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Building and Remodeling Synapses

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Abstract

Synaptic junctions are generated by adhesion proteins that bridge the synaptic cleft to firmly anchor pre- and postsynaptic membranes. Several cell adhesion molecule (CAM) families localize to synapses, but it is not yet completely understood how each synaptic CAM family contributes to synapse formation and/or structure, and whether or how smaller groups of CAMs serve as minimal, functionally cooperative adhesive units upon which structure is based. Synapse structure and function evolve over the course of development, and in mature animals, synapses are composed of a greater number of proteins, surrounded by a stabilizing extracellular matrix, and often contacted by astrocytic processes. Thus, in mature networks undergoing plasticity, persistent changes in synapse strength, morphology or number *must* be accompanied by selective and regulated remodeling of the neuropil. Recent work indicates that regulated, extracellular proteolysis may be essential for this, and rather than simply acting permissively to enable synapse plasticity, is more likely playing a proactive role in driving coordinated synaptic structural and functional modifications that underlie persistent changes in network activity.

Keywords

synapse; proteinase; cell adhesion molecule; synaptic cleft; extracellular matrix; MMP; CAM

Synapse adhesive structure

At CNS synapses, presynaptic terminals are bound to postsynaptic sites by a trans-synaptic adhesive apparatus that spans the intervening cleft. The synaptic cleft is defined by rigidly parallel membranes separated by 15–25 nm, and despite its name, is filled with proteins. High-resolution, ultrastructural techniques have revealed the presence of two sets of filaments within synaptic clefts. The first range between 4 – 6 nm and bridge the cleft (Ichimura and Hashimoto, 1988; Landis and Reese, 1983). These filaments are sparsely but evenly distributed and undoubtedly contribute mechanically to junction adhesion. Consistent with this interpretation, recent work employing a cryo-EM technique that circumvents fixation and staining entirely reveals regularly distributed clusters spanning the cleft about 8.5 nm apart (Zuber et al., 2005). The second population of filaments that have been identified runs parallel to the apposing membranes (Ichimura and Hashimoto, 1988; Lucic et al., 2005). Proteins that are enriched in this zone can be stained with EPTA or bismuth iodide (Bloom and Aghajanian, 1968; Pfenninger, 1971a; Pfenninger, 1971b), suggesting that they are rich in basic residues, but the identities of the proteins comprising either bridging or parallel filaments are unknown.

Variance according to classification and age

All CNS synapses share a similar, readily identifiable structure. This generalization also holds true for the adhesive structure of synapses, but there are particular types or classes of synapse that have noteworthy distinctions. For example, in cerebral cortex, Gray found the distance across synaptic clefts to be approximately 20nm for Type I (excitatory) synapses, but only 12nm for Type II (inhibitory) synapses (Colonnier, 1968; Gray, 1959). Excitatory synapses also appear to fall into groups based on location: those on dendritic shafts are longer and straighter than those forming on spines (Aoto et al., 2007; Zhang et al., 1999).

Both synapse structure and adhesion evolve as synapses mature. Postsynaptic densities at young synapses are thin and similar in thickness to presynaptic densities (Elste and Benson, 2006; Vaughn, 1989). This makes them appear very much like the adherens junctions that form between epithelial cells. Consistent with this similarity, actin depolymerizing agents disassemble all synapses forming between young hippocampal neurons grown in culture, and isolated synaptosomes prepared from early postnatal cortex are sensitive to calcium depletion and trypsin (Khaing et al., 2006; Zhang and Benson, 2001). In contrast, actin depolymerization in mature synapses deflates dendritic spines (Allison et al., 1998), but does not detectably alter basic synapse ultrastructure (Zhang and Benson, 2001), and synaptosomes from mature brain are resistant to calcium depletion and trypsin (Cotman and Taylor, 1972; Pfenninger, 1971b; Zhang and Benson, 2001). Thus, young and mature synapses utilize different means to stabilize trans-synaptic adhesion.

Proteins that adhere across the cleft

Several CAM families are found enriched at CNS synapses. Those that have been demonstrated to act in hippocampal neurons include the Neurexins, which bind either Neuroligins (NLs) or Leucine-rich repeat transmembrane proteins (LRRTMs), classic Cadherins, Protocadherins, SynCAMs, Synapse adhesion-like molecules (SALMs), Nectins, Netrin-Gs and Netrin-G ligands, Integrins, EphB receptors and EphrinBs (Fig. 1). Members of each of these families have been shown to influence synapse assembly, stability, and/or function, and they can all bind adhesively. Considerably less is known about their individual contributions to trans-synaptic adhesion, synapse structure, or stability and how these structural roles relate (if at all) to synapse targeting or selectivity. It is not known whether members of these families are represented at all synapses, or whether particular families form a structural core around which the others act as modifiers. Additionally, the results of a recent screen for proteins that can promote presynaptic terminal formation suggest that there are additional families that have yet to be characterized (Linhoff et al., 2009). This level of knowledge of CNS synapse composition stands in stark contrast to the clear relationships that can be drawn between molecules and structure at immune synapses, adherens junctions, and even at neuromuscular junctions (e.g. (Knight et al., 2003; Noakes et al., 1995; Patton et al., 2001)).

