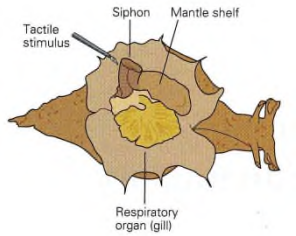
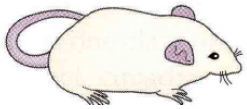
Synaptic plasticity, learning, memory and LTP

"One of the most remarkable aspects of an animal's behaviour is the ability to modify that behaviour by learning, an ability that reaches its highest form in human beings. For me, learning and memory have proven to be endlessly fascinating mental processes because they address one of the fundamental features of human activity: our ability to acquire new ideas from experience and to retain these ideas over time in memory…."

[From Eric Kandel, 2001 - Nobel Prize in Physiology or Medicine 2000]

Research on cellular basis of learning & memory mainly performed in three animal systems

Aplysia	*Drosophila*	*Mouse*
		
All neurons and synapses in behavioral circuits are identified and can be recorded easily Ideal for detailing mechanisms underlying implicit learned motor responses	Capable of learned behaviors Amenable to random mutagenesis and selection of mutants with defective behaviors	Similar anatomy to human Amenable to study of explicit memory Hippocampus amenable to electrophysiology Behavior modification of genetically modified mice

LTP

The term Long Term Potentiation is used to indicate an enduring increase in the amplitude of excitatory postsynaptic potentials as a result of high-frequency (tetanic) stimulation of afferent pathways.

- **Form of plasticity can be induced by tetanic stimulation**
- **LTP in awake animals can last many weeks, maybe a lifetime.**
- **Neurons must be active during tetanus for LTP**
- **Temporal & spatial summation required**
- **LTP is important for associations**

Long term memory in the hippocampus: potentiation at Schaffer's collateral-CA1 synapse

Early and late LTP:

the former is elicited by one single train of stimuli at 100 Hz; the latter by 4 trains at 10-min intervals.

Kandel, E.R., Science 2001, 294: 1030- 1038)

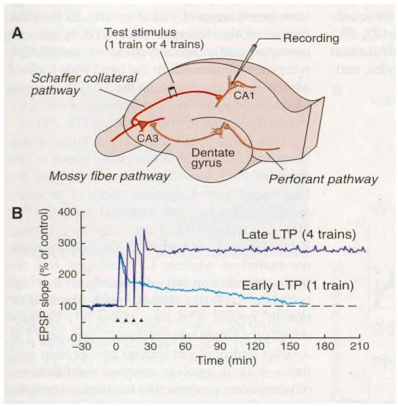
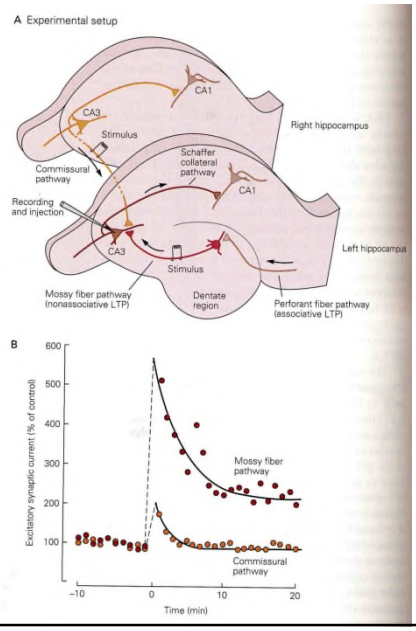


Figure 16. LTP in the hippocampus. A) The three major pathways of the hippocampus each of which gives rise to LTP.
B) The early and late phases of LTP in the Schaffer collateral pathway. A single train of stimuli for one second to 100 Hz elicits an early LTP, and four trains at 10-minute intervals elicit the late phase of LTP. The early LTP lasts about 2 hours, the late LTP more than 24 hours (from [Kandel, 2001 #261])

LTP at CA3-CA1 synapse is blocked by NMDAR antagonist APV and by inhibitors of CaM kinase

Long term memory in the hippocampus: potentiation at mossy fiber-CA3 synapses



Mechanism of long term memory in the hippocampus: The Big Question

Where does the process causing increased synaptic transmission associated with LTP takes place…: pre- or post-synaptically?

At the time of this experiment, there were 3 suggested possibilities:

1. Increased neurotransmitter release from presynaptic terminals
2. A morphological change in pre- or post-synaptic structure
3. A post-synaptic change in sensitivity to neurotransmitters

Is LTP induced Pre- or post-synaptically?

The Premise: After LTP induction, an increase in neurotransmitter release (glutamate) by the pre-synaptic neuron would result in a simultaneous increase in both NMDA and AMPA components of the EPSP.
It was already known that the non-NMDA mediated current increases after LTP, but to prove that more glutamate is released, it would have to be shown that the NMDA mediated current increases after LTP as well.

PROCEDURE: LTP is induced by Tetanic stimulation. Chemical antagonist CNQX was applied to block the non-NMDA (AMPA) receptors. The NMDA component of the EPSP was examined in isolation from the non-NMDA (AMPA) component before and after LTP using CNQX. Cells were monitored for 40 min following LTP inducing stimuli.

RESULTS: After addition of CNQX: Tetanic stimulation induced Post Tetanic Potentiation. Caused a transient increase in NMDA component, but quickly returned to baseline

INTERPRETATION: The NMDA component of the EPSP is not enhanced following LTP-inducing stimuli. Since NMDA mediated response did not change after tetanus, **an increase in glutamate release probability does not explain the changes in LTP**

