The Physiology and Pathology of Synaptic Cell Adhesion Molecules

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1 Introduction

The brain was characterized by an enormous degree of complexity and diversity of neural networks, making it one of the most complicated organs. This complexity and diversity came from the vast numbers of neurons, but also from the variety of synapses where neurons pass electrical or chemical signals to other cells. In the brain, neurons recognized each other and form stable synaptic connections through synaptic cell adhesion molecules (CAMs). Synaptic CAMs served as the “glue” that connects the pre- and post-synaptic neurons. These CAMs played important roles in 1) the initial target recognition between pre- and post-synaptic neurons during synapse formation (Sanes & Yamagata, 2009; Williams et al., 2010) and 2) enrichment of synaptic components at pre- and post-synaptic terminals in the early stages of synapse development (Dalva et al., 2007; Chavis & Westbrook, 2001). During the later stages of synapse development and in mature synapses, CAMs also regulated synaptic structure and function. Alterations in CAMs led to changes in synaptic morphology and function, leading to dysfunction of neural circuits, whose function was highly reliant on precisely controlled cell-cell adhesions. Thus, it was not surprising that many CAMs were associated with many neuropsychiatric disorders including autism, Alzheimer’s disease (AD) and schizophrenia. For example, mutations in

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neurexins (Nrxs) and neuroligins (NLs) were found in patients with autism spectrum disorder (ASD) (Südhof, 2008) and Eph receptor alterations were highly related to AD (Chen et al., 2012).

Here we would like to summarize some of the known CAMs, their physiology, and their roles in brain pathologies involving protein-protein interactions at synapses.

2 CAMs between pre- & post- synapses

2.1 Neurexin and Neuroligin

2.1.1 Physiology

Nrxs, discovered as receptors for α-latrotoxin (Südhof, 2008), were type-I transmembrane proteins localized presynaptically (Berninghausen et al., 2007). There were three different genes coding for Nrxs (Nrx1, Nrx2, Nrx3) in mammals, expressing three α-Nrxs (long form) and three β-Nrxs (short form) due to two different promoters (Baudouin & Scheiffele, 2010). NLs were also type-I proteins found on the postsynaptic membrane. At least four (in mice and rats) or five (in humans) NL isoforms had been identified (Lisé and El-Husseini, 2006; Jamain et al., 2008). Nrxs and NLs interacted with each other with high affinity via their extracellular regions (Scheiffele et al., 2000; Comoletti et al., 2006). The crystal structures of Nrxs and NLs indicated that these extracellular parts formed a trans-synaptic complex in the synaptic cleft (Araç et al., 2007). The binding of Nrxs and NLs was dependent on the extracellular Ca²⁺ (Boucard et al., 2005; Chen et al., 2008; Ichtchenko et al., 1995; Nguyen and Südhof, 1997) and splicing sites on both proteins. Splicing sites 4 (SS4) on Nrxs and splice site B on NLs controlled the binding affinity between these two proteins (Boucard et al., 2005; Chih et al., 2006; Reissner et al., 2013; Ichtchenko et al., 1995). The α-Nrxs and β-Nrxs both bound to NL1, which lacked splice site B, and were independent of SS4 in Nrxs. In the presence of splice site B, NL1 bound only to β-Nrxs, but did not bind to α-Nrxs, without SS4 (Boucard et al., 2005). This apparent splice insert dependency of Nrx/NL interaction raised a splice-code hypothesis that specific pairings of Nrx/NL complex according to their roles at different location (Nam & Chen, 2005; Boucard et al., 2005; Ichtchenko et al., 1995; Chih et al., 2006).

The C-terminal of Nrxs and NLs interacted with intracellular scaffolding proteins to mediate pre- and post-synaptic differentiation and function. Nrxs bound CASK (Ca²⁺/calmodulin-activated Ser-Thr kinase), while CASK bound Velis/MALs proteins and Mints/X11 proteins in the presynaptic terminal (Butz et al., 1998; Borg et al., 1999). At postsynaptic sites, the NLs/Nrxs interaction caused an increase in PSD-95 clustering and the recruitment of postsynaptic NMDA (N-methyl-D-aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid) receptors (Nam & Chen, 2005; Heine et al., 2008; Chih et al., 2005; Barrow et al., 2009). Thus, the binding of Nrxs and NLs to their partners helped to align the presynaptic release machinery and postsynaptic receptors.

How exactly did the Nrx/NL complex function at synapses? In vitro studies suggested that Nrx/NL interactions promoted synapse formation. Expression of NLs in non-neuronal cells induced presynaptic differentiation at the contacting axons of cultured
neurons, whereas expressing β-Nrx in non-neuronal cells induced postsynaptic differentiation at the contacting dendrites of neurons (Gokce & Südhof, 2013). Overexpression of NLs in cultured neurons increased synapse numbers in a synapse-type and NL-isoform-dependent manner (Chih et al., 2004; Chih et al., 2005; Varoqueaux et al., 2004; Levinson et al., 2005). Suppression of NLs expression by RNA interference (RNAi) or disruption of Nrx/NL interaction consistently reduced the number of synapses (Chih et al., 2005; Levinson et al., 2005).

In vivo analysis from knockout (KO) mice showed that NLs and Nrxs were essential for synaptic maturation and function (Varoqueaux et al., 2006; Missler et al., 2003; Chubykin et al., 2007). The α-Nrx KO mice showed reduced neurotransmitter release (Missler et al., 2003). The KO of NL1 in mice reduced the synaptic strength at excitatory synapses, whereas the neurons lacking NL2 showed synaptic dysfunction at inhibitory synapses. The NL1-3 triple KO mice were neonatal lethal, and massive synaptic impairments had been observed from both in vitro and in situ analysis of these mice (Varoqueaux et al., 2006). In addition, Nrxs and NLs also contributed to the long-term plasticity of synapses via an activity-dependent mechanism (Varoqueaux et al., 2004; Jedlicka et al., 2013). Constitutive inclusion of an alternative SS4 in Nrx-3 impaired the recruitment of the postsynaptic AMPA receptor (AMPAR) in mice during NMDA receptor (NMDAR)-dependent LTP (Aoto et al., 2013).

2.1.2 Pathology

Nrxs and NLs had been genetically associated with ASDs. ASDs were characterized by impairments in social interaction and communication, and were stereotypic or repetitive behaviors (Südhof, 2008). ASDs altered the connection and organization of nerve cells and their synapses in the brain. Five ultra-rare structural variants, including a predicted splicing mutation, had been found in the α-Nrx1 gene from 116 Caucasian patients with autism but only one ultra-rare structural variant occurred in controls (Yan et al., 2008). The β-Nrx1 gene had two putative missense structural variants that were detected in four Caucasian patients with autism and not in healthy controls (Feng et al., 2006). More recently, Nrx2 disruption had also been implicated to the pathogenesis of ASD (Gauthier et al., 2011). In 2012, rare Nrx3 deletions in ASD had been reported (Vaags et al., 2012). Two base pair deletions in NL4 had been found in male autistic patients, resulting in altered interactions with β-Nrxs (Laumonnier et al., 2004). The R451C and R87W substitutions in the NL3 and NL4 genes, respectively, had been associated with autistic patients (Comoletti et al., 2004; Zhang et al., 2009). This R451C mutation impaired NL3 trafficking, resulting in lower cell surface expression of NL3 and largely reducing β-Nrx1 binding activity. The R451C knock-in (KI) mice showed increased spatial learning and impairments in social interactions, accompanied by specific increases in inhibitory synaptic transmission (Tabuchi et al., 2007). Unlike the R451C knock-in mice, a loss-of-function mutation in the mouse NL4 impaired reciprocal social interactions and communication (Jamain et al., 2008).

The interactions of Nrxs and NLs not only controlled the balance between excita-
tory and inhibitory neurotransmitter release, but they also functioned in β-amyloid metabolism which was a key process in AD pathogenesis (Sindi et al., 2014). A genome-wide association study compared 1256 SNPs in Nrx1, Nrx2, Nrx3, and NL1 genes among 3009 AD patients and 3006 controls respectively, and identified AD susceptibility may increase by Nrx3 in males (Martinez-Mir et al., 2013). The NLs had been implicated a role in Aβ accumulation in AD (Scholl & Scheiffele, 2003). Recently, NL1 but not NL2 was reported to display a high affinity interaction with oligomeric forms of Aβ via its extracellular domain (Dinamarca et al., 2011; Dinamarca et al., 2012), thus indicating that NL1 stabilized oligomeric assemblies of Aβ in the glutamatergic synapse postsynaptically. Processing of Nrx3β was altered by the introduction of several PS1 mutations that cause early-onset familial AD (Bot et al., 2011). In hippocampal neurons, accumulation of Nrx C-terminal fragments was associated with the inhibition of presenilin/γ-secretase (Saura et al., 2011).

