Review

Synaptic Plasticity and Translation Initiation

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It is widely accepted that protein synthesis, including local protein synthesis at synapses, is required for several forms of synaptic plasticity. Local protein synthesis enables synapses to control synaptic strength independent of the cell body via rapid protein production from pre-existing mRNA. Therefore, regulation of translation initiation is likely to be intimately involved in modulating synaptic strength. Our understanding of the translation-initiation process has expanded greatly in recent years. In this review, we discuss various aspects of translation initiation, as well as signaling pathways that might be involved in coupling neurotransmitter and neurotrophin receptors to the translation machinery during various forms of synaptic plasticity.

It is thought that the cellular changes that underlie various forms of short-term synaptic plasticity involve covalent modifications of pre-existing proteins and are protein-synthesis independent. In contrast, it is clear that long-lasting forms of synaptic plasticity require macromolecular synthesis. For example, long-lasting, late phase long-term potentiation (L-LTP) in the hippocampus requires new protein synthesis (Frey and Morris 1997; Nguyen et al. 1997), as does long-term facilitation (LTF) in *Aplysia* (Montarolo et al. 1986). The dependence of L-LTP and LTF on protein synthesis correlates with the necessity of new protein synthesis for long-lasting memory (Davis and Squire 1984). The classical view of how new protein synthesis impacts LTP is that proteins are synthesized in the cell body and delivered to the potentiated synapses. However, it has been shown that proteins can also be synthesized locally at or near synapses (Aakalu et al. 2001). In addition, several studies have shown that synaptic activity results in enhanced protein synthesis in synaptosomes. For example, depolarization with high concentrations of K⁺ was shown to increase the synthesis of the α subunit of calcium/calmodulin-dependent protein kinase II (α -CaMKII; Bagni et al. 2000), brain-derived neurotrophic factor (BDNF) was shown to increase the synthesis of Arc (Yin et al. 2002), and stimulation of group I mGluRs was shown to increase the synthesis of the fragile X mental retardation protein (Weiler et al. 1997). These data suggest that new synthesis of proteins occurs at active synapses, which is consistent with the notion that local protein synthesis might be involved in synaptic plasticity.

Evidence in support of the idea that local protein synthesis is important for synaptic plasticity was provided in studies by Kang and Schuman (1996). These authors found that, unlike electrically-induced LTP, the initiation of long-lasting potentiation in hippocampal slices induced by either BDNF or neurotrophin 3 required protein synthesis. The protein synthesis-dependence of BDNF-induced potentiation persisted, even when the cell bodies of presynaptic and postsynaptic neurons were cut off from their dendrites (Kang and Schuman 1996), a finding that strongly suggests that this form of potentiation requires dendritic protein synthesis.

An additional form of synaptic plasticity that requires rapid, local protein synthesis is mGluR-dependent LTD (Huber et al.

2000, 2001). In hippocampal area CA1, mGluR-dependent LTD can be blocked by translation inhibitors and, similar to BDNF-induced potentiation, persists even when cell bodies are excised from their dendrites (Huber et al. 2000). Thus, the protein synthetic machinery and the mRNA(s) necessary for the induction of mGluR-dependent LTD are present in postsynaptic dendrites.

The signaling pathways that are responsible for initiating new protein synthesis after the induction of the aforementioned forms of synaptic plasticity, either at the synapse or at the cell body, are poorly understood. The initiation of translation is usually divided into three steps. First, the initiator Met-tRNA^{Met} must bind to the small 40S ribosomal subunit, forming the 43S preinitiation complex. Then, the 43S complex must bind to an mRNA and locate the initiation codon to form the 48S preinitiation complex. Finally, the large 60S ribosomal subunit is added to generate a translation-competent 80S ribosome that is now able to proceed with translation elongation. All three steps in the initiation of translation involve soluble proteins, some of which are referred to as eukaryotic initiation factors (eIFs; Hershey and Merrick 2000). In this review, we will discuss how the function of several initiation factors and other translation regulatory proteins are modulated via phosphorylation by protein kinases, and we will discuss signaling pathways that might couple glutamate, serotonin, and neurotrophin receptors to initiation factors during protein synthesis-dependent forms of synaptic plasticity in mollusks and mammals.

