The role of cell adhesion molecules in synaptic plasticity and memory

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Studies in the past few years suggest that cell adhesion molecules may play signaling as well as structural roles at adult synapses during plasticity. The observation that many adhesion molecules are expressed both pre-synaptically and post-synaptically raises the possibility that information about synaptic activity might simultaneously be communicated to both sides of the synapse, circumventing the need for distinct anterograde and retrograde messengers.

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Abbreviations

apCAM	Aplysia NCAM homolog
HAV	His–Ala–Val
IAP	integrin-associated protein
Ig	immunoglobulin
LTP	long-term potentiation
MAPK	mitogen-activated protein kinase
NCAM	neural cell adhesion molecule
RGD	Arg–Gly–Asp

Introduction

During brain development, growing axons must recognize and establish connections with the appropriate postsynaptic target neurons in order to establish the functional neural circuits that mediate animal behavior. Once these synaptic circuits are established, they can undergo modifications including the addition or deletion of synapses, or the alteration of pre-existing synapses. This capacity for change — synaptic plasticity — represents the nervous system's ability to encode and represent changes in the environment, that is the ability to learn and remember.

Adhesion molecules are known to participate in target recognition and stabilization during synaptogenesis. They are required for axonal development from the initial induction of outgrowth [1] to the guidance to the target [2,3]. In the chicken optic tectum, for example, the lamina-specific expression patterns of cell adhesion molecules [4] regulate the connectivity of ingrowing fibers [5]. In *Drosophila*, Fasciclin II, an immunoglobulin (Ig) superfamily protein is localized at synapses and controls the number of boutons and the structure of the neuromuscular junction [6–8]. Studies such as these highlight the importance of adhesion molecules in target recognition and synaptogenesis.

Because the expression of many cell adhesion molecules persists in adulthood [9,10••,11], they may play analogous roles in the activity-dependent rearrangement of synaptic structures in the adult brain. In this review, we highlight recent studies implicating cell adhesion molecules as mediators of synaptic and behavioral plasticity. The possible mechanism(s) by which these molecules participate in plasticity is also discussed.

Involvement of cell adhesion molecules in synaptic plasticity and learning

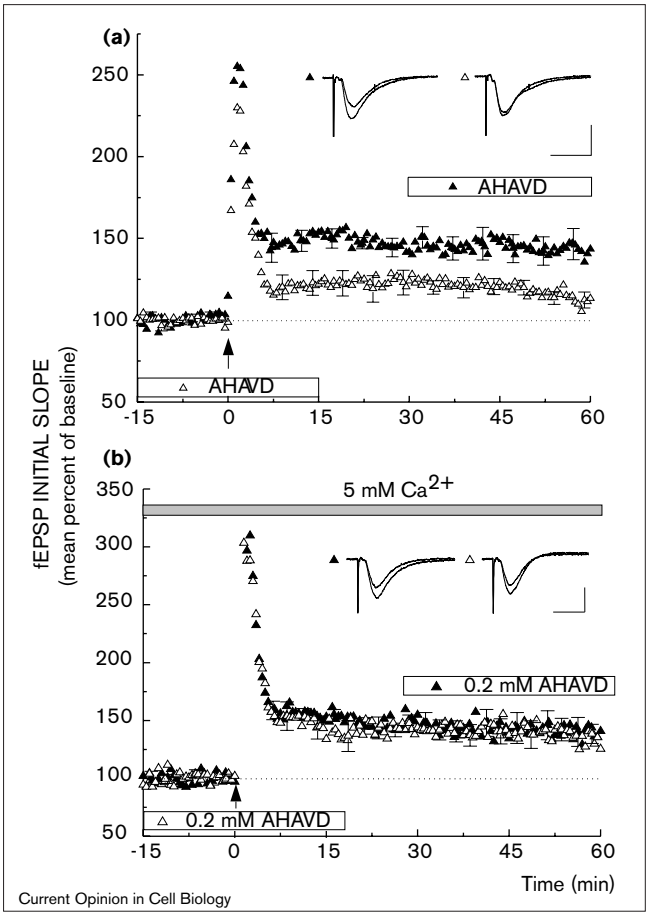
Synapses, the points of contact between neurons, undergo dynamic changes in their strength, enduring from minutes to hours to days. The presence of adhesion molecules in or near the synaptic cleft raises the possibility that, in addition to serving as recognition molecules for synaptogenesis, they may participate in initiating and maintaining synaptic changes. One prominent form of synaptic change exhibited by many different synapses is long-term potentiation (LTP), an enduring enhancement of excitatory synaptic transmission that occurs following brief episodes of synaptic activity. Since it was first discovered in the hippocampus — a brain structure implicated in memory formation — this type of synaptic plasticity has been intensively studied as a potential model for how information is stored during animal learning. Over the past few years, several studies have shown that adhesion molecules may participate in both synaptic changes, such as LTP, and behavioral changes, such as learning.

