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Synaptic adhesion molecules and excitatory synaptic transmission

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Synaptic adhesion molecules have been extensively studied for their contribution to the regulation of synapse development through trans-synaptic adhesions. However, accumulating evidence increasingly indicates that synaptic adhesion molecules are also involved in the regulation of excitatory synaptic transmission and plasticity, often through direct or close associations with excitatory neurotransmitter receptors. This review summarizes recent results supporting this emerging concept and underlying mechanisms, and addresses its implications.

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Introduction

Synaptic adhesion molecules are known to be involved in the regulation of diverse steps in synapse development and maintenance, including the initial contact between pre- and postsynaptic sides of synapses, formation of early synapses and their differentiation into mature synapses, and maintenance and plasticity of established synapses [1–3]. However, recent studies have begun to reveal a novel role for adhesion molecules in regulating excitatory synaptic transmission and plasticity. Potential mechanisms underlying these functions are often suggested to include direct interaction or close association of adhesion molecules with neurotransmitter receptors, such as NMDA (*N*-methyl-D-aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) glutamate receptors (NMDARs and AMPARs, respectively).

Synaptic adhesion molecules are thought to cluster neurotransmitter receptors by interacting with the cytoplasmic scaffolding proteins that are in complex with neurotransmitter receptors, such as PSD-95 (Figure 1a). This tripartite interaction may be sufficient for adhesion molecules to recruit neurotransmitter receptors to sites of early trans-synaptic adhesion. In addition, it would bring scaffolding protein-associated signaling molecules close to receptors. However, synaptic adhesion molecules may also require direct or close *cis* interactions with neurotransmitter receptors (Figure 1b). For instance, *cis* interactions between adhesion molecules and neurotransmitter receptors situated on the same scaffolding protein may enhance the stability of tripartite complexes or the functional interplay between them.

It should be noted that experimental evidence supporting the direct or close interactions of synaptic adhesion molecules with neurotransmitter receptors is often less compelling than that for trans-synaptic adhesions, likely because of the weak or transient nature of the interactions. In this review, we focus on summarizing results that are relatively more convincing.

Synaptic adhesion molecules that regulate excitatory synaptic transmission and plasticity

