[Frontiers in Bioscience 11, 2400-2419, September 1, 2006]

Cell adhesion molecules at the synapse

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1. ABSTRACT

Synapses are specialized intercellular junctions whose specificity and plasticity provide the structural and functional basis for the formation and maintenance of the complex neural network in the brain. The number, location, and type of synapses formed are well controlled, since synaptic circuits are formed in a highly reproducible way. This implies the existence of cellular and molecular properties that determine the connectivity of each neuron in the nervous system. Recent evidence has elucidated that these key features of the synapse are regulated by several families of cell-adhesion molecules (CAMs) enriched at synaptic junctions, including neuroligins, SynCAM, NCAM, L1-CAM, cadherins, protocadherins, and integrins. In this review we will discuss the various stages of synaptogenesis from the perspective of CAMs: Contact initiation, recruitment of presynaptic and postsynaptic proteins, synapse maturation/stabilization or elimination, and synaptic plasticity. We will also highlight some of the factors that regulate the function of these CAMs at the synapse, and discuss how dysfunction of these adhesive systems may contribute to several neurological disorders.

2. INTRODUCTION TO THE SYNAPSE

In development, synapses are thought to form when motile growth cones on the tips of extending axons reach their target cell and are transformed into stable synaptic contacts. This process requires spatially and temporally controlled changes in cell shape and structure and the recruitment of proteins to the forming synapse (1, 2). The axon terminal, or presynaptic side, is engorged with synaptic vesicles containing neurotransmitters, the chemical basis of neuron to neuron communication. These vesicles are docked on the presynaptic membrane, attached by a complex cytomatrix of proteins, and primed for the proper signal for release. At the dendrite, or postsynaptic site, neurotransmitter receptors and a wide array of transmembrane, cytoskeletal and signaling proteins are clustered and thereby poised to respond to the neurotransmitter released from the presynaptic terminal (3). This asymmetrical morphology and arrangement of proteins at the synapse makes them distinct from other cell-cell junctions. However, in addition to adhesion at synaptic sites, the presynaptic and postsynaptic terminals are connected at sites lateral to the synapse by *puntca adherentia*, a junction that is morphologically similar to

tight junctions formed between epithelial cells (4). Therefore, some basic aspects of junction assembly may be shared between synapses and other junctions, but the functional and morphological features that are unique to synapses may require neuron specific processes and proteins.

2.1 DEVELOPMENT OF THE NEUROMUSCULAR JUNCTION

Most of our knowledge of synapse formation and maturation is derived from studies on the neuromuscular junction (NMJ), contacts formed between presynaptic motoneurons which contact postsynaptic muscle cells (2, 5). Due to the large size and accessibility of this synapse, much of the physiological properties and molecules responsible for its development are well characterized. The earliest event in synapse formation at the NMJ is a rudimentary postsynaptic organization, termed pre-patterning, which occurs before arrival of the nerve axonal growth cone. In pre-patterning, acetylcholine receptors (AChRs) concentrate on the muscle fiber, independent of contact with motoneuron terminals (6-8). The mechanisms underlying pre-patterning are unclear, however data obtained from knockout mice indicate that the function of muscle-specific kinase (MuSK) is required and this process is independent of the secreted factor Agrin (6, 7). The role of pre-patterning in subsequent synapse formation also remains unclear. *In vitro,* synapse formation occurs when pre-patterning has not been observed, and incoming neurites do not preferentially contact pre-clustered AChR's (9, 10). Thus pre-patterning of AChR's is not required for subsequent synapse formation *in vitro.* However, *in vivo* AChR clusters are preferentially formed at the endplate band where innervation eventually occurs (11), suggesting that the location of synapses may not be entirely determined by the site at which the motoneuron contacts the muscle. Based on these findings, one may envision two scenarios: Motor axons ignore these preformed clusters *in vivo* just as they do *in vitro*, and use agrin to organize new clusters and a second signal is used to disperse non-synaptic clusters. Alternatively, axons might recognize these clusters or encounter them by chance, and then use agrin to enlarge and/or stabilize them. Experiments which visualize axon neurites and AChR clustering simultaneously *in vivo* are required to distinguish between these two possibilities.

Upon arrival of the motoneuron terminal, secreted molecules such as neuregulin and agrin, are released from axonal terminals and induce further clustering of AChR and maturation of postsynaptic specializations in the target muscle cells by acting through ErbB tyrosine kinase and MuSK (12-14). The motoneuron terminals of Agrin and MuSK knockout mice fail to differentiate, remaining highly dynamic, also providing evidence that postsynaptic differentiation is necessary for subsequent induction of presynaptic development (12, 15). The mechanism of the muscle-derived signal necessary for this reciprocal differentiation is not well defined, however, signaling via laminins have been implicated since laminin knock out results in perturbed presynaptic development (16-18). Furthermore, the laminin β2 directly binds to and causes clustering of voltage gated calcium channels (VGCC's) required for neurotransmitter release (19).

During early stages of development, muscle fibers are innervated by several motoneurons (polyneural innervation). A few days later, around the time of birth, synapse elimination results in the conversion of polyneural innervation to separation of motor units, and establishment of the adult pattern of mononeural innervation. This process of conversion has been shown to be regulated by the limited availability of trophic support (20, 21), as well as motoneuron activity (20, 22, 23). Together, the known interactions between the presynaptic motoneuron and postsynaptic muscle cell represent a core, albeit incomplete, understanding of the main steps in NMJ synaptogenesis. The emerging view is that the reciprocal signaling typified at the NMJ may be recapitulated for the formation of CNS synapses, but most likely with different molecular players.

2.2 DEVELOPMENT OF CNS SYNAPSES

In contrast to the NMJ, mechanisms of synaptogenesis in the central nervous system (CNS) are poorly understood (24, 25). This process is complicated by the enormous heterogeneity of the neuronal types and differences in the timing of their development. There are many types of synapses in the brain, each identified by the neurotransmitter they release. Examples include glutamate, acetylcholine, γ-aminobutyric acid (GABA), glycine, dopamine and serotonin. The effect of the neurotransmitter on the postsynaptic neuron is context specific, depending on several factors including the developmental stage of the neuron, the type and number of receptors present on the postsynaptic membrane, and neuronal activity (26). Excitatory synaptic transmission in the mammalian brain is primarily mediated by the neurotransmitter glutamate. As such, most of our knowledge of synaptogenesis in the CNS is based on research done on glutamatergic synapses. Due to the absence of evidence to the contrary, events of glutamatergic synapse formation are presumed to be similar for other types of synapses found in the CNS.

Synapse formation is thought to involve several characteristic steps: contact initiation, recruitment of presynaptic and postsynaptic proteins, and stabilization (Figure 1). First, an initial contact is made between an axon and the target postsynaptic cell. This has traditionally been described in terms of axonal growth cone that sends out filopodia searching for a prospective partner. This view is a carry over from studies of the NMJ where the target (muscle) is relatively stationary. Dendrites however, also extend growth cones and are lined with filopodia along their entire length. The dynamic protrusive behavior of these dendritic filopodia is consistent with an active ability to initiate contact formation (27, 28). Regardless of whether dendrites or axons are responsible for initiation of contact, target recognition is thought to be specific, since correct connectivity is essential to the function of a neural network. Given the large number of neuronal contact type and targets, the adhesion system(s) mediating this initial

