Local Translational Control in Dendrites and Its Role in Long-Term Synaptic Plasticity

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ABSTRACT: Local protein synthesis in dendrites has emerged as a key mechanism contributing to enduring forms of synaptic plasticity. Although the translational capability of dendrites has been appreciated for over 20 years, it is only recently that significant progress has been made in elucidating mechanisms that contribute to its regulation. It is clear from work over the last few years that the control of translation in dendrites is complex, involving a host of unique (and often surprising) mechanisms that can operate together or in parallel to tightly control gene expression in time and space. Here, we discuss the strategies used by neurons to regulate translation in dendrites and how these are implemented in the service of long-term information storage. J Neurobiol 64: 116–131, 2005

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The use-dependent modification of synaptic efficacy lies at the heart of the ability of the nervous system to encode and retain information. Two forms of synaptic plasticity in the mammalian brain, long-term potentiation (LTP) and long-term depression (LTD), have received particular attention as potential substrates of learning and memory. In each, changes in synaptic efficacy are restricted (for the most part) to activated synapses, a property referred to as input specificity. A major turning point in the study of LTP and LTD came from the discovery that both translation and transcription are required for these forms of plasticity to persist in an enduring (or late-phase) form (Frey et al., 1988; Nguyen et al., 1994). The requirement for transcription indicated a critical role for events in the cell body, which illustrated a cell-biological problem that has occupied the field ever since: How do some synapses get strengthened/weakened selectively when the gene products required for that change are potentially available to all synapses? Early on, it was assumed that transcription and translation were tightly coupled, and both likely occurred in the soma. Given this constraint, one idea that emerged is that active synapses are tagged in a protein synthesis–independent manner, which enables them to selectively capture the newly synthesized products made elsewhere (Frey and Morris, 1997). While this idea has gained experimental support (e.g., Martin et al., 1997), it is clear that there is much more to the story. We now know that transcription and translation in neurons are not necessarily coupled in time or space, and this autonomous control of gene expression can play a critical role in enduring forms of synaptic plasticity. In particular, the local translation of mRNAs in dendrites has emerged as another strategy used by neurons to solve the input specificity problem. In this review, we discuss the various strategies used by neurons to regulate local protein synthesis in dendrites and the role this plays in long-term synaptic plasticity.

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SPATIAL SPECIFICITY OF DENDRITIC PROTEIN SYNTHESIS

The first indication that dendrites have autonomous translational control came from the discovery of dendritically localized polyribosome complexes using electron microscopy (reviewed in Steward and Schuman, 2001, 2003). The existence of polyribosomes in dendrites implied not only the existence of the translational machinery, but also that this machinery was in active use for protein synthesis. The preferential location of these complexes at the base of spines in forebrain neurons further suggested that dendritic protein synthesis might be capable of modifying the composition of synapses independently of one another (Steward and Levy, 1982). In the limit, such a mechanism could allow the tuning of the translational response to the patterns of activity at a single synapse, with the resulting protein products dedicated to that synapse, and that synapse alone. Recent proteomic profiling of purified postsynaptic density (PSD) fractions have provided some evidence for this possibility, in demonstrating resident translation machinery embedded within the PSD itself (Li et al., 2004; Peng et al., 2004). Although the localization of the translation machinery itself suggests the capability of autonomous translational control at individual synapses, there is as yet no direct evidence that dendritic protein synthesis operates with this degree of spatial resolution. For example, it is not known to what extent newly synthesized proteins are shared among neighboring synapses or whether changes in activity at single synaptic sites are capable of regulating local translation *in situ*. This gap in our knowledge does not mitigate the role played by dendritic protein synthesis in establishing or maintaining input specificity, because the input selectivity of LTP itself is not absolute (Schuman and Madison, 1994; Engert and Bonhoeffer, 1997). Nevertheless, determination of the true spatial limits of dendritic protein synthesis is a fundamental issue that has yet to be resolved.

Generally, local translation could contribute to input specificity in two ways: (1) through on-site synaptic synthesis and delivery of effector proteins, or (2) by synthesis of a synaptic mark that somehow targets that particular synaptic site for the selective utilization of gene products made elsewhere (e.g., Martin et al., 1997). These mechanisms, of course, are not mutually exclusive but rather complementary, and current evidence favors the idea that each can be important for the stabilization of long-term plasticity. Another possibility, recently advanced by Moccia and colleagues (2003), is that local protein synthesis may alter the translational competency of specific synapses. In this scenario, marking a synapse might correspond to conferring on it the ability to translate a particular population of mRNAs that other neighboring synapses cannot. Input specificity aside, it is also likely that local protein synthesis in dendrites contributes to long-term synaptic plasticity in other ways; for example, though synthesis of retrograde signals that could function to direct transcriptional events at the soma, or be released to modulate the activity in the apposed presynaptic terminal.

LOCALIZATION OF THE TRANSLATION MACHINERY

The first level of regulation for dendritic protein synthesis arises from the mechanisms that localize components of the translation machinery and mRNAs in dendrites. A number of studies have demonstrated that the components necessary for translation are constitutively present in dendrites (Tiedge and Brosius, 1996; Gardiol et al., 1999; Pierce et al., 2000; Tang et al., 2002), and recent studies have suggested that some of these components exhibit activity-dependent trafficking within dendrites (e.g., Ostroff et al., 2002; Antar et al., 2004; Smart et al., 2003). Thus, the localization of the translation machinery is both a necessary prerequisite for dendritic translation and a means to dynamically regulate it.

Studies using *in situ* hybridization have identified more than 30 distinct mRNA species in dendrites (for review, see Steward and Schuman, 2003) and RNA amplification of cytoplasmic contents from neuronal processes in culture have suggested that the number of dendritically localized mRNAs might be far greater ($\approx$ 400; Miyashiro et al., 1994). For these mRNAs to function in local synthesis, they must be transported into dendrites and dock at the appropriate synaptic sites. The mechanisms responsible for trafficking mRNAs to dendrites are thought to involve the recognition of *cis*-acting elements in the 3′ untranslated region (UTR) by specific RNA binding proteins that interact with microtubule-based transport systems (Tiedge et al., 1999; but see Hachet and Ephrussi, 2004). mRNAs are transported into dendrites in RNA granules; it is thought that this structure serves to prevent premature mRNA translation/degradation during transport, and that mRNAs might be released into a translationally competent form by activity-dependent regulation (Krichevsky and Kosik, 2001). The importance of mRNA trafficking to dendrites in synaptic function is illustrated by a recent study that examined mutant mice in which the native 3′ UTR of αCAMKII mRNA was replaced with the

3′ UTR of bovine growth hormone (Miller et al., 2002). Dendritic localization of αCAMKII mRNA was completely abolished in these mice, and dendritic levels of αCAMKII protein were also severely reduced. As a consequence, these mice also showed deficits in late phase LTP and hippocampal-dependent long-term memory. Aside from the effects on plasticity, this study raises the interesting possibility that local αCAMKII translation may represent a significant (and perhaps the major) source of αCAMKII protein at synaptic sites.

