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Making memories stick: cell-adhesion molecules in synaptic plasticity

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Synapses are adhesive junctions highly specialized for interneuronal signalling in the central nervous system. The strength of the synaptic signal can be modified (synaptic plasticity), a key feature of the cellular changes thought to underlie learning and memory. Cell-adhesion molecules are important constituents of synapses, with well-recognized roles in building and maintaining synaptic structure during brain development. However, growing evidence indicates that cell-adhesion molecules also play important and diverse roles in regulating synaptic plasticity and learning and memory. This review focuses on recent advances in understanding the molecular mechanisms through which adhesion molecules might regulate synaptic plasticity.

Information is encoded in the CNS through networks of neurons that are functionally connected by synapses – adhesive junctions that are highly specialized for interneuronal signalling[1]. Brief periods of activity at a synapse can enhance or depress subsequent synaptic strength, a term that describes the magnitude of the postsynaptic response following a sequence of axon terminal depolarization, neurotransmitter release, binding to postsynaptic receptors and subsequent depolarization of the postsynaptic membrane. The particular frequency at which neural impulses arrive at an axon terminal, coupled with the level of postsynaptic depolarization, generally dictates whether synaptic strength is increased (high-frequency) or weakened (low-frequency), as well as the duration of the subsequent synaptic modification[2]. Such dynamic regulation of synaptic strength by neural activity is referred to as 'activity-dependent synaptic plasticity' and is a fundamental component of normal brain function. For example, long-term potentiation (LTP) is an experimentally induced form of synaptic plasticity in which a conditioning stimulus (usually electrical stimulation of a set of axons) leads to a rapid and sustained increase in synaptic strength (potentiation), lasting hours to days or longer. These and other properties have established LTP as a leading cellular model for how neurons enable skill learning[3] and memory formation[4]. Activity-dependent synaptic plasticity is also crucial for establishing neural circuitry during brain development[5] and for reorganizing synaptic circuitry following brain, spinal cord or peripheral nerve injury[6]. What are the molecular mechanisms that underlie synaptic plasticity? Most experimental work has focused on changes in neurotransmitter release[7] and the regulation of neurotransmitter receptor localization and function as a basis for synaptic plasticity[8]. Increasingly, however, it is becoming clear that cell-adhesion molecules (CAMs), which are crucially required for building and maintaining synaptic

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PII: S0962-8924(00)01838-9

BOX 1 – CELL ADHESION AT SYNAPSES

Several types of CAMs have been localized to CNS synapses, most of which fall into four groups: integrins, immunoglobulin superfamily, cadherins and neurexins and neuroligins.

Integrins

Integrins are heterodimeric glycoproteins comprising two noncovalently associated subunits, α and β (Ref. a; Fig. I). Each α and β subunit contains a large extracellular domain, a transmembrane domain, and a cytoplasmic domain that interacts with actin via talin, α-actinin or vinculin and numerous cytoplasmic signalling molecules. The extracellular domains of both subunits form the ligand-binding site, which, for many integrins, recognizes a sequence – Arg-Gly-Asp (RGD) – found in many matrix proteins[b]. Integrins require divalent cations for ligand binding, and their activity can be regulated by cytokines, agonists or cations (Table I). Although the classic integrin interaction is to join cells with substrates, integrins can also function in cell–cell adhesion through immunoglobulin (Ig) superfamily members or cadherins[c,d]. More than ten different integrin subunits are expressed in the brain and are differentially localized[e–g]. Electron microscopy has shown that α8 and β8 are concentrated at some post-synaptic densities[f,g].

Immunoglobulin superfamily

Ig superfamily members are either type I or GPI-linked membrane proteins having one or more Ig-like domains that mediate recognition and adhesion, and usually one or more fibronectin III repeats[h] (Fig. I). Most members have preferences for homophilic or heterophilic interactions, but many can engage in both[i], and the strength of adhesion varies widely. Some can function as co-stimulatory molecules in T-cell activation[j]. The cytoplasmic domains of some can be tethered to actin[k] and are essential for signal transduction[l,m] (Fig. I; Table I). Some members, particularly NCAM, fasciclin II (*Drosophila*) and L1 are required for aspects of axonal guidance and cell migration during development[n,o]. NCAM exists in a variety of differentially spliced and glycosylated isoforms (Box 2). In adult brains, at least one NCAM isoform becomes concentrated in some dendritic spines[p].

Cadherins

The cadherin superfamily includes classic cadherins, cadherin-like neuronal receptors (CNRs) and protocadherins[q]. All are proteins with a single transmembrane domain mediating strong, Ca^{2+}-dependent cell–cell adhesion[r] (Fig. I) via the first of five or six tandemly repeated domains[s,t]. Most interactions are homophilic, but closely related cadherins can form *cis*-heterodimers within the plane of the membrane[u] as well as engage in *trans*-heterophilic interactions across membranes[u–w] or can bind other cell-adhesion molecules[c,d]. For classic cadherins, strength of adhesion is modulated by the cytoplasmic tail through regulation of lateral clustering by interactions with p120 and δ-catenin, and through linkage to actin via α-, β- and γ-catenin[r,x–cc]. The CNRs are linked to the tyrosine kinase fyn[dd] (Fig. I; Table I). A majority of synapses in the CNS contain cadherins[ee], and different cadherins have been localized at mutually exclusive synaptic loci in the CNS[ff–ji].

