

Current Advances in Local Protein Synthesis and Synaptic Plasticity

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Local or dendritic protein synthesis is required for long-term functional synaptic change, such as long-term potentiation (LTP) and long-term depression (LTD). LTP and LTD both rely on similar signal transduction cascades, which regulate translation initiation. Current research indicates that the specificity by which new proteins participate in either LTP or LTD may be determined in part by specific RNA-binding proteins as well as activity-dependent capture.

Key words: LTP; ERK; LTD; protein synthesis; fragile X mental retardation protein; 4EBP

Persistent, activity-dependent changes at individual synapses are a mechanism by which the brain encodes and stores information. The most well established models for activity-dependent synaptic strengthening and weakening are long-term potentiation (LTP) and long-term depression (LTD), respectively. Both LTP and LTD display input, or synapse specificity, in which only the activated synapses express plasticity. How changes at individual synapses are maintained has been a subject of intense investigation. With the discovery of polyribosomes at or near synapses, it was hypothesized that neurotransmitter-stimulated synaptic or “local” protein synthesis may be a mechanism by which the protein complement of individual synapses is altered and long-term changes are maintained (Schuman et al., 2006). Support for this idea comes from studies that have demonstrated that LTP and LTD require new dendritic protein synthesis independent of transcription (Kang and Schuman, 1996; Huber et al., 2000; Cracco et al., 2005).

Because of the number of excellent reviews on local protein synthesis and synaptic plasticity in recent years (Kelleher et al., 2004b; Klann and Dever, 2004; Sutton and Schuman, 2005), this review will focus on recent advances in the field including the role of translation initiation and specific RNA-binding proteins in synaptic plasticity and the identity of candidate proteins in the stabilization of synaptic change.

Local protein synthesis is required for the persistence of synaptic change

Initial studies demonstrated a role for both translation and transcription in the maintenance of the late phase of LTP (L-LTP), and it was thought that the new proteins were derived from newly transcribed mRNA (for review, see Sutton and Schuman, 2005). However, it is now evident that the intermediate stages of L-LTP

(1–3 h) are maintained by new protein synthesis in dendrites independent of transcription (Kang and Schuman, 1996; Kelleher et al., 2004a; Cracco et al., 2005). Early LTP (E-LTP), which lasts ~1 h, is often induced with a single episode of high-frequency stimulation or tetanus and is mediated by posttranslational modifications of existing proteins. Transcription-dependent forms of L-LTP (>4 h) are recruited by repeated spaced tetani (Banko et al., 2005), but this is not essential to observe the translation-dependent component of L-LTP (Raymond et al., 2000; Pang et al., 2004; Cracco et al., 2005). Likewise, at *Aplysia californica* sensory–motor neuron synapses, the conversion of a short-term to long-term facilitation (LTF) occurs with repeated stimuli and requires transcription and protein synthesis (Kandel, 2001). Although E-LTP and L-LTP both require NMDA receptor activation, BDNF, D₁/D₅ dopamine receptors, and group 1 metabotropic glutamate receptors (mGluRs) are specifically implicated in generation of the protein synthesis-dependent phase (for review, see Sutton and Schuman, 2005). Consistent with this observation, BDNF, mGluR, and D₁/D₅ receptor agonists stimulate protein synthesis in dendrites (Aakalu et al., 2001; Job and Eberwine, 2001; Smith et al., 2005).

The findings that long-term synaptic weakening or LTD requires dendritic protein synthesis indicate that new proteins maintain synaptic change regardless of the polarity. Activation of group 1 mGluRs with either synaptic stimulation or the selective agonist *R,S*-dihydroxyphenylglycine (DHPG) induces LTD (mGluR-LTD) in hippocampal area CA1 and cerebellar Purkinje neurons that requires rapid synthesis of proteins, within minutes (Huber et al., 2000; Karachot et al., 2001). There is also evidence for a late phase of LTD (L-LTD) induced by activation of NMDA and D₁/D₅ dopamine receptors that does not require new proteins until 2–3 h after induction (Manahan-Vaughan et al., 2000; Sajikumar and Frey, 2003).