Regulation of Translation Initiation by eIF2

The initiation factor eIF2, which consists of three heterologous subunits (α , β , and γ), binds the initiator Met-tRNA^{Met} to the small ribosomal subunit in the first step of translation initiation. eIF2 must bind GTP in order to form a stable ternary complex (eIF2-GTP-Met-tRNA^{Met}), which then binds to the ribosome. After the 43S preinitiation complex binds an mRNA, base-pair formation between an AUG codon and the anticodon of Met-tRNA^{Met} induces GTP hydrolysis by eIF2 and release of a stable eIF2-GDP binary complex. The initiation factor eIF2B catalyzes guanine nucleotide exchange on eIF2 to once again form active, GTP-bound eIF2 (Dever 1999, 2002).

The guanine nucleotide exchange reaction on eIF2 is a critical translational control point. Four eIF2 kinases are known to phosphorylate eIF2 α on Ser51, which converts eIF2 from a substrate to a competitive inhibitor of the exchange factor eIF2B

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Figure 1 Regulation of translation by eIF2. The guanine nucleotide exchange factor eIF2B catalyzes the exchange of GDP for GTP on eIF2. GTP-bound eIF2 is then able to associate with the specific initiator methionyl-tRNA and form an eIF2-GTP-tRNA complex that is necessary for the ribosome to initiate translation. After the ribosome scans the mRNA and recognizes the AUG codon, the GTP is hydrolyzed and the stable eIF2-GDP complex is released. A guanine-nucleotide exchange reaction is required to form eIF2-GTP to initiate the translation of another mRNA transcript. This process is regulated by phosphorylation of eIF2, which is mediated by the four kinases HRI, PKR, GCN2, and PERK. Phosphorylated eIF2 competes with nonphosphorylated eIF2 for a binding site on eIF2B. However, phosphorylated eIF2 inhibits eIF2B activity and subsequently decreases the rate of eIF2-GTP formation and the availability of the complex for translation initiation.

(Dever 1999, 2002). Thus, phosphorylation of eIF2 α blocks guanine nucleotide exchange of eIF2, preventing formation of the ternary complex, and subsequently, obstructing new rounds of translation initiation (Fig. 1). All four of the eIF2 α kinases have been observed to be present in the brain. These include the heme-regulated eIF2 α kinase (termed HRI; Mellor et al. 1994), the RNA-dependent eIF2 α kinase (termed PKR; DeGracia et al. 1999), the amino acid-regulated eIF2 α kinase (termed GCN2; Sood et al. 2000), and the PKR-like endoplasmic reticulum eIF2 α kinase (termed PERK; Shi et al. 1998). Whether eIF2 α phosphorylation is altered during a protein synthesis-dependent form of synaptic plasticity has not yet been investigated. However, it has been shown that application of BDNF to cultured neurons results in a decrease in eIF2 α phosphorylation that correlates with increased protein synthesis (Takei et al. 2001). It remains to be determined whether altered eIF2 α phosphorylation accompanies either BDNF-induced synaptic potentiation or other protein synthesis-dependent forms of synaptic plasticity.

Regulation of Translation Initiation by eIF4E

Most mRNAs bind to the ribosome via recognition of the 5' mRNA cap (5' m⁷GpppN, where N is any nucleotide) by the cap-binding protein complex. This complex, also known as eIF4F, is a heterotrimer consisting of the initiation factors eIF4A, eIF4E, and eIF4G. eIF4A is a DEAD-box RNA helicase that is thought to unwind the secondary structure in the 5' untranslated region (UTR) of the mRNA to facilitate binding of the mRNA to the ribosome. eIF4G is a scaffolding protein that binds eIF4E and eIF4A, as well as the translation factor eIF3 and the poly(A)-binding protein (PABP), which binds to the poly(A) tail on the 3'

end of the mRNA (Sonenberg and Dever 2003). eIF4E is the cap-binding component of eIF4F. eIF4E binds directly to the 5' mRNA cap via its cap-recognition pocket, which receives the m⁷G base, the triphosphate, and the second nucleotide (Tomoo et al. 2003). mRNA cap analogs such as m⁷GpppG inhibit protein synthesis by competing with endogenous capped mRNA for eIF4E. Both mGluR-dependent LTD in the hippocampus (Huber et al. 2000) and LTF at the crayfish neuromuscular junction (Beaumont et al. 2001) are blocked by m⁷GpppG, indicating cap-dependent translation is necessary for these forms of synaptic plasticity.