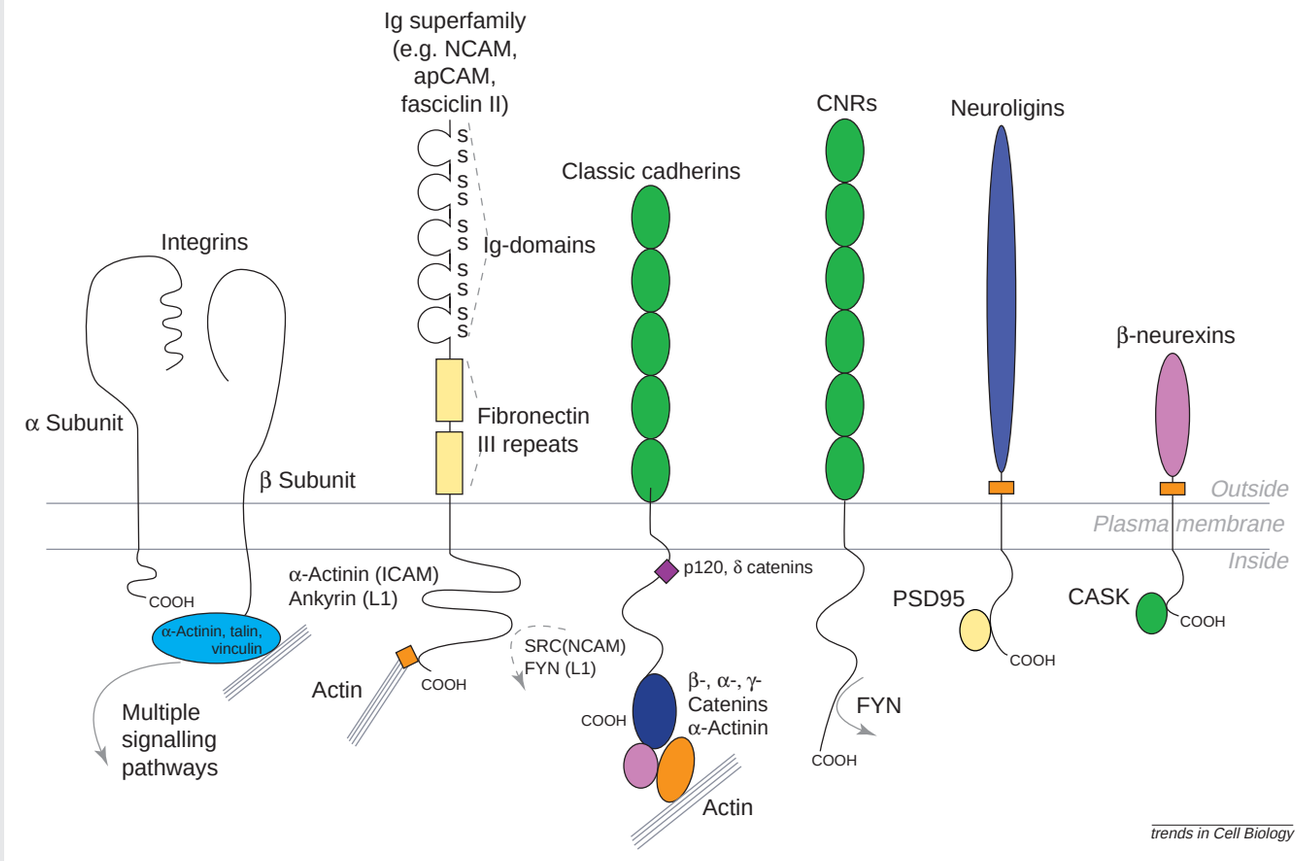

FIGURE I

Structures of neuronal cell-adhesion molecules.

BOX 1 – CONTINUED

TABLE I – COMPONENTS OF NEURONAL SIGNALLING PATHWAYS

Family	Representative neuronal members	Ligands	Cytoskeletal linkage	Signalling and regulation	Refs
Cadherins	N-cadherin, E-cadherin, CNRs	Cadherin on neighbouring cells	Actin via β- and δ-catenin	Examples include: p120 (classic) δ-catenin presenilin? PTPmu β-catenin Fyn (CNRs) bFGF (N-cadherin)	 73 74 75 76 77
Integrins	αvβ8, α8β1	Extracellular matrix proteins, ICAM, VCAM, cadherins	Actin via α-actinin, talin, vinculin and others	Multiple pathways	
Immunoglobulin superfamily	NCAM, TAG-1, neurotrimin, telencephalin, L1	Integrins, homophilic binding, other Ig members	Actin via ankyrin and spectrin (L1), α-actinin or ezrin (ICAM1, 2)	Examples include: Src (NCAM, L1) Fyn (L1) bFGF (NCAM, L1)	 78,79 79 80
Neurexins	α-, β-Neurexin	Neuroligin 1	?	via CASK?	
Neuroligins	Neuroligin 1–3	β-Neurexins	Actin via PSD95?	via PSD95?	

Abbreviations: bFGF, basic fibroblast growth factor; CNR, cadherin-like neuronal receptor; ICAM, intercellular adhesion molecule; NCAM, neuronal cell-adhesion molecule.

Neurexins and neuroligins

Neurexins are a family of brain-specific proteins that can be differentially spliced to produce an enormous variety of molecules[kk]. Alpha- and β-neurexins are presynaptic; only β-neurexins have an identified postsynaptic ligand, the neuroligins[ll]. Neuroligins 1–3 are type I membrane proteins that bind to neurexins in a Ca^{2+}-dependent manner through their extracellular N-terminal domain, which is homologous to serine esterases but lacks catalytic activity[mm]. Neurexins and neuroligins would be well situated to link pre- and postsynaptic signalling mechanisms: the intracellular C-terminus of neuroligins binds to the PDZ-containing protein PSD-95, which is thought to function as a nexus for clustering receptors and signalling molecules at the postsynaptic side of the synapse, whereas the C-terminus of neurexins binds to CASK, another PDZ-containing protein found presynaptically[nn,oo] (Fig. I; Table I).