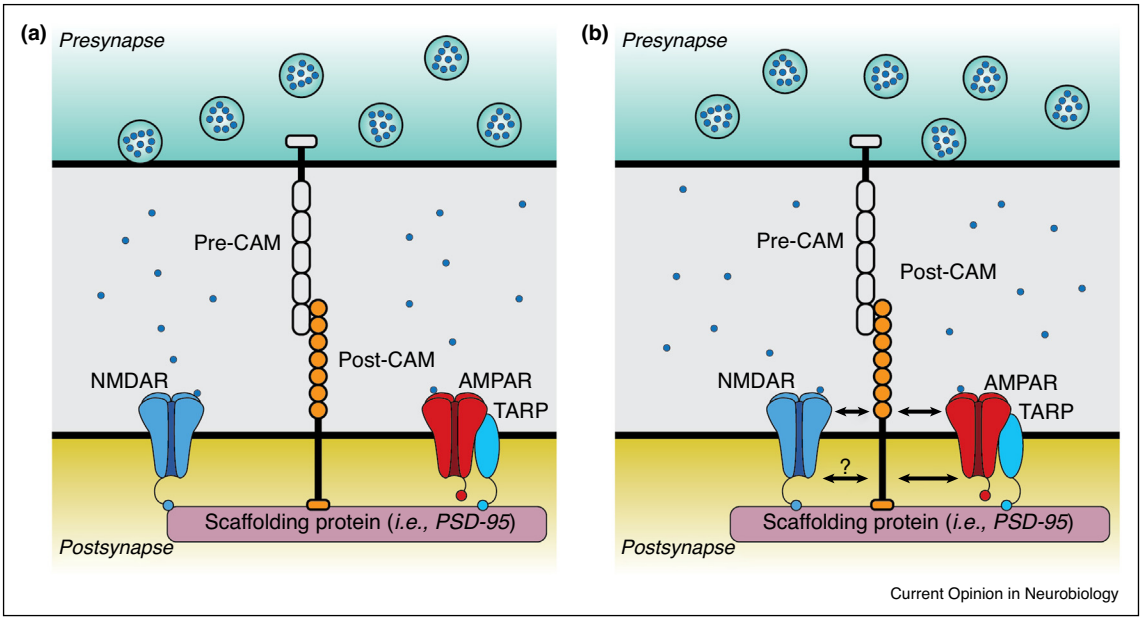
Neuroligin-1

Neuroligin-1, a prototypical postsynaptic adhesion molecule that interacts with presynaptic neurexins [1], has been strongly implicated in the regulation of NMDAR-mediated synaptic transmission and NMDAR-dependent synaptic plasticity. Supporting data have been obtained from diverse brain regions, including the hippocampus [4–10], cortex [11], striatum [12], amygdala [13], and cerebellum [14].

Neuroligin-1-dependent regulation of NMDAR function may require a complex of PSD-95, an abundant excitatory postsynaptic scaffold, with NMDARs and TARP-containing AMPARs. Recent data, however, indicate that neuroligin-1 can also associate with the GluN1 subunit of NMDARs through extracellular coupling [4]. In addition, the extracellular region of neuroligin-1 can normalize the reduction in NMDAR-mediated synaptic transmission caused by combined neuroligin-1 knockout (KO) and neuroligin-3 knockdown (KD) [15].

Notably, neuroligin-1-dependent regulation of NMDAR- and AMPAR-EPSCs (excitatory postsynaptic currents) requires a critical residue (E747) in the middle of the cytoplasmic region of neuroligin-1, but does not involve

Figure 1



Conventional and emerging views on how synaptic adhesion molecules interact with neurotransmitter receptors.
(a) Conventional view: cytoplasmic scaffolding proteins such as PSD-95, which interact with both synaptic adhesion molecules and neurotransmitter receptors, may play a role in synaptic coclustering of adhesion molecules and neurotransmitter receptors.
(b) Emerging view: synaptic adhesion molecules and neurotransmitter receptors may directly interact or closely associate with each other, thereby enhancing the stability of the complex or facilitating the functional interplay between them. Examples of such functional interplay could include regulation of trans-synaptic adhesions by ligand-bound receptors or, conversely, regulation of the pharmacological or kinetic properties of receptors by trans-synaptic adhesions

the C-terminal PDZ-binding motif [8]. In addition, an extracellular region of neuroligin-1 containing the splice insert B, known to regulate neurexin binding, is important for neuroligin-1-dependent regulation of NMDAR-EPSCs and long-term potentiation (LTP) at perforant path-dentate gyrus (DG) synapses [7], although this regulation seems to involve a reduction in excitatory synapse number rather than NMDAR content at individual synapses.

More recently, Hevin, a synaptogenic protein secreted by astrocytes, has been shown to interact with neurexin-1α and neuroligin-1B (containing splice insert B), a trans-synaptic pair that does not interact with each other, to promote presynaptic differentiation and postsynaptic clustering of proteins, including NMDARs, at thalamocortical synapses [16]. Because Hevin preferentially recruits GluN2B-containing NMDARs to synapses, the reported extracellular coupling between neuroligin-1 and the GluN1 subunit of NMDARs is unlikely to be critical [4].

Neuroligin-3 and neuroligin-4X

Neuroligin-3, present at both excitatory and inhibitory synapses [1], enhances AMPAR- but not NMDAR-mediated synaptic transmission in a manner requiring E740 (corresponding to E747 in neuroligin-1), whereas neuroligin-3 enhances inhibitory transmission through mechanisms that require the presence of neuroligin-2 [8,17].

Neuroligin-3 containing the ASD-related mutation, R451C, increases AMPAR-mediated synaptic transmission, slows NMDAR-EPSC decay, increases GluN2B-containing NMDARs, and enhances NMDAR-dependent LTP in the hippocampus [18]. Although molecular details remain unclear, these apparent gain-of-function phenotypes suggest the possibility that neuroligin-1 containing extracellular mutations can alter AMPAR- and NMDAR-mediated synaptic transmission.