A great deal of information has been published on synaptic CAMs, and most CAM families have been the subjects of in-depth reviews (e.g. (Akins and Biederer, 2006; Craig and Kang, 2007; Dalva et al., 2007; Hirano et al., 2003; Morishita et al., 2006; Scheiffele, 2003; Shapiro et al., 2007; Waite et al., 2005; Yamagata et al., 2003)). In light of this, we are outlining briefly the attributes and major interactions of the most prominent or best understood synaptic CAM families in order to provide a backdrop for subsequent discussion, but this overview is not meant to be comprehensive and the reader is referred to the reviews cited above for greater detail.

Neurexins, NLs, and LRRTMs

Presynaptic Neurexins bind to postsynaptic NLs or LRRTMs in a calcium-dependent fashion (de Wit et al., 2009; Dean et al., 2003; Ko et al., 2009; Siddiqui et al., 2010; Song et al., 1999) or to a GluD2/cerebellin1 complex in cerebellum (Uemura et al., 2010). Neurexins and NLs can be differentially spliced and this contributes to their binding selectivity (Boucard et al., 2005; Chih et al., 2005; Comoletti et al., 2006; Graf et al., 2006; Ichtenko et al., 1996; Ko et al., 2009). Interactions between Neurexins and any of their partners can induce the formation of presynaptic terminals (de Wit et al., 2009; Ko et al., 2009; Scheiffele et al., 2000). NL-2 shows a greater specificity for inhibitory synapses, and NL-1, for excitatory synapses (Chubykin et al., 2007; Graf et al., 2004; Pouloupoulos et al.; Song et al., 1999; Varoqueaux et al., 2004), while LRRTM1 and 2 and GluD2/cerebellin1 appear to act exclusively at excitatory synapses (de Wit et al., 2009; Ko et al., 2009; Siddiqui, 2010 #3447; Linhoff et al., 2009; Uemura et al., 2010). Conversely, Neurexins can stimulate the formation of a functional postsynaptic apparatus in neurons (Barrow et al., 2009; Graf et al., 2004; Nam and Chen, 2005). Interestingly, LRRTM1 can also promote glutamatergic postsynaptic differentiation (Linhoff et al., 2009), but it is not yet clear whether this action is mediated via Neurexin, which is largely presynaptic, but can also be localized to postsynaptic sites (Taniguchi et al., 2007). Synaptogenic interactions between Neurexins and either NLs or LRRTM1 and 2 have been verified by several labs and are well understood in cultured neurons, but the principal roles that these proteins play *in vivo* is less well understood. Some data support that binding between Neurexins and NLs may be more relevant for promoting activity-dependent synapse selectivity than for assembly per se (Chubykin et al., 2007; Prange et al., 2004). Consistent with this idea, mice lacking NLs1-3 can develop morphologically normal synaptic junctions, but there are clear functional abnormalities (Varoqueaux et al., 2006).

Classic Cadherins and Protocadherins

Classic Cadherins ("Cadherins") are also calcium-dependent CAMs that confer strong adhesion at synapses similar to their role at epithelial cell junctions. Adhesion is homophilic and appears to involve principally the first two extracellular Cadherin domains, which can interact in both *cis* and *trans*. *Trans* interactions are strengthened by clustering, which can be regulated by interactions with intracellular binding partners (Yap et al., 1998). Different neurons in different regions of the brain express distinct cohorts of Cadherins, and they may participate in synapse specification (Benson et al., 2001; Hirano et al., 2003; Suzuki et al., 1997). At developing synapses, Cadherin adhesion is not sufficient to induce synaptogenesis, but it is crucial for synapse adhesion (Bozdagi et al., 2004; Scheiffele et al., 2000; Togashi et al., 2002), and consistent with this role, N-cadherin is distributed evenly and throughout synaptic clefts (Elste and Benson, 2006; Yamagata et al., 1995). As synapses mature, Cadherins become dispensable for the maintenance of synaptic junctions, and become concentrated into a few discrete clusters (Elste and Benson, 2006; Uchida et al., 1996).

The clustered Protocadherin (Pcdh) gene family consists of α -Pcdh, β -Pcdh, and γ -Pcdh subfamilies. The subfamilies are organized into 14–22, 5' variable exons, each one of which encodes an entire extracellular domain. Each variable exon is controlled by a separate promoter that in the α - and β - subfamilies can be spliced to a subfamily-specific constant exon encoding a common intracellular domain. β -protocadherins are generated similarly, but do not share a constant intracellular domain (Wu and Maniatis, 1999). In addition to the 58 clustered Protocadherins, which are encoded within a gene locus and generated by alternative splicing, there are 13 non-clustered Protocadherins that are each encoded by separate genes (Morishita et al., 2006). The nature of Pcdh binding interactions is an area of active investigation in part because mutations in Pcdhs have been associated with mental

retardation, epilepsy, deafness and susceptibility to a variety of neuropsychiatric disorders (El-Amraoui and Petit, 2010). There is evidence for both heterotypic (Kazmierczak et al., 2007) as well as homotypic interactions (Fernandez-Monreal et al., 2009; Morishita et al., 2006), but generally, Pcdh interactions appear to be inherently weaker than those of classic cadherins (Kohmura et al., 1998; Triana-Baltzer and Blank, 2006). Individual neurons appear to express particular Pcdh cohorts, suggesting that Pcdhs may participate in a combinatorial recognition code (Esumi et al., 2005; Kaneko et al., 2006). Functionally, α -Pcdhs have been linked to olfactory sensory axon sorting into glomeruli within the olfactory bulb (Hasegawa et al., 2008), while γ -Pcdhs are required for survival of spinal interneurons (Wang et al., 2002), localize in part to synapses (Li et al., 2010; Phillips et al., 2003) and influence synapse development (Garrett and Weiner, 2009; Wang et al., 2002; Weiner et al., 2005). Recent work supports that γ -Pcdhs can also regulate the shape and trafficking of intracellular organelles (Fernandez-Monreal et al., 2009; Hanson et al., 2010).