Finally, it should be emphasized that mRNA trafficking into dendrites is not merely a constitutive process, but can also be regulated by synaptic activity (Tongiorgi et al., 1997; Steward et al., 1998). This point has been elegantly demonstrated in studies of the regulated delivery of the mRNA encoding Arc (activity-regulated cytoskeletal protein) to synaptic sites after high-frequency stimulation (Steward et al., 1998). In this case, *in vivo* tetanization of the perforant path induces the transcription of *Arc* mRNA in granule cells of the dentate gyrus; *Arc* mRNA then traffics into dendrites, where it localizes selectively to previously activated dendritic lamina. These results thus indicate that mRNA localization can be tightly controlled within dendrites in an activity-dependent manner and this process likely contributes to input specificity.

SIGNALING TO THE TRANSLATION MACHINERY

Given the multitude of translation regulatory mechanisms and the heavy interactions between intracellular signaling pathways, it is likely that most cytosolic signaling molecules have the capability to alter translation given the appropriate context. Nevertheless, two signal transduction pathways—the ERK-MAPK and PI3 kinase pathways—have emerged as key regulators of translational efficiency in multiple eukaryotic systems and deserve special mention. Both pathways are activated downstream of growth factors, and often serve as key intermediaries between the transduction of environmental signals and the control of both translation and transcription. In addition, both pathways have been shown to play important roles in enduring forms of synaptic plasticity and memory (English and Sweatt, 1997; Atkins et al., 1998; Lin et al., 2001) and, at least in the case of the ERK-MAPK pathway, new evidence indicates that part of this role seems to derive from the control of translation (Kelleher et al., 2004). The details of these pathways will not be considered here (for recent reviews, see Wymann et al., 2003; Thomas and Huganir, 2004), except with reference to how their downstream targets can affect translation. Another signaling molecule that appears to have a specialized role in translational regulation is the protein kinase mTOR (mammalian target of rapamycin). As its name implies, mTOR activity is the target of the protein synthesis inhibitor rapamycin, which has been shown to preferentially inhibit translation of growth-associated mRNAs in some systems (for review, see Gingras et al., 2001). mTOR plays a critical role in the induction of late-phase LTP in CA1 region of hippocampus (Tang et al., 2002; Cammalleri et al., 2003) as well as long-term synaptic facilitation at sensorimotor synapses in *Aplysia* (Casadio et al., 1999; Purcell et al., 2003), implying perhaps a conserved role for its downstream targets in long-term memory formation.

THE MACHINERY OF TRANSLATION AND ITS REGULATION

Conventionally, the process of protein synthesis is divided into three phases—initiation, elongation, and termination—and each of these phases is subject to regulation. We will briefly consider each phase to illustrate specific mechanisms that may play a role in dendritic protein synthesis. A detailed account of the core mechanisms underlying each phase is beyond the present scope, but we direct the reader to several excellent reviews that consider these mechanisms in greater detail (Welch et al., 2000; Pestova et al., 2001; Browne and Proud, 2002; Sonenberg and Dever, 2003).

Initiation

All eukaryotic mRNAs have a 7-methyl-GTP cap structure at the 5′ end and a 3′ poly (A) tail that act cooperatively in translation initiation. The 5′ cap structure is recognized by the eIF4F protein complex, which is composed of the cap-binding protein eIF4E, the RNA helicase eIF4A, and the protein scaffold eIF4G. The scaffold provided by eIF4G, in turn, recruits the 43S preinitiation complex [composed of the small 40S ribosomal subunit, the eIF2 ternary complex (GTP-bound eIF2 complexed with the initiator Met-tRNAi), and eIF3] to the mRNAs 5′ end likely through interactions with eIF3. The mRNA-bound ribosomal complex then scans down the mRNA until a context-appropriate initiation codon is reached, at which time the protein factors dissociate from the complex and the large 60S ribosomal

subunit joins in a reaction that requires the GTPase activating protein eIF5. The newly formed 80S ribosome, with the Met-tRNA in the ribosomal P site, is now initiated on the mRNA and is free to begin elongation.

The cap binding protein eIF4E is often considered to be rate limiting for translation initiation, and its regulation by phosphorylation has received special attention as a mechanism for controlling protein synthesis. The direct phosphorylation of eIF4E is controlled by the Mnk (MAPK signal integrating kinase) family of protein kinases, which can be activated downstream of both the ERK-MAPK and p38 MAPK signaling pathways. In many cases (but not all), overall translation rates are correlated with the extent of eIF4E phosphorylation (Scheper and Proud, 2002). Initially, it was reported that phosphorylation of eIF4E increased its affinity for the 5′ cap (Minich et al., 1994) and hence favored initiation by promoting cap binding of the eIF4F complex. However, recent studies suggest that phosphorylation of eIF4E actually decreases its affinity for the cap (Scheper et al., 2001; Zuberick et al., 2003), making the specific role played by eIF4E phosphorylation less clear (see Scheper and Proud, 2002). However, it is clear is that the availability of eIF4E can be strongly influenced by the activity of its binding proteins (4EBPs), which compete with eIF4G for eIF4E binding. Phosphorylation of 4EBPs causes eIF4E to dissociate and thus favors formation of the eIF4F complex; the phosphorylation of 4EBP1 appears, in most systems, to be downstream of mTOR (Gingras et al., 2001).

The regulation of eIF2 activity (when it occurs) often plays a dominant role in controlling translation initiation. In order to bind Met-tRNAi, eIF2 must be in its GTP-bound form (the GDP-bound form is inactive), but to dissociate from the ribosome and allow for 60S subunit joining, eIF2-GTP must be converted to eIF2-GDP in a reaction stimulated by eIF5. Thus, the recycling of eIF2 between its GTP- and GDP-bound forms must be tightly controlled for effective translation initiation. Phosphorylation of the alpha subunit of eIF2 potently inhibits this recycling and in sufficient amounts produces translational arrest of most mRNAs (Jefferson and Kimbal, 2003). Although sizeable phosphorylation of eIF2α is most commonly observed in pathophysiological conditions, one study found detectable levels of phosphorylated eIF2α in cultured cortical neurons under nonstressed conditions, and treatments that stimulated translation resulted in eIF2α dephosphorylation (Takei et al., 2001).