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structure during brain development, also play important and diverse roles in modulating distinct aspects of synaptic plasticity in maturity. Here, we discuss the mechanisms through which CAMs participate in the modification of synaptic strength, principally in the context of LTP, since this is one of the best-studied forms of activity-dependent synaptic plasticity.

The CNS synapse

The most common type of synapse joins a presynaptic axon terminal and a postsynaptic dendrite across a gap, the synaptic cleft, which measures between 200–300 Å. The synaptic cleft is slightly wider than the gap between adjacent apposed membranes and is filled with an amorphous, electron-dense material. The pre- and postsynaptic membranes appear

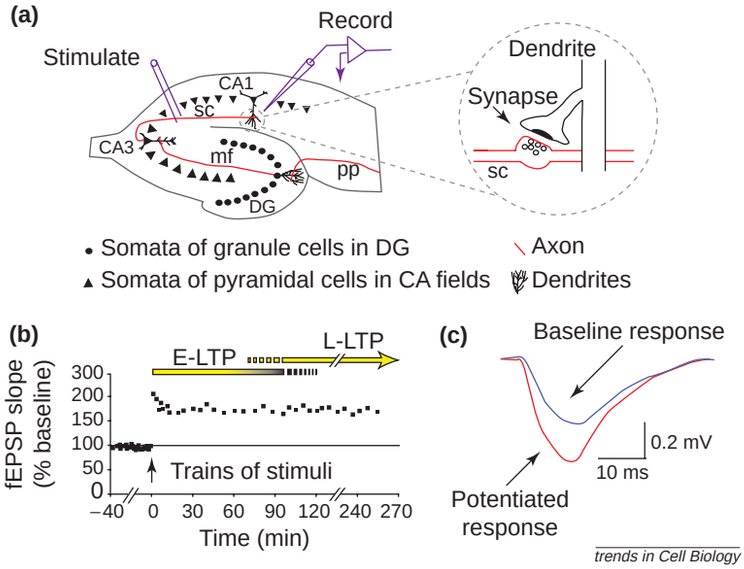

FIGURE 1

The hippocampal slice is a dominant model system for studying long-term potentiation (LTP) and the role of cell-adhesion molecules (CAMs) in synaptic plasticity. (a) Schematic diagram of a hippocampal slice showing subregions, major cell types and axon pathways, and a typical experimental setup for inducing LTP in area CA1. For clarity, only a single neuron is shown in its entirety (i.e. somata, dendrites and axon) in each subregion. Normally, information from other brain areas enters the hippocampus through the perforant path (pp), which terminates on the dendrites of granule cells in the dentate gyrus (DG). The axons of the granule cells – the mossy fibres (mf) – relay information to the dendrites of pyramidal cells in area CA3. Information is then relayed by the axons of area CA3 neurons – the Schaffer collaterals (sc) – to the dendrites of pyramidal neurons in area CA1. LTP can be elicited in all of these regions but is commonly studied in area CA1 at the synapses between Schaffer collaterals and dendrites of CA1 neurons (shown in large circle, right). Living hippocampal slices are maintained *in vitro*, where high-frequency trains of electric current are passed through a bipolar stimulating electrode placed in area CA3, depolarizing the Schaffer collaterals. A recording electrode placed in area CA1 monitors the evoked synaptic potentials and the resulting LTP. One way in which the role of CAMs in LTP has been studied is to introduce blocking reagents (e.g. antibodies against adhesion proteins) directly into the media in which the slice is maintained and then monitor the ability to induce or maintain LTP. (b) Semi-schematic representation of area CA1 field excitatory postsynaptic potentials (fEPSPs) illustrating early (E-) and longer-lasting (L-) LTP. A baseline response is established prior to applying multiple, widely spaced trains of high-frequency electrical stimulation to the Schaffer collaterals (arrow). The ensuing potentiation is seen as an immediate and sustained increase in the magnitude of the CA1 synaptic response (fEPSP slope, y-axis). The upper lines indicate the approximate start and duration of E-LTP and L-LTP. If elicited alone, E-LTP declines to baseline between ~1–2 h following the stimulus. However, in this example, L-LTP has also been induced; the transition between E- and L-LTP is not evident in the synaptic potentials because the decline of E-LTP overlaps with the onset of L-LTP. L-LTP then persists for many hours to days. (c) Superimposed, individual electrophysiological traces taken before (baseline response, upper trace) and 120 min after stimulation (potentiated response, lower trace), showing increase in synaptic strength during LTP in comparison with baseline.

thicker than the surrounding plasmalemma owing to varying amounts of dense material attached to the cytoplasmic faces on either side of the synapse. Presynaptic terminals are filled with synaptic vesicles containing neurotransmitters – glutamate, at most excitatory synapses, and gamma-aminobutyric acid (GABA) or glycine at most inhibitory synapses. A subpopulation of vesicles is docked at the membrane and ready to fuse and release neurotransmitters, thus defining the 'active zone'. Astrocytic processes are observed at the perimeter of synapses, but the extent to which they surround the active zone varies substantially[9,10].

While the synapse is highly specialized for intercellular signalling, it is also an adhesive junction, having many of the properties associated with other cell–cell junctions. In appearance, the CNS synapse is most closely related to the adherens junction between epithelial cells. The junctions span similar membrane distances; fuzzy, electron-dense material fills the intermembrane zones; and both contain cadherins, a family of Ca^{2+}-dependent CAMs (Box 1). The principal difference between these two junctional types is that adherens junctions are functionally symmetric, joining identical cell types across the same cellular domains, whereas synapses are polarized, most often joining functionally distinct cellular domains: axon to dendrite or soma.