How is binding of eIF4E to the 5' mRNA cap regulated? One way is by proteins that bind to and sequester eIF4E, thereby preventing eIF4E from binding to eIF4G (Fig. 2). Not surprisingly, these eIF4E-binding proteins (4E-BPs) are regulated by phosphorylation; when 4E-BP is phosphorylated, its binding to eIF4E is disrupted and translation is stimulated. Several protein kinases have been shown to phosphorylate 4E-BP, including mammalian target of rapamycin (mTOR), whose activity is blocked by rapamycin (Beretta et al. 1996), and the mitogen-activated protein kinases ERK1 and ERK2 (Lin et al. 1994). Thus, inhibition of mTOR should inhibit protein synthesis-dependent forms of synaptic plasticity. Several studies have shown this to be the case. In Aplysia sensory neurons, rapamycin inhibits stabilization of LTF induced by serotonin (Casadio et al. 1999) and LTF at the crayfish neuromuscular junction (Beaumont et al., 2001). Moreover, it was shown that L-LTP, BDNF-induced potentiation, and mGluR-dependent depotentiation of LTP in the hippocampus are blocked by rapamycin (Tang et al. 2002; Zho et al. 2002; Cammalleri et al. 2003). Finally, it was recently shown that mTOR phosphorylation and activation is associated with and necessary for mGluR-dependent LTD (Hou and Klann 2004). Thus, mTOR appears to be critical for forms of synaptic plasticity that require protein synthesis.

The upstream signaling cascades that trigger activation of mTOR during protein synthesis-dependent forms of synaptic plasticity are not well understood, but likely involve the phosphatidylinositol 3-kinase (PI3K)/Akt pathway (Gingras et al. 1998). Inhibitors of PI3K have been shown to block crayfish LTF (Beaumont et al. 2001) and various forms of LTP (Kelly and Lynch 2000; Sanna et al. 2002; Opazo et al. 2003). It also

Figure 2 Regulation of cap-dependent initiation. Cap-dependent translation commences when hyperphosphorylated 4E-BP is released from eIF4E and the cap-binding complex assembles on the 5' m⁷G cap of an mRNA. eIF4G provides the scaffold on which eIF4E and eIF4A bind. eIF4A unwinds any pre-emptive secondary structure of the mRNA, exposing a site for subsequent 43S ribosome joining. Phosphorylation of eIF4E on serine 209 by Mnk1, which also binds to eIF4G, destabilizes the eIF4E-5' cap interaction and may serve as a means to recycle eIF4E after the ribosome has successfully loaded onto the mRNA.

was shown that BDNF-dependent phosphorylation and activation of mTOR in cultured neurons is blocked by PI3K inhibitors (Takei et al. 2001). Inhibitors of PI3K also abolish mGluR-dependent LTD, as well as the LTD-associated increases in mTOR phosphorylation (Hou and Klann 2004). The precise delineation of the signaling cascades that couple glutamate, serotonin, and neurotrophin receptors to activation of mTOR during synaptic plasticity is an important question that remains to be addressed.