Nrxs and NLs had also been associated with schizophrenia. A whole-genome analysis identified a deletion in two affected siblings that disrupted Nrx1 (Kirov et al., 2008). Nrx1α exonic deletions had since been found in three patients with paranoid-type schizophrenia (Vrijenhoek et al., 2008). A later study of 2977 schizophrenia patients and 33746 controls examined Nrx1 for copy number variants (CNVs) and identified 66 deletions and 5 duplications in NRXN1 from the patients, confirming that Nrx1 was a risk gene for schizophrenia (Rujescu et al., 2009). Nrx3 was also shown to contribute to the degree of nicotine dependence in patients with schizophrenia (Novak et al., 2009). A loss-of-function mutation R215H in NL2 was associated with GABAergic synapse formation (Sun et al., 2011). Systematic screening had also confirmed the key role of NL4 in schizophrenia (Sand et al., 2006).

Mutations in Nrxs and NLs had been found in epilepsy. Biallelic Nrx1 deletions resulted in a severe recessive mental retardation syndrome and early onset epilepsy (Harrison et al., 2011). Furthermore, a screen in 1569 patients with idiopathic generalized epilepsy (IGE) and 6201 controls had revealed that exon-disrupting deletions of Nrx1 increased the risk of IGE syndromes (Møller et al., 2013). Furthermore, the Nrx2 expression level was elevated in the dentate gyrus in kainate- and pentylenetetrazole-induced seizures, whereas Nrx1 and 3 expression were observed no specific changes (Górecki et al., 1999). Postsynaptically, a partial NL1 deletion was found by genomic microarray in a child with seizure disorder (Millson et al., 2012). Moreover, mutations in NL4 have been associated with seizures because of its function in development of synaptic structures (Laumonnier et al., 2004).

2.2 N-cadherin/β-catenin

2.2.1 Physiology

Cadherins were transmembrane proteins containing an extracellular domain with a repeated “cadherin motif” or “cadherin repeat” sequence (Takeichi, 1988). There were more than 100 members in humans, grouping into classic cadherins and protocadherins. N-cadherin was the most abundant cadherin in excitatory synapses with a highly conserved cytoplasmic domain binding β-catenin and p120-catenin (Takeichi, 1988; Takeichi, 2007).
N-cadherin mediated Ca\(^{2+}\)-dependent homophilic protein interactions (Hirano and Takeichi, 2012). During synaptic maturation, the location of N-cadherin shifted from the cleft to the outer rims of the active zone (Uchida et al., 1996; Fannon & Colman, 1996). Classical cadherins bound to β-catenin at its central armadillo repeat domain, and β-catenin interacted with the actin cytoskeleton through α-catenin. Cultured neurons lacking N-cadherin or β-catenin showed reduced spine number, more filopodia-like spines, thinner spines, or spines with smaller heads (Mendez et al., 2010; Saglietti et al., 2007; Okuda et al., 2007). Suppression of β-catenin expression decreased the amplitude but not the frequency of spontaneous excitatory synaptic currents in cultures. Similar treatment impaired synaptic scaling induced by a two-day blockade of neural activity with tetrodotoxin or bicuculline (Okuda et al., 2007). Conditional KO mice showed reductions in the stability of coordinated spine enlargement and LTP in the CA1 region (Bozdagi et al., 2010). The LTP-induced long-term stabilization of synapses was also impaired in expression mutants or knockdown of N-cadherin (Mendez et al., 2010). Cooperation between NL1 and N-cadherin had recently been revealed that promotes the formation of glutamatergic synapses and controls vesicle clustering at nascent synapses (Aiga et al., 2011; Stan et al., 2010).

Beyond the postsynaptic functions, N-cadherin and β-catenin were also involved in regulating transmitter release. Overexpression of the extracellular domain of N-cadherin increased the frequency of miniature excitatory postsynaptic currents (mEPSCs) (Saglietti et al., 2007). The absence of N-cadherin dramatically impaired short-term plasticity from facilitation to depression at glutamatergic synapses (Jüngling et al., 2006). Mice deficient in β-catenin showed a reduction in the number of reserved pool vesicles and impairment in their response to prolonged repetitive stimulation (Bamji et al., 2003). Axonal knockdown β-catenin had been shown to affect the dynamics of vesicle release (Taylor et al., 2013). Therefore, N-cadherin and β-catenin were structurally and functionally linked in the processes of synapse stabilization as well as in the processes of synaptic transmission from both sides of the synapses.

### 2.2.2 Pathology

Many cadherin genes were found to be genetically associated with ASD. A genome-wide recurrent de novo analysis included the CDH13 gene in rare copy-number variations in autism families (Sanders et al., 2011). A scan for the IQ discrepancy in ASD patients revealed a unique truncated cadherin, cadherin 13 (CDH13) (Chapman et al., 2011). The cadherin 15 (CDH15) gene had been found in a sporadic patient with autism (Willemse et al., 2010). Cadherin 8 (CDH8), which presents in the developing human cortex, was reported as an autism susceptibility gene in other recent research (Pagnamenta et al., 2011). Moreover, variants of cadherin 11 (CDH11), cadherin 10 (CDH10) and cadherin 9 (CDH9) had been identified in ASD (Wang et al., 2009; Crepel et al., 2014). Protocadherin 10 (PCDH10), which regulates neuronal activity and controls axon outgrowth, was one potential candidate gene for autism (Morrow et al., 2008; Uemura et al., 2007). Protocadherin 19 (PCDH19) mutations had also been associated with ASD recently (van Harsssel et al., 2013).
PCDH11 had been implicated to associate with hominid speciation, language acquisition and the sexual dimorphism of brain asymmetry, thereby functioning in schizophrenia as predicted (Crow 2002). Another study was observed an increase of PCDH17 expression in schizophrenia patients in Brodmann’s area 46 (Dean et al., 2007). Furthermore, a deletion between CDH12 and CDH18 genes on 5p14 had been identified in a monozygotic twin pair discordant for schizophrenia (Singh et al., 2010). Disrupted in schizophrenia 1 (DISC1), a promising gene in schizophrenia, had been reported to regulate N-cadherin expression at the cell membrane in primary neurons, thus indicating the linkage between cadherin and schizophrenia (Hattori et al., 2010).

The contribution of cadherins in epilepsy had also been reported. In 2008, PCDH19 was first implicated in epilepsy or mental retardation (Dibbens et al., 2008). Later on, in two unrelated girls with seizures, larger genomic deletions comprising PCDH19 had been identified (Vincent et al., 2012). De novo PCDH19 mutations in epilepsy female restricted mental retardation syndrome had implicated that PCDH19 was a major gene for epilepsy (Jamal et al., 2010). Furthermore, the gonadal mosaicism of a PCDH19 mutation in a parent could be an important mechanism as reported (Dibbens et al., 2011).

2.3 Ephrins and Eph Receptors

2.3.1 Physiology

Eph receptors (EphA and B) was a family of receptor tyrosine kinases, containing an intracellular tyrosine kinase domain and a PDZ-binding motif (Kullander & Klein, 2002; Himanen, 2012). EphA receptors bound to glycosylphosphatidylinositol(GPI)-anchored proteins ephrinA, while EphB receptors bound to transmembrane ephrinB ligands. Eph–ephrin interaction also could mediate signal transductions between the receptor-expressing cell and the ligand-expressing cell in a bidirectional manner (Daar, 2012). Eph and ephrin expressions were found at both the pre- and postsynaptic membranes, and also, at least some isoforms, on astrocytes (Klein, 2009). Eph and ephrin signaling was involved in many regulation processes, including axon guidance and cell migration (Davy and Soriano, 2005; Xu and Henkemeyer, 2012; Egea & Klein, 2007). The activation of cyclin-dependent kinase 5 (Cdk5) and ephexin1 by ephrin-A1 promoted EphA4-dependent spine retraction, followed by a scaling-down of excitatory synaptic strength (Fu et al., 2007; Peng et al., 2013). EphA4 inhibited integrin signaling pathways (Bourgin et al., 2007), and EphA4 activation by ephrin-A3 reduced tyrosine phosphorylation of the scaffolding protein Crk-associated substrate (Cas), the tyrosine kinase focal adhesion kinase (FAK), and proline-rich tyrosine kinase 2 (Pyk2) while down-regulating the association of Cas with the Src family kinase Fyn and the adaptor Crk. The EphA4 receptor linked with spine-associated RapGAP (SPAR), which was activated by GTPase, regulated the activities of the Rap GTPase, and therefore neuronal morphology (Richter et al., 2007, Clifford et al., 2011). EphA–ephrinA signaling played important roles in the synaptic strength and plasticity in addition to regulating cell morphology (Hruska and Dalva, 2012). The activation of EphA4 decreased synaptic and surface GluR1, and attenuates mEPSCs amplitude (Fu et al., 2011). The Eph4-deficient hippocampal CA1 region showed altered dendritic spine
maturation (Murai et al., 2003), impaired LTP and long-term depression (LTD) (Grunwald et al., 2004). Postsynaptic expression of EphA4 and its ligand ephrin-A3 in astrocytes mediated neuron-glial interactions, which were also required for LTP expression at CA3-CA1 synapses in the hippocampus (Filosa et al., 2009).