The 40S ribosomal protein S6 is also a target of phosphorylation, and enhanced phosphorylation of S6 correlates with enhanced translation initiation, but in particular, initiation of mRNAs containing a 5′ terminal oligopyrmidine tract (known as the 5′ TOP mRNA family). The TOP family of mRNA transcripts is somewhat unique, in that the vast majority of members encode components of the protein synthetic machinery (Meyuhas, 2000); thus, S6 phosphorylation could provide a potential mechanism for regulating translational competency in dendrites. In this regard, the generation of a cDNA library of mRNAs from isolated *Aplysia* sensory neuron neurites has revealed a large proportion of extrasomatic mRNAs that encode translation-related proteins, including ribosomal proteins and canonical translation factors (Moccia et al., 2003). Among those identified was S6, which a previous study demonstrated was a target of both translational and posttranslational regulation (i.e., phosphorylation) in isolated *Aplysia* synaptosomes (Khan et al., 2001). Cytoplasmic phosphorylation of S6 is mediated by p70 S6 kinase (S6K), which in turn is regulated by mTOR as well as downstream effectors of the PI3K pathway (Meyuhas, 2000; Martin and Blenis, 2002).

Elongation

During the elongation phase, amino acids are added to the growing polypeptide as the ribosome translocates one codon relative to the mRNA. Although the regulation of elongation is much less complicated and varied than initiation, there is good evidence from a variety of eukaryotic systems (including neurons) that the ability to control translation by modulation of elongation is vitally important for cellular functioning.

At present, three canonical elongation factors have been identified in eukaryotes (Browne and Proud, 2002). Two of these factors—eEF1A and eEF1B—are responsible for recruiting a new aminoacyl-tRNA to the ribosomal A site. Phosphorylation of eEF1A/B by classical (i.e., Ca^{2+}-dependent) PKC isoforms has been shown to increase their activity in translation elongation. The third elongation factor—eEF2—is required for the translocation of the ribosome along the mRNA. Unlike eEF1A/B, phosphorylation of eEF2 strongly inhibits its activity, likely by preventing its binding to the ribosome. eEF2 kinase (eEF2K; formerly CAMKIII) appears completely dedicated to the regulation of eEF2, because this is its only known substrate. As implied by its former designation, eEF2K is a calcium-calmodulin dependent protein kinase (Nairn et al., 2001), and eEF2 phosphorylation in neurons has been shown to be regulated in an

activity-dependent manner (Marin et al., 1997; Scheetz et al., 2000).

The regulation of the phosphorylation status of eEF2 appears to be a widely used cellular strategy for controlling translation elongation. In addition to calcium-calmodulin, the activity of eEF2K can be enhanced by phosphorylation from AMP-activated protein kinase and protein kinase A (PKA) (Browne and Proud, 2002; Browne et al., 2004a). Interestingly, PKA phosphorylation renders eEF2K less dependent on Ca^{2+}-calmodulin for activity, suggesting a potential mechanism for keeping eEF2K autonomously active. Phosphorylation of eEF2K by a variety of other protein kinases produces the opposite effect, namely, an inhibition of eEF2K activity. These include members of stress-response pathways (e.g., SAPK2, p38 MAPK, and MAPKAP-K2), $p90^{RSK1}$ (downstream of the ERK-MAPK pathway), S6K, and mTOR (Browne and Proud, 2002; Browne et al., 2004b). Many of these signaling molecules are also known to play complementary roles in translation initiation, suggesting a means to coordinate the regulation of initiation and elongation to suit a particular set of environmental conditions.

Termination

Translation termination, in which the completed polypeptide is released and the ribosome dissociates from the mRNA, requires two release factors: eRF1, which recognizes all three stop codons and catalyzes the termination reaction, and eRF3, which stimulates eRF1 activity in a GTP- and ribosome-dependent manner. Still very little is known regarding how posttranslational modification of eRF1 and eRF3 affects their activity. However, it is clear from other eukaryotic systems that termination efficiency is subject to other forms of regulation: it is influenced by the context provided by nucleotides downstream of the stop codon, as well as by a number of trans-acting protein factors (Welch et al., 2000). In addition, to participate in another round of protein synthesis, the 80S ribosome must dissociate to generate free 40S subunits. Again, ribosome recycling in eukaryotes is poorly understood, but the analogous process in prokaryotes is complex, involving an interplay between initiation, elongation, and release factors. While regulation of the termination phase has yet to be documented in neuronal systems, the efficiency with which ribosomes dissociate from the mRNA and recycle into initiation-competent modes likely has a major impact on dendritic translation.

Internal Ribosomal Entry

In addition to the canonical cap-dependent scanning mode of translation initiation used by the vast majority of cellular mRNAs, a small subset of mRNAs possess the ability to recruit the 40S ribosome to an internal ribosomal entry site (IRES) usually localized just upstream from the initiation codon (Hellen and Sarnow, 2001). Because the binding of the ribosome occurs in an internal site, this mode of initiation is cap-independent and can ensue in the absence of some otherwise essential initiation factors (e.g., eIF4E). Although it is still not clear to what extent IRES-mediated translation occurs in dendrites, it is noteworthy that a number of dendritically localized mRNAs possess cap-independent activity in a well-established bicistronic reporter assay. To date, mRNAs encoding ARC (activity-regulated cytoskeletal protein), αCAMKII, dendrin, MAP2 (microtubule-associated protein 2), neurogranin, and FMRP (Fragile X Mental Retardation protein) all have the ability to initiate translation via internal ribosomal entry (Pinkstaff et al., 2001; Chiang et al., 2001). One implication of IRES activity is that it provides a potential mechanism for coupling global changes in translational efficacy with selective translation of specific mRNAs. Rendering cap-dependent translation inefficient, by reducing the activity of eIF4E, for example, could favor the translation of those mRNAs that contain IRES activity. In this regard, Dyer and colleagues (2003) have recently demonstrated that an activity-dependent form of plasticity in neuroendocrine cells of *Aplysia* is associated with a switch from cap-dependent to cap-independent translation, resulting in increased synthesis of egg-laying hormone despite overall decreases in translational efficiency. It will be interesting to see if similar mechanisms may operate in mammalian dendrites during various forms of synaptic plasticity.