Another way that binding of eIF4E to the 5' mRNA cap is regulated is via eIF4E phosphorylation (Fig. 2). Phosphorylation of serine 209 on eIF4E usually (but not always) is positively correlated with increased translation (Scheper and Proud 2002). Initial studies indicated that phosphorylated eIF4E bound to cap analogs (Minich et al. 1994). However, more recent studies indicate that phosphorylated eIF4E exhibits reduced affinity for cap analogs (Scheper et al. 2002; Zuberek et al. 2003). It has been proposed that the reduced affinity of phosphorylated eIF4E for the mRNA cap structure results in release of eIF4E, permitting reinitiation on the same mRNA or on another message (Scheper and Proud 2002), thereby resulting in increased translation activity. eIF4E has been shown to be phosphorylated by the protein kinase Mnk1 (Waskiewicz et al. 1999), which is phosphorylated and activated by the mitogen-activated protein kinases ERK and p38 (Waskiewicz et al. 1997), kinases that are known to be critical for various forms of synaptic plasticity (Bolshakov et al. 2000; Sweatt 2001; Thiels and Klann 2001; Gallagher et al. 2004). Enhanced phosphorylation of Mnk1 and eIF4E has been shown to occur in cultured neurons treated with BDNF, and the increased eIF4E phosphorylation was shown to be ERK dependent (Takei et al. 2001; Kelleher III et al. 2004). More recently, it was shown that NMDA receptor activation enhances the phosphorylation of Mnk1 and eIF4E via ERK in hippocampal area CA1 (Banko et al. 2004) and L-LTP-inducing stimulation has been shown to result in an ERK-dependent increase in eIF4E phosphorylation (Kelleher III et al. 2004). Finally, serotonin has been shown to alter eIF4E phosphorylation via activation of p38 in Aplysia neurons treated with serotonin (Dyer and Sossin 2000). Thus, phosphorylation of eIF4E by Mnk1 via activation of either ERK or p38 is another way in which translation initiation is likely to be regulated during synaptic plasticity.

S6-Directed Translation of 5'TOP mRNAs

As mentioned above, mTOR and ERK can both regulate various aspects of cap-dependent translation. An additional role for these

Figure 3 S6-directed translation. S6 kinase (S6K1) is activated by multiple kinases, including PDK-1, ERK, PKC ζ/γ , and mTOR. Activated S6K1 phosphorylates ribosomal protein S6, whose phosphorylation is correlated with the selective translation of mRNAs that contain 5'TOPs in their 5'UTR.

Table 1. Dendritic Proteins Encoded by mRNAs Containing 5' TOPs

Protein	Function	Reference(s)
Ribosomal proteins	Initiation, scanning, translocation	Steward and Levy 1982
eEF1A	Elongation of peptide chain	Asaki et al. 2003 ^a
eEF2	Elongation of peptide chain	Inamura et al. 2003
		Asaki et al. 2003
PABP	mRNA stability, circularization of mRNA	Inamura et al. 2003
		Mudashetty et al. 2002

^aPolyribosomes have been observed near dendritic spines; however, a comprehensive study to determine the localization of all ribosomal proteins has not been conducted. S6 protein has been observed in the postsynaptic density.

protein kinases in protein synthesis is the regulation of S6-directed translation (Fig. 3). Both mTOR and ERK, as well as phosphoinositide-dependent kinase 1 (PDK-1) and the ζ isoform of protein kinase C (PKC ζ), are involved in the phosphorylation and activation of p70 S6 kinase (S6K1; Dufner and Thomas 1999). S6K1 has been proposed to regulate the translation of a group of mRNAs that contain a 5'-terminal oligopyrimidine tract (5'TOP), which consists of 4 to 14 pyrimidines located at the 5' terminus of mRNAs that encode ribosomal proteins and mRNAs that encode certain other components of the translation machinery, such as elongation factor 2 (Meyhaus and Hornstein 2000). Interestingly, proteins encoded by mRNAs containing 5'TOPs have been observed in dendrites (Table 1). The precise mechanism responsible for the regulation of 5'TOP translation is not well understood. The S6K1 substrate thought to be important in regulation of 5'TOP translation is ribosomal S6 protein, whose own mRNA contains a 5'TOP (Fumagalli and Thomas 2000; Hershey and Merrick 2000); however, it was reported that regulation of 5'TOP translation was maintained in cells lacking S6K1 (Stolovich et al. 2002).

Activation of S6K1 and subsequent increases in S6 phosphorylation appears to play a role in synaptic plasticity. It was shown that L-LTP-inducing stimulation results in an mTOR-dependent increase in active S6K1 as measured by the phosphorylation of threonine 389 on S6K1 (Cammalleri et al. 2003). More recently, it was reported that L-LTP is associated with an ERK-dependent increase in S6 phosphorylation (Kelleher III et al. 2004). Serotonin, which induces LTF in Aplysia, has been shown to increase the activity of S6K1 and the subsequent phosphorylation of ribosomal protein S6 in synaptosome preparations (Khan et al. 2001). Interestingly, in the same study, it was observed that serotonin increased not only the phosphorylation of S6, but also the levels of S6 protein, which was blocked by rapamycin. Thus, it is possible that protein synthesis-dependent forms of synaptic plasticity require an increase in the synthesis of ribosomes and other components of the translation machinery. This possibility remains to be determined.