New proteins regulate trafficking of ionotropic glutamate receptors

Current evidence indicates that newly synthesized proteins maintain LTP and LTD through regulation of ionotropic glutamate receptor trafficking. DHPG treatment of cultured hippocampal

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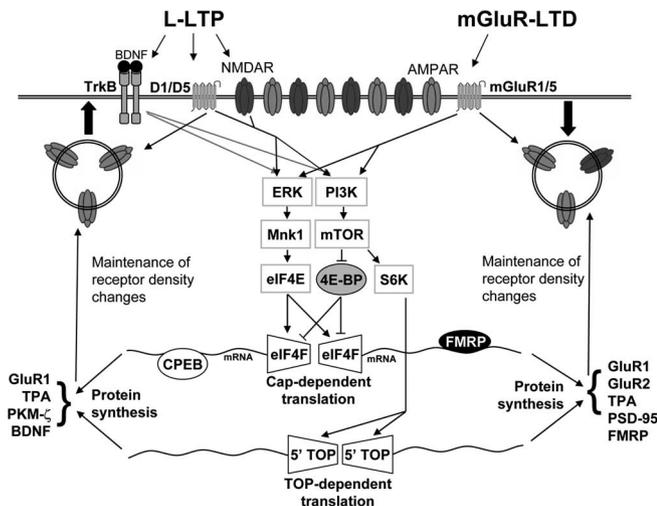


Figure 1. Convergence and divergence of mechanisms for protein synthesis-dependent LTP and LTD. Protein synthesis-dependent LTP (L-LTP) and mGluR-LTD activate and use similar, if not identical, pathways. To simplify, not all protein synthesis regulatory pathways are included, and second-messenger pathways 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 mGluR1/5 receptors initiate the internalization of glutamate receptors but similarly activate the ERK and PI3 kinase pathways. L-LTP- and mGluR-LTD-inducing stimuli phosphorylate ERK, Mnk1, and eIF4E and stimulate eIF4F initiation complex assembly. Activated PI3 kinase phosphorylates mTOR, which in turn phosphorylates and inactivates the negative regulator of cap-dependent translation initiation, 4EBP, thereby enhancing translation initiation. Activated mTOR additionally phosphorylates and activates S6K (ribosomal S6 kinase), which leads to increased TOP (5' terminal oligopyrimidine tract)-dependent translation. Proteins translated in response to synaptic activity may facilitate or maintain alterations in surface receptor number, synapse size, and/or synapse number. A few selected proteins, the synthesis of which have been demonstrated or are required for protein synthesis-dependent plasticity by the two different stimulation paradigms, are listed.

neurons or slices induces a rapid endocytosis of postsynaptic ionotropic glutamate receptors [both AMPA receptors (AMPA) and NMDA receptors (NMDARs)] that results in a decrease in surface receptor number and a decrease in the frequency of miniature EPSCs (mEPSCs) (Snyder et al., 2001; Xiao et al., 2001; Nosyreva and Huber, 2005). Initial endocytosis of AMPARs and NMDARs is independent of translation, but persistent decreases in surface expression require new proteins (Snyder et al., 2001; Nosyreva and Huber, 2005). The removal of postsynaptic AMPAR and NMDARs may lead to structural changes, such as dendritic spine elongation, which is also initiated by mGluR-stimulated protein synthesis (Vanderklish and Edelman, 2002).

In contrast, AMPAR insertion is stimulated by dopamine D_1/D_5 receptor-directed protein synthesis. D_1/D_5 activation stimulates dendritic synthesis of the GluR1 subunit of AMPARs, which results in a rapid increase in GluR1 surface expression (15 min) and an increase in mEPSC frequency (Smith et al., 2005). Therefore, newly synthesized proteins may maintain LTP and LTD by regulation of AMPAR trafficking or stabilization of structural changes that maintain receptor density at the synapse (Fig. 1).

Thus, dendritic protein synthesis functions to maintain both LTP and LTD. At what level is the specificity for synthesizing "LTP" or "LTD" proteins determined? Distinct patterns of synaptic activity may regulate distinct signaling cascades, differentially regulate translation machinery, or stimulate different RNA-binding proteins, which in turn target specific mRNAs for

translation (Fig. 1). Alternatively, when translation is stimulated in dendrites, both LTP and LTD proteins may be synthesized simultaneously, and the specific pattern of synaptic stimulation may determine which proteins are used or "captured" (Kelleher et al., 2004b; Sajikumar and Frey, 2004). As described below, recent evidence suggests that aspects of both of these hypotheses may be correct.