More recently, neuroligin-3 harboring R704C, another ASD-related mutation, was shown to enhance neuroligin-3 binding to AMPARs and promote AMPAR endocytosis, whereas the same mutation introduced into neuroligin-4X was shown to abolish wild-type neuroligin-4X–dependent suppression of AMPAR-mediated transmission [19••]. Notably, expression of wild-type neuroligin-4X in the context of reduced neuroligin expression (miR-mediated KD of neuroligins-1, -2, and -3) was found to enhance AMPAR currents, an increase that was abolished by the R704C mutation, which eliminates T707 phosphorylation by protein kinase C (PKC) [20].

Notably, the influence of neuroligin-3 or -4 mutations on AMPAR trafficking and synaptic function appear to be affected by compensatory changes during development, as supported by the observation that constitutive neuroligin-3 KO or developmentally early conditional neuroligin-3 KO has minimal effects on AMPAR function at calyx of Held synapses, whereas developmentally late conditional neuroligin-3 KO or neuroligin-3 mutations (R451C and R704C) have profound effects on AMPAR function [21].

Neurexins

Neurexins are presynaptic adhesion molecules that interact with postsynaptic proteins, including neuroligins, LRRTMs, and GluD2 [1,2]. Microspheres coated with neurexin-1β has been shown to rapidly recruit NMDARs and GluA2-containing AMPARs likely through neurexin-neuroligin interaction in an activity-independent manner [22]. In addition, mice lacking neurexin-2α, or both neurexin-2α and -2β, show reduced excitatory presynaptic release and, intriguingly, reduced postsynaptic NMDAR function [23], likely through trans-synaptic neurexin-neuroligin adhesion.

More recently, constitutive inclusion of splice site #4 (SS4) in neurexin-3 in mice has been shown to decrease postsynaptic levels of AMPARs, but not NMDARs, and suppress synaptic AMPAR recruitment during LTP [24]. Constitutive removal of SS4 from neurexin-3 by cre-recombination, however, leads to normalization AMPAR-mediated synaptic transmission [24]. It is possible that SS4 in neurexin-3 decreases postsynaptic AMPAR levels by suppressing the interaction of neurexin-3 with postsynaptic ligands such as LRRTMs/neuroligins [2]. These results suggest that alternative splicing in neurexins can regulate postsynaptic receptor levels through trans-synaptic adhesion.

LRRTMs

LRRTMs, leucine-rich repeat (LRR)-containing synaptic adhesion molecules that interact with neurexins and PSD-95 [2,25,26], have been implicated in the regulation of synapse development as well as synaptic transmission and plasticity. In support of these functions, double-KD of LRRTM1 and LRRTM2 suppresses AMPAR-EPSCs, but not NMDAR-EPSCs, at Schaffer collateral-CA1 synapses [15], whereas LRRTM2 KD suppresses NMDAR-EPSCs as well as AMPAR-EPSCs at perforant path-DG synapses [2]. In addition, double-KO of LRRTM1 and LRRTM2 suppresses hippocampal LTP [27], and LRRTM3 KO in mice decreases the amplitude of miniature EPSCs (mEPSCs) in DG granule cells without affecting LTP [28]. Lastly, LRRTM4 interacts with glypicans (presynaptic proteoglycans) and regulates excitatory synapse density, as evidenced by the fact that LRRTM4 KO [29] or KD [30] reduces mEPSC frequency in DG granule cells; in the somatosensory cortex, LRRTM4 KD suppresses mEPSC amplitude rather than frequency [30]. Although it remains largely unclear how LRRTMs regulate AMPAR/NMDAR-mediated synaptic transmission and plasticity, it is notable that the reduction in AMPAR-EPSCs induced by double-KD of LRRTM1 and LRRTM2 is rescued by overexpression of the extracellular domain of LRRTM2 [15], suggesting that extracellular LRRTM2–AMPAR coupling is important.