Cytoplasmic Polyadenylation

Translation of a subset of mRNAs can also be triggered by regulated cytoplasmic polyadenylation of the 3′ tail. This subset of mRNAs contain short nucleotide sequences in the 3′ UTR known as cytoplasmic polyadenylation elements (CPEs). These sequences are recognized by CPE-binding protein (CPEB), which normally represses translation through interacting with the protein maskin, which binds eIF4E and inhibits its association with eIF4G (Richter and Lorenz, 2002). However, phosphorylation of CPEB by the protein kinase Aurora can relieve this repression. Phosphorylated CPEB associ-

ates with cleavage and polyadenylation specificity factor (CPSF) and together, this complex recruits poly (A) polymerase (PAP) to the 3′ tail to initiate polyadenylation. The lengthened poly (A) tail is recognized by the poly (A) binding protein (PABP), which in turn associates with the 5′ cap and facilitates the displacement of maskin from eIF4E, enabling it to interact eIF4G and function in translation initiation.

One dendritically localized mRNA that can be regulated in this fashion is αCAMKII. αCAMKII mRNA contains two CPEs in its 3′ UTR (Wu et al., 1998), and these are required for αCAMKII translation driven by either visual experience or NMDA receptor activation (Wu et al., 1998; Wells et al., 2001). Moreover, NMDA receptor activation in synaptosomes has been shown to stimulate Aurora activity, the phosphorylation of CPEB, and induce αCAMKII mRNA polyadenylation (Huang et al., 2002), suggesting that this mechanism also operates at synapses to control αCAMKII synthesis. A recent study has also demonstrated that, like Aurora, CAMKII itself can also phosphorylate CPEB at synapses, leading to enhanced CPEB-induced translation (Atkins et al., 2004). This reciprocal regulation between CAMKII and CPEB could provide a mechanism for CAMKII to regulate its own synthesis. A final twist to the story has been provided recently by Si and colleagues (2003), who demonstrated that the local translation of CPEB in *Aplysia* sensory neuron neurites is required for long-term synaptic facilitation. These results underscore the point made earlier when considering translation of TOP mRNAs—local protein synthesis may serve to regulate the translational capability of particular synaptic sites by virtue of their prior history of activity.

NEUROMODULATORY REGULATION OF DENDRITIC TRANSLATION

Brain-Derived Neurotrophic Factor

Brain-derived neurotrophic factor (BDNF) belongs to the neurotrophin family of growth factors. Growth factors, in general, are known to promote structural changes in the nervous system, which has inspired wider interest into their potential role as regulators of synaptic plasticity. Studies of BDNF knockout mice suggested a specific role for this factor in enduring, protein synthesis–dependent forms of synaptic plasticity (Korte et al., 1996; Patterson et al., 1996), and the application of BDNF to hippocampal slices induces a form of LTP that is dependent on protein synthesis (Kang and Schuman, 1995, 1996). BDNF application induced LTP even in dendrites that were surgically isolated from their parent cell-bodies, and importantly, it was still blocked by protein synthesis inhibitors (Kang and Schuman, 1996). These results indicate that BDNF induces a form of synaptic plasticity that relies on dendritic protein synthesis.

Studies of BDNF's effect on translational responses in neurons indicates that it is a strong activator of both overall translation in the cell body, as well as local translation in dendrites. Application of BDNF strongly enhances the protein incorporation of radiolabelled amino acids in cortical (Takei et al., 2001, 2004) and hippocampal (Kelleher et al., 2004) neuronal cultures, and produces a rapamycin-sensitive increase in the proportion of mRNAs associated with polysomes (Schratt et al., 2004). Using microarray profiling of polysome-associated mRNAs isolated from cultured cortical neurons, Schratt and colleagues (2004) have recently identified numerous mRNAs whose translation is enhanced by BDNF. Interestingly, unique populations of mRNAs were affected by BDNF at different developmental ages, with larger representation of proteins with a role in axon guidance or those important for synaptic function in young and mature neurons, respectively. The ability of BDNF to induce robust activation of translation in neurons seems to result from the concerted regulation of a number of proteins important for translation initiation, and recent studies implicate the protein kinase mTOR as a particularly important signaling intermediary (Takei et al., 2001, 2004; Schratt et al., 2004). In both cortical and hippocampal neurons, for example, BDNF induced the phosphorylation of both eIF4E, through an ERK-MAPK–dependent mechanism, as well as 4EBP1 (Takei et al., 2001; Kelleher et al., 2004). In cortical neurons, the phosphorylation of 4EBP1 was dependent on a PI3K-mTOR signaling cascade and independent of ERK-MAPK, which is a profile that is typical of most other eukaryotic cells (Gingras et al., 2001; Scheper and Proud, 2002). In hippocampal neurons, however, 4EBP1 phosphorylation was also dependent on ERK-MAPK activation, suggesting differential coupling of the ERK-MAPK pathway to the translation machinery in these neurons. BDNF also stimulated the phosphorylation of ribosomal protein S6 in hippocampal neurons in an ERK-MAPK–dependent manner, and caused the dephosphorylation of eIF2α in cortical neurons. It will now be of interest to determine the extent to which these changes occur in dendrites and how much they contribute to long-lasting changes in synaptic efficacy. Speaking to the latter point, Purcell and colleagues (2003) have recently demonstrated

that BDNF can facilitate the induction of long-term synaptic facilitation in *Aplysia* via an ERK-MAPK–dependent mechanism, although it is unclear whether such facilitation by BDNF is the result of translational or transcriptional regulation. In addition, Tang and colleagues (2002) demonstrated that inhibiting mTOR activation with rapamycin blocks long-term synaptic potentiation by BDNF in hippocampal slices in a manner reminiscent of other protein synthesis inhibitors, suggesting a link between BDNF-induced translational regulation via mTOR and the induction of long-lasting synaptic plasticity.

In addition to its effect on overall neuronal protein synthesis, it is now clear that BDNF also regulates local protein synthesis in dendrites. In one study, BDNF enhanced the incorporation of radiolabelled amino acids in isolated dendrites and synaptoneurosomes (Takei et al., 2004), suggesting a broad stimulation of local protein synthesis. However, in other studies, the translational enhancing effects of BDNF in synaptoneurosomes was limited to a subset of proteins, including the immediate early gene Arc (Yin et al., 2002), the synaptic scaffold protein Homer 2, and the GluR1 subunit of AMPA receptors (Schratt et al., 2004). These particular targets, given their established role in synaptic function, provide perhaps the first clue as to the mechanism by which BDNF-induced translational activation contributes to synaptic plasticity.