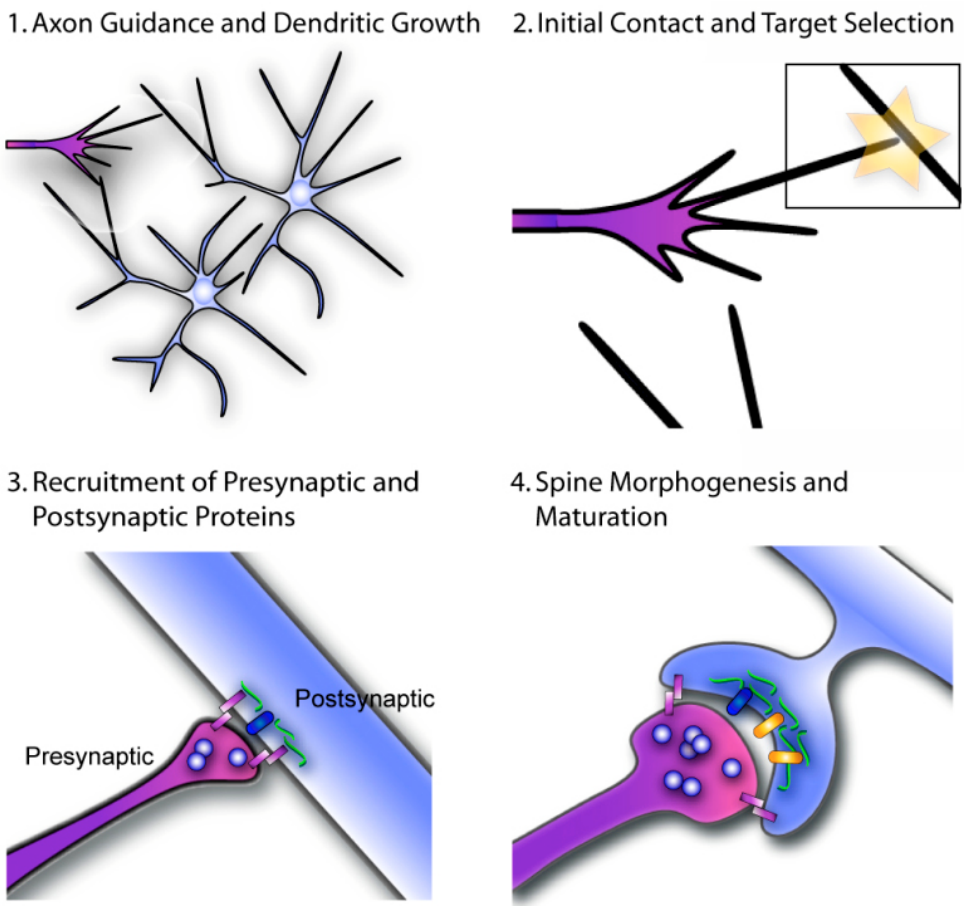

Figure 1. Development of glutamatergic synapses in the central nervous system. (1) Axons often travel long and arduous pathways before reaching their target field. Dendrites also undergo complex branching. Some of the cell adhesion molecules implicated in this stage include ephrins, L1, fasciclin, and integrins. (2) Both axons and dendrites extend long protrusions called filopodia which are believed to be actively searching for appropriate targets. Several homophilic cell adhesion molecules such as cadherins, protocadherins, integrins, and sidekick, are thought to play important roles in regulating target recognition. (3) After contact formation between appropriate presynaptic and postsynaptic targets, proteins important for the development of functional synapses are recruited. On the presynaptic side, vesicles containing neurotransmitters and the machinery mediating vesicle fusion are recruited. Directly apposed on the postsynaptic side, neurotransmitter receptors and scaffolding proteins are clustered. (4) As synapses mature, additional recruitment of presynaptic and postsynaptic proteins leads to further stabilization of the contact. Other recruited molecules modulate synapse morphology. Most mature glutamatergic synapses occur on mushroom-shaped protrusions known as spines, and many cell adhesion molecules have been shown to play a role in this process via modulation of the actin cytoskeleton. Examples include cadherins, integrins, neuroligin/neurexin, L1, nectins, and NCAM.

contact is predicted to be complex and this requirement could only be met by polymorphic adhesion proteins that offer sufficient combinatorial possibilities. This 'lock and key' mechanism was first hypothesized by Sperry (1963), which implies the existence of specific adhesion molecules pair axons with their targets for the configuration of synaptic connections (29).

The second step in synaptogenesis is thought to involve recruitment of pre- and postsynaptic components at the site of initial contact. This includes recruitment of presynaptic release machinery and postsynaptic neurotransmitter receptors and associated signaling molecules. Recruitment of different proteins to presynaptic and postsynaptic sites suggests involvement of trans-synaptic adhesion molecules able to interact with distinct scaffolding and signaling proteins at the pre- and postsynaptic sides. These trans-synaptic signals would also require specificity, the ability to recruit the appropriate neurotransmitter on the presynaptic side and their cognate receptors on the postsynaptic side, in order to avoid mismatching. Much work in this field focused on the order of recruitment of presynaptic and post synaptic proteins, however, consensus on the hierarchal recruitment of individual proteins remains elusive.

After recruitment of pre- and postsynaptic proteins, these newly formed synapses may be further stabilized or lost, in an effort to fine tune neuronal circuitry. Transformation of the stabilized contacts to

mature synapses also involves coordinated changes in the size and content of pre- and postsynaptic sites, and is also thought to involve recruitment of specific cell adhesion complexes.

Although not required for initial steps of synapse formation (30), the process of synapse elimination or strengthening is thought to, in part, depend on external stimuli and synaptic activity. For instance, in the rodent barrel cortex, which receives somatosensory input from the whiskers, sensory deprivation via trimming of the whisker (loss of external stimuli), and results in decreased stable synaptic connections (31). In contrast, stimulation of the whisker has been shown to increase the number of synapses (32). Therefore, adhesion systems important for these processes are likely to be modulated by synaptic activity, leading to changes in protein levels or in their adhesive properties.

Each of the steps of synaptogenesis outlined herein requires cohesion and reciprocation between two cells, and this is a fundamental property of all cell adhesion molecules. Conceptually synaptogenesis is described as individual steps, but are in fact part of a synaptogenic continuum. As such, molecular players in one step are likely to have additional roles in other steps. The multiplicity, in number and function, of adhesion complexes makes them both interesting and difficult to study. Although all CAMs share the ability to induce adhesive contacts, individual CAMs may have developmentally regulated functions that range from contact initiation to stabilization and plasticity. Recent *in vitro* studies showed that several of the identified CAM's can modulate synaptic contact number, morphology and function, however a strong evidence that any of these molecules is indispensable for synapse formation *in vivo* is lacking, suggesting a redundancy in their function. Thus, synapse formation and maturation may rely on the collective action of several of CAMs and their interacting proteins (Figure 2). Whether the numerous adhesion families act in parallel or in a hierarchical manner is unknown, and future study will be required to tease apart the nuances of how these adhesion systems work together in the establishment and function of the synapse.

3. CELL ADHESION MOLECULES IN EXCITATORY SYNAPSE DEVELOPMENT

3.1. TARGET RECOGNITION AND INITIATION

An important aspect of synaptogenesis is the ability of axons to grow to their target fields and synapse with the correct postsynaptic cell type. These axons often travel long and arduous pathways before reaching their final target, and although they come in contact with a multitude of potential postsynaptic partners along the way, they do not establish synapses on inappropriate cells. For instance, motoneuron axons from the ventral horn of the spinal cord delay synapse formation until they reach the proper muscle target. Furthermore, these axons may delay synapse formation for days, even weeks, when within these target regions (2). Thus, precise axon guidance by cues alone is not sufficient for target-specific synapse formation and suggests that other factors must contribute (33). Such events could be mediated by intrinsic genetic programs, but there is no evidence yet to support this mechanism. Several target-derived factors have been identified, and many adhesion molecules have been implicated in this process including cadherins, protocadherins, and sidekick. The molecular diversity and differential distribution of these synaptic adhesion molecules satisfies the requisite specificity for synaptic connectivity.

Due to their existence in multiple isoforms, matching cadherins in axons and dendrites is believed to promote selective adhesion between appropriate partners. All three major subtypes of cadherins are expressed in the brain: classical cadherins, cadherin-related proteins, and protocadherins. The expression and subcellular distribution of classical cadherins, and their intracellular binding partners, catenins, varies with neuronal cell type and developmental stage, suggesting that cadherins may play a role in the specificity of synapse connectivity (34, 35). For instance, cadherin-6 is expressed in functionally connected neurons in the auditory system (36).