Translation initiation is implicated in LTP and LTD

New evidence indicates that LTP and mGluR-LTD both regulate cap-dependent translation initiation and in turn are affected by manipulations of translation initiation machinery. NMDA treatment, E-LTP-inducing, and L-LTP-inducing protocols increase phosphorylation of Mnk1, eIF4E, 4EBP, and p70 S6 kinase and stimulate formation of the translation initiation (eIF4F) complex, all of which function to enhance translation initiation and the global translation rate (Banko et al., 2004, 2005; Kelleher et al., 2004a; Klann and Dever, 2004; Wells, 2006). Interestingly, DHPG treatment, which leads to mGluR-LTD, also results in phosphorylation of Mnk1, eIF4E, and 4EBP and stimulates eIF4F complex formation (Banko et al., 2006). In both LTP and LTD paradigms, Mnk1 and eIF4E phosphorylation depends on extracellular signal-regulated kinase (ERK) (Banko et al., 2004, 2005; Kelleher et al., 2004a). During mGluR-LTD, phosphatidylinositol-3 kinase (PI3 kinase) and mammalian target of rapamycin (mTOR) stimulate phosphorylation of eIF4E-binding protein (4EBP), which is thought to gate eIF4E phosphorylation by ERK (Banko et al., 2006). Consistent with these biochemical findings, inhibition of PI3 kinase, mTOR, or ERK prevents protein synthesis-dependent LTP and mGluR-LTD (Tang et al., 2002; Gallagher et al., 2004; Hou and Klann, 2004; Kelleher et al., 2004a) (Fig. 1).

Recent studies demonstrate that genetic deletion of two suppressors of translation initiation, 4EBP2 and an eIF2a kinase, GCN2, similarly affect LTP and hippocampal-dependent memory (Banko et al., 2005; Costa-Mattioli et al., 2005). A single tetanus, which elicits only E-LTP in wild-type (WT) mice, results in a translation-dependent L-LTP in 4EBP2 and GCN2 knock-out (KO) mice, suggesting that the threshold for L-LTP is reduced. mGluR-LTD is also enhanced in the 4EBP2 knock-out mice (Banko et al., 2006). Surprisingly, spaced trains of 100 Hz stimulation, which elicit L-LTP in WT mice, cause little or no potentiation in mutant mice. As a result, both of these KO mice lines show a deficit in hippocampal-dependent memory tasks. The reduced L-LTP in response to space trains could be attributable to the elevated level of eIF4F initiation complexes formed in the absence of 4EBP and nonselective translation of mRNAs or repressors of LTP (Banko et al., 2005; Costa-Mattioli et al., 2005).

RNA-binding proteins differentially regulate LTP and mGluR-LTD

As highlighted in the accompanying review by Wells (2006), translation of specific mRNAs can be regulated by RNA-binding proteins. Recent studies have demonstrated a role for cytoplasmic polyadenylation element-binding protein (CPEB) and Fragile X mental retardation protein (FMRP) in LTP and mGluR-LTD, respectively (Huber et al., 2002; Alarcon et al., 2004). CPEB binds to specific 3' CPE sequences and at a basal state is thought to suppress translation of its mRNA targets. In response to extracellular stimuli, CPEB acts to facilitate polyadenylation and translation initiation by recruitment of PABP (polyA-binding protein) and eIF4G, respectively (Wells, 2006). Genetic deletion of one isoform of CPEB, CPEB1, resulted in a deficit in some, but

not all, forms of protein synthesis-dependent LTP, suggesting that CPEB1-regulated polyadenylation of mRNAs contributes to the synthesis of proteins required for LTP (Alarcon et al., 2004). Likewise, downregulation of CPEB in *Aplysia* sensory neurons blocks LTP (Si et al., 2003). These results suggest that CPEB may specifically regulate proteins required for synaptic strengthening.