The Silent Synapse Hypothesis of LTP

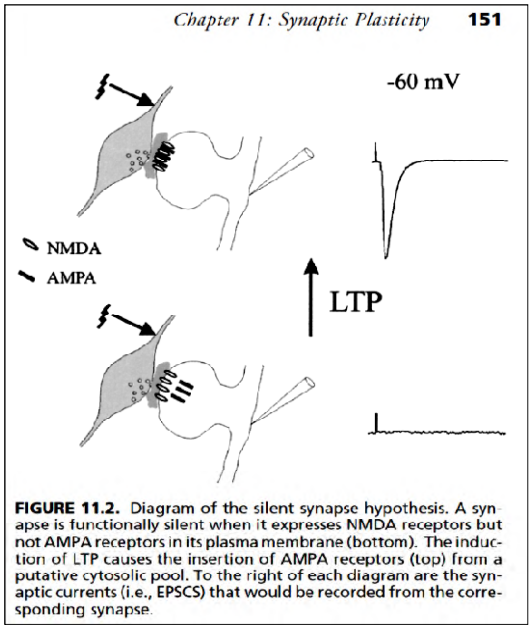
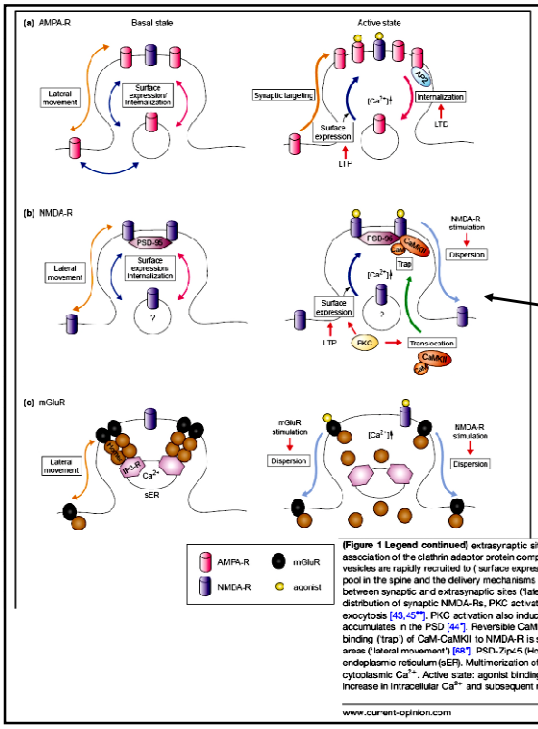


FIGURE 11.2. Diagram of the silent synapse hypothesis. A synapse is functionally silent when it expresses NMDA receptors but not AMPA receptors in its plasma membrane (bottom). The induction of LTP causes the insertion of AMPA receptors (top) from a putative cytosolic pool. To the right of each diagram are the synaptic currents (i.e., EPSCS) that would be recorded from the corresponding synapse.

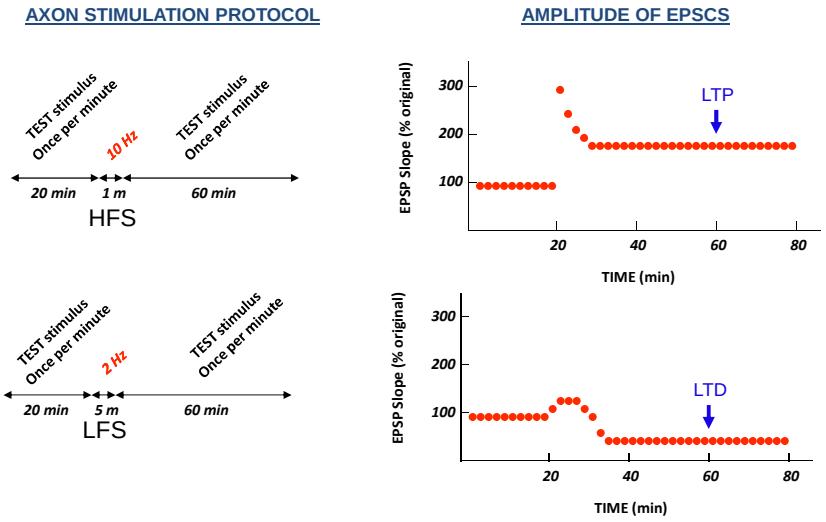


(Figure 1 Legend continued) extrasynaptic site. NMDA-R-dependent 'internalization' of AMPA-Rs provides a possible mechanism for LTD. Direct association of the clathrin adaptor protein complex (AP2) with AMPA-R is essential for this internalization [47••]. **(b)** Basal state: NMDA-Rs in transport vesicles are rapidly recruited to ('surface expression') and internalized from ('internalization') the synaptic membrane [13••]. The nature of the vesicular pool in the spine and the delivery mechanisms of NMDA-Rs are not well understood (see update). NMDA-Rs can also move on the neuronal surface between synaptic and extrasynaptic sites ('lateral movement'), at the basal state. Active state: although neuronal stimulation does not affect the distribution of synaptic NMDA-Rs, PKC activation or LTP induction can increase NMDA-R 'surface expression' through SNARE-dependent exocytosis [43,45••]. PKC activation also induces rapid 'dispersion' of NMDA-Rs from synaptic sites (not shown, whereas in contrast, CaMKII accumulates in the PSD [44•]. Reversible CaMKII 'translocation' is also achieved through NMDA-R stimulation, and requires CaM binding. Direct binding ('trap') of CaM-CaMKII to NMDA-R is sustained [60,62••]. **(c)** Basal state: mGluR clusters themselves are highly mobile about perisynaptic areas ('lateral movement') [58•]. PSD-Zip45 (Homer 1c) binds to both type-I mGluRs (mGluR1/5) and IP_3Rs on the surface of Ca^{2+}-enriched smooth endoplasmic reticulum (sER). Multimerization of PSD-Zip45 molecules leads to the clustering of mGluRs, and enhances IP_3 R dependent increases in cytoplasmic Ca^{2+}. Active state: agonist binding to mGluR5 promotes mGluR5 cluster 'dispersion' [56•]. NMDA-R stimulation entails both a slow increase in intracellular Ca^{2+} and subsequent mGluR cluster 'dispersion' [55].

The lability of AMPA relative to NMDA receptors is thought to contribute to synaptic plasticity

PSD-95 family members might stabilize the NMDA receptors arrayed in the center of the PSD while allowing AMPA receptors arrayed around the periphery to turn over more quickly.

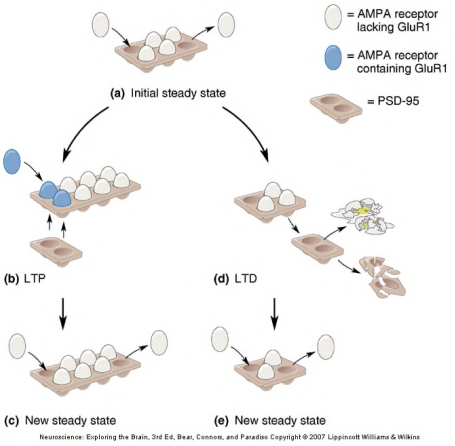
Synapses sensitive to LTP are also sensitive to long-term depression (LTD)



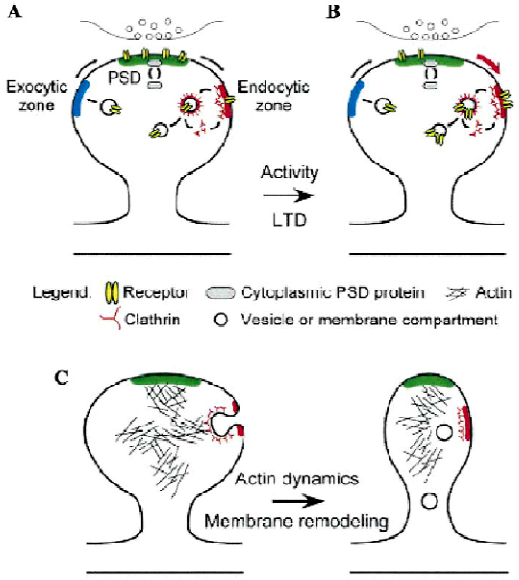
Vertebrate Models of Learning: role of scaffold protein PSD95