Integrin superfamily

Integrins are a family of proteins that interact with extracellular matrix proteins. A highly conserved five amino acid residue sequence, including Arg–Gly–Asp (RGD), is found in most of the ligands of integrins; this sequence is known to be critical for ligand binding to integrins. Blocking integrin function with a peptide containing the RGD sequence causes a decay of LTP in the CA1 region of adult rat hippocampus [12]. The peptide-mediated inhibition of LTP was time-dependent: the application of the antagonist peptides 10 minutes, but not 25 minutes, after LTP induction was effective in blocking LTP, suggesting that integrin function is required for a very early stage of LTP stabilization [13]. Integrins also participate in a form of short-term synaptic plasticity termed stretch-induced enhancement of neurotransmitter release at frog motor nerve terminals [14]. At this synapse, a transient force applied to the muscle results in an increase in the frequency of miniature end-plate potentials. The application of RGD peptides can block the stretch-induced enhancement of synaptic strength.

In *Drosophila*, the locus linked to a mutant called *Volado*, which displays impaired olfactory associative memory, was found to encode two isoforms of a new type of integrin,

Figure 1



Peptides containing the sequence HAV (in the single letter code for amino acids) perturb the induction of LTP but not the maintenance of LTP. **(a)** Superimposed ensemble averages from two-pathway experiments conducted in the same slices. Bath application of an AHAVD (in the single letter code for amino acids) peptide for 20 minutes prior to tetanus significantly reduces LTP in pathway 2 (open triangles) whereas application of the same peptide 30 minutes after LTP induction in pathway 1 has no significant effect on established potentiation (black triangles). **(b)** Ensemble averages for two-pathway experiments in which the HAV peptide was applied either 30 minutes before (open triangles) or after (black triangles) LTP induction by tetanus in an altered artificial cerebrospinal fluid containing 5.0 mM Ca^{2+}. Individual superimposed representative electrophysiological traces are shown for each experimental group 10 minutes before and 50–60 minutes after LTP induction. Scale bar is 0.5 mV/20 msec. Reprinted with permission from [10••].

α-integrin [15••]. The *Volado* gene product is expressed in the mushroom body, an area known to be important for learning in insects. Conditional expression of the wild-type *Volado* transgene in the *Volado* mutants can rescue the memory impairment, suggesting that the lack of integrin function is indeed the cause of memory interference [15••]. What particular aspect of integrin function is important for learning in *Drosophila*? A morphological analysis in this same study revealed no gross structural abnormalities in the mushroom bodies of the mutants. A more detailed analysis of the synaptic and subsynaptic structures is needed before a morphological alteration can be ruled out. Nevertheless, these results suggest the possibility that integrin signaling, rather than integrin structural support, is required for memory in *Drosophila*.

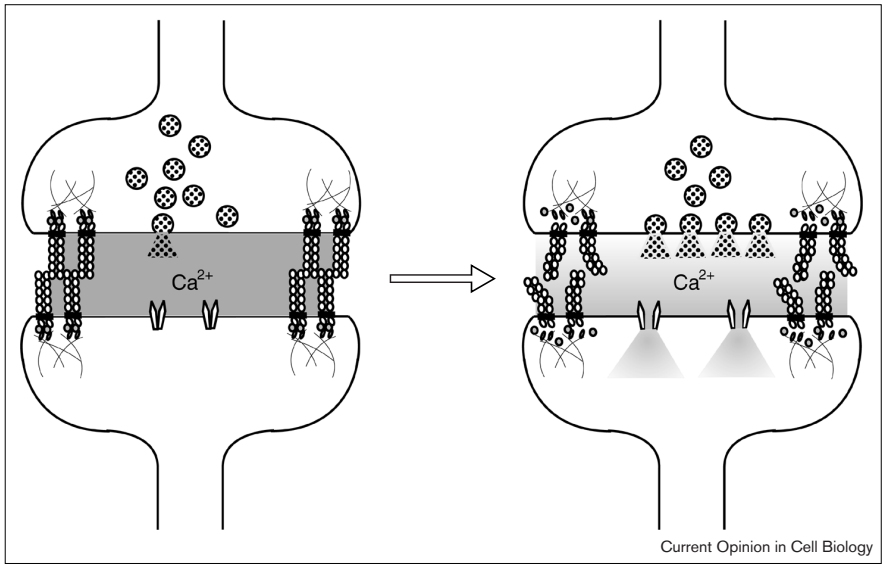
Related to the above point, an integrin-associated protein (IAP), which was recently found to be involved in tyrosine kinase signaling [16], appears to influence memory performance in rats [17•]. Differential display was used to compare hippocampal cDNAs from rats that perform poorly versus those that perform well on an inhibitory avoidance learning task [17•]. Three cDNAs corresponding to splice variants of IAP exhibited elevated expression in the hippocampus of the rats with a good memory. Injection of antisense oligonucleotides to IAP into the hippocampus impaired memory retention and also reduced the magnitude of LTP recorded *in vivo*. Future studies are needed to determine the subcellular localization of IAP(s) in the hippocampus and whether IAP works together with integrins during plasticity or independently.