Like CPEB, FMRP is an RNA-binding protein that may suppress translation of its mRNA targets as well as act as a switch to stimulate protein synthesis in response to extracellular signals (Todd et al., 2003; Weiler et al., 2004; Grossman et al., 2006). Interestingly, the mRNA for FMRP is present in dendrites, and FMRP is synthesized in response to mGluR activation (Weiler et al., 1997; Antar et al., 2004). FMRP, in turn, regulates mGluR-LTD. In mice lacking FMRP (*Fmr1* KO mice), mGluR-LTD is enhanced and does not require new protein synthesis (Huber et al., 2002; Koekkoek et al., 2005; Nosyreva and Huber, 2006). This result suggests in the absence of FMRP there is an uncoupling of synaptic protein synthesis from activity as well as an abundance of proteins that maintain LTD without new synthesis. Although NMDAR-dependent LTP and LTD are unaffected in the hippocampus of *Fmr1* KO mice (Godfraind et al., 1996; Huber et al., 2002), LTP in the amygdala and neocortex is absent (Li et al., 2002; Larson et al., 2005; Zhao et al., 2005). It is unclear whether this is caused by a deficit in a protein synthesis-dependent component of LTP. In the hippocampus, however, current data indicate that CPEB and FMRP may each specifically regulate the synthesis of proteins for L-LTP and mGluR-LTD, respectively.

Local protein synthesis and synaptic tagging

Frey and Morris (1997) observed that L-LTP induction at a subset of synapses stimulated the synthesis of new proteins that could be subsequently captured at a second independent set of synapses by a single tetanus, converting E-LTP to L-LTP (Frey and Morris, 1997). They hypothesized that a single tetanus generates a synaptic “tag” that mediates the capture of recently translated proteins, termed plasticity-related proteins (PRPs), from the soma or elsewhere in the dendrite. Similarly, proteins induced by prior L-LTD can be captured by E-LTD stimuli at independent synapses (Sajikumar and Frey, 2004). Surprisingly, there is evidence for what has been termed “cross-tagging” by L-LTD and L-LTP (Sajikumar and Frey, 2004). That is, E-LTP can be consolidated to L-LTP by the capture of proteins generated by previous L-LTD-inducing stimulation, and vice versa. This raises the intriguing possibility that the same proteins are synthesized in response to either L-LTP- or L-LTD-inducing stimuli and the synaptic tag determines the direction of synaptic change consolidated.

Candidate PRPs

The PRPs for LTP and LTD may be the same or similar proteins and simply function to stabilize synaptic changes initiated by E-LTP and E-LTD induction. Recent evidence indicates there are different PRPs for LTP and LTD. Protein kinase M ζ (PKM ζ) is a constitutively active isoform of PKC and is induced by L-LTP-inducing stimulation, and its activity is required for the maintenance of L-LTP but not L-LTD (Sajikumar et al., 2005). These results suggest that PKM ζ is a specific PRP for L-LTP. Other recent work demonstrates that exogenous application of BDNF is sufficient to maintain L-LTP in the presence of protein synthesis inhibitors, suggesting that BDNF is the only essential PRP (Pang et al., 2004). There is much less known about the PRPs for LTD. A number of studies have demonstrated synthesis of proteins with mGluR activation (DHPG), such as GluR1, GluR2, TPA (tissue

plasminogen activator), and PSD-95 (postsynaptic density-95), but the role of these proteins in mGluR-facilitated LTP or mGluR-LTD is unknown (Kacharina et al., 2000; Todd et al., 2003; Ju et al., 2004; Shin et al., 2004). The fact that all of these proteins are implicated in LTP maintenance suggests that, in addition to inducing LTD, DHPG stimulates the synthesis of proteins required for both LTP and LTD, lending support to the notion of selective capture (Kelleher et al., 2004b; Sajikumar and Frey, 2004).

Summary and perspectives

It is well established that new proteins are required to maintain the persistence of synaptic strengthening and weakening. Interestingly, similar signal transduction cascades are used to activate translation initiation by both LTP- and LTD-inducing stimulation. New data indicate that RNA-binding proteins and capture of new proteins contribute to the specificity of long-term synaptic change (Fig. 1). Because FMRP is implicated in human mental retardation, this suggests that misregulation of protein synthesis-dependent plasticity contributes to human cognitive function and neurological disease (Bear et al., 2004; Koekkoek et al., 2005).

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