Ig Superfamily

The Ig superfamily is exceptionally large and diverse, but all members share Ig domains, which are thought to confer recognition and adhesion.

Neural cell adhesion molecule (NCAM) was the first CAM identified in the nervous system (Thiery et al., 1977). In cultured hippocampal neurons, NCAM is rapidly recruited to newly forming synaptic contacts (Sytnyk et al., 2002) and postsynaptically can selectively promote the generation or stabilization of excitatory synapses (Dityatev et al., 2000). NCAM participates in the normal development of presynaptic mossy fiber terminals in CA3 and plays a central role in long term potentiation (LTP) at these synapses (Cremer et al., 1998; Eckhardt et al., 2000). At the neuromuscular junction, NCAM is required for sustained neurotransmitter release and presynaptic terminal maturation (Polo-Parada, et al, 2001), but it is not yet known whether it is utilized similarly at central synapses. NCAM and SynCAM1 are also the principal sites for the addition of polysialic acid (PSA) (Galuska et al.; Rutishauser, 2008), which contributes to both the proper assembly of hippocampal circuits and long term plasticity (Eckhardt et al., 2000). Members of the L1CAM family play broad roles in circuit assembly (e.g. (Cohen et al., 1997; Dahme et al., 1997; Demyanenko and Maness, 2003), but may also prove to be important generally for positioning inhibitory synapses: mice lacking Close Homolog of L1 (CHL1) show an increase in the size and density of perisomatic inhibitory synapses in hippocampus, and Neurofascin is required for proper targeting of GABAergic synapses to Purkinje cell axon initial segments (Ango et al., 2004; Nikonenko et al., 2006).

SynCAMs (or NECLs), when expressed in heterologous cells, can induce the formation of excitatory presynaptic terminals. Individual SynCAMs show heterophilic binding preferences (Fogel et al., 2007; Spiegel et al., 2007). In neurons, overexpression of SynCAM1 increases excitatory synapse function, but does not influence synapse number (Sara et al., 2005) suggesting that *in vivo* it may act to promote maturation rather than assembly.

Synapse adhesion-like molecules (SALMs) are postsynaptic CAMs that were identified by their interactions with postsynaptic scaffolding proteins, SAP97 and PSD-95. In addition to an extracellular Ig domain and fibronectin repeat, SALMs have several LRR domains. SALM-3 and -5 can promote the formation of excitatory and inhibitory presynaptic terminals, but only SALM-3 binds to PSD95 (Mah et al., 2010). SALM4 and 5 can bind homophilically in trans, but the other SALMs cannot (Seabold et al., 2008). Other SALM family members may regulate synapse maturation: SALM1 interacts with and can recruit NMDARs while SALM2 can recruit AMPARs and regulates postsynaptic recruitment of

PSD95. SALM2 knockdown in cultured hippocampal neurons decreases the frequency of EPSCs (Ko et al., 2006; Wang et al., 2006).

The Nectin family is related to the SynCAM family. Nectins work coordinately with Cadherins to form adherens junctions between epithelial cells. Both Nectins-1 and-3 concentrate at developing mossy fiber synapses in hippocampus (Mizoguchi et al., 2002; Tachibana et al., 2000), but as synapses mature, Nectins are excluded from active zones and concentrate at adjacent adherens junctions (Mizoguchi et al., 2002). This developmentally regulated synapse distribution pattern bears some similarity to that for Cadherins and suggests that the two families may cooperate during synapse assembly. Additionally, binding between presynaptic Nectin-1 and postsynaptic Nectin-3 in cultured hippocampal neurons contributes to axon-dendrite recognition, an essential step in the polarization of synaptic junctions (Togashi et al., 2006).

Netrin-G ligands (NGLs)

Postsynaptic NGL-2 contains a LRR and an Ig domain and can induce the formation of presynaptic terminals. It can bind to Netrin-G2 (or Laminin-2), a GPI-linked protein located presynaptically, but Netrin-Gs may utilize a co-receptor as their binding alone appears insufficient to account for a presynaptic induction event (Kim et al., 2006; Lin et al., 2003b; Nishimura-Akiyoshi et al., 2007). NGL-Netrin-G interactions are modestly adhesive (Kim et al., 2006), and they are expressed in distinct neuronal populations (Kim et al., 2006; Nakashiba et al., 2002; Nishimura-Akiyoshi et al., 2007; Yin et al., 2002), suggesting they will play a role in synapse specification.