At individual synapses, classical cadherins are detected pre- and postsynaptically (37-39). In development, N-cadherin and β-catenin are distributed diffusely along the length of dendritic motile filopodia and upon contact with an axon, the cadherin complex accumulates at points of contact (38, 39). Studies using a dominant negative approach (N-cadherin lacking ectodomain), demonstrated that blockade of N-cadherin function results in loss of spines and appearance of filopodia-like protrusions (38). These effects are more dramatic in younger neurons, further demonstrating that cadherins are more active at earlier stages of synapse development. Interfering with cadherins function suggests that these molecules are more likely involved in regulation of target specificity, rather than induction. For example, initial synaptic assembly is delayed but not blocked in neurons that are transfected with dominant-negative cadherin (40). Moreover, in the retino-tectal system, addition of antibodies that block N-cadherin function causes retinal ganglion cells to overshoot their target and form exuberant synapses (41). Thus, evidence indicates that cadherins are important for target recognition, but they are not essential for synapse differentiation, a process which may require other adhesion systems.

Protocadherins have been also implicated in target selection. About 70 protocadherins are known in mouse and human, and many of these are expressed in the nervous system in largely overlapping patterns, with some regional and cell-type differences in strength of expression (42, 43). Unfortunately, deletion of all of the variable exons in the protocadherin-γ cluster leads to apoptotic degeneration of interneurons and neonatal lethality (44), making it impossible to assess their role in target specificity. However, when combined with a mutation that prevents apoptosis, further analysis revealed that *Pcdh-γ* mutant neurons made significantly fewer synapses than wild-type neurons (45). Although this data circumvents the

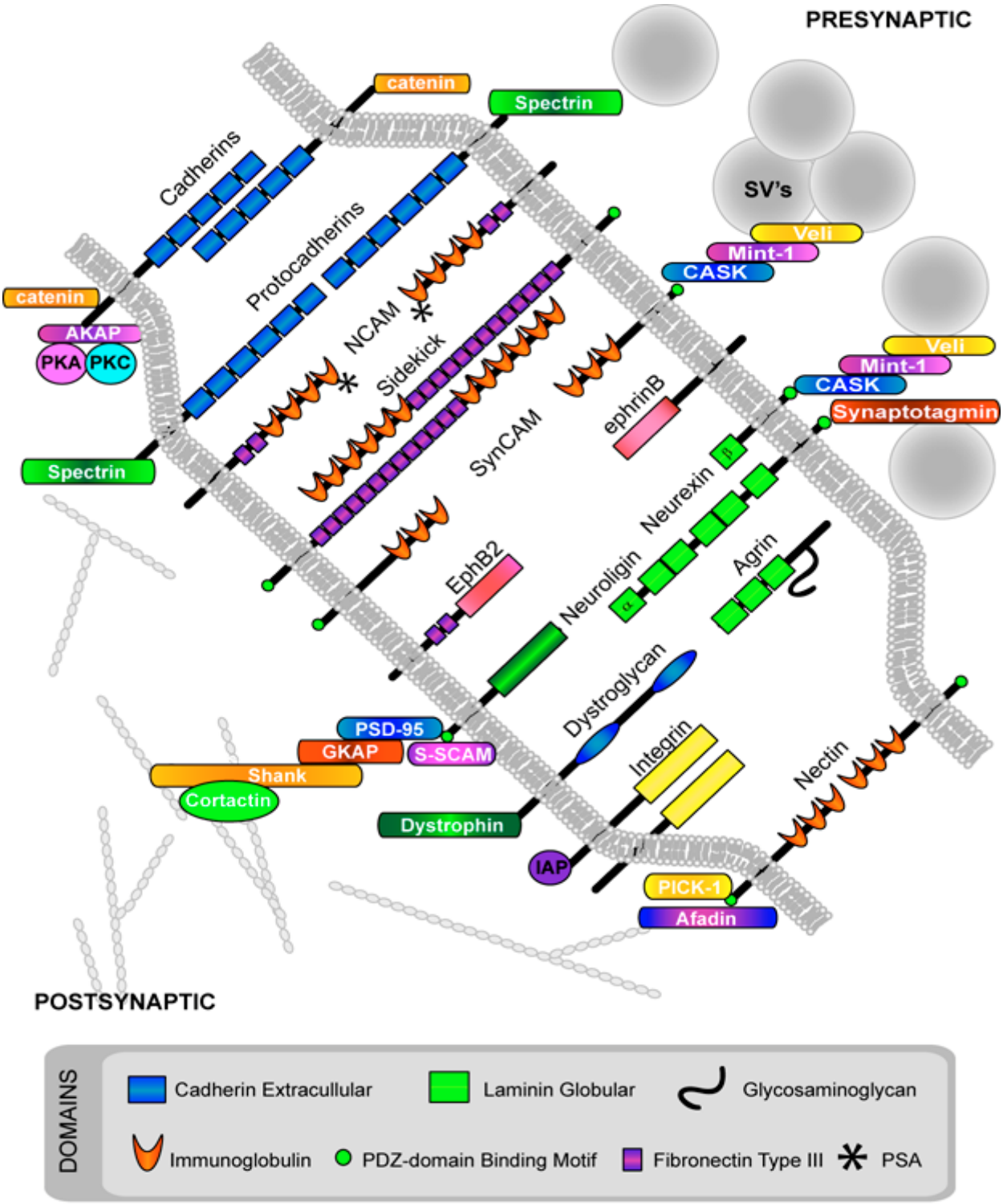

Figure 2. Diverse adhesion complexes implicated in synapse formation. The bottom side shows CAMs that are present predominantly on the postsynaptic membrane and the top side shows CAMs present at the presynaptic membrane. Domains important for the function of several CAMs are shown. Several adhesion molecules contain a C-terminal PDZ binding motif which allows interaction with PDZ domain-containing scaffolding proteins; some of them are listed. Neuroligin/neurexin and SynCAM are the only adhesion molecules shown to be sufficient to drive synapse formation *in vitro*.

problem of lethality to examine synapses in protocadherin knock-outs and implies their importance in synapse formation, this does not impart how protocadherins are exerting their function. Conclusive data to support the role of protocadherins in issuing target specificity will probably require the development of transgenic mice in which the repertoire of *Pcdh-γ* genes is altered. Correlating expression pattern of certain isoforms to neuronal subsets for which the pattern of connectivity is known may also help to answer this question, particularly if miss-expression of another isoform can be shown to shift connectivity.

The expression pattern and consequences of its miss-expression on connectivity have been demonstrated for the adhesion molecule sidekick. Sidekick is a member of the immunoglobulin superfamily of proteins and contains 6 Ig domains and 13 fibronectin III repeats, and was identified based on its ability to regulate photoreceptor differentiation in Drosophila (46). In mammals, sidekick -1 and -2 concentrate at pre- and postsynaptic sites respectively, in largely non-overlapping subsets of retinal neurons (47). Cells transfected with sidekick-1 or sidekick-2 form separate aggregates of these proteins, indicating a homophilic association. This ability is thought to be mediated through the first two Ig domains of sidekick, since deletion of these domains results in abolishment of adhesion (48). Sidekick-rich synapses are concentrated in narrow sub-laminae of the inner plexiform layer of the visual system, suggesting that sidekick interactions may promote laminae specific connectivity. Indeed, over-expression of sidekick in the retina has been shown to divert neuronal processes (46, 47).

Interestingly, synapse assembly may be potentiated by a third cell. Neurons in the egg laying circuit of *C.elegans*, form synapses in a stereotypical pattern that is not target dependent, but rather, dependent on the vulval epithelial cells. The signal responsible for this was determined to be due to the neuronal adhesion molecule SYG-1 and its epithelial counterpart SYG-2, transmembrane members of the immunoglobulin superfamily. SYG-1 and -2 are not essential for synapse formation per se, but data from the SYG mutant worms point to the importance of synaptic "guideposts" to ensure formation of functional circuits (49, 50). Further research is required to determine if non-target guideposts are important for target recognition in other neuronal circuits.

3.2 RECRUITMENT OF PRESYNAPTIC AND POSTSYNAPTIC MOLECULES

Several molecules have been identified as synapse inducers, proteins that mediate the recruitment of pre- and postsynaptic molecules important for the function of an active synapse. Several CAM's have been demonstrated to fulfill this role. In particular, SynCAM and neuroligins are the only CAMs so far to demonstrate the ability to promote presynaptic differentiation at contacts between axons and heterologous cells, and that drive the recruitment of synaptic proteins at sites of contact (51-53). This suggests that at least some cell adhesion molecules are sufficient to drive recruitment of synaptic proteins to contact sites.