CAMs modulate short- and long-lasting forms of synaptic plasticity

At least two temporally and mechanistically distinct processes contribute to activity-dependent synaptic plasticity, which lasts from tens of minutes to hours or more[11]. Short-lasting forms of synaptic plasticity can be induced quite rapidly, do not require protein synthesis, and are not sustained beyond a few hours. Such rapidly induced, but short-lasting, forms of synaptic plasticity probably reflect changes in the strength of preexisting synapses through posttranslational modifications and translocation of pre- and postsynaptic proteins[12]. By contrast, long-lasting changes in synaptic strength, ones that might endure for several hours to days, require gene transcription and protein synthesis. Such long-lasting forms of synaptic plasticity can be associated with structural remodelling of synaptic architecture and the formation of new synaptic contacts[13]. There is growing evidence that CAMs play important roles in modulating both short-lasting synaptic plasticity at preexisting synapses and long-lasting synaptic plasticity in which synaptic structural changes and new synapse formation can also occur.

In the mammalian brain, the contribution of CAMs to synaptic plasticity has been studied mostly in the context of LTP. LTP can be induced at many different types of synapses throughout the brain[14] but is best characterized in living brain-slice preparations of the hippocampus, a structure crucial for memory formation[15]. Figure 1a illustrates the principal circuitry of the hippocampus and a commonly used experimental set-up for inducing LTP of the excitatory synapses in area CA1. Trains of electrical stimuli applied to the axons (the Schaffer collaterals) of area CA3 neurons produce LTP of the synapses between the axons of CA3 neurons and the dendrites of CA1 neurons. When brief, high-frequency trains of stimuli (tetanizing stimuli) are used, a rapid-onset, short-lasting form of LTP (lasting 1–2 h) is induced that does not require protein synthesis. This form is called early (E)-LTP and very likely involves rapid changes in the strength of preexisting synapses[12]. By contrast, when multiple,

BOX 2 – MODIFICATION OF NCAM ADHESION BY POLYSIALIC ACID

Polysialic acid (PSA) is a simple, linear homopolymer of α2,8-linked sialic acid. In vertebrates, it is found almost exclusively in association with NCAM[a], where it is attached via typical N-linked core glycosylation of the fifth immunoglobulin (Ig) domain (Box 1; Fig. I) through the expression of two sialyl transferases (PST and STX) that are each differentially regulated during development[b]. Functionally, PSA was recognized initially by its ability to decrease NCAM-mediated adhesion[c], but subsequent work has indicated it can indirectly decrease adhesion mediated by other Ig superfamily molecules as well. Although the mechanism by which it acts to decrease NCAM adhesion is not perfectly understood, it probably involves steric hindrance created by its extensive negative charge and large hydration volume[d]. It is currently thought that PSA-NCAM represents a less-adhesive form of NCAM, one that would be appropriate for facilitating the synaptic/structural reorganization that occurs during brain development and under conditions of synaptic plasticity in maturity[e]. In support of this, PSA expression is more widespread throughout the brain during development[f], where it plays an essential role in a variety of events. For example, pathfinding in a number of systems involves cycles of fasciculation where axons travel together in closely apposed bundles, and defasciculation where they separate and rearrange. When PSA is removed from growing axons in a number of regions [by using the enzyme endoneuraminidase N (endo N), which selectively removes PSA], the axons fail to defasciculate or form collaterals and pathfinding errors result[g]. When removed from regions where both axons and recipient cells express PSA-NCAM, axons defasciculate more extensively[h,i] (although see also Ref. j). Migration of some cell populations, most notably those of the olfactory bulb, are impaired by injections of endoneuraminidase N (endo N) and in mice deficient in NCAM[k,l]. By adulthood, PSA is largely absent in the brain[m], but expression remains in certain brain regions characterized by ongoing neuronal and synaptic plasticity. For example, PSA expression remains high in the mature olfactory bulb and dentate gyrus, which continually undergo cycles of neural regeneration[n]; it remains highly expressed in the mature hypothalamus, which undergoes hormone- or salt-regulated changes in synapse number[o], and it remains highly expressed in the mature hippocampus, which undergoes synaptic remodelling[e,j].

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widely spaced trains of high-frequency stimuli are used, both E-LTP and a subsequently developing, longer-lasting form of LTP (L-LTP) are induced, the latter lasting several hours to days or more (Fig. 1b). L-LTP requires gene transcription and protein synthesis and has been associated with growth of new dendritic spines[16] and formation of new synapses[17,18]. Each of the major families of CAMs has been shown to play a role in the induction or maintenance of E- and/or L-LTP.