EphB–ephrinB signaling promoted excitatory synaptogenesis. EphrinB binding to the EphB receptor elevated excitatory synapse formation via degradation of Ephexin5, a RhoA guanine nucleotide exchange factor (Margolis et al., 2010). Suppression of the expression of the EphB receptor reduced excitatory synapses and the clustering of NMDARs and AMPARs, and altered dendritic spine formation as well (Henkemeyer et al., 2003). The PDZ domain of EphB2 also controlled localization of the AMPA-type glutamate receptor, while the ephrin binding domain of EphB2 initiated presynaptic differentiation (Kayser et al., 2006). EphBs were thought to control synaptogenesis by associating the motility of filopodia and the binding ability of ephrin (Kayser et al., 2008). The Rho-GEF kalirin, Rac1, and its effector PAK were involved in the ephrinB-EphB signaling pathway during spine development (Penzes et al., 2003). Suppression of EphB2 expression by siRNA in the postsynaptic neuron reduced mEPSCs frequency in cultured cortical neurons (Kayser et al., 2006). EphB2 deficient mice showed reduced NMDA-mediated synaptic responses and impaired LTP (Henderson et al., 2001), which could be rescued by expressing C-terminal truncated EphB2 (Grunwald et al., 2001). The tyrosine phosphorylation sites in ephrinB2 were necessary for maintaining LTP but not LTD, whereas the C-terminal PDZ interaction site was required for both (Bouzioukh et al., 2007). EphrinB3-deficient mice showed reduced amplitude of mEPSCs, but increased NMDA/AMPA ratios in CA1 neurons (Antion et al., 2010). Blocking the interaction between EphRs and the PDZ protein GRIP or extracellular application of soluble forms of B-ephrins (presynaptic ligands for the EphB receptors) reduced mossy fiber LTPs in the CA3 region, suggesting a requirement for trans-synaptic interactions between EphB receptors and B-ephrins (Contractor et al., 2002). Replacement of the cytoplasmic C-terminal signaling domain of the ephrinB3 with β-galactosidase selectively blocked mossy fiber LTPs (Armstrong et al., 2006). Therefore, trans-synaptic ephrin–Eph adhesion regulated synaptic maturation and plasticity in a bidirectional way in both developing and adult brains.

2.3.2 Pathology

Copy number variations in ephrinA5 were associated with schizophrenia in 2006 (Wilson et al., 2006). EphrinB2 was suggested to be a schizophrenia susceptibility gene on chromosome 13q33 in the Han Chinese population (Zhang et al., 2010). Loss of function of ephrinBs blocked the phosphorylation of Dab1 by Reelin, which was associated with epilepsy, schizophrenia and AD (Sentürk et al., 2011). Morphological abnormalities of spines were closely associated with mental retardation and schizophrenia (Wong & Guo, 2013), where ephrin-Eph receptor signaling was indicated in these processes via the regulation of Rho GTPase (Irie & Yamaguchi, 2004). The up-regulation of EphA10 and ephrinA4 were observed after status epilepticus (SE), suggesting their involvement in the
pilocarpine-induced epileptogenesis (Xia et al., 2013). Moreover, receptor EphA5 and ligand ephrin-A3 functionally retarded the development of behavioral seizures induced by perforant path stimulation (Xu et al., 2003).

Dysfunctions in Ephs and ephrins signaling pathways had been found to be involved in the pathogenesis of AD (Chen et al., 2012). In AD model mice, abnormal expression of EphA4 and EphB2 were detected much earlier than the decrease in synaptic proteins and the onset of cognitive decline (Simón et al., 2009), indicating that Eph receptors may act as early stage markers of AD. EphA4 had been reported to be one of γ-secretase’s substrates (Inoue et al., 2009), the key enzyme that cleaved amyloid precursor protein (APP) to generate Aβ. However, familial mutations in PS1 in AD patients slowed down this process of EphA4, resulting in a reduced formation of dendritic spines. The amount of Rac1 decreased dramatically corresponding with the level of EphA4-ICD in AD patients (Matsui et al., 2012). The processing of the EphB2 receptor was also regulated by γ-secretase and inhibited by familial AD mutations of PS1 (Litterst et al., 2007). The Aβ peptide bound to the extracellular domain of EphB2 and triggers EphB2 degradation in the proteasome, leading to a decrease in surface and total EphB2 in neurons. A lack of EphB2 expression caused neuronal dysfunction and memory impairments through the NMDAR dependent pathway (Cissé et al., 2011). More interestingly, increasing EphB2 level could reverse these impairments.

With limited research results, Eph and ephrin were also considered as potential risking genes in ASD. Decreased expression levels of EphrinB3 were identified in the autistic group than in the controls by real-time reverse-transcriptase PCR (Suda et al., 2011). EphB/Ephexin5 signaling during the development of synapses affected cognitive function in ASD in another study (Margolis et al., 2010). However, the association still remained to be confirmed.

2.4 NCAM

2.4.1 Physiology

The neural cell adhesion molecule (NCAM) was a glycoprotein expressed in both the pre- and postsynaptic membranes. The extracellular part of NCAM had five Ig domains that bound to NCAM, and two fibronectin type III (FNIII) domains related to neurite outgrowth. At least 27 alternatively spliced NCAM mRNAs were present in rat brains (Reyes et al., 1991). Numerous studies had shown that NCAM regulated synapse formation, maturation, and function through homo- and heterophilic interactions (Bukalo and Dityatev, 2012). The ablation of NCAM reduced the number of synapses (Dityatev et al., 2000). NCAM associated with the postsynaptic spectrin-based scaffold to form a complex that was responsible for recruiting NMDARs and Ca\(^{2+}\)/calmodulin-dependent protein kinase II alpha (CaMKIIalpha) to synapses, and was important for NMDAR-dependent LTP and LTD (Sytnyk et al., 2006; Bukalo et al., 2004; Muller et al., 1996). NCAM also had presynaptic functions (Rafuse et al., 2000; Polo-Parada et al., 2001). Deleting NCAM at the neuromuscular junction (NMJ) led to smaller NMJs with impaired accumulation of presynaptic proteins, reduced number of docked vesicles, and altered paired-pulse facilitation.
The C-terminal of NCAM played a key role in maintaining effective transmission via a pathway involving myosin light chain kinase (MLCK) and probably MLC and myosin II (Polo-Parada et al., 2005). Chromaffin cells showed impairment of catecholamine granule trafficking in the absence of NCAM, resulting in a reduced rate of granule fusion under physiological stimulation. These findings suggested that NCAM was involved in vesicle recycling in both neuronal and endocrine cells (Chan et al., 2005).

2.4.2 Pathology

NCAM had long been implicated in various neurological disorders. Embryonic NCAM dysfunction was linked with schizophrenia more than 20 years ago (Conrad & Scheibel, 1987). Unlike the case of ASD patients (Plioplys et al., 1990), NCAM levels in serum and cerebrospinal fluid (CSF) increased in schizophrenic patients (Lyons et al., 1988; Poltorak et al., 1996). Interestingly, the hippocampus of schizophrenic patients showed a reduction of polysialylated NCAM (PSA-NCAM) (Barbeau et al., 1995). An increase in the cytosolic isoform of NCAM had also been observed in the hippocampus of schizophrenia patients (Vawter et al., 1998b). An increase in the cytosolic NCAM/synaptophysin ratio was demonstrated in the hippocampus of schizophrenia patients (Vawter et al., 1999). Similarly, the cingulate cortex of schizophrenics also showed elevated NCAM/synaptophysin ratios (Honer et al., 1997). In another study, ChAT/NCAM ratios were reduced in the frontal and temporal cortices of AD patients as compared to controls (Aisa et al., 2010). Besides schizophrenia, the levels of NCAM serum fragment had also been found significantly decreased in autistic patients compared with age-matched controls (Plioplys et al., 1990).

The cytosolic NCAM isoform (cN-CAM) underwent a tremendous reduction in BP disorder (-140%) in hippocampal tissue (Vawter, 2000). Quantitative western blot analysis had revealed that cytosolic NCAM protein and mRNA levels increased in the hippocampus and prefrontal cortex in patients (Vawter et al., 1998b). Interestingly, NCAM infusion reduced astrocyte division, while BP disorder decreased glia numbers (Krushel et al., 1995; Ongür et al., 1998). Recently, novel variants of ST8SIA2, a BP disorder related gene, in its region of interaction with NCAM1 had been described in 48 Caucasian cases with BP disorder (Shaw et al., 2014).

Interestingly, reduced CSF-NCAM-1 concentration was found in either epileptic group compared to the control group or in the drug-refractory epilepsy group compared to the drug-effective epilepsy group, therefore indicating CSF-NCAM-1 as a potential biomarker for epilepsy (Wang et al., 2012). Approximately 10 years ago, a largely increased number of highly PSA-NCAM positive cells in the bilateral dentate gyrus were observed in rats with repeated exposure to amygdaloid kindled generalized seizures (Sato et al., 2003). Later, degeneration of CA3 neurons and dentate gyrus granule cells in the epileptic focus and early onset of focal seizures were induced by the inactivation of PSA-NCAM by endoneuraminidase (EndoN) administration into the contralateral ventricle of kainic acid-treated mice, suggesting that PSA-NCAM mediated GDNF signaling to transport neuroprotective signals into the lesioned hippocampus (Duveau & Fritschy, 2010). Planexin, a NCAM-derived peptide that mimicked trans-homophilic NCAM interaction,
represented protective roles for immature neurons in vivo after status epilepticus (Zellinger et al., 2011).