Integrins

Integrins are a large family of membrane-spanning, heterodimeric (α - β) receptors for proteins of the extracellular matrix (ECM) and other proteins including CAMs (Hynes, 1992). Many of the ~20 subunits known have been found in hippocampus, although in area CA1, α 3, α 5, α 8, α v, β 1 and β 5 are the dominant Integrin subunits (Pinkstaff et al., 1999). In mice lacking β 1-integrin in forebrain excitatory neurons throughout development, synapses can assemble but show diminished AMPAR-mediated synaptic transmission, impaired responses to high-frequency stimuli and exhibit decreased LTP (Chan et al., 2006; Huang et al., 2006). Mice having a conditional deletion of α 3-integrin show similar deficits in LTP with no alterations in basal synaptic transmission (Chan et al., 2007), suggesting the impact on LTP is separable, an interpretation that is also consistent with findings following pharmacological blockade of β 1- or α 3-integrins (Chun et al., 2001; Kramar et al., 2002; Kramar et al., 2006).

Intriguingly, mice lacking either β 1- or α 3-integrins exhibit normal behavior in hippocampal dependent spatial and contextual memory tasks and show deficits only in a hippocampal dependent working memory task (Chan et al., 2007; Chan et al., 2006; Huang et al., 2006). Thus, Integrins appear to participate in functional differentiation and synapse plasticity. Work in cultured hippocampal neurons supports that β 3-integrins can promote synapse differentiation (Chavis and Westbrook, 2001) and regulate the surface expression and composition of AMPARs (Cingolani et al., 2008). Despite the clear importance of this family to synapse maturation and function, little is known about the localization of Integrins at synapses (Einheber et al., 1996).

Ephs and Ephrins

Interactions between postsynaptic EphB receptor tyrosine kinases and presynaptic Ephrin B1 or 2 promote the formation of glutamatergic terminals in dissociated hippocampal neurons (Kayser et al., 2006; McClelland et al., 2009). Postsynaptic EphrinB3 selectively

promotes the formation of glutamatergic synapses that form on dendritic shafts (Aoto et al., 2007). EphBs also promote postsynaptic morphological and functional maturation (Henkemeyer et al., 2003). Mice lacking single EphB receptors do not show obvious synapse deficits, but mice lacking EphB1-3 have reduced synapse numbers and diminished spine size suggesting there is functional redundancy between these family members (Henkemeyer et al., 2003; Kayser et al., 2006)]. EphB/ephrinB binding is modestly adhesive (Pfaff et al., 2008), but more significantly, their interaction promotes forward and reverse signaling that could stimulate the recruitment of other adhesive families.

Extracellular Matrix (ECM)

A number of glycoproteins and proteoglycans, particularly chondroitin sulfate proteoglycans, constitute the neural ECM (Dityatev and Schachner, 2003; Ruoslahti, 1996; Viapiano and Matthews, 2006). These and other ECM proteins, including Reelin, Tenascins, Thrombospondins and Agrin, among others, are an important component of the extracellular space in both developing and mature brain, which occupies a volume fraction of between 15 and 30% in normal adult brain tissue (for review, see (Sykova and Nicholson, 2008)). A variety of functions have been attributed to brain ECM, including mechanical support and stabilization of synapses and processes, control of the diffusion characteristics of extracellular ions and other molecules, cell signaling, and compartmentalization of cell surfaces (for review, see (Gundelfinger et al., 2010)). At mature synapses, synaptic cleft proteins are largely resistant to hyaluronidase treatment, suggesting that hyaluronic acid-based ECM is probably not concentrated within the synaptic cleft (Bloom and Aghajanian, 1968). Consistent with this, localization studies of ECM components indicate that most ECM surrounds and supports cell somata, dendrites, and mature synapses in the form of peri-neuronal nets (Celio et al., 1998; Matthews et al., 2002; Thon et al., 2000; Yamada et al., 1997), and may function here both to constrain spine morphological dynamics (Oray et al., 2004) as well as control mobility of cell-surface proteins such as glutamate receptors (Frischknecht et al., 2009). Similarly, Reelin, which is secreted by GABAergic interneurons in mature brain (Alcantara et al., 1998; Pesold et al., 1998), has been implicated in the regulation of synapse and spine number, NMDA receptor subunit trafficking and composition, and synaptic plasticity (Beffert et al., 2005; Groc et al., 2007; Niu et al., 2008; Pujadas et al., 2010). At developing synapses, some ECM proteins may function within the synaptic cleft. For example, neuronal Pentraxins can bind and cluster surface AMPARs at synapses (O'Brien et al., 1999) and mice lacking Laminin β 2 show a greater variability in synaptic cleft width and PSD length in hippocampus (Egles et al., 2007). The ECM also plays a pro-active role in assembly of synapse structure and function during development. For example, Versican secreted by interneurons of the developing chick optic tectum can promote presynaptic differentiation of innervating axons from retinal ganglion cells (Yamagata and Sanes, 2005) and Thrombospondins secreted by astrocytes promote differentiation of presynaptic terminals in several brain regions by interactions with GABA_A receptor α 2 δ -1 (Christopherson et al., 2005; Eroglu et al., 2009). Additionally, ECM proteins and peri-neuronal nets, in particular, may be important for regulating the timing of the critical period of heightened experience-dependent plasticity in developing sensory neocortex (McRae et al., 2007).

