellular molecules to elucidate their various contributions on synaptic functioning. These molecules have been found to affect all components of the tripartite synapse and to regulate neurotransmission. Many of these molecules were previously known to be synaptogenic or to have other effects in the synapse, but were mainly considered in a neurocentric context where other constituents of the brain, such as (astro)glial cells or the ECM, were largely ignored. The importance of understanding astrocytic function and dysfunction in the synapse has been underscored by the recently recognized role of astrocytes in a number of synaptic pathologies (Chung et al., 2015), such as schizophrenia (Berretta, 2012; Halassa et al., 2007; Osborn et al., 2016; Pekny et al., 2016; Sofroniew and Vinters, 2010; van Dijk et al., 2016; Xia et al., 2014). In the case of autism, a significant number of the molecules discussed here have been pinpointed as autism risk genes, specifically neurexins and neuroligins (Kleijer et al., 2014; Krueger et al., 2012), Cntns (Kleijer et al., 2014, 2015; Zuko et al., 2016), NCAMs (Petit et al., 2015; Zhang et al., 2014a), integrins (Schuch et al., 2014), cadherins and protocadherins (Butler et al., 2015; Cappelletti et al., 2015; Chen et al., 2014; Crepel et al., 2014; Rivero et al., 2015; Stewart, 2015; van Harssel et al., 2013), connexins (Avendano et al., 2015; Fatemi et al., 2008; Petit et al., 2015), thrombospondin (Lu et al., 2014), and laminins (Kim et al., 2015). Research on new astrocytic therapeutic targets for the treatment of CNS pathologies (Giralt et al., 2010; Rappold and Tieu, 2010) may therefore benefit markedly from additional identification of astrocyte-expressed synaptic molecules. This is greatly facilitated by transcriptome databases like such used in this review (Cahoy et al., 2008; Han et al., 2014; Orre et al., 2014; Zhang et al., 2014b).

The molecules discussed in this review provide clear examples of how regulation of synaptic transmission is established by close cooperation of neurons and astrocytes. Studies on these molecules do not only improve our knowledge on the role of astrocytes in neuronal connectivity and functioning, but may also lead to a better appreciation of the integration of the brain's functional elements, which include other cell types and molecules also. The rapidly growing wealth of research into the tripartite synapse represents an important step towards this new view on brain functioning. By summarizing recent findings and proposing potential additional players, the importance of the complex and diverse actions of astrocyte-derived CAMs and matricellular factors in the tripartite synapse is underscored. Further insights in the integration of neurons and astrocytes at the level of the tripartite synapse may provide novel outlooks on synaptic physiology and plasticity in both the normal and diseased brain.

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