2.5 L1-CAMS

2.5.1 Physiology

L1-CAMS was a family of transmembrane proteins, with at least four members in vertebrates: L1CAM, close homolog of L1 (CHL1), NgCAM-related cell adhesion molecule (NrCAM), and neurofascin. The L1-CAMS were involved in many neuronal functions, including axonal guidance, neurite outgrowth and fasciculation, and cell migration (Chang et al., 1987; Lindner et al., 1983; Fischer et al., 1986; Maness & Schachner, 2007). L1-deficient mice showed a significant reduction in frequency of miniature inhibitory postsynaptic currents (mIPSCs) and a reduction in the amplitude of putative unitary IPSCs (Saghatelyan et al., 2004). However, the conditional inactivation of L1 in the adult brain increased the basal excitatory synaptic transmission and decreases anxiety in the open field, which differed from the response seen in L1 constitutive KO mice (Law et al., 2003). The ankyrin-mediated localization of L1CAMs was implicated in the organization of GABAergic synapses in Purkinje neurons (Ango et al., 2004). Loss of the L1/ankyrin interaction impaired branching of GABAergic interneurons and specifically reduced the number of perisomatic synapses (Guan & Maness, 2010).

CHL1 was implicated in synaptogenesis of inhibitory interneurons, although it functioned differently from L1. The hippocampal CA1 region in juvenile CHL1 mutant mice showed an increase in IPSCs and a decrease in LTP at CA3-CA1 synapses. The length and linear density of active zones and the numbers of perisomatic puncta containing inhibitory axonal markers were also increased (Nikonenko et al., 2006). CHL1 also maintained inhibitory synapses between stellate axons and Purkinje dendrites, indicating a role in connecting glia and neuron (Ango et al., 2008). CHL1-deficient mice showed enhancement of basal synaptic transmission in the lateral and medial perforant path projections to the dentate gyrus, while reactivity to environmental stimuli and social behaviors were altered (Morellini et al., 2007).

2.5.2 Pathology

L1-CAMS was largely increased in the CSF of AD patients, independent of age and gender (Strekalova et al., 2006). CHL1 was detected to co-localize with β-site APP-cleaving enzyme (BACE1) in the terminals of hippocampal mossy fibers, olfactory sensory neuron axons and growth cones of primary hippocampal neurons (Hitt et al., 2012) Moreover, L1-CAMS and CHL1 were cleaved by BACE1 physiologically (Zhou et al., 2012). After four months of L1-CAMS injection into adult AD model mice, Aβ plaque load, levels of Aβ42, Aβ42/40 ratio, and astrogliosis were reduced and densities of inhibitory synapses on pyramidal cells in the hippocampus were increased as compared to control, implying L1-CAMS as a candidate to ameliorate the pathology of AD (Djogo et al., 2013).

In 2002, three novel L1-CAM variations were determined in exon 18, intron 11, and
intron 25 from Japanese schizophrenic patients (Kurumaji et al., 2001). A missense polymorphism of CHL1 in the signal peptide region was observed in 24 Japanese patients with schizophrenia in another study (Sakurai et al., 2002). This positive association between CHL1 gene and schizophrenia was confirmed by further analyzing SNPs in the gene in the Han Chinese population (Chen et al., 2005). L1-CAM was also suggested to regulate schizophrenia with NCAM. Increased N-CAM and decreased L1-CAM antigen in CSF of schizophrenia patients were reported (Poltorak et al., 1997). The correlation between expression levels of L1-CAM and NCAM had been impaired in schizophrenia patients (Vawter et al., 1998a).

2.6 Nectins

2.6.1 Physiology

Nectins (Nectin 1-4) were Ca\(^{2+}\)-independent Ig-CAMs (Takai et al., 2003). Nectins form homo-cis dimers followed by \textit{trans}-interaction in an either heterophilic or homophilic manner through their extracellular domains (Mizoguchi et al., 2002). Nectins interacted with actin-binding protein afadin, an \(\alpha\)-catenin interact protein, through the C-terminal PDZ binding domain (Giatzoglou et al., 2009). Similar to N-cadherin, Nectin-1 mainly located at matured excitatory synapses (Lim et al., 2008). The CA3 area of the adult hippocampus showed an asymmetric localization of Nectin-1 and -3 at the pre- and postsynaptic sides. Reduction in nectin-based adhesion led to a decrease in synapse size and an accompanying increase in synapse number, suggesting a role of the nectin-afadin system in synaptogenesis (Mizoguchi et al., 2002). Mice deficient in either Nectin-1 or Nectin-3 showed a reduced number of puncta adherentia junctions (PAJs) and abnormal mossy fiber trajectory (Honda et al., 2006). Conversely, conditional inactivation of afadin reduced the signal of nectins, N-cadherin, \(\beta\)-catenin and disrupts PAJs, whereas it increased the numbers of perforated synapses. Thus, the nectin-afadin interaction appeared to participate in synaptic remodeling by regulating the stability of synaptic junctions (Majima et al., 2009).

The nectin-afadin complex also interacted with many synaptic proteins that function at synapses. The synaptic scaffolding molecule (S-SCAM) had been reported to co-localize with nectins via the PDZ-binding domain of the latter (Yamada et al., 2003). S-SCAM was involved in the presynaptic vesicle clustering mediated by N-cadherin and NL-1 cooperation (Stan et al., 2010). Thus, several CAMs could function either separately or synergistically in synapse maturation (Sakisaka et al., 2007).

2.6.2 Pathology

Nectin-1 and -3 served as substrates for PS/\(\gamma\)-secretase proteolytic activity (Kim et al., 2002; Kim et al., 2011). Recently, an association between reduced expression of Nectin-3 in the stratum lacunosum moleculare and the triggering of tauopathy had been suggested (Maurin et al., 2013). In AD, the excessive production of A\(\beta\) peptide could be prevent by
ADAM10-mediated α-secretase activity toward APP (Postina et al., 2004). Reduced expression of Nectin-1 had been revealed in ADAM10 conditional KO mice recently, suggesting the involvement of Nectin-1 in AD (Prox et al., 2013). However, more investigations would be necessary to uncover the mechanisms of nectins in diseases.

2.7 Contactins

2.7.1 Physiology

Contactins (CNTN) were a group of GPI-linked Ig-CAMs containing six N-terminal Ig-like domains and four fibronectin III-like domains. Six members were recognized in the CNTN family: CNTN-1, CNTN-2/TAG-1, CNTN-3/BIG-1, CNTN-4/BIG-2, CNTN-5/NB2, and CNTN-6/NB3. Both CNTN-1 and CNTN-2 were involved in axon growth and guidance (Buttiglione et al., 1996; Perrin et al., 2001). CNTNs may therefore function at both pre- and postsynaptic sites, although the mechanisms remain unclear. CNTN-6 was prominently expressed presynaptically in the developing nervous system. CNTN-6 deficient mice showed increased numbers of immature granule cells in the internal granule cell layer (IGL) (Sakurai et al., 2009) and a decreased density of excitatory but not inhibitory synapse density (Sakurai et al., 2010). CNTN 4 and 5 were also involved in synapse differentiation, especially at early stages (Mercati et al., 2013). Unlike the presynaptic localization of CNTN-6, CNTN-1 had been detected in PSD in CA1 pyramidal cells. Inactivation of CNTN-1 expression affected PPF and NMDA receptor-dependent LTD, without altering synaptic morphology (Murai et al., 2002). In adult mice, overexpression of contactin increased LTP as well as spatial and object recognition memory (Puzzo et al., 2013).

2.7.2 Pathology

CNTN was another family of CAMs heavily related to ASD. CNTN4, CNTN5, and CNTN6 were suggested as potential risking genes. For example, a deletion at the 5' end of the CNTN4 gene had been identified in an autism patient (Cottrell et al., 2011). Disruption of the CNTN4 gene caused 3p deletion syndrome and impairs normal CNS development (Fernandez et al., 2004). Rare copy number variations (CNVs) in CNTN4 had been reported to influence autism susceptibility in Asian populations (Guo et al., 2012). A loss of CNTN5 co-segregated with autism in one family, as well as one de novo CNV and one non-cosegregating inherited CNV in CNTN6, was found in a Utrecht cohort (van Daalen et al., 2011). Mice models based on clinic observations on CNTN had been generated (Momoi et al., 2009), and more investigations were needed to reveal the underlying mechanism between these molecules and ASD.