LTP, LTD, and Glutamate Receptor Trafficking

- Egg carton model of AMPA receptor trafficking at synapse
- Size of scaffold – *slot proteins*
- Scaffold like egg carton
- Slot proteins form egg cups
- AMPARs are the eggs
- LTP increase scaffold
- LTD decrease scaffold
- *PSD-95* may be egg carton
- New AMPARs have GluR1



1124 BIOL PSYCHIATRY 2004;55:1121–1127 Thomas A. Blanpied and Michael D. Ehlers

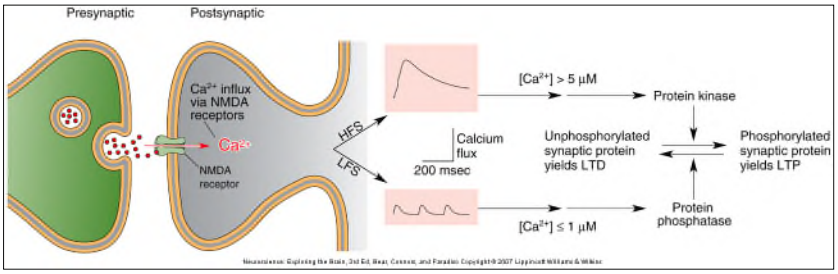


The positioning of the endocytic zone near to but distinct from the PSD suggests a general model of synaptic membrane traffic in which receptors move into synaptic membranes via perisynaptic regions

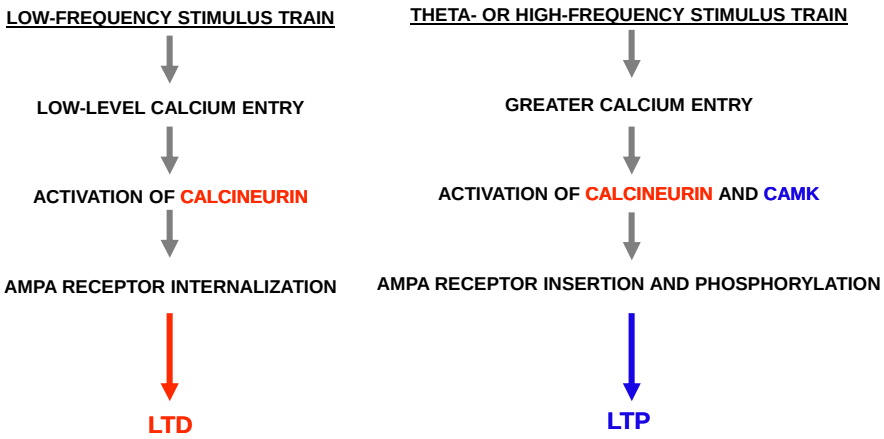
Figure 2. Role of spine microanatomical zones in synaptic plasticity and spine morphologic dynamics. **(A)** Proposed model whereby spines contain a number of domains dedicated to protein trafficking. Internalization of synaptic receptors and other membrane proteins occurs at the endocytic zone (red), where clathrin and endocytic proteins recycle (Blanpied et al 2002). Receptors are hypothesized to be inserted in the membrane at an exocytic zone (green) and moved laterally into the synapse, whereas cytosolic proteins can be directly added to and removed from the PSD (green). Equipped with functional domains to insert, stabilize, and remove receptors, each spine retains autonomous control over the strength of transmission at its synapse. **(B)** Activity-dependent synaptic plasticity, such as long-term depression (LTD), produces a net decrease in the number of synaptic receptors. The presence of a constitutively operating endocytic zone suggests that synaptic receptors translocate from the PSD to the endocytic zone before endocytosis. **(C)** A model for coordinated regulation of actin and endocytosis during spine morphologic change. We propose that actin-dependent changes in spine shape may involve membrane removal by endocytosis. PSD, postsynaptic density.

Vertebrate Models of Learning

- LTP, LTD, and Glutamate Receptor Trafficking



LTD has a lower calcium concentration threshold than LTP, but LTP is dominant



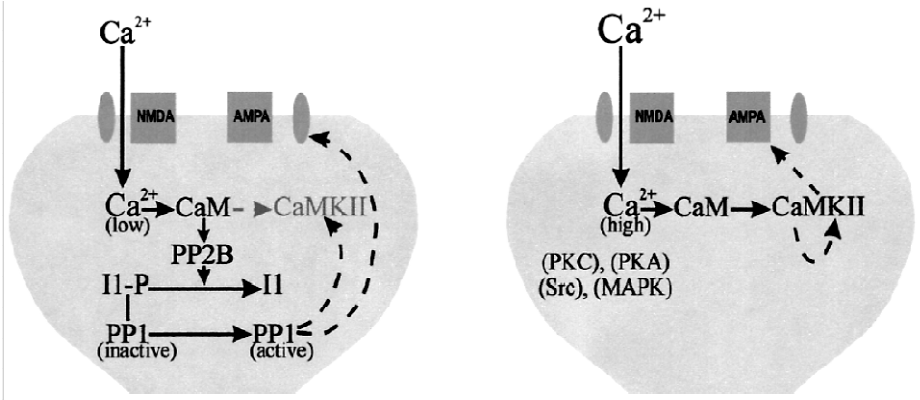


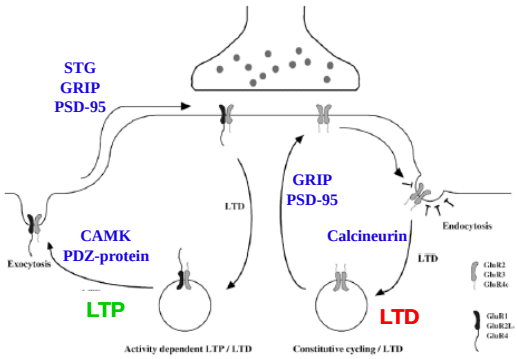
FIGURE 11.3. Model for the signaling cascades responsible for LTD and LTP. LTD is generated when a low rise in Ca^{2+} binds to calmodulin (cam) and activates calcineurin (PP2B). Calcineurin then dephosphorylates inhibitor 1 (I1), which therefore no longer inhibits protein phosphatase 1 (PP1). Active PP1 may act on any number of substrates including camkii or AMPA receptors (*left*). LTP is generated when a high rise in Ca^{2+} activates camkii. Other protein kinases that may also be involved in triggering LTP are protein kinase C (PKC), cAMP-dependent protein kinase (PKA), the tyrosine kinase src (Src), and MAP kinase (MAPK)(*right*).