What is the minimal adhesive unit?

The minimal functional adhesive unit required to generate a synapse is not known, but several lines of data indicate that it is composed of several CAM families and that the process is hierarchical (Benson et al., 2001; Scheiffele, 2003; Vaughn, 1989) (Fig. 2). Experiments using heterologous co-cultures of neurons and either HEK cells or COS cells expressing synaptic CAMs indicate that ligation to a synaptogenic protein is required (Biederer and Scheiffele, 2007). However, formation of a presynaptic terminal can also be

induced by a poly-L-lysine-coated bead, suggesting that initial formation, or at least the induction of a presynaptic terminal, is not necessarily specific (Burry, 1980; Lucido et al., 2009; Peng et al., 1987). This idea gains weight from studies of neurons grown in culture where it has been observed that synapses can often form with neurons that would never be a native target *in vivo*. A low level of specificity for initiation would be expected to be accompanied by synapse elimination as inappropriate contacts are lost, and this appears in fact to be the case: *in vivo*, dendritic filopodia innervated by multiple axons become single synapses over time (Fiala et al., 1998), and synapse loss occurs at a higher rate in younger relative to older cultured neurons (Sebeo et al., 2009; Ziv and Smith, 1996). This idea is also consistent with the labile nature of first-formed synapses—a property that allows inappropriate contacts to be readily eliminated.

Co-culture experiments also suggest that a synaptogenic protein alone is not sufficient to generate a junction, and that even young, labile junctions must be composed of more than a single CAM family. The pseudosynapses that can be induced to form between HEK or COS cells expressing synaptogenic proteins remain susceptible to F-actin depolymerization (Wittenmayer et al., 2009). The Cadherins and Integrins expressed endogenously in HEK and COS cells are not sufficient to induce synapse formation, but recent work shows that in cultured neurons, Cadherin expression is required for NLs to promote synaptogenesis (Stan et al., 2010). Consistent with this, we find that neither SynCAMs nor NLs, when expressed in cell lines lacking Cadherins, can generate presynaptic terminals in neurons (Mesias and Benson, unpublished data). Thus, it would seem that members from at least two different CAM families are required to initiate synaptic junction assembly.

As synapses mature, synaptic adhesive structure is strengthened, and this reflects in part the addition of several different CAM families each of which is anchored by cytoskeleton and/or a dense protein scaffold. While each adhesive grouping may operate as an independent unit, some recent work suggests that they may act cooperatively (Siddiqui et al., 2010). Several studies that have reported very modest changes in synapses following the deletion of a single synaptic CAM also support that individual CAM family members can substitute for one another. Even the loss of several CAM family members, such as in mice lacking NLs1-3 or EphBs1-3, results in relatively modest effects in light of the severity of the manipulation—synaptic transmission can be affected, synapse number and even size can be reduced, but overall pre- to postsynaptic cleft morphology remains similar to wild type animals (Henkemeyer et al., 2003; Kayser et al., 2006; Pouloupoulos et al., 2009; Varoqueaux et al., 2006).

Confocal studies that have examined synaptic distribution of various CAM family members support that several families will be present within synapses, but it remains to be determined which CAM groupings are essential, which provide type-specific characteristics, how they are organized (or not) within the synaptic cleft, and probably most importantly, how their intrasynaptic distribution impacts the organization of pre- and postsynaptic scaffolds attached to their cytoplasmic tails.

Synapse function and structure remain plastic into maturity

Developmental periods of synapse and circuit assembly are associated with a heightened capacity for structural and functional plasticity (Hubel et al., 1977). However, the mature synaptic neuropil remains functionally and structurally dynamic, but in a manner that reflects the constraints of supporting an established network (Buonomano and Merzenich, 1998). Such dynamic behavior is thought to be the basis for how new information is learned and stored within cortical circuits (Morris et al., 2003). Persistent changes in synaptic strength, such as LTP or long-term depression (LTD), are thought to arise from rapid

posttranslational modifications and trafficking of synaptic proteins that are coordinated with morphological changes in synapse structure that require modifications of the synaptic adhesive network (Malenka and Nicoll, 1999; Yuste and Bonhoeffer, 2001). There is a large literature documenting synaptic structural remodeling with LTP or LTD, particularly that studied in young neurons, including changes in numbers of dendritic spines or filopodia (Engert and Bonhoeffer, 1999; Hosokawa et al., 1995; Maletic-Savatic et al., 1999; Nägerl et al., 2004); expansions or contractions of spine-heads (Kopec et al., 2006; Matsuzaki et al., 2004; Yang et al., 2008; Zhou et al., 2004); formation of new presynaptic boutons (Antonova et al., 2001; Bozdagi et al., 2000; Colicos et al., 2001); increases in the frequency of perforated or multi-synapse boutons (Toni, 1999); and, in maturity, changes in synaptic morphology and curvature (Desmond and Levy, 1986; Weeks et al., 2000) and spine expansion (Bozdagi et al., 2010). Many such synaptic alterations, but not all, have been linked to learning, experience, or other natural behaviors in a variety of contexts. For example, inhibitory avoidance training, a form of fear-conditioning, is associated with LTP in area CA1 *in vivo* at spatially restricted synaptic sites and drives certain biochemical changes to glutamate receptors identical to those induced by tetanically-evoked LTP (Whitlock et al., 2006). Additionally, growth or elimination of spines and synapses, changes in spine-head volume, or changes in spine motility have been associated with motor skill learning (Harms et al., 2008; Kleim et al., 1996; Xu et al., 2009; Yang et al., 2009) and with visual, somatosensory or exploratory experience (Kitanishi et al., 2009; Lendvai et al., 2000; Mataga et al., 2004; Oray et al., 2004; Wilbrecht et al., 2010). On the presynaptic side, axon branches and presynaptic boutons are also capable of significant structural remodeling over time in adult neocortex (De Paola et al., 2006; Marik et al., 2010; Stettler et al., 2006; Yamahachi et al., 2009). Thus, coordinated synaptic structural and functional remodeling is a mechanism common to many forms of enduring behavioral experience.