Adhesion proteins modulate E-LTP at preexisting synapses

Classic cadherins (N- and E-cadherin), a cadherin-like protein (arcadlin) and some CAMs of the Ig superfamily (NCAM, L1 and telencephalin; Box 1) have been shown to play a role in the induction of E-LTP (Refs 19–23). When hippocampal slices are pretreated with function-blocking antibodies against adhesion proteins, synthetic blocking peptides or recombinant protein fragments, LTP either fails to develop or the post-tetanic potentiation decreases rapidly back to baseline. Exposure to such blocking reagents generally does not affect basal synaptic properties, although antibodies to arcadlin reduce normal synaptic transmission as well as prevent LTP[23]. Thus, the data suggest that these adhesion proteins contribute to the earliest mechanisms leading to enhanced synaptic strength. When blocking antibodies or peptides are applied 10–30 minutes after LTP induction, there are no further effects on synaptic strength. This could either reflect a specific role limited to the earliest phases of LTP or that the blocking reagents become ineffective in attenuating E-LTP after it is established because of changes in the conformation or accessibility of the adhesion proteins. A role for NCAM in LTP induction suggested by NCAM antibody-blocking experiments[21] is corroborated by studies showing an inability to induce LTP in area CA1 after enzymatic removal of the polysialic acid (PSA) that is attached to certain isoforms of NCAM (PSA-NCAM; Box 2) or in transgenic mice carrying a targeted deletion of the gene encoding NCAM[20]. These studies have raised the question of whether LTP in area CA1 depends mostly on PSA, rather than on NCAM *per se*. Additionally, NCAM-deficient mice also exhibit a decrease in the magnitude of LTP in area CA3 elicited by stimulation of mossy fibres[24], although other studies have failed to find any differences in LTP between wild-type and NCAM-deficient mice[25]. Because NCAM-deficient mice display marked developmental abnormalities in the morphology and distribution of the presynaptic mossy fibre terminals[24,26,27], an additional question has been raised as to whether the impaired area CA3 LTP in NCAM-deficient mice simply reflects abnormal development of the presynaptic input. However, a recent study has clarified both the roles of NCAM and PSA in LTP and the issue of whether NCAM is directly involved in synaptic plasticity or indirectly affects LTP in area CA3 through its important role in development of this brain region. Cremer and colleagues[28] engineered transgenic mice carrying a targeted deletion

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of the gene encoding one of two identified polysialyltransferases that are responsible for attaching PSA to NCAM. The deleted gene, *ST8SiaIV/PST-1*, is expressed predominantly during postnatal development and remains highly expressed in mature hippocampus, whereas the other (intact) gene, *ST8SiaII/STX*, is expressed predominantly during embryonic and very early postnatal development throughout many brain regions, including the hippocampus[29]. In contrast to NCAM-deficient animals, the brains of *ST8SiaIV/PST-1*-deficient animals – and in particular area CA3 – display normal neuroanatomical features and normal levels of PSA at early stages of postnatal development, presumably attributable to expression of ST8SiaII/STX. However, because of the gene deletion, the level of PSA in brain gradually decreases during subsequent postnatal development. The level of NCAM expression in the brains of mutant animals is identical to that in wild-type animals at all ages. In area CA1, LTP is indistinguishable in two-week-old mutant mice in comparison with age-matched controls but is significantly impaired by four weeks of age and later, thus paralleling the gradual postnatal disappearance of PSA. By contrast, LTP in area CA3 appears normal at all ages examined. Thus, in area CA1, PSA plays an essential role in LTP, whereas, in area CA3, NCAM, but not PSA, appears to be essential for LTP.

Integrin-mediated adhesion (Box 1), by contrast, plays a role in the early stabilization of E-LTP but little or no role in its induction. Disrupting integrin-mediated adhesion by exposing hippocampal slices to antagonistic peptides containing the integrin recognition sequence Arg-Gly-Asp (RGD) up to 10 min following induction of E-LTP causes a gradual decay in synaptic strength over a ~40 min period, without affecting the initial establishment of E-LTP[30].

In contrast to diminished LTP following treatment with antibodies against N-cadherin[19], a recent study of synaptic plasticity in cadherin-11-deficient mice has shown an enhanced level of LTP in hippocampal area CA1 (Ref. 31). The basis for enhanced plasticity in these animals is unknown. Synaptic organization appears normal, which might indicate that altered cadherin-mediated signalling rather than developmental abnormalities in synapse number or structure is responsible. Beyond obvious methodological differences, the seemingly opposite effects on LTP obtained by blocking N-cadherin or cadherin-11 function suggest that different classic cadherins have unique roles in synaptic signalling.