In another study, BDNF was found to enhance the translation of a fluorescent reporter in dendrites of cultured hippocampal neurons (Aakalu et al., 2001). This enhancement was observed in dendrites still connected to the cell body, in optically isolated dendrites (in which the fluorescent signal from the soma is continuously eliminated by photobleaching), and in transected dendrites that were physically isolated from their cell bodies. In addition to overall increases in reporter expression in dendrites, BDNF induced the formation of hot-spots of reporter expression—these hot-spots colocalized with both pre- and postsynaptic markers, as well as with a ribosomal marker, suggesting that they may reflect synaptic sites of enhanced protein synthesis. A recent study has suggested another class of mechanism for local control of translation by BDNF. In this study (Smart et al., 2003), BDNF induced the translocation of eIF4E into cytoskeletal fractions enriched in mRNA granules, an effect involving integrin signaling and F-actin dynamics. BDNF also increased the concentration of eIF4E present in dendritic spines, suggesting a potential link between the biochemical studies and recruitment of the translation machinery to synaptic sites.

When considered together, the work summarized above implicates a role for BDNF in initiating translation-dependent processes required for L-LTP. However, a new study (Pang et al., 2004) has suggested that BDNF also acts as a newly synthesized product that acts downstream of translation during the maintenance of L-LTP. In this study, exogenous application of BDNF restored L-LTP in the presence of protein synthesis inhibitors, implying that BDNF (and the proteolytic enzymes responsible for BDNF maturation) are the only targets of protein synthesis necessary to maintain L-LTP. This result is consistent with the previous observation of Kang and colleagues (1997) that TrkB receptor-bodies, which quench BDNF in the extracellular space, could reverse previously established LTP. However, other proteins synthesized in response to L-LTP stimulation, such as protein kinase Mζ (Osten et al., 1996), have also been shown to be necessary and sufficient to maintain L-LTP (Ling et al., 2002). While these observations suggest that the role of translational regulation in maintaining L-LTP is unlikely limited to single protein targets, the new results provided by Pang and colleagues (2004) implicate BDNF as one target that appears to play a pivotal role.

Dopamine

The neurotransmitter dopamine has a rich history in the field of synaptic plasticity and memory. Dopamine can bind to five different receptors which are classically divided into two families based on positive (D1, D5) or negative (D2–D4) coupling to adenylate cyclase. A number of studies have demonstrated a key role for D1/D5 receptor signaling in the induction of L-LTP. D1/D5 antagonists (Frey et al., 1991) or inhibitors of PKA (Frey et al., 1993) selectively block late-phase LTP and mutant mice lacking the D1 receptor do not express L-LTP (Matthies et al., 1997). Conversely, D1/D5 agonists (Huang and Kandel, 1995) and cAMP analogues (Frey et al., 1993) both induce long-lasting synaptic potentiation in hippocampal slices that requires new protein synthesis. These observations raise the question of whether D1/D5 receptor activation regulates dendritic protein synthesis and, if so, what functional impact does this have on synaptic transmission. A recent study has suggested some answers to these questions. Using cultured hippocampal neurons (which express both D1 and D5 receptors), Smith and colleagues (2004) first demonstrated that D1/D5 agonists enhanced the dendritic synthesis of a GFP-based translation reporter. To examine the synthesis of endogenous proteins, they utilized a fluorescein-conjugated derivative of puromycin (F2P) as a marker for translation

of endogenous mRNAs. Puromycin is a tRNA-mimetic that becomes incorporated into elongating polypeptides during protein synthesis, and in its native form, blocks protein synthesis by preventing peptide bond formation. In control experiments, they demonstrated that the majority of F2P signal was protein synthesis–dependent, and that bath application of D1/D5 agonists enhanced the F2P signal in a protein synthesis–dependent fashion. In addition, local perfusion of dendrites with a D1/D5 agonist along with F2P induced a protein synthesis–dependent increase in incorporated fluorescence, suggesting that D1/D5 receptor activation enhances local protein synthesis in dendrites. Furthermore, they demonstrated that D1/D5 receptor activation enhanced the frequency of miniature excitatory synaptic events, the surface expression of the GluR1 subunit of AMPARs, and the association of surface GluR1 with synaptic markers. All of these effects required new protein synthesis, suggesting that D1/D5 receptor signaling converts inactive synapses to active ones through changes in dendritic protein synthesis. This study, therefore, suggests a link between two mechanisms thought to operate during LTP: the conversion of silent synapses to active synapses (Liao et al., 1995) and the necessity of new protein synthesis for its stabilization (Frey et al., 1988).

ACTIVITY-DEPENDENT REGULATION OF DENDRITIC PROTEIN SYNTHESIS

Activation of Ionotropic Glutamate Receptors

Because new protein synthesis is clearly required for long-lasting activity-dependent changes in synaptic transmission, the manner by which neuronal activity engages the translational machinery is key to our understanding of long-term information storage. A number of studies have demonstrated that exposing brain slices or cultured neurons to glutamate strongly inhibits the incorporation of radiolabelled amino acids into protein (Orrego and Lipman, 1967; Vornov and Coyle, 1991; Marin et al., 1997). For example, Marin and colleagues (1997) found that a variety of pharmacological treatments that stimulate glutamate neurotransmission, including KCl depolarization, as well as AMPA, NMDA, and glutamate application, produced a rapid inhibition of overall protein synthesis in cultured cortical neurons in a Ca^{2+}-dependent fashion. Moreover, the relative efficacy of each of these treatments in inhibiting protein synthesis was highly correlated with the extent of eEF2 phosphorylation induced by each treatment. This overall inhibition of protein synthesis seen with bath application of glutamate agonists in this study involved both AMPA receptors (AMPARs) and NMDA receptors (NMDARs), but not metabotropic receptors. Although the kinetics of translation inhibition by glutamate were not examined in detail, Marin and colleagues (1997) demonstrate that the phosphorylation of eEF2 induced by such treatment is rapid (within 30 s). It is important to note here that in the above studies, these treatments produce global and prominent increases in cytosolic Ca^{2+} and were studied in the context of pathophysiology, not synaptic plasticity. However, it is noteworthy that short (30 s) exposure to bath-applied glutamate at 50 μM (half the concentration used by Marin et al., 1997) induces LTP of mEPSC (miniature excitatory postsynaptic current) frequency in cultured hippocampal neurons (Margaroli and Tsien, 1992), suggesting that the conditions used by Marin and colleagues (1997) may bear some relevance to plasticity, as well. Consistent with this idea, a recent study has shown that induction of a protein synthesis–dependent chemical LTP (by pairing KCl depolarization with the adenylate cyclase activator forskolin) produces a decrease in overall translational efficacy 1 h posttreatment in hippocampal slices (Chotiner et al., 2003). Similar to Marin and colleagues (1997), this decrease in protein synthesis was associated with increased phosphorylation of eEF2, suggesting potential regulation of translation elongation.