Constraints on synaptic structural remodeling

How such structural remodeling occurs is largely unknown, but mechanisms *must* exist to enable dynamic, perhaps transient membrane-membrane associations between neurons and/or between neurons and glia. That structural plasticity occurs at all in adult cortical regions is remarkable given two observations. First, depending on the brain region, astrocytic membranes can associate with perisynaptic membrane to greater or lesser degrees (for review, see (Reichenbach et al., 2010)). The occurrence of puncta adherens junctions—spot welds of strong adhesion—between such astrocytic and neuronal membranes (Spacek and Harris, 1998) suggests, in theory at least, a potential physical restraint on overt synaptic remodeling. The proportions of synapses bearing some degree of astrocytic association or coverage varies widely across brain regions; in some areas, like structures of the olfactory system that exhibit robust structural plasticity throughout life, none of the synapses are ever fully covered (Raisman, 1985); in hippocampus and neocortex, about 60% of the synapses have some degree of partial coverage, but virtually none are fully covered (Spacek and Harris, 1998; Ventura and Harris, 1999; Witcher et al., 2007); in cerebellum, parallel fiber synapses with Purkinje cells are almost fully covered (Grosche et al., 2002; Grosche et al., 1999). Second, ECM proteins in mature brain are often inhibitory to process growth and regeneration (Silver and Miller, 2004), and in some models of experience-dependent plasticity (like ocular dominance plasticity), appear inhibitory to such plastic processes (Berardi et al., 2003). Collectively, these data point strongly to mechanisms that regulate CAMs and/or the ECM in enabling synaptic plasticity. Indeed, many of the CAM families that collaborate in building synapses during circuit assembly have been implicated in such flexibility in synapse structure and function later in life, and there have been several recent, comprehensive reviews on how individual CAMs or CAM families participate in these processes, particularly in the context of loss-of-function effects on LTP at young synapses (Arikkath and Reichardt, 2008; Benson et al., 2000; Dityatev et al., 2008; Tai et al., 2008).

Similarly, ECM molecules such as Laminin, Tenascins, Fibronectin, Brevican, Neurocan, Reelin, Agrin and other ECM glycoproteins have been implicated, in ways yet to be fully defined, in synaptic plasticity (Dityatev and Schachner, 2003). One of the key, open questions is what are the endogenous mechanisms that are engaged during synaptic plasticity, either elicited experimentally or during learning, that could account for local regulation of the synaptic adhesive and/or ECM microenvironment?

Proteolytic cleavage and synaptic plasticity

One long-standing hypothesis is that synaptic plasticity is enabled in part by local proteolysis. This idea had origins in the early recognition of a relationship between synaptic plasticity and proteolytic cleavage, where, for example, Lynch and colleagues proposed an LTP-associated activation of Calpain within the postsynaptic spine as a mechanism for releasing a reserve pool of glutamate receptors for insertion into the postsynaptic density (Lynch and Baudry, 1984).

More recent investigation of this idea has focused on local, extracellularly-mediated proteolysis of CAMs and/or ECM molecules as a mechanism to relieve physical/neurochemical constraints on plasticity (thus acting permissively) and/or initiate signaling cascades that drive downstream pathways that promote plasticity (thus acting proactively). Conceptually, this latter scenario could occur by liberation of latent bioactive protein fragments or growth factors normally sequestered in the matrix that activate cell-surface receptors, as one example.

It is now clear that there are several families of extracellularly acting proteases that are regulated by synaptic activity and may serve to coordinate structural and functional plasticity by local remodeling of the perisynaptic microenvironment. For example, tissue-type Plasminogen activator (tPA), a serine protease, is an immediate-early gene that is upregulated by LTP- or LTD-inducing synaptic activity, and when blocked either pharmacologically or genetically, impairs the maintenance of these forms of plasticity as well as performance in certain memory tasks (Baranes et al., 1998; Calabresi et al., 2000; Centonze et al., 2002; Huang et al., 1996; Qian et al., 1993). Additionally, recent studies suggest that tPA modulates stress-induced plasticity in the amygdala (Skrzypiec et al., 2008) and experience-dependent pruning of dendritic spines in visual cortex during the critical period for monocular deprivation (Mataga et al., 2004; Oray et al., 2004). The mechanisms behind these contributions are not clear, but may involve tPA-dependent activation of BDNF (Pang et al., 2004). Neuropsin, also a serine protease, has also been shown to regulate the induction of hippocampal LTP as well as contribute to certain forms of memory (Tamura et al., 2006), possibly through NMDA receptor-dependent proteolytic degradation of L1CAM (Matsumoto-Miyai et al., 2003). Together, these data strongly implicate extracellular proteolysis in the mechanisms of synapse and behavioral plasticity. However, it has been difficult to determine whether such proteolytic activities are permissive, thus allowing plasticity to proceed, or are in fact also contributing proactively, thus driving synaptic alterations directly. Some clues to the answer to this question come from recent studies of Neurotrypsin, a serine protease, as well as a family of extracellular proteolytic proteins called Matrix Metalloproteinases (MMPs) (Fig. 3).