EphBs and ephrin-Bs

EphB receptor tyrosine kinases (EphBs), known to regulate dendritic spines, also regulate the trafficking and function of NMDARs and AMPARs [31–33]. Ephrin-B-bound EphBs directly interact with NMDARs through extracellular domains and phosphorylates the GluN2B subunit of NMDARs at cytoplasmic tyrosine residues through Src tyrosine kinases, promoting synaptic localization of NMDARs and NMDAR-dependent calcium influx through suppression of calcium-dependent desensitization [31,32,34]. EphBs associate with SAP102, a PSD-95 relative known to regulate NMDAR trafficking [35], to regulate synapse development through PAK signaling [36]. EphBs also regulate NMDAR-dependent synaptic plasticity through mechanisms involving the extracellular domain but not the tyrosine kinase domain [31,32]. Clinically, the surface interaction between EphBs and NMDARs has been associated various brain disorders [31,33], including encephalitis involving NMDAR autoantibodies that weaken the surface interaction [37]. Ephrin-B3, which can be postsynaptically localized for reverse signaling [32], *cis*-interacts with EphBs and inhibits EphB-dependent phosphorylation of GluN2B [38]. Ephrin-B3 also directly interacts with PSD-95 in a phosphorylation-dependent manner to promote synaptic localization of PSD-95 [39], an important regulator of excitatory synaptic strength and plasticity [35], and with Erk kinases to inhibit postsynaptic mitogen-activated protein kinase signaling and regulate excitatory synapse density [40].

N-cadherin

N-cadherin, an Ig domain-containing homophilic adhesion molecule in complex with β-catenin, is thought to stabilize neuronal synapses and regulate excitatory synaptic transmission and plasticity [2,3]. N-cadherin-dependent regulation of excitatory synaptic function is supported by the observations that dominant-negative N-cadherin decreases mEPSC frequency and amplitude [41], and conditional KO (*Camkii-Cre*) of N-cadherin decreases CA1 LTP [42]. Intriguingly, N-cadherin directly interacts with the extracellular N-terminal domain of the GluA2 subunit of AMPARs and suppresses lateral diffusion of GluA2 on neuronal cell surfaces [43]. In addition, N-cadherin enhances surface expression of GluA1 in heterologous cells [44].

β3 integrin

β3 integrin, an extracellular matrix receptor, is localized to postsynaptic sites and regulates AMPAR trafficking and synaptic plasticity [45]. β3 integrin directly interacts with the GluA2 subunit of AMPARs through the transmembrane or intracellular domains of both proteins [46]. These results, together with the abovementioned extracellular coupling between N-cadherin and GluA2, suggest the interesting possibility that GluA2 may form a tripartite complex with N-cadherin and β3 integrin, although the functional consequences of these potential interactions remain unclear.

MDGA2

MDGAs (MAM domain-containing glycosylphosphatidylinositol [GPI] anchors) are Ig domain-containing, GPI-anchored adhesion molecule known to interact in *cis* with neuroligins and block neuroligin interactions with neurexins at both excitatory and inhibitory synapses [47•,48,49]. In support of a role for MDGA2 in the inhibition of AMPAR-mediated synaptic transmission, a haploinsufficiency of MDGA2 has been shown to increase mEPSC frequency and amplitude and enhance AMPAR-EPSCs, without affecting mIPSCs, in hippocampal slices [47•].

FLRT3

KD of FLRT3 (fibronectin leucine-rich transmembrane protein 3), an LRR-containing postsynaptic adhesion molecule that interacts with presynaptic latrophilins [2], decreases mEPSC frequency and amplitude in dissociated hippocampal neurons, and decreases AMPAR-EPSCs and NMDAR-EPSCs at perforant path-DG synapses [50]. This suggests that FLRT3 likely regulates both synapse development and synaptic transmission, although the underlying mechanism is unclear.

IgSF11

IgSF11 (immunoglobulin superfamily member 11) is a novel Ig domain-containing synaptic adhesion molecule that interacts with PSD-95 and has been implicated in synaptic stabilization of AMPARs [51•]. In support of this, a high-throughput single-molecule tracking approach has shown that KD of IgSF11 in cultured neurons decreases mEPSC frequency and amplitude and increases surface mobility of the GluA2 subunit of AMPARs [51•]. *Igsf11* KO in mice decreases mEPSC amplitude, but not frequency, in DG granule cells, whereas it suppresses LTP at Schaffer collateral-CA1 synapses. Re-expression of IgSF11 in IgSF11-deficient DG granule cells rescues mEPSC amplitude, whereas a mutant IgSF11 lacking the C-terminal PDZ domain-binding motif partially rescues mEPSC amplitude, suggesting that both PSD-95-dependent and -independent mechanisms are involved. Although, IgSF11 forms a complex with AMPARs in the brain, a direct or close *cis* interaction between IgSF11 and AMPARs has not been demonstrated.