Cytoplasmic Polyadenylation and CPEB

Regulation of translation initiation also occurs via polyadenylation of the 3' end of mRNAs (Fig. 4). Polyadenylation is regulated by two sequences in the 3' untranslated region (3'UTR) of mRNAs, the cytoplasmic polyadenylation element (CPE; sequence of UUUUUAU or similar) and AAUAAA. The critical regulatory protein in polyadenylation is CPE-binding protein (CPEB), which binds to CPEs (Richter 2000). CPEB is phosphorylated by

Figure 4 Regulation of translation initiation by polyadenylation. The 3'UTR of a select group of mRNAs contains sequences that permit the binding of CPEB and CPSF. Transcripts bound by CPEB and its binding partner maskin are inhibited from beginning cap-dependent translation until the addition of the poly(A) tail. Phosphorylation of CPEB by the protein kinase Aurora facilitates the interaction between CPEB and CPSF, which in turn, promotes recruitment of PAP to lengthen the poly(A) tail and destabilizes the interaction between maskin and eIF4E. Following release of eIF4E from maskin, the cap-binding complex assembles and translation is initiated. As indicated, PABP interacts with eIF4G to circularize the mRNA and enhance translation.

the protein kinase Aurora (Mendez et al. 2000a), which induces CPEB to interact with cleavage and polyadenylation-specificity factor (CPSF) on the AAUAAA sequence, thereby recruiting poly(A) polymerase (PAP) to lengthen the poly(A) tail of the mRNA (Mendez et al. 2000b). The process of polyadenylation is thought to increase translation by counteracting maskin, a protein that binds both CPEB and eIF4E (Stebbins-Boaz et al. 1999). Maskin, similar to 4E-BP, is a repressor of translation because it prevents binding of eIF4E to eIF4G. Polyadenylation causes maskin to dissociate from eIF4E, permitting the binding of eIF4E to eIF4G, and the subsequent recruitment of ribosomes to increase translation (Cao and Richter 2002).

The poly(A) tail of the mRNA and the 5' cap interact synergistically to stimulate translation (Gallie 1991). PABP interacts with both the poly(A) tail and eIF4G (Sachs 2000), which serves to circularize the mRNA (Wells et al. 1998). Although the nature of the synergism between the poly(A) tail and the 5' cap is unknown, an intriguing possibility is that the poly(A) tail enables ribosomes to efficiently recycle on the same mRNA via the interaction of PABP with eIF4G, thereby bringing the 3' and 5' ends into proximity with one another.

Several recent studies have demonstrated the importance of CPEB for synaptic plasticity. In *Aplysia*, serotonin induces an increase in CPEB levels that is both mTOR and PI3K dependent (Si et al. 2003). In the same study, the authors found that CPEB antisense nucleotides blocked LTF, indicating that CPEB is required for the stabilization of LTF (Si et al. 2003). CPEB also appears to be required for normal mammalian synaptic plasticity. Recently, it was shown that mice that have the CPEB-1 gene deleted have impaired LTP (Alarcon et al. 2004). These findings suggest that one subset of mRNAs that are likely translated during synaptic plasticity are synaptically localized mRNAs that contain CPEs.