A homozygous mutation of CNTNAP2 in Old Order Amish children with focal epilepsy was reported (Strauss et al., 2006). The CNTNAP2 gene had emerged as a genetic risk in both autism and schizophrenia (Burbach & van der Zwaag, 2009). CNTN2, together with CNTN associated protein-like 2 (CNTNAP2) were required for maintaining voltage-gated potassium channels at the juxtaparanodal region, was reported to be associated with seizures as well (Stogmann et al., 2013).
A downstream of CNTN2 that was linked to three conserved SNPs in the 3'-UTR of CNTN2 was significant following random effects meta-analysis, thus suggesting CNTN2 as a new biomarker in AD (Medway et al., 2010). A recent study demonstrated CNTN2 levels were decreased in AD brain samples, whereas BACE1 levels increased in the same samples, therefore indicating CNTN2 as a physiological substrate for BACE1 and presenting the possibility that CNTN2 regulated AD via BACE1-mediated pathway (Gautam et al., 2014).

2.8 LRRTMs

2.8.1 Physiology

The LRRTM (LRRTM 1-4) proteins were a group of PSD-enriched type-I transmembrane proteins that contained extracellular leucine rich repeats and a short cytoplasmic tail (Laurén et al., 2003). Non-neuronal cells expressing LRRTMs induced presynaptic differentiation when cocultured with neurons (Linhoff et al., 2009). Knocking down LRRTM2 reduced, whereas overexpression of LRRTM2 increased, the number of excitatory synapses, but not inhibitory synapses in a cultured system (de Wit et al., 2009; Ko et al., 2009). The extracellular LRR domain of LRRTM2 mediated this excitatory presynaptic differentiation (Siddiqui et al., 2013). LRRTM4-Null dentate gyrus granule cells showed reduced numbers of excitatory synapses and impairments in both mEPSCs and action-potential-evoked EPSCs (Siddiqui et al., 2013). LRRTM2 bound Nrxs, and the LRRTM-Nrx interaction played a key role in regulating excitatory synapse formation (Ko et al., 2009). Single, double, or triple knockdowns of LRRTM1, LRRTM2 and NL-3 in cultured hippocampal neurons had no effect on synapse numbers, whereas triple knockdown (TKD) of two LRRTMs and NL-3 in cultured NL-1 KO neurons led to a ~40% reduction in excitatory synapses (Ko et al., 2011). Knockdown of LRRTM1 and LRRTM2 selectively reduced AMPA receptor-mediated synaptic currents, while knockdown of both LRRTMs, together with NL-3, reduced AMPAR and NMDAR-mediated currents in NL-1 deficiency mice in the synapses forming stage (Soler-Llavina et al., 2011), suggesting a functional redundancy between NLs and LRRTMs in developing excitatory synapses. In mature synapses, LRRTMs acted in a NLs-independent manner. For example, inactivation of LRRTM expression, starting from P21 to P35-40, had no effect on excitatory synaptic transmission, while KO of NL1 reduced the NMDAR/AMPAR ratio at similar ages (Soler-Llavina et al., 2011). LRRTM1-KO mice exhibited an increase in the size of presynaptic terminals in the hippocampal CA1 region, and an extraordinary phenotype where the animals showed avoidance of small enclosures, an increase in social interaction, and a decrease in nest building (Linhoff et al., 2009; Voikar et al., 2013). In acute hippocampal slices, double knockdown of LRRTM1 and LRRTM2 impaired LTP, which could be rescued by expression of the LRRTM2 extracellular domain (Soler-Llavina et al., 2013). These results indicated that LRRTMs not only played a key role in synapse development and maturation, but they were also directly involved in synaptic transmission and more complicated behaviors.
2.8.2 Pathology

LRRTMs had been implicated in several neurologic disorders by limited evidences. LRRTM1, considered the first potential genetic influence on human handedness and first putative genetic effect on variability in human brain asymmetry, was associated with schizophrenia (Francks et al., 2007). LRRTM3 was reported to promote APP processing by β-site APP-cleaving enzyme 1 (BACE1) (Majercak et al., 2006). LRRTM3 bound to presenilin-1 and is implicated in the clearance of Aβ deposition (Edwards et al., 2009). Moreover, a family-based association study implicated LRRTM3 in ASD susceptibility (Sousa et al., 2010).

2.9 SynCAM

2.9.1 Physiology

Synaptic cell adhesion molecules (SynCAM1-4) was a family of type-1 transmembrane proteins with three extracellular Ig-like domains (Thomas et al., 2008). All SynCAMs were highly enriched in the brain, and SynCAM 1 was also found in the lung and testis (Fogel et al., 2007). Like the NLs, SynCAM recruited synaptic proteins and promoted neuron differentiation presynaptically in co-culture assays (Sara et al., 2005). During synapse development, SynCAMs were located in both pre- and postsynaptic compartments and underwent homo- and heterophilic adhesive interactions. SynCAMs also bound many other proteins via the C-terminal domain. SynCAMs bound to the scaffold proteins syntenin and CASK via the C-terminal PDZ domain, and recruited CASK to the plasma membrane (Biederer et al., 2002). SynCAM1 also bound to protein 4.1B intracellularly, which, in turn, recruited NMDAR to the postsynaptic plasma membrane, resulting in an increase in the frequency of NMDAR-mediated mEPSCs in cultured hippocampal neurons (Hoy et al., 2009). In vivo studies had revealed a role for SynCAM 1 in the regulation of synapse numbers and plasticity. Mouse neurons formed fewer excitatory synapses in the absence of SynCAM 1 (Giza et al., 2013), while overexpression of SynCAM 1 resulted in an increase in excitatory synapse number. The LTD and spatial learning were also regulated by the expression of SynCAM 1 (Robbins et al., 2010).

2.9.2 Pathology

The involvement of SynCAM in diseases was still not well investigated. The intracellular domain of APP could form a complex with Mint1 and Cask and be replaced by SynCAM sequences, thus implicating a possible involvement of SynCAM in AD (Wang et al., 2009). In a culture system, more polysialylation of SynCAM 1 occured in the presence of ST8SIA2, a gene associated with schizophrenia, suggesting SynCAM may be involved in schizophrenia through an indirect manner (Rollenhagen et al., 2012). Thereby more investigations would be needed in this area.
2.10 SALMs

2.10.1 Physiology

Synaptic adhesion-like molecules (SALMs) were a newly discovered family of adhesion molecules with at least five members. SALMs 1-3 contained an extracellular region consisting of a leucine-rich repeat (LRR), a fibronectin type III domain, Ig-like domains, a transmembrane domain, and a C-terminal PDZ-binding motif that interacted with PSD-95. SALMs 4 and 5 lacked the PDZ-binding domain (Seabold et al., 2008). SALMs 1-3 bound to each other, while SALMs 4 and 5 formed homomeric complexes. Transfected heterologous cells showed that only SALMs 4 and 5 formed homomeric associations mediated by the extracellular N terminus (Seabold et al., 2008). SALMs bound to many synaptic proteins. SALM1 interacted with postsynaptic NMDA receptors, possibly through the extracellular or transmembrane regions, and with scaffold proteins PSD-95, SAP 97, and SAP 102 via the PDZ-binding domain. Immunostaining experiments showed that SALM1 recruited PSD-95 and NMDA receptors to postsynaptic sites (Wang et al., 2006; Seabold et al., 2012). SALM2 interacted with PSD-95 and other postsynaptic proteins, including guanylate kinase-associated protein (GKAP) and AMPA receptors (Ko et al., 2006). SALM3 and SALM5 recruited vesicular glutamate transporter (VGlut) and vesicular GABA transporter (VGAT), the presynaptic vesicle protein synaptophysin, and the presynaptic active zone protein Piccolo (Mah et al., 2010). Functional assays revealed that overexpression of SALMs promoted neurite outgrowth in cultured neurons (Wang et al., 2008a). Suppression of SALM2 expression decreased the number of excitatory synapses and dendritic spines, and selectively reduced the frequency but not the amplitude of mEPSCs (Ko et al., 2006). Knockdown of SALM5 reduced both spontaneous excitatory and inhibitory synaptic transmissions, affecting both frequency and amplitude (Mah et al., 2010). Thus, SALMs regulated excitatory and inhibitory synapse function through distinct mechanisms.

2.10.2 Pathology

The reports of SALMs involvement in neurologic disorders were also quite limited now. In a 19-year-old severely autistic and mentally retarded girl, SALM5 was observed to have a 10-fold decreased expression compared to control in fibroblasts (de Bruijn et al., 2010). In another study, SALM5 had been suggested in familial schizophrenia by using rare copy number variant and linkage scans (Xu et al., 2009).

2.11 NGLs

2.11.1 Physiology

NGL (netrin-G ligand) proteins were a family of LRR-containing CAMs with three members: NGL1-3. NGLs were mainly located postsynaptically at excitatory synapses. NGL-1 and -2 bound to netrin-G1 and netrin-G2 through their cytosolic tails in an isoform-specific manner (Kim et al., 2006). The LRR domain of NGL-3 interacted with presynaptic
LAR protein to induce synapse formation (Kwon et al., 2010). PTPσ interacted with NGL-3 to promote a bidirectional synapse formation, whereas PTPδ-NGL-3 interaction induced presynaptic differentiation in a unidirectional manner. Receptor tyrosine phosphatases LAR, the NGL-3 binding partner, was also required for maintaining the number of excitatory synapses and dendritic spines (Dunah et al., 2005). Overexpression NGL-2 in cultured neurons showed increased number of dendritic protrusions. Suppression or competitive inhibition of NGL-2 reduced the number of excitatory synapses (Kim et al., 2006) and decreased EPSCs (Kim et al., 2006; Woo et al., 2009). In the retina, loss of NGL-2 impaired branching of horizontal cell axons that stratified in the outer plexiform layer and reduced synapse formation between horizontal cell axons and rods (Soto et al., 2013). LAR knockdown reduced both the amplitude and frequency of mEPSCs (Dunah et al., 2005). Thus, like other cell adhesion molecules, NGLs were also involved in synaptic maturation and transmission.