Neuroligins were first identified for their ability to bind all three isoforms of β-neurexin, a presynaptic transmembrane protein (54). The interaction between neuroligin and β-neurexin has been demonstrated to increase the size and number of presynaptic terminals (55, 56), as well as potentiate the clustering of the postsynaptic protein PSD-95 under some circumstances (52). Conversely, β-neurexin presented to dendrites via heterologous cells or beads has been demonstrated to recruit postsynaptic proteins (57, 58).

SynCAM is a transmembrane member of the Ig superfamily that shows homophilic, calcium-independent binding, contains 3 Ig-domains, and an intercellular C-terminal PDZ-binding motif which binds to the synaptic scaffolding proteins CASK and syntenin. SynCAM overexpression in cultured neurons promotes synapse formation, and overexpression in non-neuronal cells rapidly induces formation of active presynaptic terminals in axons contacting these heterologous cells (53). There are three other genes encoding SynCAM, and heterophilic adhesion between the various SynCAM isoforms has been demonstrated (59). The role that the other SynCAM isoforms play and the consequences of heterophilic binding between them have not been studied in neurons.

Although both SynCAM and neuroligins are both strong inducers of synapses, it appears that synapses induced by these CAMs are functionally distinct (60). Artificial presynaptic terminals induced by both of these CAMs onto heterologous cells have been shown to be identical in all parameters measured to each other, and to true synapses. Overexpression in neurons however, produced a different story, as well as some controversy. Only expression of SynCAM increased synaptic function by electrophysiological measures, whereas morphological analysis revealed the opposite, only neuroligin increased synapse number (60). In contrast, other studies have used electrophysiology to show increased synaptic function in neuroligin over-expressing neurons (55, 56), and that knockdown of neuroligin diminishes synaptic function and activity (61). The differences of these observations may be explained by the developmental and cell-type differences of the neurons studied. The generation of mutant animals will help determine whether these proteins are essential for synapse development *in vivo*.

A sequential order for the recruitment of synaptic proteins and whether they are recruited as preassembled complexes or as individual molecules has been an area of intense study. Recruitment of individual molecules probably contributes to presynaptic assembly, however studies from several laboratories have suggested that vesicular delivery plays a prominent role. The fusion of dense core vesicles carrying structural components of the presynaptic active zone, such as piccolo and bassoon, has been observed shortly after initial contact (62). Another population of precursor presynaptic vesicles containing proteins important for active neurotransmitter release, such as VAMP and synaptophysin, has also been observed to be recruited shortly after initial contact formation (63). The order of assembly of these two populations of presynaptic

transport packets has not been directly compared, and the driving force for their recruitment is unknown. Cell adhesion complexes have often been implicated, however, the hierarchal nature and delivery mode for most adhesion molecules during synapse formation has not determined. For instance, β-neurexin and SynCAM are potent inducers of presynaptic active zone assembly onto heterologous cells, and it can be presumed that their delivery is an early event resulting in the transformation of a nascent contact to a functional presynaptic zone. However, it is unclear whether these molecules are already at the plasma membrane and cluster through lateral movement, or whether they are directly delivered as clusters via vesicular transport mechanisms. Overexpression studies showed that PSD-95 enhances recruitment of endogenous neuroligin-1 at excitatory contacts and this process correlates with an increase in size of the presynaptic terminals (55). These data suggest that clustering of postsynaptic elements may enhance recruitment of the presynaptic release machinery and that this process is required for stabilization of newly formed contacts. Moreover, recent data show that in young hippocampal neurons neuroligin-1 is associated with the scaffold molecule PSD-95, in the absence of an active presynaptic terminal. Time-lapse imaging performed by our group also revealed the presence of a preformed complex of scaffold proteins containing neuroligin-1, which preceded the recruitment of presynaptic vesicle proteins and the machinery required for active recycling of neurotransmitter. In this case, the presence of postsynaptic proteins such as neuroligin-1 may facilitate the recruitment of presynaptic proteins important for vesicular release (64). In contrast with these results, previous studies have demonstrated that the recruitment of PSD-95 occurs after the establishment of an active presynaptic terminal (63, 65, 66). Although the role of adhesion complexes was not studied, the presumed role of neuroligin-1 would be to recruit PSD-95 to these sites. Another study looking at new contacts made by axonal filopodia demonstrated the rapid recruitment of NMDA-type glutamate receptors independent of PSD-95, and before the establishment of an active presynaptic terminal (67). These forms of recruitment are illustrated in Figure 3, and raise several questions. How are these processes of recruitment developmentally and spatially regulated? What are the adhesion systems involved, and when? Regardless of whether the postsynaptic density or the presynaptic active zone is assembled first at the nascent contact, the resultant young synapse is subject to maturation/stabilization or elimination.

3.3. MATURATION AND SPINE MORPHOGENESIS

A feature of synaptic formation is a prolonged maturation phase, where synapses are stabilized, and maturation of pre- and postsynaptic sites occurs in a coordinated fashion. The number of synaptic vesicles in the presynaptic compartment increases, as well as the size and protein content of the postsynaptic density (68, 69). The high correlation between the size of the pre- and postsynaptic compartment suggests that the coordinated actions of a trans-synaptic adhesion complex are important for this process. Not surprisingly, several CAM's involved in earlier steps of synaptogenesis, serve roles in the maturation of synapses. For instance, addition of antibodies that block N-cadherin function causes the formation of widely separated synaptic clefts in the chick retinal-tectal tract (70). Miss-localization of β-catenin, through disruption of its interaction with the intracellular tail of cadherin, results in abnormal distribution patterns of synapsin and PSD-95, decreases in FM 4-64 uptake, and a decline in presynaptic activity (71). Furthermore, EM analysis has shown a reduction in synaptic vesicles in neurons of the β-catenin conditional knock out mice (72). Thus, adhesion systems like the cadherin-catenin complex can properly co-ordinate the maturation of pre- and postsynaptic elements.

The most dramatic example of synapse maturation is the transformation of an immature glutamatergic postsynaptic compartment into a mature spine, an actin-based protrusion from the dendrites with a bulbous head. Glutamatergic synapses initially form on dendritic filopodia and shafts, and overtime, are proposed to develop into spines. By having an enlarged head attached to the dendritic shaft by a small neck, spines provide biochemical as well as spatial compartmentalization. This morphological change of the postsynaptic compartment is regulated by numerous mechanisms that signal through proteins that regulate the actin cytoskeleton such as the Rho family GTPases, and several actin-binding proteins such as Arp2/3 and cortactin (73). In addition to their adhesive properties, many CAM's interact with these proteins that affect the actin cytoskeleton, and thus are poised to mediate this maturational change. For instance, in epithelial cells, adhesion by the cadherin complex mediates profound changes in the actin cytoskeleton through several effectors including cortactin, Arp1/3, formin-1, and the Rho family of GTPases. Whether cadherin similarly affects these proteins at the synapse remains unknown, however, it appears very likely since cortactin, Arp1/3, and several Rho GTPases are known to alter spine morphology and stability (74, 75).

Several adhesion complexes have been shown to affect spine morphology or the actin cytoskeleton, including neuroligins, cadherins, integrins, syndecans, as well as numerous members of the immunoglobulin superfamily (73). For example, Nectins are members of the immunoglobulin superfamily which functions in concert with cadherins in various types of adherens junctions including the puncta adherentia of synapses (76), are also believed to play an important role in the actin cytoskeleton rearrangement. Four nectin genes are known, and each contain 3 Ig domains, and a short cytoplasmic tail containing a PDZ domain binding motif (77). Each nectin is expressed in several splice variants, and forms *cis* homodimers and interact in *trans* in a homo- and heterophilic manner. Afadin, which contains an actin-binding and a PDZ domain, provides a direct link to the cytoskeleton. Nectins also affect the actin cytoskeleton via activation of Rac1 and Cdc42 (78). The effect of nectin in spine morphogenesis has yet to be investigated, however, inhibiting nectin-1 has been shown to cause abnormal