One mRNA that appears to be regulated by polyadenylation during synaptic plasticity in *Aplysia* is N-actin mRNA, which contains a CPE in its 3'UTR (DesGroseillers et al. 1994). The poly(A) tail of N-actin RNA has been shown to be elongated in response to stimulation with serotonin (Liu and Schwartz 2003; Si et al. 2003). Another likely target to be regulated by polyadenylation during mammalian synaptic plasticity is the mRNA that encodes the α subunit of CaMKII. The mRNA for α -CaMKII contains two CPEs in its 3'UTR (Wu et al. 1998). These sequences are required for increased polyadenylation of α -CaMKII mRNA and subsequent synthesis of α -CaMKII that is associated with NMDA receptor-dependent synaptic plasticity in the visual cortex (Wells et al. 2001). In the hippocampus, increased α -CaMKII synthesis also has been observed with LTP induced by high-frequency stimulation (Ouyang et al. 1997) and LTP induced by pairing θ -pulse stimulation with β -adrenergic receptor activation (Giovannini et al. 2001). The increased α -CaMKII synthesis observed in the latter study was found to be ERK dependent. Thus, plasticity-induced increases in α -CaMKII synthesis may require not only polyadenylation of the 3' end of the α -CaMKII mRNA, but also ERK-dependent changes in the phosphorylation of initiation factors such as eIF4E that would regulate binding of the 5' cap of α -CaMKII mRNA to the cap-binding complex.

Regulation of Internal Translation Initiation

Several mRNAs are able to bind to the 40S ribosome subunit independent of the 5' m⁷GpppN cap by using an internal ribosome entry site (IRES). A small number of cellular mRNAs have been reported to have IRES elements. These mRNAs appear to contain secondary structures or multiple AUG codons that normally would block the 43S ribosome from scanning the mRNA. Binding of the ribosome to an IRES element located in an internal position on the mRNA provides it access to the appropriate AUG start codon (Hellen and Sarnow 2001). Five mRNAs found in dendrites have been reported to contain IRES elements that might mediate cap-independent translation (Table 2). Although cap-independent translation during synaptic plasticity has not been reported, it was shown that electrical activity that induces a form of neuronal plasticity in *Aplysia* bag cell neurons results in the dephosphorylation of eIF4E, triggering IRES-mediated translation (Dyer et al. 2003). Interestingly,

Table 2. Dendritic mRNAs Containing IRESs

mRNA	Protein Function	Reference(s)
Activity-regulated cytoskeletal protein (Arc)	Actin-binding synaptic junctional protein	Pinkstaff et al. 2001
α -CaMKII	Multifunctional kinase, calcium signaling	" "
Dendrin	Unknown	" "
Microtubule-associated protein 2 (MAP2)	Microtubule assembly and scaffolding protein	" "
Neurogranin (RC3)	Calcium/calmodulin-binding protein	" "

Figure 5 Model of FMRP function during mGluR-LTD. Under basal conditions, FMRP is thought to dimerize and assemble into a granule complex with mRNAs, mRNA-binding proteins, FMRP-associated proteins, and ribosomes, tonically inhibiting the translation of specific mRNAs in the granule complex. This FMRP complex can be transported from the soma into dendrites. Stimulation of group I mGluRs results in a yet-to-be-determined modification of FMRP, permitting FMRP-bound mRNAs to be translated. The proteins translated from these mRNAs then mediate protein synthesis-dependent mGluR-LTD. Among the mRNAs targeted by FMRP is its own mRNA; this newly synthesized FMRP may then turn off further translation by once again binding its target mRNAs.

α -CaMKII mRNA contains an IRES element (Pinkstaff et al. 2001) and as mentioned above, LTP-inducing stimulation stimulates the translation of α -CaMKII (Ouyang et al. 1997). It is not known whether the LTP-induced translation of α -CaMKII is via either a cap-dependent mechanism or a cap-independent, IRES-mediated mechanism. Thus, whether synaptic plasticity induces translation of mRNAs that have IRES elements such as α -CaMKII via a cap-independent initiation mechanism remains to be investigated.

Regulation of Translation by FMRP

Fragile X mental-retardation syndrome is caused by a trinucleotide repeat expansion mutation in the *FMR1* gene (Antar and Bassell 2003). *FMR1* (referred to as *Fmr1* in the mouse) encodes Fragile X mental-retardation protein (FMRP), an RNA-binding