These studies thus suggest that global stimulation of excitatory drive in both brain slices and cultured neurons is associated with decreases in overall protein synthesis. However, other studies have demonstrated that global increases in activity can also enhance certain aspects of protein synthesis in neurons. For example, Kelleher and colleagues (2003) demonstrated that disinhibiting cultured hippocampal neurons with bicuculine enhanced protein synthesis of a transfected synthetic mRNA. Moreover, Schratt and colleagues (2004) have shown that K^+ depolarization of cultured cortical neurons increases the fraction of mRNA associated with polysomes, and Banko and co-workers (2004) have shown that NMDA stimulation of hippocampal slices induces eIF4E phosphorylation in area CA1, an effect typically associated with enhanced translation initiation. Thus, in contrast to the studies described above, these results suggest that global increases in excitatory neurotransmission enhance overall protein synthesis. Although it is not yet clear what factors account for these different results, one intriguing possibility is that global increases in neuronal activity enhance pro-

cesses responsible for translation initiation, but strongly depress the elongation step, leading to a net inhibition of overall protein synthesis. This could, in principle, account for the increased association of mRNAs with polysomes found by Schratt and colleagues (2004), because inhibiting elongation will lead to ribosomal stalling on the mRNA and increase the size of polysome complexes.

While it is unclear how global increases in excitatory neurotransmission impact on overall protein synthesis, the effect of spatially restricted changes in activity are perhaps more relevant to our understanding of input-specific forms of plasticity. In this regard, Kelleher and colleagues (2003) report that Schaeffer collateral stimulation of hippocampal slices sufficient to induce late-phase LTP is associated with global increases in radiolabelled amino acid incorporation in both CA1 and CA3 fields. An increase in the synthesis of the GluR1 AMPAR subunit has also been demonstrated in CA1 minislices, but this increase in newly synthesized GluR1 appears secondary to transcriptional regulation (Nayak et al., 1998). L-LTP induction in CA1 also is accompanied by translocation of polyribosomes from dendritic shafts into dendritic spines (Ostroff et al., 2002), suggesting enhanced local protein synthesis at synaptic sites. At least one target of this local protein synthesis is αCAMKII, because αCAMKII expression increases rapidly (within 10 min) and selectively in stimulated areas after LTP induction in a protein synthesis–dependent manner (Ouyang et al., 1999).

Biochemical studies also support the view that glutamatergic stimulation can regulate local protein synthesis. For example, Bagni and colleagues (2000) demonstrated that stimulation of synaptosomes with KCl depolarization or glutamate/glycine increased the association of αCAMKII mRNA with polysomes, suggesting enhanced translation initiation. This effect appeared specific for αCAMKII mRNA because the relative amount of *Arc* and type 1 inositol 1,4,5-triphosphate receptor mRNAs associated with polysomes were not changed by stimulation. Similarly, Scheetz and colleagues (2000) show that NMDA stimulation of synaptoneurosomes prepared from developing superior colliculi induces rapid αCAMKII synthesis. This triggered αCAMKII synthesis was associated with, paradoxically, increased phosphorylation of eEF2 and $> 50\%$ decrease in overall protein synthesis. Moreover, treatment with low doses of the elongation inhibitor cyclohexamide produced an expected decrease in overall synthesis, but surprisingly, also a specific increase in αCAMKII synthesis. These observations thus suggest that, at least under certain circumstances, an inhibition of overall protein synthesis itself can be a trigger for the preferential translation of specific mRNAs.

Activation of Metabotropic Glutamate Receptors

Metabotropic glutamate receptors comprise a family of eight known members that are categorized into three groups based on their coupling to specific signal transduction pathways (Coutinho and Knöpfel. 2002). For simplicity, we will use the generic term metabotropic glutamate receptors (mGluRs) to refer to Type 1 receptors because this mGluR family appears to play a pivotal role in translational regulation and synaptic plasticity. For example, activation of mGluRs in hippocampal slices primes the induction of LTP in CA1 by prolonging the persistence of LTP induced by weak stimulation protocols (Cohen and Abraham, 1996). This facilitating effect of mGluR activation on LTP persistence requires protein, but not mRNA synthesis, demonstrating a role for the translation of preexisting mRNA in this effect (Raymond et al., 2000). In addition to a role in LTP, mGluR activation underlies an NMDAR-independent form of LTD in the CA1 region (Oliet et al., 1997). In a series of elegant experiments, Huber and colleagues (2000) demonstrated that this form of LTD requires rapid dendritic protein synthesis. They showed that mGluR-LTD was not affected by inhibiting transcription, but was blocked by inhibitors of translation, including infusion of an inhibitory cap-analogue directly in the postsynaptic cell. They also showed that mGluR-LTD could be induced in surgically isolated dendritic fields, indicating that the source of protein synthesis was in the dendrites. Unlike the role for protein synthesis in the late phase of LTP, which is revealed after 1 to 3 h, the effects of protein synthesis inhibitors on mGluR-LTD become evident within 20 min. This feature of mGluR-LTD makes the task of linking local dendritic translation of specific mRNAs with plasticity considerably more tractable. Accordingly, understanding the mechanisms and targets of translational regulation by mGluR activation has become an issue of great interest.