NMDAR-induced CAMK activity acts on AMPA receptors in two ways to promote LTP

CAMK phosphorylates an unknown protein, enabling a PDZ-protein that interacts with long tail on GluR1 to deliver receptor TO EXTRASYNAPTIC SITE

Delivered receptors migrate (randomly?) into post-synaptic density, where interactions of receptor-associated GRIP and STG and the major postsynaptic matrix protein PSD-95 anchor receptor to synapse

Newly delivered GluR1-containing AMPA receptors can be phosphorylated directly by CAMK, which increases unitary conductance of the receptor



Calcineurin activation promotes internalization of AMPA receptors containing only short-tail subunits, thereby promoting LTD

WHEN HIGH CALCIUM ENTRY ACTIVATES BOTH CALCINEURIN AND CAMK, CAMK-MEDIATED GluR1-CONTAINING AMPAR EXOCYTOSIS EXCEEDS CALCINEURIN-MEDIATED SHORT TAIL-ONLY AMPAR ENDOCYTOSIS

The Molecular Basis of Long-Term Memory

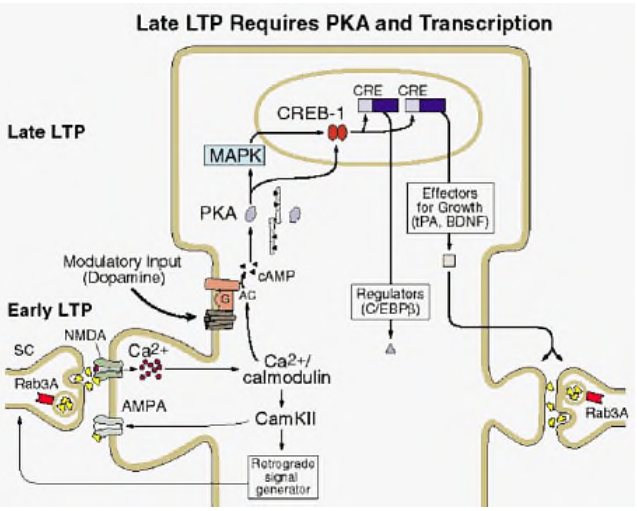
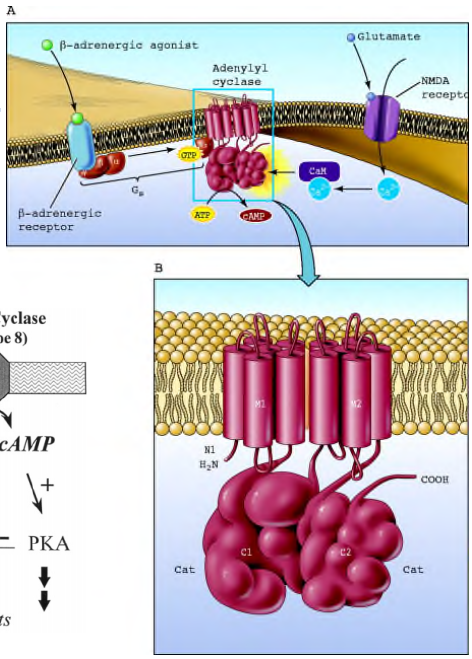
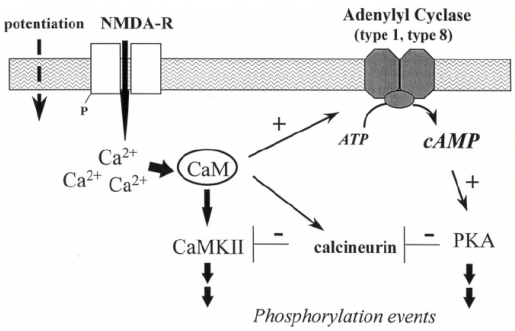


Figure 17. A model of the late phase of LTP in the Schaffer collateral pathway. A single train of action potentials initiates early LTP by activating NMDA receptors, Ca2+ influx into postsynaptic cell, and the activation of asset of second messengers. With a repeated trains of action potentials the CA2+ influx also recruits an adenylyl cyclase (AC), which activates the cAMP-dependent protein kinase. The kinase is transported to the nucleus where it phosporylates CREB. CREB in turn activates targets, as BDNF, that are thought to lead to structural changes. Mutation in mice that block PKA or CREB reduce or eliminate the late phase of LTP (from Kandel, 2001).

The Molecular Basis of Long-Term Memory:

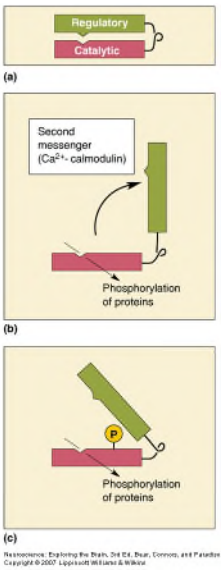
Ca^{2+}Calmodulin and Adenylyl Cyclase



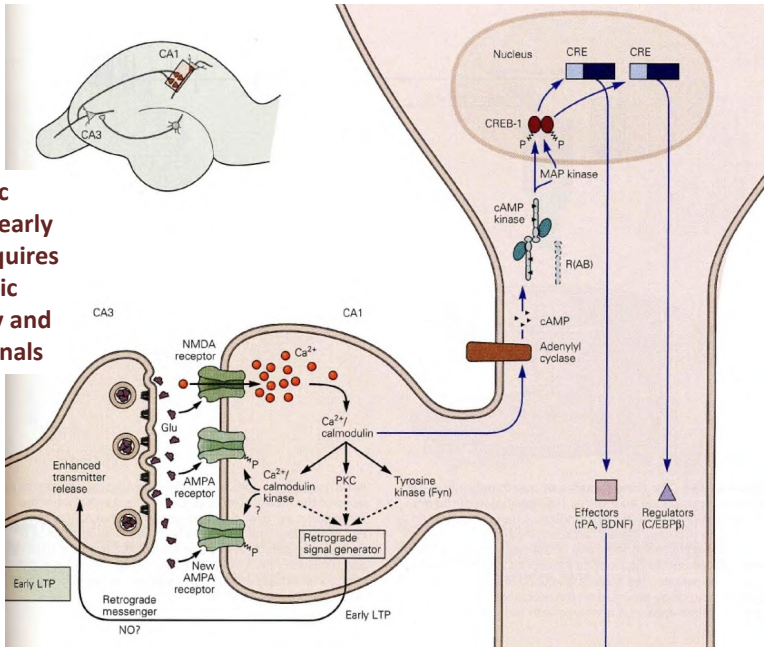


The Molecular Basis of Long-Term Memory
Why are kinases involved?