protein that is thought to function as a translation repressor (Lagerbauer et al. 2001; Li et al. 2001; Zhang et al. 2001). FMRP is found predominantly in the cytoplasm, where it is thought to dimerize and form a granule complex that contains mRNAs, mRNA-binding proteins, FMRP-associated proteins, and ribosomes, tonically inhibiting the translation of the mRNAs in the granule complex (Jin and Warren 2003). Interestingly, FMRP and *Fmr1* mRNA have been shown to be present in dendrites (Feng et al. 1997; Weiler et al. 1997), and stimulation of mGluRs has been shown to result in a rapid translation of FMRP in synaptosomes (Weiler et al. 1997). Huber et al. (2002) showed that *Fmr1* knockout mice exhibit enhanced hippocampal mGluR-dependent LTD. These investigators proposed that mGluR-LTD might normally enhance the synthesis of FMRP, which then would serve to limit expression of LTD by inhibiting translation of other synaptic mRNAs (Fig. 5). Many of the mRNAs that bind to FMRP encode proteins important for synaptic function (Table 3). Examination of the role of these proteins in mGluR-dependent LTD should provide insight into how specific mRNAs are translated in response to synaptic stimulation that ultimately results in synaptic plasticity.

Regulation of Translation Elongation

Although the focus of this review has been regulation of translation initiation, translation may also be regulated during synap-

tic plasticity at the elongation step via phosphorylation of eukaryotic elongation factor 2 (eEF2). eEF2 is a GTP-binding protein that mediates the translocation of peptidyl-tRNA from the A site to the P site on the ribosome (Moldave 1985). Phosphorylation of eEF2 by eEF2 kinase, a Ca^{2+} /calmodulin-dependent enzyme, results in an inhibition of eEF2 activity and a general reduction of peptide elongation (Ryazanov and Davydova 1989; Carlberg et al. 1990; Redpath et al. 1993). Several studies have been reported that implicate eEF2 phosphorylation in synaptic plasticity. In intact tadpole tecta, NMDA receptor activation was shown to increase the phosphorylation of eEF2 (Scheetz et al. 1997). The same group found that stimulation of synaptoneurosomes from rat superior colliculus also results in increased eEF2 phosphorylation, which was correlated with increased synthesis of α -CaMKII (Scheetz et al. 2000). It was reported that glutamate

Table 3. Examples of FMRP-Binding mRNAs That Encode Proteins Involved in Synaptic Function

mRNA	Protein Function	Reference(s)
Microtubule-associated protein 1B (MAP1B)	Regulate synaptic structure and morphology	Zhang et al. 2001
SAP90/PSD-95-associated protein 4 (SAPAP4)	Maintenance of postsynaptic density structure	Zalfa et al. 2003
FMRP	mRNA-binding protein, mRNA trafficking, translation repressor	Brown et al. 2001
Munc 13	Mediate neurotransmitter release	Ashley Jr. et al. 1993; Brown et al. 1998; Zhang et al. 2001

enhances the phosphorylation of eEF2 via NMDA receptors in cultured cortical neurons (Marin et al. 1997). Finally, it was shown that chemically induced LTP elicits an inhibition of de novo total protein synthesis, coincident with increased phosphorylation of eEF2 and increased protein levels of Arc and Fos (Chotiner et al. 2003). Taken together, these findings suggest that phosphorylation of eEF2 during certain forms of synaptic plasticity results in a decrease in overall protein synthesis, while at the same time increasing the translation of specific mRNAs. It remains to be determined whether this type of translation regulation occurs in other forms of protein synthesis-dependent synaptic plasticity.

Concluding Remarks

It is widely accepted that protein synthesis is required for many forms of synaptic plasticity, as well as for long-term memory. To understand how the translation of new protein occurs during various forms of synaptic plasticity, it is critical to understand how translation initiation is regulated. A gap in our current knowledge and a major challenge for investigators in this regard is the identification of the signaling cascades that couple neurotransmitter and neurotrophin receptors to the initiation factors that regulate translation initiation. Fortunately, a number of laboratories have recently taken up this challenge and have begun to identify the signaling molecules involved in regulating translation initiation during various forms of synaptic plasticity, including spatial (soma vs. dendrite) and temporal aspects of this regulation (Cushman 2003). Although these initial findings are promising, careful studies will be required to determine the similarities and differences in the biochemical sequelae that link neurotransmitter and neurotrophin receptors to the translation initiation machinery during protein synthesis-dependent forms of synaptic plasticity.

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