SALM1

SALM1 (also known as LRFN2) is a member of the SALM (synaptic adhesion-like molecule) family of LRR-containing proteins [52]. Among the five known SALMs, SALM3 and SALM5 interact with presynaptic LAR family receptor tyrosine phosphatases (LAR-RPTPs) and have strong synaptogenic activities [53,54], but minimal effects on synaptic strength, as supported by the decrease in the frequency, but not amplitude, of mEPSCs in *Salm3*-KO CA1 pyramidal neurons [53]. Other SALMs (SALM1, -2, and -5), however, have been implicated in the regulation of AMPAR- or NMDAR-mediated synaptic transmission, as demonstrated by SALM2-dependent synaptic localization of AMPARs in dissociated hippocampal neurons [52] and SALM5-dependent promotion of AMPAR-EPSCs through trans-synaptic interactions with LAR-RPTPs in hippocampal slice culture [54]. In addition, SALM1 associates with and induces dendritic clustering of NMDARs through mechanisms requiring the C-terminal PDZ-binding motif of SALM1, which interacts with PSD-95 [52]. However, SALM1 can also interact with the extracellular and/or transmembrane domain of the GluN1 subunit of NMDARs in heterologous cells, indicative of extracellular coupling.

NGL-2

Netrin-G ligands (NGLs) are LRR-containing excitatory postsynaptic adhesion molecules that interact with PSD-95 and presynaptic netrin-Gs/LAR-RPTPs. The netrin-G2 ligand, NGL-2, also known as LRRC4 (leucine-rich-repeat–containing 4) associates with and induces dendritic clustering of NMDARs and PSD-95, but not AMPARs, in dissociated neurons. NGL-2 KD or KO induces input-specific decreases in excitatory transmission, as evidenced by suppression of NMDAR-EPSCs and AMPAR-EPSCs at Schaffer collateral-CA1, but not TA-CA1, synapses by in utero KD of NGL-2, and by Schaffer collateral pathway-specific reduction in excitatory synaptic transmission in *Lrrc4*-KO mice [55]. However, whether NGL-2 and NMDARs/AMPARs interact extracellularly has not been determined.

Elfn1

Elfn1 (extracellular leucine-rich repeat fibronectin containing 1), an LRR-containing postsynaptic adhesion molecule expressed in somatostatin-positive interneurons in the hippocampus, localizes to excitatory synapses that receive input from hippocampal pyramidal neurons [56,57•]. Elfn1 is thought to regulate presynaptic release through trans-synaptic recruitment of metabotropic glutamate receptor 7 (mGluR7) and GluK1/2-containing kainite receptors [56,57•]. Although it is unclear whether this trans-synaptic interaction is direct, it clearly represents an example of trans-synaptic modulation of neurotransmitter receptors by synaptic adhesion molecules.

Perspectives

Although evidence implicating synaptic cell adhesion molecules in the regulation of synaptic transmission and plasticity through direct or close interactions with neurotransmitter receptors is accumulating, additional and stronger evidence is required to make this emerging concept more compelling. Such evidence could be obtained through real-time imaging of close protein-protein interactions on the cell surface, or using biochemical methods, such as enzymatic biotinylation of nearby proteins. In addition, crystallographic or cryo-electron microscopic analyses of protein-protein complexes could be attempted. Lastly, functional consequences of *cis* interactions could be explored. For instance, conformational changes in neurotransmitter receptors induced by ligand binding may modulate the strength or specificity of trans-synaptic adhesions, as demonstrated by the observation that, upon NT-3 binding, the receptor tyrosine kinase TrkC associates more strongly with presynaptic PTPσ (a LAR-RPTP) [58•,59]. Conversely, and perhaps more interestingly, synaptic adhesions may regulate the pharmacological and/or kinetic properties of neurotransmitter receptors.

Conflict-of-interest statement

None.

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