- Phosphorylation is a long term mechanism that overrides transient stimuli and turnover rates
- Persistently Active Protein Kinases
  - Phosphorylation maintained: Kinases stay "on"
    - CaMKII and LTP
      - Molecular switch hypothesis



Presynaptic component of early and late LTP requires postsynaptic cAMPK activity and retrograde signals

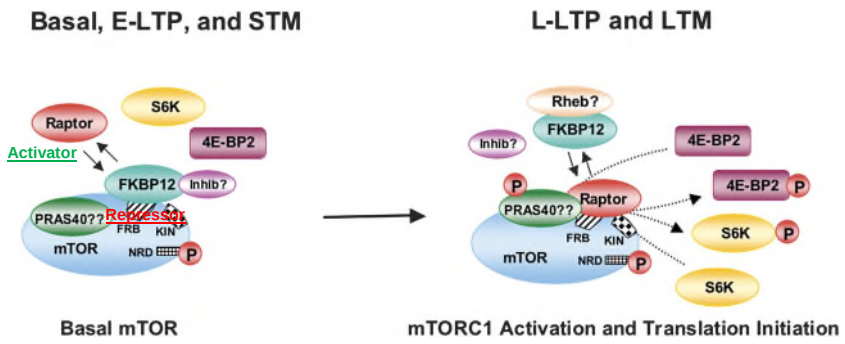


The Molecular Basis of Long-Term Memory

Protein Synthesis

- Requirement of long-term memory
  - Synthesis of new protein
- Protein Synthesis and Memory Consolidation
  - Protein synthesis inhibitors
    - Deficits in learning and memory
- CREB and Memory
  - CREB: Cyclic AMP response element binding protein

Proposed mechanism for mTORC1 activation following stimulation that induces L-LTP or after a training that triggers long-term memory formation.



FKBP12 serves as an intracellular scaffold for either an mTOR inhibitory factor(s) or directly competes with Raptor for the mTOR FRB site.

Stimulation that induces translation initiation (either electrical stimulation that induces L-LTP or training that induces LTM), signals either (1) the displacement of the inhibitory factor(s) interacting with FKBP12, or (2) the sequestration of FKBP12 from mTOR, thereby permitting Raptor access to the FRB. Translation-inducing signaling promotes mTOR access to 4E-BP2 and S6K, possibly through activation of additional mTORC1-associated scaffolds (i.e., PRAS40), allowing translational initiation. Ras-homolog enriched in the brain (Rheb), proline-rich Akt/PKB substrate-40 kd (PRAS-40), FKBP12-binding domain (FRB), KIN (mTOR kinase catalytic domain), NRD (domain, site of serine 2448 phosphorylation).

Joel D. Richter, and Eric Klann Genes Dev. 2009;23:1-11

High CaMK activity induced during late LTPis also mediated by new Cam-kinase protein synthesis near the synapse

Most mRNAs have 3' polyA tail, which is necessary for initiation of the mRNA's translation

Neurons contain some mRNAs that are not polyadenylated, are not translated, and are transported along dendrites to areas near dendritic spines

NMDA receptor activation and calcium entry activates a protein kinase called AURORA

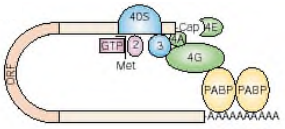
Aurora kinase activates translation of nearby dormant mRNAs

ONE OF THESE DORMANT RNAs ENCODES CAM KINASE

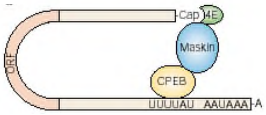
Because of its dendritic localization, new CAMK synthesis is restricted to the synapse undergoing LTP

The dendritic localization of dormant CAMK RNA and its activation during LTP are mediated by Cytoplasmic Polyadenylation Element Binding (CPEB) protein

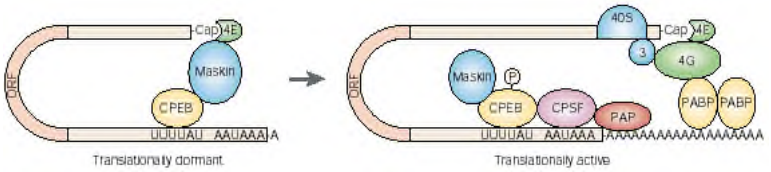
How does CPEB protein control RNA dormancy and activation in neurons?



PolyA is needed for assembly of 5' translation initiation complex



CPEB protein binding to 3' CPE helps mask RNA 5' end

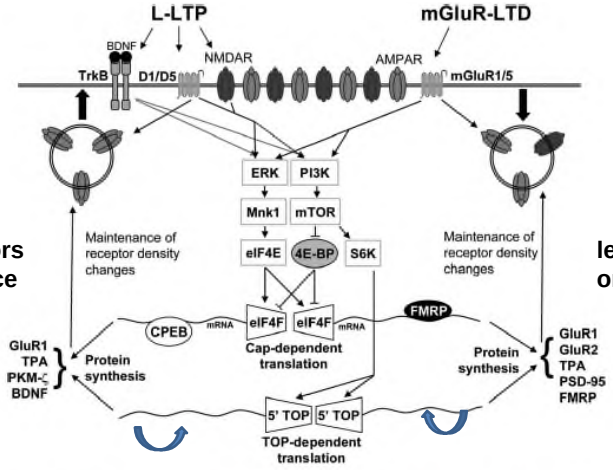


CPEB phosphorylation by Aurora allows for recruitment of polyA polyermerase (PAP)

Polyadenylation of dormant RNA allows assembly of 5' translation initiation complex