2.11.2 Pathology

NGL-1 localized at chromosome 1p13, a risk region with schizophrenia reported previously (Ohtsuki et al., 2008). Decreased mRNA expression levels of NGL-1 and NGL-2 were observed in the brains of schizophrenia and BP disorder patients (Aoki-Suzuki et al., 2005). Moreover, NGL-1 had been reported to be phosphorylated via the interaction with cyclin-dependent kinase-like 5, and the phosphorylation of NGL-1 stabilized the association between NGL-1 and PSD95, thereby arguably suggesting a role for NGL-1 in disorders like autism and early-onset intractable epilepsy beyond its synaptic functions (Ricciardi et al., 2012).

2.12 IgLONs

2.12.1 Physiology

IgLONs were a group of GPI-anchored proteins with three extracellular C2 domains. Four genes were identified in this family: LAMP (limbic system-associated membrane protein), OBCAM (opioid-binding cell-adhesion molecule), NTM (neurotrimin), and Kilon. The LAMP, NTM, and OBCAM molecules interacted homophilically with themselves and heterophilically with each other (Lodge et al., 2000; Gil et al., 2002). The IgLONs were implicated in synaptogenesis. Overexpression of LAMP or OBCAM increased the synapse number in cultured hippocampal neurons (Hashimoto et al., 2009). Consistently, down regulation of OBCAM expression reduced the synapse number (Yamada et al., 2007). Overexpression of Kilon reduced the synapse number at early stages but increased the number of dendritic synapses in mature neurons with the alteration of lipid raft dependence (Hashimoto et al., 2008).

2.12.2 Pathology

IgLONs were implicated in the neuronal disorders with limited researches. Down-regulation of OBCAM was determined in the cerebral cortex, frontal lobe, and meninges, but
not in cerebellum in most cases of brain tumors (Reed et al., 2007). Stronger expression of NTM was also identified in nervous tumors than that in normal brain tissues (Liu et al., 2004). Additionally, NTM and OBCAM had been suggested as having a role in developmental delay (Minhas et al., 2013).

2.13 LAR-RPTPs

2.13.1 Physiology

Leukocyte antigen-related receptor protein tyrosine phosphatases (LAR-RPTPs) were type-I transmembrane proteins with two intracellular PTP domains (Pulido et al., 1995). Three vertebrate members (LAR, PTPδ, and PTPσ) and a few invertebrate members had been identified (Chagnon et al., 2004). LAR and PTPσ were enriched in glutamatergic synapses, and LAR was associated with AMPARs (Wyszynski et al., 2002; Takahashi et al., 2011); whereas PTPδ was mainly localized in inhibitory synapses (Takahashi et al., 2012). LAR-RPTPs regulated synapse formation via various protein interactions. Overexpression of dominant-negative LAR impaired the normal function of β-catenin–cadherin complex that regulated synaptic differentiation (Brigidi & Bamji, 2011). EPSCs were dramatically impaired by overexpression of LAR dominant-negative constructs (Dunah et al., 2005). Loss of LAR-RPTPs reduced the amplitude and frequency of mEPSCs. Mice deficient in PTPδ showed increased PPF and LTP in the hippocampus (Uetani et al., 2000). Receptor protein tyrosine phosphatase σ (RPTPσ) null mice showed an increase in PPF and mEPSCs frequency, but reduced LTP (Horn et al., 2012). PTPσ and PTPδ were required for excitatory and inhibitory synaptic differentiation, respectively, via interactions with Slit- and Trk-like proteins (Slitrks), a family of proteins belonging to the LRR superfamily (Yim et al., 2013). Activation of LAR-RPTPs resulted in specific mAChR-LTD, but not mGluR-LTD (Dickinson et al., 2009). Mice lacking LAR phosphatase domains exhibited spatial learning impairment in Morris water maze, and were more active in exploration and nest-building (Kolkman et al., 2004). Similar learning impairment had been found in mice lacking PTPδ (Uetani et al., 2000). On the contrary, loss of RPTPσ in mice caused an enhancement in novel object recognition memory (Horn et al., 2012).

2.13.2 Pathology

With very few research results, LAR-RPTPs seem to play a role in neuropsychiatric disease. PS/γ-secretase sequentially cleaved LAR and controlled LAR-β-catenin interaction (Haapasalo et al., 2007). On the other hand, Slitrks, which interacted with PTPσ and PTPδ, were linked to schizophrenia and Tourette syndrome (Hayashi-Takagi & Sawa, 2010; Bloch et al., 2011). Moreover, the Slitrk5 mutant mice had caused a reduction in striatal volume and dendritic complexity of striatal medium spiny neurons and an increase in neuronal activity in orbito-frontal cortex, indicating its role in human obsessive-compulsive disorder (OCD) (Ting & Feng, 2011).
<table>
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<tr>
<th>Mole.</th>
<th>Synaptic Location</th>
<th>Interaction</th>
<th>Functions</th>
<th>References</th>
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</table>
| Nrxs  | pre               | $\alpha$-latrotoxin, CASK, NLs, LRRTMs, GABA$_A$-receptor | $\alpha$-latrotoxin receptor  
Maintained presynaptic differentiation, the basal synaptic transmission and long-term plasticity of synapses  
$\uparrow$PSD-95, $\uparrow$NMDA and AMPA receptors  
Related to ASD, AD, schizophrenia & epilepsy  
Induced postsynaptic differentiation ($\beta$-Nrx)  
Impaired the recruitment of the postsynaptic AMPAR (Nrx3) | Südhof, 2008  
Levinson et al., 2005; Varoqueaux et al., 2004; Varoqueaux et al., 2006  
Barrow et al., 2009; Chih et al., 2005; Heine et al., 2008; Nam & chen, 2005  
Harrison et al., 2011; Reissner et al., 2013; Sindi et al., 2014; Südhof, 2008  
Gokce & Südhof, 2013  
Aoto et al., 2013 |
| NLs   | post              | Nrxs, PSD-95 | Induced pre- and postsynaptic differentiation and function  
Maintained the numbers of synapses, the basal synaptic transmission and long-term plasticity of synapses  
$\uparrow$PSD-95, $\uparrow$NMDA and AMPA receptors | Chih et al., 2005; Gokce & Südhof, 2013  
Varoqueaux et al., 2004; Varoqueaux et al., 2006  
Barrow et al., 2009; Chih et al., 2005; Heine et al., 2008; Nam and chen, 2005 |

