Molecular mechanisms for activity-regulated protein synthesis in the synapto-dendritic compartment

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The creation of enduring modifications in synaptic efficacy requires new protein synthesis. Neurons face the formidable challenge of directing these newly made proteins to the appropriate subset of synapses. One attractive solution to this problem is the local translation of mRNAs that are targeted to dendrites and perhaps to synapses themselves. The molecular mechanisms mediating such local protein synthesis, notably CPEB-mediated cytoplasmic polyadenylation, are now being elucidated.

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Abbreviations

α-CaMKII	α subunit of calcium/calmodulin-dependent kinase II
CPE	cytoplasmic polyadenylation element
CPEB	CPE-binding protein
CPSF	cleavage and polyadenylation specificity factor
CREB	cAMP-response-element-binding protein
eIF	eukaryotic initiation factor
FMRP	fragile X mental retardation protein
GABA	γ-aminobutyric acid
LTD	long-term depression
LTP	long-term potentiation
MAP2	microtubule-associated protein 2
mGluR	metabotropic glutamate receptor
NMDA	*N*-methyl-D-aspartate
PSD	postsynaptic density
RAFT1	rapamycin and FKBP12 target 1
UTR	untranslated region

Introduction

Synapses are the pre-eminent mediators of information processing in the nervous system. These remarkable structures utilize a host of morphological and biochemical strategies to accomplish efficient neurotransmission. Synapses also possess a rich capacity for use-dependent modification. Such plasticity is crucial for information processing and storage in the brain. These modifications take place over a vast range of time frames. For example, paired-pulse facilitation is initiated in milliseconds and decays rapidly. The early stages of long-term potentiation (LTP) or long-term depression (LTD) are initiated within seconds to minutes of appropriate synaptic stimulation and (in the absence of new protein synthesis) decay within 1–2 h. Finally, an important class of synaptic modifications can last for days to years — and perhaps even for the life of the individual [1]. These long-term changes in synaptic strength are thought to be the basis for memory storage [2,3].

Although shorter-term synaptic modifications may be brought about by covalent modification of existing proteins, long-lasting changes require new protein synthesis [4–6]. These new polypeptides undoubtedly play a key role in synaptic modification; some of them are likely to be incorporated into the synapses, whereas others may be necessary for transmitting signals to the soma [7,8].

Neurons employ at least three strategies for the activity-dependent regulation of protein synthesis and targeting. First, some proteins are translated in the soma from newly transcribed mRNAs. For example, transcription factors such as CREB (cAMP-response-element-binding protein) and C/EBP (CCAAT enhancer binding protein) are activated in response to particular forms of synaptic stimulation [9]. CREB also plays a key role in the formation of long-term memories in fruit flies [10]. The processes by which such remotely synthesized proteins are delivered to the appropriate synapses are not yet fully understood, but seem likely to involve the creation of 'tags' at the activated synapses [11]. Second, newly transcribed mRNAs may be transported to activated synapses, where they are thought to be translated. This mechanism has been recently described for *Arc*, an immediate-early gene whose transcription is tightly regulated by synaptic activity [12••]. The shunting of mRNAs into the dendritic region is presumably accompanied by concomitant protein synthesis upon their arrival at the appropriate target synaptic region.

A third strategy for achieving activity-dependent regulation of protein synthesis and targeting — which is the focus of this review — is by the regulated translation of mRNAs localized at synapses. This mode is suggested by the observations that dendritic shafts contain polyribosomes, tRNAs, initiation factors, and specific mRNAs [13–15]. As polyribosomes are frequently found at the base of synaptic spines, they may service restricted domains of the synapto-dendritic compartment — even individual synapses. Although several mRNAs are known to be localized to dendrites *in situ*, including those encoding microtubule-associated protein 2 (MAP2), *Arc*, fragile X mental retardation protein (FMRP), and the α subunit of calcium/calmodulin-dependent protein kinase II (α-CaMKII), the total dendritic complement is likely to be far richer. For example, a host of other mRNAs have been identified in the dendrites of cultured neurons [8,16].

Local mRNA translation at synapses

Recent work has established a direct link between local mRNA translation and synaptic plasticity. In an elegant set

of experiments, Kandel and co-workers [7] have shown that protein synthesis inhibitors, when selectively applied to the synapse, block long-lasting, long-term facilitation (L-LTF) in cultured *Aplysia* neurons. In vertebrates, dendritic protein synthesis seems likely to play a role in long-lasting hippocampal L-LTP as well. For example, high-frequency stimulation of hippocampal slices induces localized, NMDA-receptor-dependent α-CaMKII translation in dendrites [17,18•]. Dendritic translation of the mRNA encoding FMRP is stimulated by activation of metabotropic glutamate receptors (mGluRs) [19,20]. Further, a rapid onset, protein-synthesis-dependent, long-lasting synaptic potentiation can be induced by the neurotrophin BDNF (brain-derived neurotrophic factor), even when dendrites are severed from their neuronal soma [21,22]. This form of potentiation is not dependent upon glutamate receptor activation, and its relationship to other forms of long-lasting synaptic modification is currently not known.