The first clue that mGluR activation could regulate local protein synthesis came from the observation that treating synaptoneurosomes with mGluR agonists produced a rapid increase in RNA loading on polyribosomes (Weiler and Greenough, 1993). More recently, Job and Eberwine (2001) demonstrated that the mGluR agonist DHPG induces a rapid increase in dendritic expression of a GFP-based translation reporter in cultured hippocampal neurons; the major-

ity of this increase was due to new synthesis because it was strongly inhibited by two protein synthesis inhibitors. Similar to the effects of BDNF (Aakalu et al., 2001), DHPG treatment induced hot-spots of reporter expression in dendrites, and these colocalized with ribosomal markers. Recent work has shed light on the signaling cascades that are important for both translational activation and LTD induced by mGluR activation. The mGluR agonist DHPG induced ERK-MAPK, but not p38-MAPK, phosphorylation in hippocampal slices and specific inhibitors of MEK (the upstream kinase that activates MAPK) blocked mGluR-LTD (Gallagher et al., 2004). Moreover, treatment of hippocampal slices or synaptoneurosomes with DHPG induced activation of the PI3K signaling pathway, including the protein kinase mTOR, and PI3K inhibitors or the mTOR inhibitor rapamycin each blocked the induction of mGluR-LTD (Hou and Klann, 2004). These studies thus suggest that mGluR activation signals to the translation machinery via both ERK-MAPK and PI3K signaling pathways, and both pathways play a role in the establishment of mGluR-dependent synaptic plasticity.

The studies summarized above provide important insight into the mechanism by which mGluR activation induces translational activation and synaptic plasticity, but determining the precise relationship between the two will require identification of the specific targets of mGluR-induced translational activation and how these contribute to changes in synaptic efficacy. A number of specific proteins have already been identified as targets of mGluR translational regulation, and this list will almost certainly grow in the coming years. In cultured cortical neurons, mGluR activation rapidly upregulates expression of the synaptic scaffolding protein PSD-95 by a mechanism that requires protein, but not mRNA, synthesis (Todd et al., 2003a). Activation of mGluRs has also been shown to enhance the synthesis of tissue plasminogen activator in cultured hippocampal neurons and synaptoneurosomes by a mechanism involving cytoplasmic polyadenylation (Shin et al., 2004). Another target of mGluR-activated translation, interestingly, is FMRP. DHPG-treated synaptoneurosomes demonstrate increased FMR1 mRNA associated with polysomes and increased levels of FMRP protein assayed by Western blotting (Weiler et al., 1997). In addition, DHPG induces a marked and rapid increase in FMRP expression in cultured cortical neurons which is blocked by the translation inhibitor puromycin, but not the transcription inhibitor actinomycin D (Todd et al., 2003a). mGluR-dependent translation of FMRP has also been observed in the barrel cortex of rats following unilateral whisker stimulation; this increase in FMRP protein was observed even though levels of *FMR1* mRNA remained unchanged (Todd et al., 2003b). Interestingly, the ability of mGluR activation to stimulate the translation of PSD-95 is lost in FMRP knockout mice (Todd et al., 2003a), suggesting that the mGluR-dependent regulation of PSD-95 is secondary to its effects on FMRP. Moreover, the ability of DHPG to stimulate both the association of mRNA with polysomes and the incorporation of radiolabelled amino acids in synaptoneurosomes is also lost in FMRP knockout mice (Weiler et al., 2004). Thus, although much more work is required in this area, current data suggests that FMRP plays a primary role in the translational response induced by mGluR activation, raising the general question of whether it has a role in mGluR-dependent plasticity. In this regard, Huber and colleagues (2002) have shown FMRP may actually play an inhibitory role because mGluR-dependent LTD is enhanced in FMRP knockout mice. Whether this enhancement of mGuR-LTD by FMRP is related to altered translational induction is currently unknown.

The finding that mGluR activation stimulates translation would seem at odds with the finding that one target of this regulation, FMRP, is a known translational repressor (Zalfa et al., 2003). However, because FMRP regulates the translation of its own mRNA, it is possible that the enhanced translation of FMRP by mGluR activation reflects a more generalized mechanism where the translational repression conferred by existing FMRP is temporarily relieved. In support of this notion, a recent study has demonstrated that mGluR activation also has a potent effect on the trafficking of *FMR1* mRNA and FMRP protein in cultured hippocampal neurons (Antar et al., 2004). In this case, mGluR activation enhanced trafficking of both the protein and mRNA into dendrites, but also induced a redistribution of FMRP protein (but not *FMR1* mRNA) away from synaptic sites. This redistribution of FMRP could be a potential mechanism to enable a short time-window of local protein synthesis at synaptic sites, which would be limited by the replenishment of synaptically localized FMRP through local synthesis.

Chronic Changes in Neuronal Activity

In addition to changes in synaptic efficacy that are induced rapidly such as LTP and LTD, chronic changes in neuronal activity can lead to compensatory changes in synaptic strength that develop gradually (Turrigiano et al., 1998; Murthy et al., 2001). These forms of so-called synaptic scaling are also

associated with large-scale remodeling of the postsynaptic density (Ehlers, 2003), suggesting that they may arise via local changes in synaptic architecture. One change that might be particularly important for the scaling up of synaptic responses during chronic activity blockade is increased expression of glutamate receptors, which has been reported previously (O'Brien et al., 1998). Moreover, synthesis and membrane insertion of epitope-tagged GluR2 subunits has been observed after mRNA transfection of isolated dendrites (Kacharmina et al., 2000), suggesting the possibility that regulated synthesis of GluR subunits in dendrites could contribute to synaptic scaling (as well as other forms of plasticity). Ju and colleagues (2004) have recently provided the important link between these findings. Using a novel labeling system developed by Tsien and colleagues (Griffin et al., 1998) in which a tetracysteine motif introduced into recombinant proteins can bind spectrally distinct biarsenical dyes, Ju and co-workers (2004) report that the dendritic synthesis of GluR1, but not GluR2, is upregulated by chronic (72 h) blockade of neuronal activity with the voltage-gated Na^+ channel blocker tetrodotoxin (TTX) and the NMDAR antagonist APV. Thus, local protein synthesis in dendrites may prove to be an important mechanism contributing to synaptic scaling.

Miniature Synaptic Transmission—Quantal Regulation of Dendritic Protein Synthesis?

The preceding discussion indicates that dendritic protein synthesis is regulated by both increases and decreases in neuronal activity. This raises the general question of how large these changes in synaptic activity need to be in order for the translational machinery to respond. A recent study has suggested that these changes may in fact be surprisingly small — presynaptic release of single vesicles (i.e., single quanta) are capable of regulating dendritic protein synthesis in the postsynaptic cell. Under conditions where all evoked synaptic transmission is blocked with TTX, additional blockade of miniature excitatory synaptic events (minis) produced a rapid increase in dendritic synthesis of a GFP-based translation reporter in cultured hippocampal neurons (Sutton et al., 2004). This effect was observed regardless of whether the postsynaptic detection of miniature events were blocked (with glutamate receptor antagonists) or whether the presynaptic release of such events were blocked (with Botulinum Toxin A), and these effects occluded one another. Conversely, increasing the frequency of miniature events (with low concentrations of α-latrotoxin) produced the opposite effect, that is, a significant inhibition of dendritic protein synthesis. Importantly, neither blocking minis (with GluR antagonists) or increasing their release (with α-latrotoxin) affected reporter degradation, demonstrating that the effects on reporter expression owe to changes in its rate of synthesis.