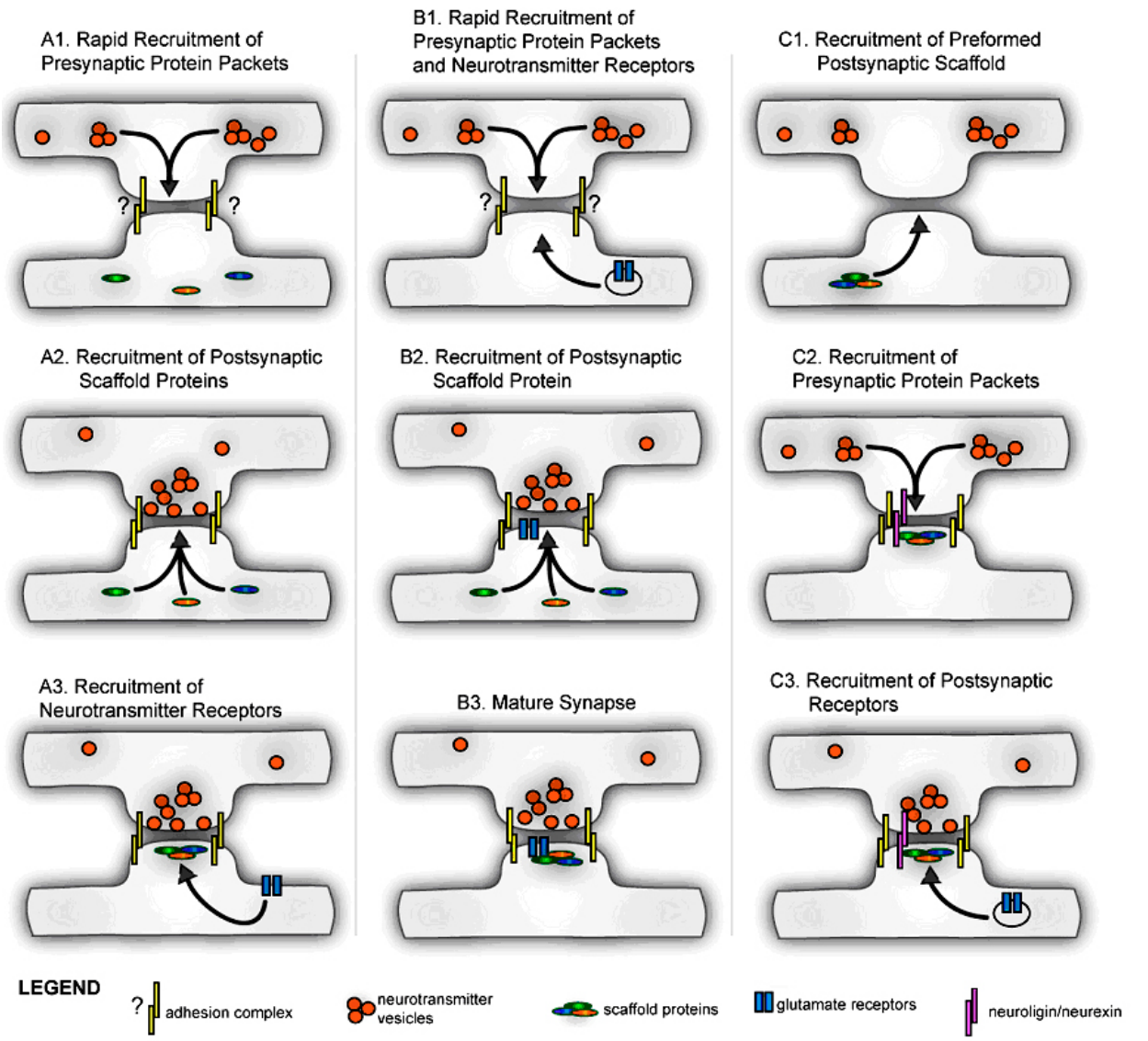

Figure 3. Three proposed hierarchical models for recruitment of proteins at glutamatergic synapses upon contact formation. (A1-A3) illustrates a model where presynaptic recruitment precedes the recruitment of postsynaptic neurotransmitter receptors and scaffolding proteins. (A1) At the presynaptic side, molecules such as VAMP and synaptophysin as well as the active zone scaffold proteins, piccolo and bassoon, are recruited to initiate assembly of vesicles and control neurotransmitter release. (A2) Postsynaptic scaffolds are recruited from diffuse cytosolic pool, directly apposing the active presynaptic terminal. (A3) Recruitment of postsynaptic receptors via gradual clustering of individual channels. (B1-3) illustrates a model where recruitment of glutamate receptors occurs rapidly after contact formation, preceding the recruitment of postsynaptic scaffolding molecules and presynaptic active zone proteins. (B1) Rapid recruitment of glutamate receptors from a highly mobile vesicular pool of receptors to new contacts between a dendrite and axon filopodia. (B2) Recruitment of postsynaptic scaffolding molecules occurs independently of receptor recruitment. (B3) Recruitment of neurotransmitter vesicles able to undergo active release occurs after delivery of glutamate receptors. (C1-3) Illustrates a model where preassembled postsynaptic scaffolding molecule recruitment precedes the assembly of a functional presynaptic terminal. (C1) Postsynaptic proteins are present in preformed complexes and are recruited to sites of contact. (C2) Adhesion complexes are clustered and functional presynaptic terminals are recruited to sites directly apposed to postsynaptic scaffold. (C3) Glutamate receptors are recruited at later stages independently.

distribution of synaptic proteins and a decrease in synapse size with a concomitant increase in synapse number (76).

Interestingly, several lines of evidence implicate adhesion with the extracellular matrix as important regulators of spines. Two integrin ligands have been demonstrated to affect dendritic spines: laminin increases spine density, whereas reelin promotes spine stability (73). In addition, overexpression of the transmembrane proteoglycan syndecan induces early transformation of

filopodia protrusions into mature mushroom-shaped spines (79). Although the examples presented herein are far from complete, and many details of the molecular events that are affected are still unknown, it is clear that the cascades initiated by adhesion complexes play an important role in spine morphogenesis.

3.4. ELIMINATION

Most work has focused on the processes of synapse formation and maturation, however, synapse elimination is equally an important developmental process (5). The initial number of synapses in development is greater than the number retained into adulthood, highlighting that synapse elimination is a crucial step in normal brain development (80, 81). Pruning of synapses is a common theme during early activity-dependent refinement of neuronal circuitry. There are two proposed mechanisms of synapse removal: Input elimination and synapse disassembly. During input elimination a presynaptic cell loses all synaptic contacts with a postsynaptic target, leading to functional and anatomical uncoupling of the cells, although contact with other targets persists (82). Input elimination is thought to require the rapid and complete disassembly of multiple synapses and has been studied at the NMJ, cerebellar climbing fibers, the visual and auditory system (2, 80, 83, 84). In contrast, synapse disassembly refers to the deconstruction of individual synaptic contacts, and thus represents a mechanism for modulating the strength of connectivity between two cells. This has been observed at the NMJ and CNS synapses in invertebrates (5).

The molecular mechanisms that drive synapse disassembly and input elimination remain unclear. Examination of fixed preparations suggests that elimination of synapsin and presynaptic vesicle associated proteins precede the removal of postsynaptic receptors (85, 86). The speed of synapse disassembly can be substantially faster than the rate of protein turnover, indicating destabilizing mechanisms rather than removal of trophic support (87). One would predict that loss of adhesion would play an integral part of synapse destabilization. Indeed, long term depression in sensory neurons in aplysia results in the removal of apCAM, an NCAM-like adhesion molecule, before the retraction of the presynaptic terminal (88). Work on the NMJ has eluded involvement of extracellular proteases as a 'punishment' signal (89), and matrix metalloprotease-3 is able to remove agrin at NMJ's and subsequently ACh receptors from the postsynaptic membrane (90). Whether proteases work similarly at CNS synapses to cleave adhesion complexes and initiate synapse elimination remains to be determined. However, in HEK293 or COS cells transiently or stably over-expressing individual protocadherin-γ (*Pcdh-γ)*, it was found that the γ-Pcdh ectodomain was cleaved at the cell surface, and that this cleavage could be blocked by inhibitors of matrix metalloproteinases (91, 92). These results suggest a very interesting paradigm where the cleavage of protocadherin-γ may play an important role in disengaging synaptic contacts. Whether protein cleavage is a general mechanism for releasing the attachment between other adhesion molecules remains to be determined.