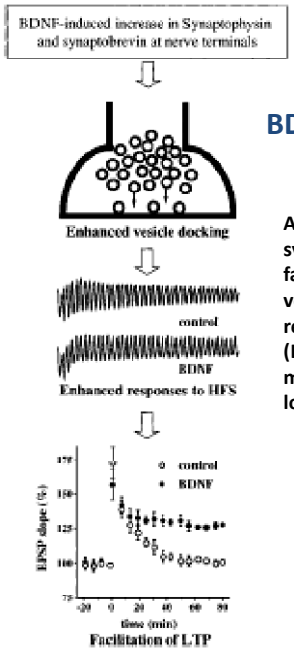
Convergence and divergence of mechanisms for protein-synthesis dependent LTP/LTD

more receptors on cell surface



less receptors on cell surface

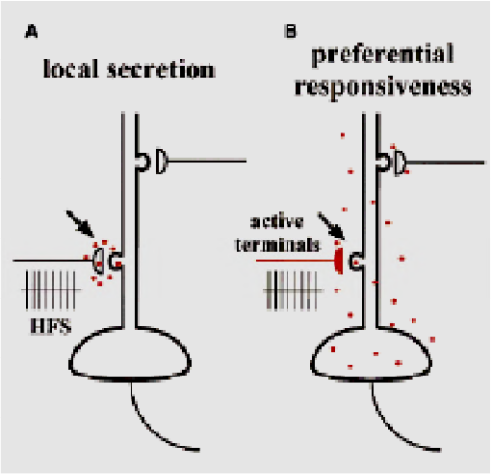
Figure 1. Convergence and divergence of mechanisms for protein synthesis-dependent LTP and LTD. Protein synthesis-dependent LTP (L-LTP) and mGluR-LTD activate and use similar, if not identical, pathways. To simplify, not all protein synthesis regulatory pathways are included, and second-messenger pathways upstream of ERK and PI3 kinase (PI3K) are omitted. Coactivation of NMDARs and dopamine D_1/D_5 receptors initiates the insertion of glutamate receptors to the synaptic surface and stimulates both ERK and PI3 kinase. Alternatively, agonists of



BDNF modulation of synaptic plasticity in hippocampal CA1 synapses.

A BDNF induced increase in the vesicle proteins synaptophysin and synaptobrevin at nerve terminals may facilitate vesicle docking. Synapses with more docked vesicles in the presynaptic active zone will undoubtedly respond better to high frequency tetanic stimulation (HFS). An enhancement of synaptic responses to tetanus may contribute, at least in part, to BDNF modulation of long-term potentiation (from[Lu, 1999 #204]).

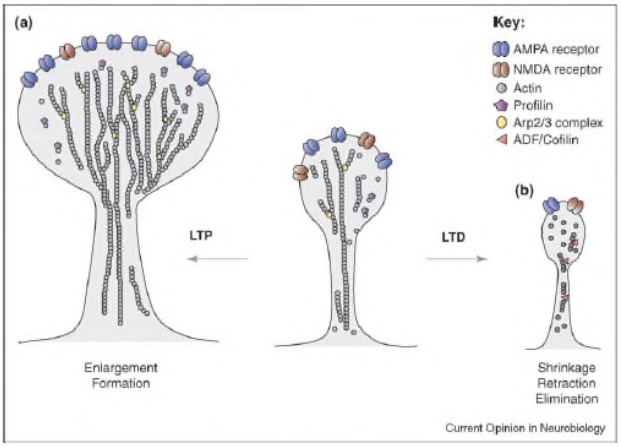
Two possible mechanisms to ensure synapse specificity of BDNF modulation.



A) Local secretion model. BDNF is secreted only at or near active synapses.

B) Preferential responsiveness model. Active presynaptic neurons/terminals respond better to widely diffused BDNF. Red dots represent BDNF molecules (from [Lu, 1999 #204]).

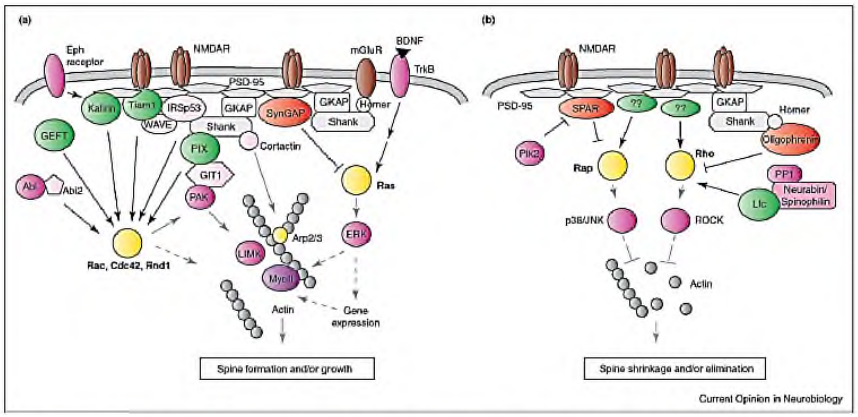
LTP and LTD are accompanied by intense cytoskeleton changes



Changes in actin polymerization and spine morphology with LTP and LTD. **(a)** LTP is associated with a shift of actin equilibrium toward F-actin (F-actin is depicted as linear chains of monomeric G-actin [single circle]) in spines, enlargement of the spine head, and recruitment of more AMPA receptors to the postsynaptic membrane. Profilin promotes actin filament assembly by increasing the availability of actin-ATP for polymerization. The Arp2/3 complex stimulates nucleation of new actin filaments and formation of branches. **(b)** By contrast, LTD stimulation shifts the equilibrium toward actin depolymerization, resulting in shrinkage or loss of spines. The actin severing protein ADF/cofilin might be involved in spine shrinkage.

Tada & Sheng, 2006

Figure 2



Small GTPase signaling pathways that regulate spine morphology. **(a)** Activation of Rac1, Cdc42, Rnd1 and Ras promote spine formation and growth. Cell surface receptors (Eph receptors, NMDA receptors) activate guanine nucleotide exchange factors (GEFT, kalirin, Tiam1, PIX; shown in green) to stimulate Rac1, Cdc42 and/or Rnd1. Rac and Cdc42 regulate actin cytoskeleton, in part by stimulating PAK and myosin II activity. IRSp53, Abi2 and WAVE are adaptor proteins involved in signaling to Rac and Cdc42. WAVE and cortactin regulate the Arp2/3 complex and actin branching. NMDA receptors and TrkB (BDNF receptor) stimulate the Ras-ERK MAP kinase pathway, which is inhibited by the RasGAP SynGAP (red). **(b)** Activated Rap and RhoA induce shrinkage and loss of spines. The RapGAP SPAR promotes spine growth, and is targeted for degradation by polo-like kinase Plk2. The RhoGEF Lfc and RhoGAP oligophrenin bidirectionally regulate Rho. Other RhoGEFs and RapGEFs (indicated by '??') probably exist in the PSD. p38, JNK MAP kinases and Rho-associated kinase (ROCK) might play a role in the inhibition of spine morphogenesis by Rap and Rho, respectively.