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<tr>
<td>N-cadherin</td>
<td>post</td>
<td>β-catenin, AMPAR subunit, GluA2, NL1</td>
<td>Related to ASD, schizophrenia &amp; epilepsy</td>
<td>Millson et al., 2012; Sand et al., 2006; Sindi et al., 2014; Sudhof, 2008</td>
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<tr>
<td>N-cadherin</td>
<td>post</td>
<td>β-catenin, ACIR</td>
<td>Maintained the development of postsynaptic spines and the number of reserved pool vesicles</td>
<td>Taylor et al., 2013</td>
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<tr>
<td>Eph Receptors</td>
<td>both</td>
<td>Ephrin, SPAR</td>
<td>Mediated axon guidance, cell migration, presynaptic differentiation and spine maturation</td>
<td>Clifford et al., 2011; Davy &amp; Soriano, 2005; Egea &amp; Klein, 2007; Murai et al., 2003; Xu &amp; Henkemeyer, 2012</td>
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<td>Mediated neuron-glia interactions (EphA4)</td>
<td>Filosa et al., 2009</td>
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<td>↓mEPSCs, ↓LTP &amp; LTD (EphA4)</td>
<td>Fu et al., 2011; Grunwald et al., 2004</td>
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<td></td>
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<td>Maintained excitatory synapses and the clustering of NMDARs and AMPARs (EphB)</td>
<td>Henkemeyer et al., 2003</td>
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<td>↓mEPSCs (EphB2)</td>
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<td>Cdk5, Eph</td>
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<td>Ephrins</td>
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<td>Cdk5, Eph</td>
<td>Mediated axon guidance, cell migration</td>
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<td>Maintained NMDA-meciated current and LTP (ephrinB2)</td>
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<td>↓mEPSCs, ↑NMDA/AMPA ratios, ↓mossy fiber LTPs(EphrinB3)</td>
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<td>Related to ASD, AD, schizophrenia &amp; epilepsy</td>
<td>Chen et al., 2012; Sentürk et al., 2011; Suda et al., 2011</td>
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<td>N-CAM</td>
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<td>homo- &amp; heterophilic interactions</td>
<td>Maintained synapses number, ↑NMDA receptor, ↑CaMKII Alpha, ↑vesicle recycling, ↓vesicle recycling</td>
<td>Bukalo et al., 2004; Muller et al., 1996; Sytnyk et al., 2005; Chan et al., 2005; Polo-Parada et al., 2001; Polo-Parada et al., 2005; Rafuse et al., 2000; Conrad &amp; Scheibel, 1987; Vawter et al., 1998b; Wang et al., 2012</td>
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<td></td>
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<td>Linked with schizophrenia, epilepsy &amp; BP</td>
<td>Chang et al., 1987; Fischer et al., 1986; Lindner et al., 1993; Maness &amp; Schachner, 2007</td>
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<td></td>
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<td>Controlled axonal guidance, neurite outgrowth and fasciculation, and cell migration</td>
<td>Saghatelian et al., 2004; Ango et al., 2008; Morellini et al., 2007; Nikonenko et al., 2006</td>
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<td>↓inhibitory synaptic response (L1)</td>
<td>Djogo et al., 2013; Sakurai et al., 2002; Strelkova et al., 2006</td>
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<td>L1-CAMS</td>
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<td>Nectins</td>
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<td>afadin, N-cadherin-catenin complex, S-SCAM</td>
<td>Initial synapses formation</td>
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<td>Regulated the stability of synaptic junctions</td>
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<td>Related to AD</td>
<td>Kim et al., 2002; Kim et al., 2011</td>
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<td>Contactins</td>
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<td>Mediated axon connections</td>
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<td>Buttilgione et al., 1996; Perrin et al., 2001</td>
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<td>↑PPF, ↑LTD, ↑LTP &amp; spatial and object recognition memory (CNTN-1)</td>
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<td>Murai et al., 2002; Puzzo et al., 2013</td>
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<td>Extended the length of neurites (CNTN-4)</td>
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<td>Mercati et al., 2013</td>
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<td>↑root (CNTN-5)</td>
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<td>Postnatal glutamatergic synapse development (CNTN-6)</td>
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<td>Maintained excitatory synapses numbers and synaptic transmission (LRRTM2 &amp; 4)</td>
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<td>SynCAM</td>
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<td>CASK, protein 4.1B &amp; NMDAR, heterophilic interactions</td>
<td>recruited synaptic proteins and promotes neuron differentiation</td>
<td>Sara et al., 2005</td>
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<td>Postsynaptic scaffolding. NMDAR trafficking, ↑NMDAR-mediated current, ↓LTD, not LTP in CA1 (SynCAM-1)</td>
<td>Biederer et al., 2002; Hoy et al., 2009</td>
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<td>↑Vesicle recycling, ↑number of presynaptic terminals, ↑excitatory synapse number &amp; synaptic transmission (SynCAM-1 &amp; 2)</td>
<td>Fogel et al., 2007; Robbins et al., 2010; Sara et al., 2005</td>
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<td>SALMs</td>
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<td>PSD-95, SAP 97, SAP 102, NMDAR, GkAP, AMPAR</td>
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<td></td>
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<td>↑frequency of mEPSCs</td>
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<td>Postsynaptic scaffolding (SALM-2)</td>
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<td>Postsynaptic scaffolding. recruit presynaptic proteins (SALM-3)</td>
<td>Mah et al., 2010</td>
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<td>↑frequency and amplitude of mEPSCs</td>
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<td>Postsynaptic scaffolding. recruit presynaptic proteins (SALM-5)</td>
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<td>Related to ASD &amp; schizophrenia</td>
<td>de Bruijn et al., 2010; Xu et al., 2009</td>
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<td>NGLs</td>
<td>post</td>
<td>netrin-G, LAR, PTPσ, PTPδ</td>
<td>Postsynaptic scaffolding</td>
<td>Dunah et al., 2005; Kwon et al., 2010</td>
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<td>Maintained excitatory synapses &amp; synaptic currents</td>
<td>Kim et al., 2006; Soto et al., 2013</td>
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<td>Induces branching of horizontal cell axons (NGL-2)</td>
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<td>Maintained excitatory synaptic currents (NGL-3)</td>
<td>Woo et al., 2009</td>
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<td>IgLONs</td>
<td>both</td>
<td>homo- and heterophilic interactions</td>
<td>Related to schizophrenia &amp; BP</td>
<td>Aoki-Suzuki et al., 2005</td>
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<td>Postsynaptic scaffolding</td>
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<td>↑ synapse number (LAMP, OBCAM)</td>
<td>Hashimoto et al., 2009</td>
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<td>↓ synapse number at early stages, ↑ increases number of dendritic synapses in mature neurons (Kilon)</td>
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<td>Related to brain tumors</td>
<td>Reed et al., 2007</td>
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<td>LAR-RPTPs</td>
<td>post</td>
<td>NGL-3, Slitrks</td>
<td>maintained excitatory synapses and dendritic spines, AMPAR trafficking, ↑ AMPAR-mediated current (LAR)</td>
<td>Dunah et al., 2005</td>
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<td>excitatory synaptic differentiation ↑ PPF, mEPSCs frequency, ↓ LTP (PTP0)</td>
<td>Horn et al., 2012; Yim et al., 2013</td>
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<td>inhibitory synaptic differentiation ↑ PPF, LTP (PTPδ)</td>
<td>Uetani et al., 2000; Yim et al., 2013</td>
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<td>Related to AD &amp; OCD</td>
<td>Haapasalo et al., 2007; Ting &amp; Feng, 2011</td>
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pre: presynaptic; post: postsynaptic; both: pre- & postsynaptic; ND: non-determined; ↑: increase; ↓: decrease

**Table 1:** Interactions and functions mediated by CAMs between pre & post synapses
3 CAMs between synapses & ECM or others

3.1 Integrins

3.1.1 Physiology

Integrins were transmembrane receptors forming heterodimers with two type-I transmembrane chains, the α and β subunits. At least 19 α and 8 β subunits were known, resulting in 25 unique heterodimers in mammals (Humphries, 2000). Some integrin subunits were concentrated at synapses. For example, postsynaptic β3 integrin bound to the GluA2 subunit of AMPARs through their cytoplasmic tails (Cingolani et al., 2008; Pozo et al., 2012). Overexpression of β3 integrin in the postsynaptic neurons reduced the amplitude of mEPSCs and altered the subunit composition of AMPAR, while inactivation of β3 integrin abolished the synaptic scaling induced by pharmacological silencing of neuronal activity (Harburger & Calderwood, 2009). Homeostatic synaptic scaling required β3 integrin, but the function of this protein in synaptic transmission was still not very clear. Excitatory synaptic currents in primary hippocampal pyramidal neurons were increased or decreased by overexpression of wild type or dominant-negative β3 integrin, respectively (Cingolani et al., 2008). However, expressing β3 integrin mutants, including wild-type, in constitutively inactive or constitutively active mutants had no differential effects in excitatory synaptic responses (Pozo et al., 2012). Deletion of β3 integrin also left LTP, LTD, and short-term plasticity unaltered (McGeachie et al., 2012). Therefore, more investigations were needed to determine the exact role of integrins in synaptic transmission.

3.1.2 Pathology

Integrins had been involved in AD. The α4 integrin and a fibronectin specific antibody were detected at the tau positive plaques in AD patients (Van Gool et al., 1994). High stained level of vitronectin and its receptor β3 integrin were found in senile plaques and neurofibrillary tangles in Alzheimer brain tissue (Akiyama et al., 1991). A recent study demonstrated that the inhibition of Aβ in LTP could be eliminated by α5 integrin in both the dentate gyrus in vitro and the CA1 in vivo (Wang et al., 2008b). Integrins had also shown their importance in the process that Aβ increases NMDA evoked neuronal activity (Uhász et al., 2010). In addition, APP was specifically colocalized with α1β1 and α5β1 integrins at the cell surface of rat hippocampal neurons and rat cortical astrocytes (Yamazaki et al., 1997).

The contributions of integrins in epilepsy had been confirmed with numerous researches. Native low expression of β1 integrin could be strongly enhanced in hippocampal neurons and astroglial cells induced by seizure (Pinkstaff et al., 1998). Moreover, α2 integrin and laminin β1 were intensely increased in the anterior temporal neocortex tissue of patients with intractable epilepsy as compared with controls (Wu et al., 2011). In reactive astrocytes after pilocarpine-induced SE, immunoreactivity for α1, α2, α4, α5, β1, β3, and β4 integrin was intensely detected (Fasen et al., 2003). Similarly, an increase in α6
integron was observed in both seizure-induced neurons and glia (Gall & Lynch, 2004). In schizophrenia studies, the potential importance of integrins had been announced. The localization of integrins in the hippocampus had been considered to be functionally correlated with their roles in neuronal epileptiform activities (Grooms & Jones, 1997). In 2002, an increase of α2b and β3a integrin expression was described in the platelet of patients with schizophrenia (Walsh et al., 2002). Genetic analysis showed variants of β3 integrin associated with age at onset of schizophrenia (Wang et al., 2013). Recently in another study, gender-specific altered α8 integrin was found in schizophrenia (Supriyanto et al., 2013). Furthermore, Reelin, a glycoprotein that bound to integrin receptors, was decreased in the prefrontal cortex of patients with schizophrenia (Guidotti et al., 2000).