Neurotrypsin is synthesized by neurons and released in an activity-dependent manner from presynaptic terminals, where it accumulates briefly at synapses (Frischknecht et al., 2008; Gschwend et al., 1997). Its only known substrate is the ECM protein Agrin (Reif et al., 2007), which is expressed widely in the CNS (Ksiazek et al., 2007). Recent studies show that upon presynaptic release, Neurotrypsin cleaves Agrin, resulting in a 22 kDa, C-terminal bioactive fragment (Agrin-22) (Stephan et al., 2008) (Fig. 3B). Interestingly, such Agrin

cleavage requires postsynaptic NMDA receptor activity (Matsumoto-Miyai et al., 2009), which may indicate that postsynaptic activity is required to convert an inactive form of Neurotrypsin into a proteolytically competent form, or modifies accessibility of Agrin for Neurotrypsin cleavage. In any event, recombinant Agrin-22, when applied to hippocampal slices, induces formation of dendritic filopodia through unknown mechanisms (Matsumoto-Miyai et al., 2009). These results suggest a proactive role for Neurotrypsin-dependent, Agrin-22-mediated signaling in driving new dendritic protrusions (Fig. 3B), some of which may be precursors of new spines and synapses (Fiala et al., 1998). However, the significance of such Neurotrypsin-dependent activities for synaptic function is at present unclear, as synaptic neurotransmission and LTP are unimpaired in Neurotrypsin-deficient mice (Matsumoto-Miyai et al., 2009). Nevertheless, mutations affecting the protease domain of Neurotrypsin in humans is associated with severe mental retardation (Molinari et al., 2002), thus Neurotrypsin proteolysis is crucial for normal brain function.

MMPs are a large family of zinc-dependent, mostly secreted proteolytic enzymes whose canonical substrates include CAMs and ECM proteins (for a comprehensive review on MMP biology, see (Dzwonek et al., 2004; Sternlicht and Werb, 2001). In brain, MMPs (and in particular, MMP-9) are secreted by neurons and glia in an inactive (pro) form, becoming proteolytically active when the propeptide is removed in response to specific stimuli (Ethell and Ethell, 2007). Studies in acute slices or in adult rats *in vivo* have shown that MMP-9 is rapidly activated perisynaptically in area CA1 by LTP-inducing tetanic stimulation of Schaffer collateral-CA1 synapses (Bozdagi et al., 2007; Nagy et al., 2006) (Fig. 3C) or, along with MMP-3, by different types of associative and non-associative learning and memory tasks (Brown et al., 2008; Nagy et al., 2007; Olson et al., 2008; Wright et al., 2007). Loss-of-function approaches, which have included pharmacological blockers, neutralizing antibodies, or genetic deletion, confirm that in the absence of MMP proteolysis, LTP of synapses in hippocampus and other cortical areas is transient (Bozdagi et al., 2007; Meighan et al., 2007; Meighan et al., 2006; Nagy et al., 2006; Okulski et al., 2007; Wang et al., 2008), and behavioral performance in various learning and memory tasks is impaired (Brown et al., 2008; Nagy et al., 2007; Olson et al., 2008; Wright et al., 2007). Additional studies have shown that the stability of spine expansion that typically accompanies LTP (Matsuzaki et al., 2004; Yang et al., 2008) is also dependent on MMP-9 proteolysis (Wang et al., 2008), indicating that the long-term stability of both functional and structural synaptic plasticity depends on MMP-9.

These data raise the important question of whether the contribution of a synaptically localized, proteolytically-active MMP to synaptic plasticity is permissive and/or instructive. A gain-of-function approach, in which active MMP-9 was applied locally to single spines of CA1 pyramidal cells visualized by 2-photon time-lapse microscopy, in combination with whole cell recording, demonstrated that active MMP-9 *by itself* both potentiated synaptic strength and, concurrently, induced expansion of spine-head volume (Wang et al., 2008) (Fig. 3C). Both functional and structural forms of MMP-9-mediated plasticity required β 1-containing Integrins and actin polymerization, the latter presumably reflecting an MMP-mediated, Integrin-dependent inactivation of the actin depolymerizing factor, Cofilin, within spines heads (Wang et al., 2008). These data confirm earlier demonstrations that β 1-containing Integrins are critical for consolidation of LTP (Chan et al., 2003; Chan et al., 2006; Chun et al., 2001; Staubli et al., 1998), and extend this idea by suggesting that LTP-activated, perisynaptic MMP-9 couples both functional and structural plasticity through activation of Integrin receptors. Once activated, Integrins engage a number of downstream signaling pathways (Bernard-Trifilo et al., 2005) that affect synaptic glutamate currents (Kramar et al., 2003; Lin et al., 2003a), and influence LTP-associated spine actin dynamics (Kim and Lisman, 1999; Kramar et al., 2006; Krucker et al., 2000; Lin et al., 2005). Additionally, recent studies in which MMP-9 was applied locally to neuronal cultures

demonstrated that MMP-9 increased lateral diffusion rates of NR1-containing NMDA receptors in a β 1-containing Integrin-dependent manner (Michaluk et al., 2009) (Fig. 3C). Taken together, these data suggest that the role of MMP-9 proteolysis in synaptic functional and structural plasticity is instructive via β 1-Integrin signaling, although an additional permissive role is not ruled out.