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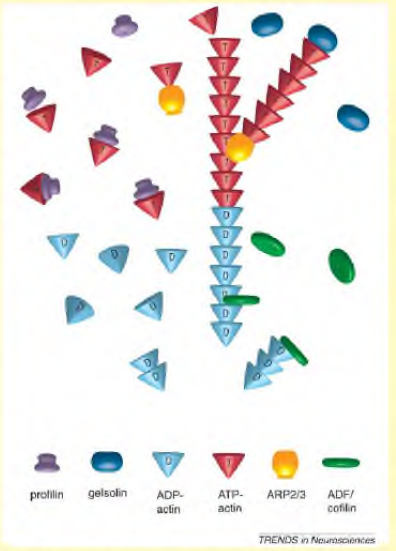
Tada & Sheng, 2006

Current Opinion in Neurobiology 2006, **16**:95–101

Box 1. Regulation of actin dynamics

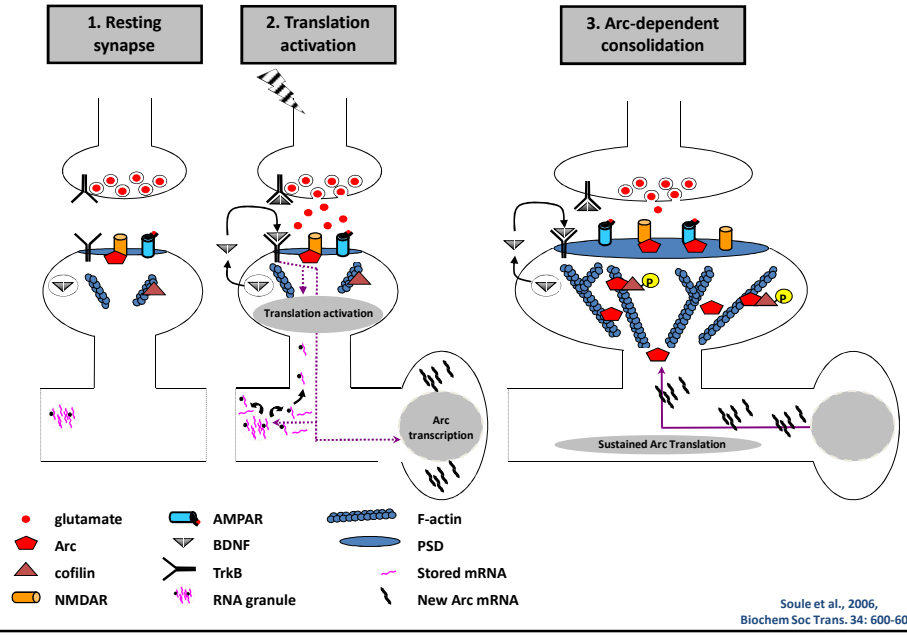
Filamentous actin (F-actin) is a double-stranded chain-like structure of monomeric actin subunits (G-actin) that grows in a polarized fashion (Figure I). F-actin is in a continuous state of turnover, with new subunits added to the barbed end of the filament and older subunits removed from the pointed end in a treadmill process [61]. Growth of filaments depends on the availability of actin monomers with bound ATP (actin-ATP). When subunits are incorporated into filaments, slow hydrolysis of actin-ATP to actin-ADP is catalyzed, which stabilizes the filamentous form. A variety of actin-binding proteins regulate and shape the treadmilling process, and thereby the cytoskeleton. The F-actin-severing protein ADF/cofilin binds to actin monomers with a higher affinity for actin-ADP than for actin-ATP. Binding of ADF/cofilin to actin-ADP changes the twist in the actin helix and promotes severing [62–64]. In this manner, ADF/cofilin catalyzes disassembly of the older, pointed ends of actin filaments. Phosphorylation of ADF/cofilin at Ser3 inhibits its ability to bind to actin [65]. Thus, depolymerization of actin can be regulated by cytosolic signaling pathways. Profilin stabilizes actin filaments by catalyzing exchange of ADP for ATP on actin monomers, maintaining a pool of actin-ATP monomers that can be added to the growing end of filaments [66]. In addition, profilin potentiates treadmilling by 'sequestering' actin monomers in a form that can bind to the barbed end, but not the pointed end, of a filament [67]. The rate of filament growth is also controlled by capping proteins such as gelsolin, which sever existing filaments and block addition of actin monomers to the barbed end [68,69]. Nucleation of new actin filaments, formation of branches on actin filaments, and cross-linking of filaments into networks are achieved through the highly regulated ARP2/3 complex. Activated ARP2/3 acts as a template for assembly of new filaments and caps the pointed ends of F-actin, allowing elongation of the barbed end. It can also initiate branching points on existing filaments. ARP2/3 can be activated by SCAR/WAVE, WASP, VASP or cortactin [54]. Binding of these proteins to ARP2/3 might also anchor the actin cytoskeleton at specific cellular locations [70,71].



Carlisle & Kennedy, 2005

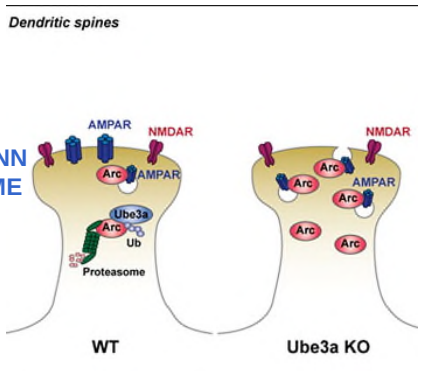
Figure I. Control of actin assembly and disassembly (based on a figure from Ref. [61]). The growing (or 'barbed') end of the filament is extended by addition of actin-ATP (T, red) to the existing filament; cofilin severs actin-ADP (D, light blue) from the older 'pointed' end.

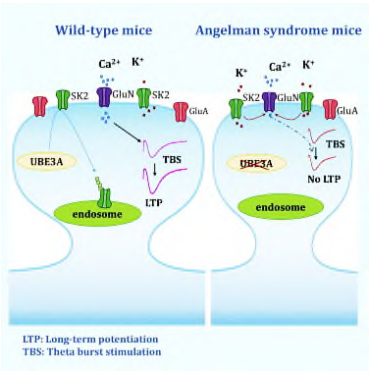
Arc-dependent synaptic consolidation (LTP)



Soule et al., 2006,
Biochem Soc Trans. 34: 600-604.