Due to the presumed stochastic nature of miniature synaptic transmission, it is surprising that this noise would influence such an energy-intensive, and exquisitely regulated, process such as translation. In somatic whole-cell voltage clamp recordings in cultured hippocampal neurons or hippocampal slices, the overall frequency of excitatory mEPSCs is typically in the range of 1 to 10 Hz. Given that an individual hippocampal pyramidal neuron receives roughly 10^4 glutamatergic synapses, an estimated overall mini frequency of 10 Hz would suggest that the rate of miniature transmission at a given synapse is likely to be quite low ($\sim$0.001 Hz). On the timescale of synaptic transmission, these events seem far too small and unreliable to make a significant impact on postsynaptic function. However, *in vivo* dendritic recordings in cat neocortex reveal much higher mini frequencies (10–20 Hz) than is observed in somatic recordings (Paré et al., 1997). Moreover, pharmacological mini blockade produced an approximately 50% increase in dendritic input resistance, suggesting that the local excitatory drive produced by these events can be substantial. Other studies have demonstrated a distance-dependent enhancement of unitary synaptic conductance in CA1 pyramidal dendrites that maintains similar somatic EPSP amplitudes for proximal and distal inputs (Magee and Cook, 2000). Together, these studies illustrate that estimating the features of mEPSCs by somatic electrophysiological recordings likely underestimates their impact as local excitatory signals.

Although a role for miniature synaptic events in regulating dendritic protein synthesis was surprising, perhaps even more surprising was the finding that NMDA receptor–dependent minis also contributed to the effect. In neurons treated with TTX and with physiological levels of Mg^{2+} (2 m*M*) present in the extracellular solution, application of the NMDA receptor antagonist APV alone induced a significant increase in dendritic protein synthesis. While this treatment was less effective than blocking both AMPA- and NMDA-receptor–mediated miniature events, even a partial role for NMDA receptors is unexpected, given that these channels are presumably blocked by Mg^{2+} ions at rest. These results raise the possibility that receptor binding *per se*, rather than

ion flux, is important for the inhibition of protein synthesis by minis. However, if this were true, the effects of AMPAR antagonists (e.g., CNQX) should add to (rather than occlude) the effects of APV in stimulating dendritic protein synthesis because depolarizing current through the AMPAR is required for removing the Mg^{2+} block, but not for glutamate binding, of NMDARs. Contrary to this prediction, neurons treated with CNQX alone (in the presence of TTX) showed an increase in dendritic translation that was of similar magnitude than cells treated with both CNQX and APV together, suggesting an occlusion of the effects of APV. An alternative possibility is that the current through AMPARs by a single quantum of glutamate is sufficient to (at least partially) remove the Mg^{2+} block of NMDARs, and the resulting NMDAR-mediated mEPSC is contributing to the inhibition of dendritic protein synthesis. Supporting this possibility are a number of studies demonstrating (in the presence of physiological levels of external Mg^{2+}), NMDAR-mediated Ca^{2+} transients in individual spines elicited by single presynaptic action potentials, each of which presumably release a single quantum (Wang et al., 1999; Yuste et al., 1999; Emptage et al., 2003).

What is the function of the regulation of dendritic protein synthesis by minis? Although this is still an open question, previous studies suggest some possibilities. For example, McKinney and colleagues (1999) demonstrated that minis are sufficient to maintain dendritic spine density in organotypic slice cultures in the face of long-term (7 day) activity blockade. Moreover, miniature synaptic transmission at the *Drosophila* neuromuscular junction is both necessary and sufficient to induce GluR clustering (Saitoe et al., 2001). These studies suggest that miniature events may convey information regarding the functional integrity of synaptic components during activity blockade. Thus, in the absence of evoked synaptic transmission, the presence of minis may favor a wait-and-see approach before large-scale rearrangements are made to the synaptic architecture at considerable metabolic cost. When such signals are removed, however, so to is the information regarding synaptic integrity, and synapses may respond by locally synthesizing the necessary components for establishing novel presynaptic contacts.

Another possibility is that the tonic inhibition of dendritic protein synthesis by minis serves to prime stimulus-induced local protein synthesis by maintaining a pool of free ribosomes and translation factors, allowing these to be recruited rapidly to recently activated synaptic sites during plasticity. Recent studies have, in fact, demonstrated that the location of the translation machinery in dendrites is not fixed, but rather can rapidly redistribute to (and presumably from) synaptic sites given the appropriate signals (e.g., Ostroff et al., 2002). Alternatively, minis may simply raise the threshold for translational control at synaptic sites, ensuring that only particular patterns of synaptic activity are capable of altering the complement of mRNAs in the activity-translating pool. Although the precise functional role played by this form of translational control is unknown, it is clear that ongoing miniature synaptic transmission can alter the translational capabilities of the local synaptic environment.

PERSPECTIVE

As illustrated throughout this review, we are only beginning to realize the full complexity underlying the regulation of local protein synthesis in dendrites. For example, consider what is already known regarding the activity-dependent translation of αCAMKII mRNA (which might best be described as the prototype for our understanding of local translation). It is clear that neurons do not use a single strategy for translating this single mRNA species, but rather make use of a host of distinct mechanisms to tightly control the expression of this protein in both time and space. Local αCAMKII synthesis in dendrites is regulated first by general dendritic mRNA trafficking and also likely through another mechanism for finer spatial localization (e.g., synapse-specific) within the dendrite. Cytoplasmic polyadenylation can induce its translation, and likely also alters its stability. This polyadenylation, in turn, is also subject to regulation from CAMKII itself, thereby providing a mechanism for CAMKII to control its own translation as well as other CPEB targets. In addition, local αCAMKII translation may be induced by a decrease in elongation efficiency. Finally, αCAMKII mRNA contains an IRES, and could thus alternate between cap-dependent and -independent modes of translation initiation as another potential means to regulate its expression. Determining how these unique modes of translational regulation interact to control the translation of αCAMKII and other dendritic mRNAs during synaptic plasticity is the challenge that lies ahead.

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