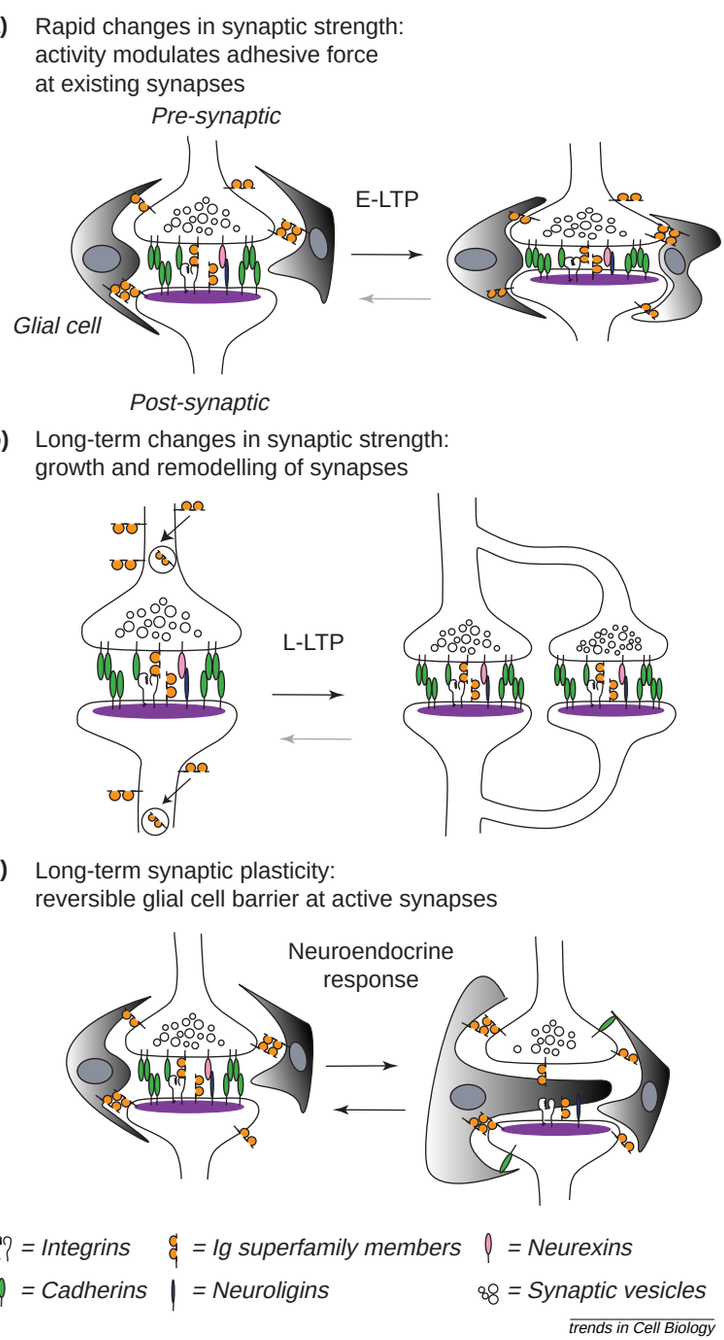
What are the mechanisms through which these adhesion proteins contribute to the induction and stabilization of rapid-onset, activity-dependent synaptic plasticity? A recent study has shown that N-cadherin and L1 are physically associated with NMDA-type glutamate receptors in large, multiprotein complexes isolated from mouse brain[32]. Since NMDA receptors are required for LTP induction[12], this important finding supports the possibility of a direct link between NMDA receptor activation during LTP induction and modulation of adhesion protein function at the synapse. For example, one consequence of a physical–functional linking is that NMDA receptor-mediated synaptic activity during the induction of LTP might rapidly alter the strength of the adhesive force that maintains apposition between pre- and postsynaptic membranes or between neuronal and surrounding glial membranes. Tanaka *et al.*[33] showed that strong depolarization of cultured hippocampal neurons by treatment with either high concentrations of K^+, the glutamate receptor agonist NMDA or the spider toxin α-latrotoxin causes synaptically localized N-cadherin to dimerize and acquire resistance to degradation by proteases, two molecular changes that, in other systems, are well-established indices of augmented and stable adhesive force[34,35]. These molecular changes to N-cadherin are prevented when neurons are stimulated in the presence of APV, an NMDA receptor antagonist. Since in the study of Tanaka *et al.*[33] the neurons were grown and maintained in the absence of direct contact with glial cells, the data indicate that NMDA receptor-mediated synaptic activity augments the cadherin-mediated adhesive force that holds pre- and postsynaptic membranes in apposition. Activity is likely to play a role in modulating the adhesive affinity of other adhesion proteins as well. The adhesive binding affinity of integrins, for example, might be altered by agonist-activated intracellular signalling pathways that cause a conformational change in the integrins to allow high-affinity binding. The classic example of this kind of inside-out signalling occurs in platelets. On a resting platelet, the integrin αIIβ3 exists in a low-affinity state and is unable to bind to soluble fibrinogen. After platelet activation (by agonists such as thrombin, collagen, ADP or epinephrine), αIIβ3 undergoes a conformational change to a high-affinity state and binds to soluble fibrinogen, causing platelet aggregation[36,37]. Ligand binding can also be regulated by integrin clustering (avidity modulation)[37].

How could activity-induced changes in adhesive strength affect synaptic physiology? There are several possibilities (Fig. 2a):

- adhesion proteins might, in turn, directly modulate glutamate receptor channel properties, a possibility suggested by the physical association of N-cadherin and L1 with NMDA receptors in large, multiprotein complexes[32]. This would place adhesion molecules directly in the initial signalling events responsible for LTP;
- the distance between pre- and postsynaptic membranes (the synaptic cleft) might be altered. This could affect the cleft glutamate concentration, which is increased at potentiated synapses[38];
- the size of the apposed active zones in the pre- and postsynaptic membranes might be altered. This could affect the density, compartmentation or composition of postsynaptic glutamate receptors[39,40];
- the extent to which glial cell (astrocyte) processes surround the edges of the synapse might be altered by changes in the strength of adhesion between neuronal and glial membranes[41]. This could modify the rate of glutamate re-uptake from the

FIGURE 2

Models of how cell-adhesion molecules (CAMs) could modify synaptic strength. (a) During rapid synaptic plasticity, such as early long-term potentiation (E-LTP), synaptic activity might modulate the strength of adhesive force between pre- and postsynaptic membranes. This, in turn could activate or alter intracellular signalling cascades that are linked to adhesion proteins (see Box 1). In one kind of example, signalling between adhesion proteins and the actin cytoskeleton could result in changes in the physical dimensions of the synapse active zone or the cleft distance, or changes in the apposition of glial cell membranes. Functionally, these kinds of changes might affect cleft glutamate concentration or the density or compartmentation of neurotransmitter receptors. In another kind of example, altered signalling by adhesion proteins could modulate the functional properties of neurotransmitter receptors or other signalling pathways directly. (b) In long-term synaptic plasticity, such as L-LTP, adhesion proteins might play an additional role during the assembly of new synaptic junctions. The surface expression of some adhesion proteins could be downregulated (internalized adhesion protein shown by small arrows in left panel) to promote process growth, whereas other adhesion proteins could be upregulated and/or recruited from existing pools to sites of newly forming synapses (right panel). The grey arrows [(a), (b)] indicate the uncertainty in mechanisms for reversing E-LTP and L-LTP; de-potentiation could occur by a reversal of the processes depicted in the models. (c) Other forms of long-lasting synaptic plasticity could involve changes in adhesion between perisynaptic neuronal membranes and the normally contiguous glial cell membranes that wrap around the synapse. In the hypothalamus, glial processes form a reversible barrier to synaptic communication, presumably enabled by changing levels of neuronal–glial membrane adhesion.