4. CELL ADHESION MOLECULES IN INHIBITORY SYNAPSE DEVELOPMENT

One critical aspect of synaptogenesis is specificity, and the mechanisms that determine whether a nascent contact develops into an excitatory or inhibitory synapse remain unknown. This is an amazingly precise process considering that a neuron may receive tens of thousands of heterogeneous synaptic inputs, yet virtually no mismatches between pre- and postsynaptic elements occur.

Most inhibitory neurotransmission in the vertebrate CNS is mediated by the neurotransmitter γ-aminobutyric acid (GABA), which is responsible for modulation of every aspect of brain function. The action of GABA is mediated by ionotropic (GABAA) and metabotropic (GABAB) receptors, which are ubiquitously expressed in the CNS (93, 94). GABAergic function is fine-tuned at multiple levels, including transmitter synthesis by two isoforms of glutamic acid decarboxylase (GAD); vesicular storage; Ca^{2+} dependent and independent release; re-uptake in neurons and glial cells; and the activation of receptors localized pre-, post-, and extrasynaptically (95).

An ensemble of hundreds of proteins has been identified at the PSD of excitatory synapses, based on proteomics analysis of biochemically purified synaptic preparations (96, 97). However, postsynaptic fractions of inhibitory synapses cannot be isolated selectively, and accordingly, much less is known about their molecular constituents. The available data indicate that the main difference is the apparent absence of proteins with PDZ domains mediating protein-protein interactions (98). At GABAergic synapses, the scaffolding protein gephyrin is concentrated within the postsynaptic domain and is reported to be important for synaptic clustering of GABAA and glycine receptors at inhibitory synapses in hippocampal neurons (99, 100). However, when other regions of the brain were examined, gephyrin was found to be only partially required for receptor clustering in the retina and spinal cord (101, 102).

The popular model for inhibitory synapse formation is thought to be initiated by GABAA receptor activation and signal transduction through the activation of G-proteins and phosphatidylinositol 3-kinase (95). However, the limited information available on the constituents of inhibitory contacts have hindered our understanding of the mechanisms that govern inhibitory synapse formation and maturation, including identification of the cell adhesion molecules directly involved in this process.

Several CAM's have indirectly been implicated in inhibitory synaptogenesis, specifically dystroglycan, L1, N-CAM, and protocadherins. Dystroglycan was the first identified adhesive macromolecule at mature GABA synapses, and was found to accumulate at synaptic loci after synaptic vesicles, GAD, GABAA receptors, and gephyrin (99, 103). Dystroglycan is composed of an

extracellular α-subunit and a transmembrane-containing β-subunit derived by proteolytic cleavage and glycosylation of a single precursor protein. Dystroglycan binds several extracellular matrix molecules such as agrin, laminin and perlecan, and intracellularly binds to dystrophin and utrophin (104). Importantly, dystroglycan binds to two proteins involved in synaptogenesis, namely agrin and β-neurexin (105, 106). Despite the potential of dystroglycan as an inhibitory synaptic adhesion protein, studies on neurons obtained from mutant mice indicate that this protein is not essential for synapse formation, since clustering of many proteins at inhibitory synapses is not affected (103). These findings suggest that dystroglycans may play a more prominent role in maturation of inhibitory contacts.

L1-CAMs are expressed by almost all post-mitotic neurons in the CNS at the onset of differentiation, but not by glia. During development it has been shown to be important in neuronal migration, neurite outgrowth, fasciculation and guidance, survival and myelination in the PNS, and some of their roles in the CNS, particularly at synapses, have recently been elucidated. Studies on hippocampal slices from adult constitutively L1-deficient mice showed no significant changes in long-term potentiation (LTP) induced by theta-burst or high frequency stimulation in the CA1 region (107). These findings were re-capitulated in juvenile mice, but interestingly, perisomatic inhibition was noticeably impaired. This was manifested as a decrease in both frequency and amplitude of inhibitory postsynaptic currents, as well as a reduction in the number of inhibitory synapses (108). These results reveal that L1-CAMs can modulate the function as well as the number of inhibitory synapses. However, it remains unclear at which step of synapse formation L1-CAM exerts these effects. One clue comes from study on neurofascin, a member of the L1-CAM family (109). The precise localization of neurofascin by the membrane adaptor protein ankyrinG, is responsible for establishment of a gradient of this CAM at the initial axon segment of cerebellar purkinje cells. Disruption of the gradient of neurofascin results in disturbance of the subcellular localization of GABAergic synapses on the axonal initial segment (109). These data suggest that L1 may be important for recognition of inhibitory terminals at specific locations to form a synapse on a target neuron, and warrants further study in other neuronal circuits.

Protocadherins appear to be important for inhibitory synapse development in the spinal cord. Spinal cord neurons cultured form *pcdh-γ* mutant mice show a decrease in the number of GABAergic terminals. Electrophysiology analysis also revealed a decrease in both the spontaneous and evoked inhibitory currents (45). It will be interesting to examine whether protocadherins are important for inhibitory synapse development in the brain.

The first direct evidence of a CAM *driving* formation of inhibitory synapses was a surprising result. Neuroligin-1, a well-characterized CAM mainly enriched at glutamatergic synapses, can also induce formation of GABAergic presynaptic contacts when overexpressed in hippocampal neurons (55, 110, 111). Later, it was discovered that this was a property of all members of the neuroligin family and their presynaptic binding partner β-neurexin (56, 57, 61). Endogenously however, neuroligin-1 and -3 are enriched at excitatory synapses, whereas neuroligin-2 is enriched at inhibitory synapses (56, 112, 113). Interestingly, the ability of neuroligins to drive formation of excitatory and inhibitory synapses seems to require interaction with β-neurexin, the same presynaptic partner for which it was originally identified. Treatment of cultured neurons with a soluble form of β-neurexin blocks the formation of both excitatory and inhibitory synapses (52, 56). Another surprising new finding is that neuroligins can also interact with α-neurexin, and this process is regulated by alternative splicing (114, 115) These data suggest that the properties of a particular synapse may be dictated by a specific combination of neuroligins and neurexins at certain neuronal contacts. How neuroligins are able to drive the formation of both excitatory and inhibitory synapses using the same presynaptic partner remains unclear. Secondary presynaptic binding partners or cross-talk with other adhesions systems may account for this phenomenon, but this remains to be determined.

5. PLASTICITY AND SIGNALLING

Expression of many cell adhesion molecules persists into adulthood, and as such, has been hypothesized to play a role in the activity-dependent rearrangement of synaptic contacts, which in turn play a role in modulating the change in synaptic strength associated with learning and memory. Indeed, several adhesion complexes are capable of sensing synaptic activity and transmitting this information to both pre- and postsynaptic compartments through signal transduction cascades, which ultimately can change the physiology of the synapse. The expression level of several CAMs is regulated by activity, and these newly synthesized molecules can participate in modification of synapse content and activity. For instance, N-cadherin, NCAM and L1 are up-regulated by distinct firing patterns of action potentials (116), in addition, the promoter for NCAM is sensitive to AMPA receptor activity (117). Function blocking antibodies, peptides, and gene knockout approaches have been used to study several CAMs, including integrins, cadherins, ehprins and NCAM in the modulation of synaptic plasticity and animal behavior. Some of the roles of these CAMs in the establishment and maintenance of synaptic plasticity are discussed below.

Integrins potentially play an important role in modulating synaptic plasticity due to their multiple roles in adhesion, signal transduction and cytoskeletal organization. Several subunits are expressed in neurons and glia of the developing and adult brain (118), and several isoforms have been localized to synapses of the NMJ and CNS (119, 120). Interestingly, blocking integrin function in the adult rat hippocampus with an RGD sequence peptide, which interferes with integrin binding to it's endogenous ligands in the extracellular matrix, causes a decay of long-term potentiation (LTP), an enduring enhancement of excitatory synaptic transmission extensively studied as a potential

correlate of learning and memory (121, 122). The molecular correlate of this decay in LTP may be due to changes in the composition or properties of the synapse. Indeed, chronic blockade by RGD peptides, or by functional antibodies against β3 integrin subunit, has been demonstrated to prevent activity-dependent reduction in the probability of release of glutamate and the switch in subunit composition of NMDA receptors from NR2A to NR2A/B (123). These results demonstrate the importance of integrins in plasticity. RGD peptides causes an increase in the tyrosine phophorylation and activity of several kinases, resulting in enhanced phosphorylation of NMDA receptors, a greater NMDA response, and a subsequent insertion of additional AMPA receptors which can act as a feed-forward mechanism for the expression of more integrin proteins (124-127). Integrin-associated protein (IAP) has been shown to be involved in tyrosine signaling and influences memory performance, in LTP in rats (128). In *Drosophila*, the locus linked to the *Volado* mutant encodes two isoforms of α-integrin expressed in the olfactory mushroom bodies. The *Volado* mutant has impaired olfactory associative memory, and interestingly no gross structural abnormalities (129). Thus, integrin signaling rather than structural support may be predominant for its role in LTP and associative memory. Whether the signaling of integrins is a universal phenomenon important for other forms of plasticity such as long-term depression (LTD) remains to be determined.