Integrins had been involved in ASD. An association between β3 integrin and ASD was suggested (Napolioni et al., 2011). An association between α4 integrin and levels of a serum autoantibody directed to brain tissue was identified to relate α4 integrin to the etiology of autism (Correia et al., 2009). Similar with NL3 R451C KI mice, a significant reduction in total brain volume and a lack of preference for social novelty were detected in β3 integrin KO mice (Ellegood et al., 2012).

3.2 Telencephalin

3.2.1 Physiology

Telencephalin (TLCN), also known as intercellular adhesion molecule 5 (ICAM5), was a type I transmembrane glycoprotein expressed only in the soma and dendritic membrane in brain (Oka et al., 1990). This dendritic distribution was mainly decided by its C-terminal sequence (Mitsui et al., 2005). Neuronal surface expressed TLCN exhibited homophilic binding ability between neurons, and heterophilic binding ability between neurons and leukocytes (Tian et al., 2000). TLCN also interacted with multiple proteins. An interaction between TLCN and ERM (ezrin/radixin/moesin) family proteins indicated the linkage of actin cytoskeleton and membrane proteins (Furutani et al., 2007). TLCN was reported to interact with β(1) integrins and stimulate β(1) integrin-dependent phosphorylation of cofillin (Conant et al., 2011).

TLCN played a role in neuronal development. In cultured hippocampal neurons, TLCN promoted dendritic elongation and branching (Tian et al., 2000). Overexpression of TLCN increased the density of dendritic filopodia and decreased the density of spines simultaneously. Consistently, TLCN-deficient neurons showed decreased density of filopodia displayed (Matsuno et al., 2006). Furthermore, the neurons lacking TLCN retracted the growth of spine heads and spine numbers in contrast to WT neurons in response to NMDA stimulation (Tian et al., 2007). TLCN also functioned in the synaptic plasticity. In TLCN-deficient hippocampal neurons, LTP induced by tetanic stimulation had been largely enhanced, while the basal synaptic transmission was normal, suggesting a TLCN-regulation of synaptic plasticity by determining the dynamic range of synaptic efficacy (Nakamura et al., 2001).
3.2.2 Pathology

TLCN may play an important role in AD development by preventing the processing of APP by \( \gamma \)-secretase (Annaert et al., 2001). TLCN was revealed to functionally but not structurally bound with Presenilin 1 and 2 (PS1 and PS2) (Annaert et al., 2001). Interestingly, APP competed the same binding region of PS1 with TLCN. This binding region of PS1 was often mutated in AD patients. In the brain of AD patients, the immunoreactivity of TLCN was decreased dramatically (Hino et al., 1997).

Several observations also suggested a role of TLCN in epilepsy. The concentrations of sTLCN were reduced in epilepsy patient plasmas, concomitant with an increase of TARC (thymus and activation regulated chemokines, CCL17) concentrations. Therefore raising a hypothesis that the ratio of TARC/sICAM5 distinguished between patients and controls (Pollard et al., 2013). Furthermore, TLCN was found in response to temporal-lobe dysfunction as well. The concentration of soluble TLCN (sTLCN) in serum and cerebrospinal fluid increased in adult temporal lobe epilepsy patients (Rieckmann et al., 1998). In localization-related epilepsy and secondarily generalized seizures patients whose TLCN was detected, lower functional MRI activation in the frontotemporal region was found concomitantly, making TLCN a potential biomarker in localization-related epilepsy (Jansen et al., 2008).

3.3 MHC-1

3.3.1 Physiology

Major histocompatibility complex (MHC) proteins were first identified in immune systems that mediated interactions of leukocytes. Three subgroups of MHC proteins had been found: class I, class II, and class III. In these three classes of proteins, class I MHC (MHC-1) was expressed in neurons as well (Corriveau et al., 1998). In addition, both \( \beta_2 \)-microglobulin, a cosubunit of MHC-1, and CD3\( \zeta \), a component of a receptor complex for MHC-1, were expressed in neurons, indicating MHC-1 signaling may also be mediated in the neuronal system in addition to immune system. Later, MHC-1 was shown colocalization with PSD-95 at excitatory synapses postsynaptically (Goddard et al., 2007). MHC-1 was negative controlling glutamatergic and GABAergic synapse density (Glynn et al., 2011). Moreover, MHC-1 was reported to be necessary and sufficient for synapse elimination in the retinogeniculate system (Lee et al., 2014).

Functionally, MHC-1 was involved in regulating synaptic transmission and plasticity. Reducing the MHC-1 expression level resulted in a significant increase in mEPSC frequency, a modest enlargement of presynaptic buttons and an increase in vesicle numbers (Goddard et al., 2007). Neural homeostatic plasticity could also be mediated by MHC-1. Reduced MHC-1 expression led to a failure to induce the increase of mEPSC amplitude and frequency by TTX treatment (Goddard et al., 2007). These results thereby suggested that MHC-1 controlled presynaptic release properties and retrogradely translated a signal across the synapse. In MHC-1 deficient hippocampal neurons, the AMPA/NMDA ratio was decreased (Fourgeaud et al., 2010), NMDA-dependent LTP was increased and LTD was blocked (Huh et al., 2000). Furthermore, in Purkinje cells lacking
MHC-1, a lower threshold for induction of LTD was exhibited, correlating an alteration of motor learning (McConnell et al., 2009).

3.3.2 Pathology

MHC-1 (human leukocyte antigen, HLA) A2 allele, but not B alleles, was reported an increased frequency of inheritance for autistic children (Torres et al., 2006). Conversely, the expression of MHC-1 was decreased in the dorsolateral prefrontal cortex but not in the orbitofrontal cortex in nonsmoking schizophrenia patients (Kano et al., 2011). MHC-1 mRNA expression was largely increased in the dentate gyrus 9 hours after kainic acid injection, indicating its role in seizures (Corriveau et al., 1998).

4 Perspective

The most remarkable feature of the brain was the large scale neuron-connected network. To transfer the information flows from one to another in the network, neurons had to form synapses. The synapse was thus considered the key structure for conveying the neural signal. It had been found that the CAMs mediate protein-protein interactions in the synaptic cleft and were involved in the recognition and localization of pre- and postsynaptic sites, as well as trans-synaptic signaling. Alterations in CAMs led to changes in synaptic morphology and function, and were associated with many neurological disorders, including autism, AD, schizophrenia and so on. Current data clearly showed that multiple mutations in different CAMs could lead to a single disease (e.g., ASD), but how these mutant proteins could synergistically affect the brain to present a common human behavior deficit seen in patients was still a mystery.

As was stated in this chapter, there was still no crystal-clear picture of how CAMs worked to initiate/regulate synapse formation, and how dysfunction of these molecules affected the function of brain circuit and behavior. In view of the large variety of synapses in the brain, the number of known synaptogenic molecules was surprisingly low and none of these mutants abolished the synapse formation either in vitro or in vivo. Thus, more efforts were expected to 1) study the precise function of the known CAMs in the synaptogenesis process, and 2) search and identify the new molecules in determining/regulating synapse formation by means of genome-wide screening, genetic engineering, and structural and functional analysis in animal models.

Acknowledgement

We sincerely apologize to the many authors whose works were not cited in this review due to space considerations. This work was supported by grants to Drs. Zhang Chen & Yang Xiaofei from National Basic Research Program of China (2011CB809102, 2014CB942804 and 2014BAI03B01), and National Science Foundation of China (31222025, 31171025 and 31300892), and National Science Foundation of Hubei (2014CFA027), and
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<tr>
<td>Integrins</td>
<td>both</td>
<td>cadherins, AMPAR</td>
<td>AMPAR trafficking ↓amplitude of mEPSCs altered the subunit composition of AMPAR ↑excitatory synaptic currents (Integrin-β3) Related to ASD, AD, schizophrenia &amp; epilepsy</td>
<td>Cingolani et al., 2008; Harburger &amp; Calderwood, 2009</td>
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<td>Telencephalin</td>
<td>ND</td>
<td>ERM, β(1) integrins</td>
<td>slowed spine maturation LTP↓ Relate to AD &amp; epilepsy</td>
<td>Matsuno et al., 2006; Nakamura et al., 2001; Annaert et al., 2001; Jansen et al., 2008</td>
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<td>MHC-1</td>
<td>post</td>
<td>β2-microglobulin, CD3ζ</td>
<td>negative controlling glutamatergic and GABAergic synapse density, synapse elimination mEPSC frequency ↓, AMPA/NMDA ratio ↓, LTP ↓ Related to ASD, schizophrenia &amp; epilepsy</td>
<td>Glynn et al., 2011; Lee et al., 2014; Fourgeaud et al., 2010; Goddard et al., 2007; Huh et al., 2000; Corriveau et al., 1998; Kano et al., 2011; Torres et al., 2006</td>
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pre: presynaptic; post: postsynaptic; both: pre- & postsynaptic; ND: non-determined; ↑: increase; ↓: decrease

**Table 2:** Interactions and functions mediated by CAMs between synapses & ECM or others.

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