synaptic cleft by affecting the density or proximity of glutamate transporters, which are localized predominantly to the perisynaptic astrocytic processes[42];

- finally, altered 'outside-in' signalling by adhesion proteins could produce rapid effects on other signalling pathways. Integrin clustering, for example, leads to tyrosine phosphorylation of a variety of proteins[43]. Although integrin cytoplasmic tails lack endogenous kinase activity, they interact with a number of proteins [e.g. focal-adhesion kinase (FAK), paxillin, integrin-linked kinase (ILK)], which in turn interact with many classic signalling pathways such as mitogen-activated protein kinase (MAPK), Rho and protein kinase C (Ref. 43). In addition, many adhesion proteins can associate with other transmembrane or membrane-associated proteins. For example, recent studies show that the deficient LTP observed in hippocampal slices prepared from NCAM-knockout mice can be rescued by exogenous application of brain-derived neurotrophic factor (BDNF), suggesting crosstalk between NCAM and growth-factor-related signalling[44].

Adhesion proteins regulate new synapse formation during long-lasting forms of synaptic plasticity

Formation of new synaptic sites as well as the loss of old ones occurs throughout life and represents another aspect of synaptic plasticity in which synaptic communication is modified for long-term periods. What are the proteins that enable new synapse assembly in the mature brain to ensure that pre- and postsynaptic membranes link-up appropriately, stabilize and become functional? Synaptic adhesion proteins are of particular interest in this context because pre- to postsynaptic membrane adhesion is one of the initial events in the construction of a synaptic junction during brain development[45] and remains a fundamental component of the maintenance of synapses in maturity. Thus, the molecular adhesive machinery required for synapse assembly in development would be expected to have an essential role in modulating synaptic architecture in the context of plasticity-related structural remodelling (Fig. 2b).

Consistent with this, Bozdagi *et al.*[17] has provided evidence suggesting that N-cadherin is synthesized

and recruited to new synapses as they are assembled during the induction of L-LTP in hippocampal slices. That study found that, during the induction of L-LTP, there was an ~27% increase in N-cadherin protein levels and an enhancement in N-cadherin dimerization, thus suggesting that augmented synaptic adhesion contributes to the potentiated state. Additionally, in the potentiated slices, there was a ~30% increase in numbers of synaptic junctions (synaptic 'puncta'), which were identified by confocal microscopic immunolocalization of the synaptic molecular markers synaptophysin (a presynaptic vesicle protein) and N-cadherin. The increase in numbers of synaptic puncta was blocked by inhibitors of protein synthesis, consistent with the requirement for protein synthesis in the expression of L-LTP[46]. Treating slices with function-blocking antibodies against N-cadherin prevented the induction of L-LTP, without affecting normal synaptic neurotransmission. Taken together, these data provide compelling evidence that N-cadherin adhesion contributes crucially to long-lasting synaptic potentiation as new synapses are formed or remodelled during the reshaping of synaptic architecture. Other adhesion proteins very likely play similar roles in reshaping synaptic structure during long-lasting synaptic plasticity. For example, changes in integrin levels are seen after hippocampal seizures[47], which involve synapse remodelling[48], and increased levels of NCAM are observed in the dendritic spines of hippocampal neurons 24 h after induction of LTP[49]. Additionally, L-LTP enhances the association of neuroplastin-65, an adhesion protein of the Ig superfamily, with a postsynaptic density (PSD)-enriched fraction, and L-LTP is blocked by treating hippocampal slices with antibodies against neuroplastin-65 (Ref. 50). It is likely that adhesion proteins affect synaptic structural remodelling through their links to the actin cytoskeleton (Box 1). It is well established that both integrin- and cadherin-based adhesion can initiate changes in cell morphology during tissue morphogenesis, cell migration and metastasis[51]. This raises the possibility for an active role for CAMs in changing spine number, morphology or motility, alterations that are associated with long-lasting synaptic plasticity[52]. In neurons, it is possible that adhesion protein-activated changes in synaptic morphology could be mediated through several signalling pathways (Table 1) that can converge on one of the members of the Rho subfamily of small GTPases, which regulate the assembly of distinct actin-based structures[53]. Actin-binding proteins, such as α-actinin-2, which tether both neurotransmitter receptors and adhesion molecules to actin, are also likely points for coordinated convergence of activity, adhesion and morphological changes to synapses or spines[54].

The foregoing discussion emphasizes that many adhesion molecules are upregulated during synaptic remodelling, presumably in order to stabilize newly forming synapses. However, surface expression of some adhesion molecules is downregulated to facilitate long-lasting synaptic plasticity, which is thought to diminish the strength of membrane adhesion that might normally act to constrain process outgrowth (Fig. 2b). For example, the gill-withdrawal reflex in the marine snail *Aplysia* is enhanced for days following a brief period of repetitive tail stimulation. The neural basis for this augmented behavioural response is a type of synaptic plasticity called long-term facilitation. Like L-LTP in the mammalian hippocampus, long-term facilitation requires gene transcription and protein synthesis and arises through the formation of new synapses[55]. The sequence of new synapse formation during long-term facilitation requires downregulation of apCAM, an NCAM-related adhesion protein, by increased internalization and degradation of apCAM on the membrane surface of the presynaptic axon[56–58]. This, in turn, is thought to decrease homophilic binding between closely apposed groupings (fascicles) of sensory axons, thereby promoting individual axons to separate from the larger group (defasciculation), which is necessary to allow terminal axon outgrowth as a requisite step towards forming new synaptic contacts[55]. Long-lasting synaptic plasticity in mammals probably also requires mechanisms for downregulating surface expression of adhesion proteins in order to promote process rearrangement. The induction of LTP in the dentate gyrus of the hippocampus, for example, is associated with the transient appearance of a 115-kDa fragment of NCAM in the extracellular space, suggesting enhanced proteolytic cleavage[59].