Many studies on synaptic plasticity have focused on two members of the Ig superfamily, NCAM and L1. NCAM is encoded by a single gene located on chromosome 11, and as a result of alternative splicing, is synthesized in three main membrane-bound isoforms (NCAM-120, NCAM-140, and NCAM-180) which differ in their C-terminals. NCAM-180 and -140 are transmembrane proteins, with different length intracellular domains, whereas NCAM-120 is attached to the membrane by a glycosylphosphalitdyl-inositol (GPI) anchor. All three isoforms have a conserved extracellular domain consisting of 5 Ig domains followed by 2 fibronectin type III repeats. Initial studies *in vitro* demonstrated a reduction in LTP when antibodies to NCAM were injected during induction (130, 131). Further studies in constitutive and conditional NCAM knockout mice showed impairments in LTP (132, 133). Since NCAM is the only carrier of polysialic acid (PSA) in mammalian brains, significant efforts have been made to determine its function. Enzymatic removal of PSA inhibits LTP and LTD in the hippocampus, as well as suppresses spatial learning (134-136). Similarly, implication of the interaction between L1 and NCAM in the establishment of LTP was first established *in vitro,* where antibodies that block L1 and NCAM interaction were specific to LTP, as no change was noted in the basal level of synaptic transmission, resting membrane potential, shape of the action potential, or input resistance of the affected pyramidal cells (130).

In vivo, antibodies against L1 or NCAM infused into the hippocampus of rats, decreases efficiency of spatial learning tasks such as the Morris water maze (137) L1 knockout mice show similar learning impairments (138), but surprisingly, L1 knock-out mice show no defects in the establishment or maintenance of LTP in hippocampus (107), and the observed learning impairment may be due to dysfunction in other brain regions. This apparent contradiction with L1 antibody experiments may be due to compensation by other adhesion systems in L1 knockout mice or activation of L1 signaling by the antibody. Whether L1 activation is relevant in normal synaptic transmission remains to be determined.

The membrane associated Eph receptor tyrosine kinases (RTK's) have been also implicated in synaptic plasticity. Ephrins are a large family of 14 receptors, and 8 ligands known as ephrins. Eph receptors and ephrin ligands are expressed through out the developing and mature nervous system and were initially characterized based on their ability to guide axons to their proper targets. Later studies revealed that these proteins are present at synapses (139-141). Because both Eph receptors and ephrin ligands are membrane associated, they are able to mediate cell-cell adhesion. Eph receptors are divided into two classes: transmembrane EphA and GPI-linked EphB, which bind ephrin A and ephrin B respectively. Ephrins must be clustered to bind and activate their cognate receptor (142). The EphB-ephrinB receptor-ligand pair is of particular interest due to their ability for bidirectional signaling (139), and this ability for reciprocal signaling has been hypothesized to co-ordinate changes in the presynaptic and postsynaptic terminals during LTP. On the postsynaptic membrane, addition of ephrin B induces interaction between EphB and NMDA-type glutamate receptors, an increase in NMDA-mediated calcium influx and gene expression (143, 144), consequentially potentiating the response of the postsynaptic neuron to synaptic activity. Disruption of Eph/ehprin signaling by interfering peptides has been demonstrated to interfere with the retrograde signaling through ephrin B, blocking long term changes in release probability thus blocking LTP at mossy fibers in the hippocampus (145). Although these studies showed that ephrin B act presynaptically, other groups demonstrated that ephrin B plays a role at postsynaptic sites. Ephrin B2 interacts with postsynaptic metabotropic receptors which have previously implicated in LTP (129). Ephrin B2 also interacts with NMDA receptors, and this interaction was demonstrated to be important during induction of LTP (146, 147). Regardless of the orientation of the ephrinB/EphB, this adhesion system has offered insight into some of the trans-synaptic signaling cascades associated with activity-based synaptic plasticity such as LTP. The two apparently apposing hypotheses of presynaptic versus postsynaptic induction of LTP have been brought together by knowledge gained form the study of a trans-synaptic adhesion complex.

Despite the fact that inhibitory synapses are essential for proper functioning of a neural network, little attention has been given to describing and characterizing the forms of plasticity at inhibitory synapses. Both LTP and LTD of inhibitory synapses has been reported in a variety of brain regions, including the hippocampus, cortex, cerebellum and brain stem (148). In common with plasticity at excitatory synapses, all forms of plasticity at

inhibitory synapses are triggered by a rise in intracellular calcium. For instance in the neonatal rat, the same conditioning protocol can lead to either LTP or LTD at GABAergic synapses, depending on whether the source of calcium influx is through voltage-dependent calcium channels or NMDA receptors respectively (149, 150). Interestingly, recent studies showed that the probability of triggering LTP at GABAergic synapses is restricted to the first postnatal week in the hippocampus (151). In the future, it will important to determine the roles and consequences of activity-dependent plasticity of inhibitory synapses in the development and function of neural networks.

6. MODULATION OF THE FUNCTION OF CELL ADHESION MOLECULES BY SCAFFOLDING PROTEINS

The number of excitatory versus inhibitory (E/I) contacts that a single neuron receives dictates neuronal excitability and function. Precise control systems must be established in each neuron to maintain appropriate numbers of excitatory and inhibitory synapses. The new finding that neuroligins can induce both excitatory and inhibitory synapses, makes them attractive candidates to regulate the E/I ratio. Recent studies show that all neuroligin family members have the inherent ability to affect both excitatory and inhibitory synapse formation, however it is apparent that interplay between neuroligins and their synaptic partners can restrict their influence to a particular synapse type. For instance, over-expression of neuroligin-1 or -2 with the excitatory scaffold PSD-95, restricts neuroligins to induce only excitatory contacts (55, 56). By assembling a core complex containing stargazin, AMPA receptors, and cell adhesion molecules, proteins such as PSD-95 may then determine excitatory synapse identity, whereas other unidentified adaptor proteins may control sorting and stabilization of cell adhesion molecules at inhibitory postsynaptic sites (152).

As previously eluded to, the scaffold molecule PSD-95 is implicated in excitatory synapse development. PSD-95 is a member of the MAGUK (membrane-associated guanylate kinases) family of synaptic proteins. MAGUKs share a common domain organization, with one or three N-terminal PDZ (PSD-95, Dlg and ZO-1) domains, an SH3 domain, and a C-terminal region homologous to guanylate kinases. PDZ domains mediate protein-protein interactions and typically bind to short amino acid motifs at the C-termini of interacting proteins that include certain ion channels and receptors (153). PSD-95 has been implicated in synapse development since it clusters at synapse precursors before many other postsynaptic proteins (25), and because discs-large (DLG), a PSD-95 homolog in *Drosophila*, is necessary for proper development of larval neuromuscular junctions (154). Significantly, PSD-95 is able to mediate changes in postsynaptic components which are accompanied by enhanced presynaptic maturation, indicating that PSD-95 induces the assembly of necessary molecules at the PSD to co-ordinate the maturation of pre- and postsynaptic elements (155). The requirement for PDZ domains in this process suggests the involvement of PDZ-interacting proteins in synapse maturation. PSD-95 may mediate this cross-synaptic maturation by the recruitment of adhesion molecules**.** At the PSD, neuroligin-1 associates, through its C-terminal PDZ-binding site, with the third PDZ domain of PSD-95, and the first PDZ-binding domain of S-SCAM (156, 157). The interaction between neuroligin-1 and these scaffolding molecules may co-ordinate recruitment of other synaptic proteins.