Immunoglobulin superfamily

Some studies have suggested that the neuronal Ig superfamily is involved in both synaptogenesis and synaptic plasticity. Mice with a targeted deletion of the NCAM (neural cell adhesion molecule) gene showed an impairment of axonal growth and synaptogenesis in the hippocampal mossy fiber axon system [18,19]. (Mossy fibers are usually restricted to the proximal dendrites of CA3 cells.) Axons in the mutant CA3 hippocampus are no longer fasciculated and mossy fiber presynaptic terminals are present ectopically in the CA3 cell body layer and throughout the CA3 region. Despite these morphological abnormalities, basal synaptic transmission and short-term synaptic plasticity were normal in the mutant mice [19]. LTP however, was abolished in these mice in both area CA3 [19] and CA1 [20]. These observations are supported by an earlier study showing that application of function-blocking antibodies to either NCAM or L1, an Ig family member, were found to inhibit LTP induction in area CA1 [21]. When LTP was examined in a different NCAM knockout mouse, however, a different result was obtained [22•]. LTP in area CA1 was indistinguishable in homozygous, heterozygous and wild-type animals, despite the fact that the knockout animals share the same morphological abnormalities in area CA3 reported in the other NCAM knockout [18,19]. Strain differences may account for this discrepancy, as the age of the animals as well as the stimulation parameters were similar in the two studies.

In addition, NCAM knockout mice exhibited deficits in performance on the Morris water maze, a spatial memory task [23]. In this task, animals are required to swim and find a platform hidden below the surface of an opaque pool. Control animals show improved performance, (e.g. decreased latency to the find the platform) with repeated trials [24]. In addition, on probe trials after training, following removal of the platform from the pool,

Figure 2



Scheme of cell adhesion molecule participation in synaptic plasticity. A model of how Ca^{2+}-dependent adhesion molecules may sense activity at synapses is shown. Activity in the synapse results in a transient depletion of Ca^{2+} (indicated by lighter shading), destabilizing adhesion-molecule bonds. This destabilization may alter intracellular signaling elements on both sides of the synapse. New adhesive interactions may occur following synaptic activity and plasticity.

control animals spend more time in the vicinity of the previous platform location. The NCAM knockout mice exhibited longer latencies to find the platform during training, as well as less time in the correct platform location following training [23].

Cell–cell adhesion mediated by Ig superfamily members can be found not only between neurons but also between neurons and glia. The adhesive interactions between neurons and glia cells may also be involved in synaptic modulation. For example, in transgenic mice ectopically expressing L1 in astrocytes, a significant reduction in LTP magnitude in area CA1 was observed, without any alteration in basal synaptic properties [25]. A behavioral analysis of these same mice revealed some interesting features of their ability to learn and remember in the Morris water maze. The transgenic mice showed a more rapid acquisition of learning on the first day of training; they also showed greater flexibility in learning when the platform was moved to a new location [26]. Taken together, the results of the LTP and water maze studies indicate that reductions in LTP in area CA1 are not necessarily predictive of learning and memory deficits. This dissociation between synaptic and behavioral plasticity has been observed for other molecules as well [27], for example, glutamate receptors and Thy-1. In the present example, the ectopic expression of L1 in glia reduced the magnitude of LTP, but did not prevent it. This raises the possibility that a modicum of synaptic plasticity in the hippocampus is sufficient to support learning.

Cadherin superfamily

Although cadherins are known to play important roles in cell recognition and adhesion during development, cadherins continue to be expressed in many tissues during adulthood [28]. For example, cadherins are expressed in the adult hippocampus and forebrain and localized at synaptic sites [4,9,10••,11,29]. A recent study has examined cadherin localization during synaptogenesis in detail [30•]. In embryonic day (E) 18 cultured hippocampal neurons, cadherins are initially diffusely distributed but become increasingly localized to both presynaptic and postsynaptic sites during the period of time synapses are being formed. Interestingly, a progressive loss of cadherin from γ-aminobutyric acid (GABA)ergic synaptic sites was also noted, such that cadherins became restricted to excitatory synapses by 2–3 weeks in culture.