Challenges that remain

There are many open questions that are raised, and that remain, in understanding the role of regulated, perisynaptic proteolysis in enabling synaptic functional and structural plasticity. Key among them, for certain proteases, is the identity of the target substrates. In the case of the MMPs, it will be important to identify the target substrate(s) that MMP-9 acts upon in response to LTP-inducing stimuli that then presumably binds to and activates Integrins. It is known that in neurons and other cell types, MMPs can cleave Cadherins, some proteins of the ECM, the adhesion protein ICAM-5 (Telencephalin) and other cell-surface signaling molecules such as β -Dystroglycan (Conant et al., 2010; Ethell and Ethell, 2007; Marambaud et al., 2002; Michaluk et al., 2007; Monea et al., 2006). Whether or how any of these potential target molecules are related to the effects of MMP-9 on LTP, NR1 surface mobility, spine plasticity, or learning and memory is presently unknown.

Equally relevant are the changes that occur across the synaptic adhesive matrix in response to plasticity-inducing stimuli. On the one hand, it would be expected that increases in synapse size and/or changes in spine/synapse morphology would be supported by the insertion of additional functional CAM units, while on the other hand, loss of some CAM units might be expected in order to enable local flexibility in membrane-membrane associations required for structural remodeling (Huntley et al., 2010; Mayford et al., 1992). Conversely, decreases in synapse size must be preceded by the disassembly and degradation of functional CAM units. New synapse formation presumably progresses hierarchically as it does during development, but in a mature environment, it is anticipated that there would be fewer errors and the process of synapse maturation may be accelerated.

Another important question will be to determine whether or how proteolytic activity affects glial processes, particularly those intimately associated with synapses undergoing plasticity. It is well-documented that perisynaptic astroglia are dynamically responsive in a variety of plasticity-related contexts, including reactive synaptogenesis (Witcher et al., 2007), learning and experience (Jones and Greenough, 1996), estrus cycle-related fluctuations in synapse density (Klintsova et al., 1995), and LTP (Wenzel et al., 1991). It would not be surprising to discover that the dynamic glial-neuronal structural interactions that have been described in several brain areas undergoing plasticity (Genoud et al., 2006; Haber et al., 2006; Langle et al., 2003) are regulated by proteolytic remodeling of local glial-neuronal contacts.

In a broader context, it will also be important to build a comprehensive understanding of how all of the various proteases that are activated during synaptic plasticity or training in a memory task work together to regulate brain function, either as semi-independent cascades (e.g. Fig. 3) or perhaps combinatorially, over time and spatially with respect to different cellular or synaptic microdomains.

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Figure 1. Schematic diagram illustrating examples of key synaptic CAM families. Shared domains are colored similarly. Postsynaptic membrane and associated proteins are shown at left, apposed to presynaptic membrane, at right. However, it should be noted that in some cases proteins shown on one side can be located on either pre- or postsynaptic sides (e.g. EphBs). For clarity, the majority of intracellular binding partners is not shown. Abbreviations are as indicated in the text.

Figure 2.

Minimal adhesive unit. Diagram of a synapse shows hypothetical distribution of CAM interactions that are known to span synaptic clefts and could act coordinately. Molecule placement along the length of the cleft is based in part on published literature showing immunogold localization (e.g. (Buchert et al., 1999; Einheber et al., 1996; Elste and Benson, 2006; Fux et al., 2003; Petralia et al., 2005; Tremblay et al., 2007)) and unpublished data (Benson, Mortillo and Elste).

Figure 3.

Extracellular proteolytic cascades drive synaptic structural and functional modifications locally in response to plasticity-inducing stimuli. Schematic diagram depicts a “resting synapse” (A) and subsequent changes to synapse structure/function following activity- and NMDA-receptor-induced activation of Neurotrophin (B) or LTP- or learning-induced activation of MMP-9 (C). Neurotrophin, which is released from presynaptic terminals upon activity (B), requires subsequent NMDA receptor activity by the postsynaptic neuron in order to cleave full-length Agrin, producing several cleavage fragments including bioactive Agrin-22. Agrin-22 then induces formation of dendritic filopodia through as-yet uncharacterized mechanisms. In contrast, MMP-9 is activated by LTP or inhibitory avoidance learning, where it signals through integrins to potentiate synaptic responses and enlarge dendritic spine heads, both of which require actin polymerization, as well as increase lateral mobility of NMDA receptors (C). See the text for further details of these and other proteolytic cascades, including relevant citations. Note however, that some of the molecular steps in these models are speculative.