ANGELMANN SYNDROME





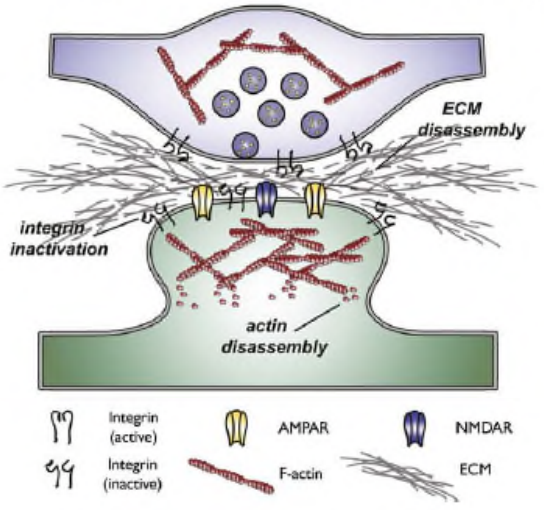
UBE3A also ubiquitinates and promotes the degradation of Arc (activity-regulated cyto-skeleton-associated protein). Arc is only found in the brain and is rapidly upregulated in response to increases in neuronal activity. UBE3A regulates AMPAR (AMPA receptor) endocytosis by controlling the amount of Arc. By doing so, UBE3A helps to restructure pre-existing synapses and this allows the development of functional neural circuits.

In cases where there is excessive Arc, endocytosis of GluA1-containing AMPARs from glutamatergic synaptic sites is unusually high. This leads to a reduction in excitatory synaptic transmission and also an increase in the number of silent (AMPAR-lacking) synapses. The defective synapses and neural circuits could be the possible cause to the various Angelman Syndrome phenotypes, such as intellectual and developmental delay, and impaired social skills.

Mabb et al.also mentioned that the UBE3A protein interacts with the tumor suppressor protein p27. In the cortex, p27 protein promotes neuronal differentiation and migration in cortical projection neurons. With the absence or low amount of the UBE3A protein, there is an increase in the p27 protein level, which might cause the premature migration and differentiation of cortical neuronal progenitors, and also change the laminar architecture of the cortex.

LTP phases are accompanied by changes in ECM

a Immediately after LTP induction - inactivation/disassembly



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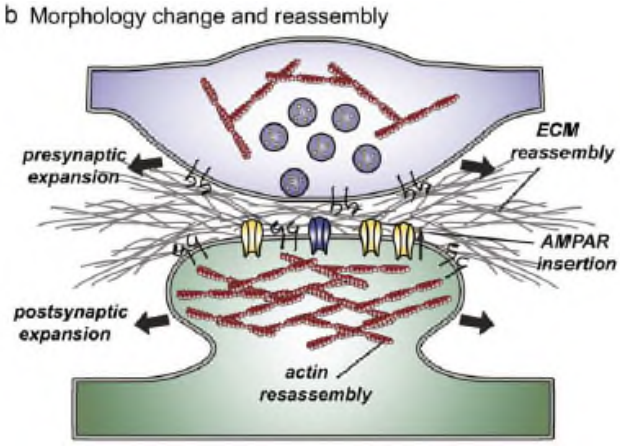
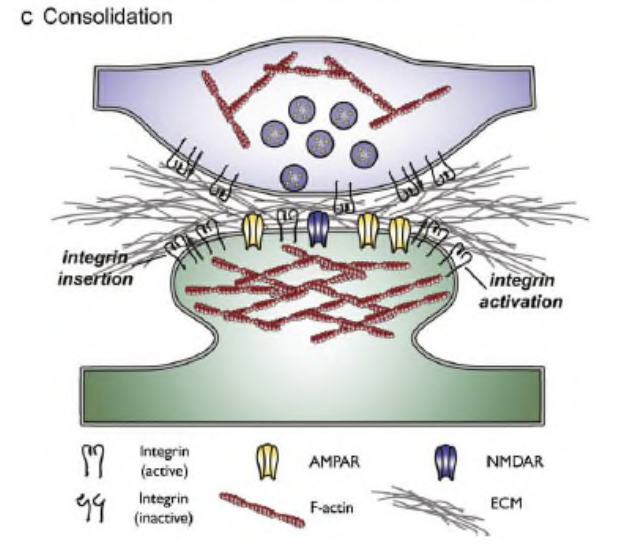
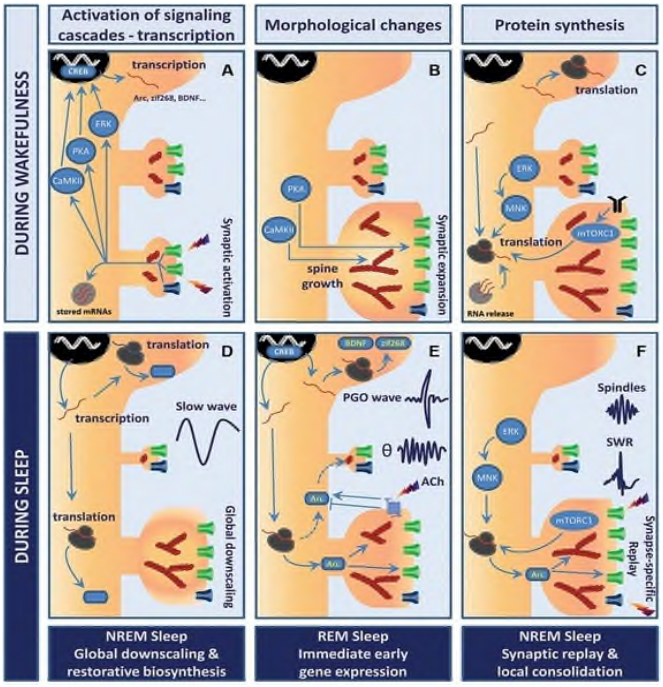


Fig. 1. Model of how integrins might consolidate LTP. (A) Synapse immediately after the induction of LTP, showing the presynaptic axon terminal (top, blue) filled with synaptic vesicles, and the postsynaptic compartment (bottom, green) with ionotrophic glutamate receptors at the cell surface and actin cytoskeleton, both of which are normally stabilised by integrin interactions with the extracellular matrix. LTP induction results in the disengagement of integrins, and disassembly of both the postsynaptic actin network and ECM. (B) Morphological changes and reassembly after LTP induction: disengagement of integrins, and depolymerisation of the postsynaptic actin network allows for the physical expansion of the postsynaptic compartment (which is associated with a concurrent expansion of the presynaptic terminal), and accommodates the insertion of AMPARs into the postsynaptic membrane. Integrin signalling then controls the polymerisation of the actin cytoskeleton. ECM is reassembled. (C) Consolidation: after a period of instability new integrins are inserted and engage with the ECM to stabilise the new synaptic morphology and function. See text for details. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



The Molecular Basis of Long-Term Memory: consolidation in sleep



Ponto-geniculo-occipital waves (**PGO waves)** are phasic field potentials originating in the pons, the lateral geniculate nucleus (LGN), and the occipital cortex. Most prominent in the period right before rapid eye movement sleep (or REM sleep)

Lesson (20)

All-together-now!

https://www.youtube.com/watch?v=SM8S4Y7FPMk

Synaptic plasticity