The persistent synaptic localization of cadherins suggests a potential role for them in synaptic plasticity. Tang and colleagues [10••] found that blocking cadherin function with either specific antibodies or a peptide that contains a highly conserved extracellular tripeptide sequence, His–Ala–Val (HAV), had no effect on normal synaptic transmission or short-term synaptic plasticity in area CA1 of the hippocampus. Significant inhibition of LTP, however, was observed if the peptide or antibody was present during the induction of LTP [10••]. Delaying the application of the HAV peptide to 30 minutes after LTP induction had no effect on established LTP. These results suggest that the electrical stimuli used to induce LTP might render the cadherin bonds sensitive to inhibition by the peptide. For example, electrical activity might transiently deplete or reduce extracellular calcium ions due to flux through voltage-gated Ca^{2+} channels and NMDA (*N*-methyl-*D*-aspartate) channels [31,32]. Because the structure of the cadherin extracellular domain is highly Ca^{2+}-dependent [33,34•], reductions in Ca^{2+} might destabilize cadherin bonds allowing the antibodies or peptides to gain access and interfere with adhesion. Consistent with this idea, the blocking effect of the HAV peptide could be overcome by raising the extracellular Ca^{2+} concentration to

a range where the stimulation-induced depletion would probably not be low enough to affect cadherin stability [33]. These results suggest the possibility that cadherins might be capable of sensing synaptic activity and transmitting this information simultaneously to both the presynaptic and postsynaptic compartment.

As blocking cadherin function only affects LTP but not basal synaptic properties [10••], it is possible that cadherin plays a signaling, rather than merely structural, role in synaptic plasticity. Catenins, a family of cytoplasmic proteins that interact with cadherins, are the mediators of signaling events triggered by cadherins. Catenins are present at synaptic sites [30•] in young and adult [10••] neurons. In addition, β-catenin is known to play an important role downstream of Wnt signaling during development [35]. Although β-catenin directly binds to cadherins, once released this protein can travel to the nucleus and act as a transcription factor through is interactions with lymphoid enhancer factor/T cell factor (LEF/TCF) [36]. This cytoplasmic mobility of β-catenins raises the possibility that it may be a dynamic downstream reporter of cadherin-mediated signaling. Indeed, a recent study has shown that β-catenin becomes clustered in response to alterations in extracellular calcium or electrical stimulation [37]. This finding suggests that β-catenin localization is dynamically regulated by synaptic activity and potentially by plasticity.

Activity-dependent modulation of cell adhesion molecule expression

As described above, function blocking studies using antibodies, peptides, or gene knockout approaches have demonstrated the involvement of cell adhesion molecules in both behavioral and synaptic plasticity. It is still not known, however, whether these molecules mediate a rearrangement of synaptic structures during memory formation. If the expression of cell adhesion molecules can be regulated by activity, then newly synthesized molecules might participate in the formation or modification of synapses. Indeed, the expression levels of some cell adhesion molecules have been reported to change in an activity-dependent manner. For example, the expression patterns of N-cadherin, NCAM and L1 can be regulated by distinct patterns of action potentials [38,39]. In addition, the promoter of the NCAM gene is sensitive to AMPA (α-amino-3-hydroxy-5-methyl-isoxazole-4-proprionic acid) receptor activity [22•]. Consistent with these observations, immunostaining following LTP has shown that the proportion of NCAM containing synapses is increased [40]. In the case of apCAM, the Aplysia homolog of NCAM, the downregulation of expression and internalization of pre-existing molecules are observed, instead of increased level of expression [41]. It has been demonstrated that either a point mutation of the apCAM phosphorylation site(s) for mitogen-activated protein kinase (MAPK) or the application of a MAPK inhibitor can block the internalization of apCAM following long-term plasticity [42]. Another study showed that an Aplysia homolog of MAPK, apMAPK can induce the phosphorylation of apCAM, as well as two transcription factors, apCREB (Aplysia homolog of cAMP response element binding protein) and apC/EBP (Aplysia homolog of CCAAT/enhancer binding protein) [43].

Conclusions and future directions

The above studies suggest that cell adhesion molecules participate in adult synaptic and behavioral plasticity. Early responses of adhesion molecules to neural activity may include dynamic changes in structure and/or signaling whereas later responses may include altered patterns of adhesion molecule expression. With a few exceptions, perturbing the function of adhesion molecules either genetically or pharmacologically appears not to influence normal synaptic transmission or short-term (e.g. 1–5 minute) plasticity. What is affected by such manipulations, however, is the capacity for synapses to exhibit long-lasting changes in synaptic strength. Further studies are needed to ascertain the degree to which particular adhesion molecules play structural versus signaling roles at the synapse. Current approaches may not provide the resolution to dissociate, or associate, these two roles. In addition, experiments in which the dynamics of cell adhesion molecules and their associated intracellular partners are monitored will provide a more realistic picture of the moment-to-moment fluctuations and transitions that occur during synaptic transmission and plasticity.

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- •• of outstanding interest

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