The regulation of adhesion between neuronal and glial cell membranes is also important in remodelling synaptic architecture (Fig. 2c). In the supraoptic nucleus of rat hypothalamus, lactation or chronic osmotic stimulation induces a retraction of the glial (astrocytic) processes that normally wrap contiguously around dendritic and somatic neuronal membranes, resulting in an increase in the number of synapses upon the exposed neuronal membrane surfaces[60]. Upon cessation of the stimulation, the process reverses. Both neurons and glia in the supraoptic nucleus express high levels of PSA-NCAM (Ref. 61), an isoform having reduced adhesivity in comparison with non-sialylated isoforms and therefore thought to represent an NCAM isoform that is permissive for structural remodelling[62] (Box 2). When the sialic acid residues are enzymatically removed by intrahypothalamic injection of endoneuraminidase N (endo N), the glial processes fail to retract in response to stimulation, preventing the increase in synapse number[63]. A similar mechanism appears to orchestrate an oestrogen-mediated fluctuation in numbers of inhibitory synapses in the hypothalamic arcuate nucleus[64]. These data support the idea that PSA-NCAM is permissive to growth and retraction of processes, which underlie new synapse formation or loss, suggesting an important role for dynamic modulation of neuronal–glial membrane adhesion in regulating synapse number in response to physiological stimuli (Fig. 2c).

Perturbing the function of CAMs affects learning and memory

The importance of CAMs to synaptic function and plasticity is underscored by the behavioural deficits

in learning and memory that result from altering cell-adhesion function. In *Drosophila*, Davis and colleagues[65] identified a gene locus linked to the memory mutant *Volado*, which encodes two isoforms of a member of the alpha integrin subunit family. The protein products encoded by *Volado* are enriched in the neuropil of the mushroom body, a brain region important for learning in insects. *Volado* mutants have impairments in olfactory memories. The memory impairment is rescued by conditional expression of a *Volado* transgene, indicating a crucial role for the integrins in the processes underlying the formation of olfactory memories. Although the mechanism through which the *Volado* integrins participate in memory formation is unknown, histological analyses of the brains of the *Volado* mutants suggest normal neuronal architecture, raising the possibility that impaired integrin signalling, rather than overt synaptic structural changes, might be responsible.

Altering L1 and NCAM function affects learning and memory both at an early, acquisition phase and in a later, memory-consolidation phase. Transgenic mice engineered so that their astrocytes express L1 ectopically, learn the position of a hidden platform faster than control mice when tested in the Morris water maze[66], a test of spatial memory. By contrast, NCAM-knockout mice show impaired spatial learning when tested in the Morris water maze[67], while similar deficits in spatial learning are evident in rats following enzymatic removal of sialic acid from PSA-NCAM (Ref. 68). In other studies, memory retention in chicks is impaired 24 h following a visual categorization task when antibodies against L1 are injected intracranially at any one of three restricted time-periods: before, 5.5 h after and 15–18 h after training[69]. Similarly, intraventricular injections of antibodies against NCAM ~6–8 h following passive avoidance training in chicks[70] or rats[71] impairs retention of the avoidance response but is without effect if injected during the training period. In these tasks, the level of polysialylation of NCAM increases over a period of hours following training in rats[72], suggesting that NCAM gradually acquires a less-adhesive state in order to promote structural remodelling[62]. It is possible perhaps that the antibodies against NCAM impede polysialylation and thereby prohibit potential structural changes in synaptic architecture required for retention of the avoidance response. It should be emphasized, however, that the precise mechanistic links between altered adhesion protein function and enhanced or diminished behavioural learning are unknown.

Future directions

Synaptically localized CAMs should be viewed not as static players whose job is simply to maintain the structural scaffolding upon which synaptic signalling occurs but, rather, as active participants in the signalling process itself, capable of modulating functional and structural aspects of synaptic plasticity. A number of technological and methodological advances are now at hand to define more clearly the precise nature of adhesive changes at the synapse as a consequence of neural activity and the signalling pathways that are modified by changing the force of synaptic adhesion. Elucidating such intracellular signalling pathways will be crucial for understanding the relationship between extracellular adhesive interactions and gene transcription and protein synthesis, both of which are required for long-term changes in synaptic function. Finally, advances in gene targeting and transient transfection techniques as well as the development of more reliable inducible promoters will allow a clear elucidation of how CAMs contribute specifically to synaptic signalling and plasticity without the potentially confounding abnormalities in circuit formation and gene compensation that can arise during development and are often encountered in animals with gene knockouts. Such future lines of investigation will be crucial for developing a comprehensive view of synapse physiology that integrates neurotransmission, intracellular signalling pathways and cell adhesion.

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Acknowlegdements

Personal work supported by grants from the NIH (NS34659 to G.W.H. and NS37731 to D.L.B.), and the National Science Foundations (IBN-9728003 to D.L.B.). We aplogoize to those authors whose work we were unable to cite because of space constraints.

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