Similar to neuroligins, neurexins also contain PDZ-binding motifs that bind to type II PDZ domains present in CASK and syntenin (158, 159). Association of β-neurexin to a tripartite protein complex formed of CASK, Mint-1 and Veli has been proposed to act as a nucleation site for coupling cell adhesion molecules to synaptic vesicle exocytosis (160). Neurexins are also directly coupled to synaptotagmins, core molecules of the synaptic vesicle release machinery (161). The *Drosophila* protein DLG, is found on both sides of the synapse, and this is also true for the mammalian homologue SAP-97 (162). Interestingly, presynaptic expression of DLG rescues the postsynaptic structural defects better than when it is expressed postsynaptically (163). Thus, assembly of postsynaptic scaffolding proteins and trans-synaptic cell adhesion molecules may help coordinating recruitment of pre- and postsynaptic elements and synapse maturation.

Interactions between adhesion and scaffold proteins are not restricted to the neuroligin-neurexin adhesion complex. For instance, nectins also contain an N-terminal PDZ domain that interacts with PICK-1 in epithelial junctions (164), however, the role of this complex has not been assessed in synapses. The C-terminal region of cadherin interacts with A-kinase-anchoring protein (AKAP) 79/150. It has been shown that AKAP organizes a scaffold of cAMP-dependent protein kinase (PKA), protein kinase C (PKC), and protein phosphatase 2B/calcineurin, that regulates phosphorylation pathways underlying neuronal LTP and LTD (165). The scaffold protein spectrin has also been shown to be important for the accumulation of pre- and postsynaptic proteins in *Drosophila* and mammals (166, 167). Trans-golgi organelles are linked via spectrin to NCAM in the plasma membrane of hippocampal neurites, and these complexes can be relocated and trapped at initial sites of contact (168). In addition, spectrin directly binds to NMDA receptors, and can be co-isolated with L1 (169, 170). Thus, we are just beginning to understand the complex interactions between adhesion complexes and scaffolding complexes and further research is required to determine the functional relevance of these interactions.

Another important theme emerges from recent findings is that stoichiometry between adhesion molecules and scaffolding proteins may regulate their targeting to and/or retention at contact sites, thereby dictating the number and type of synapses formed. Whether scaffolding molecules cooperate or compete with one another to regulate adhesion molecules at the synapse remains to be determined. Competitive interactions may be determined by differential affinities of postsynaptic scaffolding proteins for certain adhesion molecules, whereas

scaffolding proteins present at presynaptic terminals, such as Bassoon and Piccolo, may then indirectly cooperate with postsynaptic scaffolding proteins such as PSD-95 and Shank, to stabilize synapses (171). The importance of scaffold proteins in adhesion is an attractive hypothesis since they may represent a vehicle for crosstalk between different sets of adhesion molecules at the synapse, thus coordinating the multiple proteins and events of synaptogenesis.

7. SYNAPTIC IMBALANCE IN PSYCHIATRIC DISORDERS

As outlined previously, several CAM's function to drive the formation of excitatory and inhibitory synapses, and as such, dysfunction of these adhesion systems are believed to play important roles in the etiology of several developmental psychiatric disorders, such as autism and schizophrenia, which are thought to be caused by abnormal neuronal wiring and imbalance in E/I ratio (172).

Autistic disorder is a chronic and debilitating syndrome characterized by complex behavioral and cognitive deficits including abnormal social interaction and communication, repetitive behavior and atypical information processing (American Psychiatric Association: 1994). A number of studies have confirmed that autism has an important genetic component, since twin studies show high concordance rates for monozygotic twins. It has been proposed that autism may be due to a disruption in postnatal, or experience-dependent synaptic activity, and recent investigations indicate that an imbalance between excitatory and inhibitory synaptic transmission (173). Thus the model proposed suggests enhanced E/I neurotransmission due to either enhanced excitation or reduced inhibition, and this enhanced excitability may interfere with memory formation and results in defects manifested in the social and behavioral abnormalities associated with this disorder. Therefore, molecules important in the proper establishment and function of synapses are expected to play a potential role in the expression of autism. Mutations in neuroligin-3 and -4 have been identified in some autistic patients (174-176), and the ability of neuroligins to form both excitatory and inhibitory synapses, as described herein, makes them attractive candidates for the etiology of autism. Indeed, *in vitro* studies using neuroligin with the aforementioned mutations leads to decreased surface expression, although the few mutant neuroligin molecules recruited to the cell surface were still able to induce synapse formation (177-179). However more recent studies indicate that mutations in the genes encoding neuroligin are not common among all autistic patients (180-183). The result that autism is not due to a mutation of a single gene is not surprising considering the heterogeneity of autism' expression, however, it is likely that additional candidates within the cell adhesion families will be implicated due to their prominent role in synaptogenesis.

Schizophrenic illnesses occur in all populations with a characteristic and sex-dependent distribution of ages of onset. Dysregulation of several synaptic proteins, and in particular NCAM, have been associated with schizophrenia in numerous studies. A soluble NCAM fragment containing most of its extracellular region (NCAM-EC) is elevated in postmortem brain and the cerebral spinal fluid of affected patients (184, 185). NCAM-EC does not arise from the secreted splice-variant, but appears to be derived from proteolytic cleavage (185). Although the enzyme responsible is unknown, it may be related to the metalloprotease cleavage of NCAM implicated in LTP (186, 187). It is hypothesized that NCAM-EC acts as a dominant-negative to inhibit NCAM interactions leading to functional changes that underlie the disease state of schizophrenia. The molecular and functional rearrangements underlying this were explored using transgenic mice expressing NCAM-EC. These mice displayed a striking reduction in GABAergic synapses in specific areas of the brain, as well as, excitatory synapses as measured by decreases in dendrite spine number. Behavioral analysis of these mice demonstrated abnormalities, such as higher basal locomotor activity and enhanced responses to amphetamine that are relevant to schizophrenia and other neuropsychiatric disorders (188). NCAM null mice also have morphological changes in brain regions implicated in schizophrenia, but surprisingly, these mice show no alterations in sensory gating, a behavioral hallmark in schizophrenic patients (189). An explanation for this lack of phenotype may lie in the two-hit hypothesis for schizophrenia where a single intervention early in development, such as a genetic dysfunction, may not be sufficient to induce schizophrenia, but only increases the susceptibility. It is only in combination with other events in life that this vulnerability may lead to the development of the disease (190). Interestingly, stress is the often cited 'second hit'. Stress has profound effects on brain structure and function. The neural remodeling that is induced by prolonged stress involves the functional destabilization of membrane proteins in the organization and maintenance of neural circuits, and the simultaneous interaction with the actin cytoskeleton. Ideal candidates for such functions are CAMs, and recent evidence has implied L1 and NCAM. Chronic stress in animal models leads to decreased expression of NCAM-140 in the hippocampus, but increases in the expression of PSA-NCAM and L1 (191, 192). These changes in CAM expression are believed to be the basis of impaired synaptic plasticity and cognitive function that are associated with chronic stress. The role of other adhesion molecules in schizophrenia and stress has not been explored, but it is evident that at least NCAM an L1 are implicated in both the genetic predisposition and environmental stimuli hypothesized to be responsible for this neuropsychiatric disease.

8. CONCLUSIONS

Cell adhesion molecules play a prominent role in all stages of synapse assembly, from contact initiation to stabilization, and several CAM's play roles at multiple steps in this process. Recent research into the roles of adhesion molecules in synapse formation has brought much insight into the basic principles governing the formation of the NMJ, glutamatergic, and GABAergic synapases.

However, considering the existence of numerous cell adhesion molecules, it is clear that our knowledge has barely scratched the surface of the potential these molecules have in regulating the formation of synapses. Moreover, the adhesion systems governing the formation of many other types of synapses, such as dopaminergic and serotonergic synapses, remains largely unknown. Through continued work discovering the many interactions and signaling cascades, as well as, elegant imaging studies in the trafficking of these proteins, we will have a deeper understanding of the nuances governing synapse formation, and how disruption of their function may underlie neurological disorders.

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Key Words: Synapse Formation, Adhesion, CNS, Central Nervous System, NMJ, Review

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