Cellular and molecular requirements for local mRNA translation

For mRNA translation to occur at the synapse, the neuron must first target and transport specific mRNAs to the dendrite, then dock or store them in the synapto-dendritic domain, and finally trigger their translation following appropriate synaptic stimulation. mRNA targeting to synapses has been the subject of several recent reviews [23–25]. The targeting signals can reside in either the 3′-untranslated region (UTR) [26] or the 5′ region [27]. Steward and colleagues [12••,28] have shown that some mRNAs are targeted to dendrites in an activity-dependent fashion. Recently, a 640 nucleotide sequence in the 3′UTR of MAP2 has been shown to direct its dendritic localization [29]. At least some targeting mechanisms may involve a mammalian homologue of staufen, a double-stranded RNA-binding protein that is localized to the dendrites in cultured hippocampal neurons [30•]. In *Drosophila*, staufen is required for the proper sorting (or localization) of some maternal mRNAs in the oocyte [31] and in neural precursors [32–34]. Although staufen is a microtubule-binding protein [35,36] — and thus a good candidate for an mRNA transporter — its role in targeting and translational regulation in neurons has yet to be shown. Finally, Bassell and colleagues [37] have recently shown that neurotrophin-3 (NT-3) can promote the targeting of β-actin mRNA to growth cones of neurons in culture. This targeting is specific for the β-isoform of actin and is regulated by cAMP-dependent protein kinase (PKA) activation. Taken together, these data suggest that there are probably several mechanisms involved in the targeting of specific mRNA species to peripheral compartments within neurons.

Until recently, the mechanisms by which dendritic mRNAs become translationally active have been unknown. However, recent data indicate that one key mechanism for such translational regulation employs regulated polyadenylation by CPEB (cytoplasmic polyadenylation element binding protein) [38••]. Our understanding of the role of CPEB in the neuron is based largely on its well-characterized role in oocyte maturation. Therefore, before we discuss how CPEB may regulate local mRNA translation in the brain, we will first review the basic features of cytoplasmic polyadenylation-induced translation in early development (for reviews, see [39,40]).

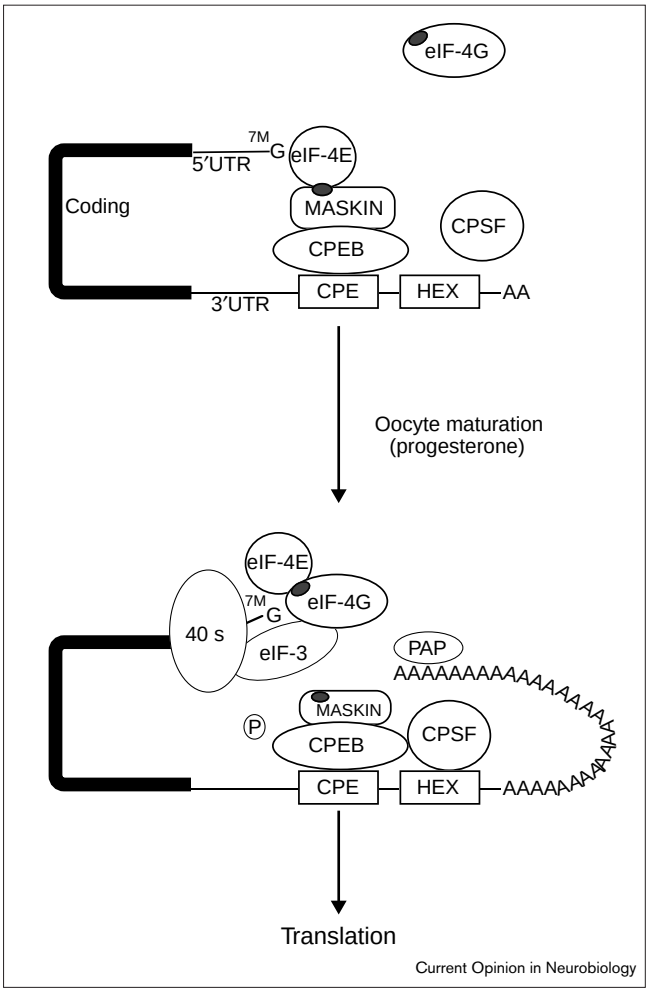
Polyadenylation and control of translation during early development

The oocytes of both vertebrates and invertebrates contain a stockpile of dormant mRNAs that are transcribed during the very long period of oogenesis and then cached in the cytoplasm. Some of these dormant mRNAs have relatively short poly(A) tails; these are usually fewer than ~20–40 nucleotides in length. After oogenesis, when the oocyte resumes meiosis (an event known as oocyte maturation), a subset of these mRNAs undergoes poly(A) tail elongation and translational activation [41–45]. Other mRNAs maintain their short poly(A) tails and remain dormant during maturation, but undergo polyadenylation-induced translation after fertilization [46]. Thus, there are two varieties of polyadenylation, one that is maturation-specific and one that is embryo-specific. For simplicity, we will focus on maturation-specific polyadenylation.

Maternal mRNAs which contain two *cis* elements will undergo cytoplasmic polyadenylation (Figure 1) and subsequent translation. The first *cis* element is the hexanucleotide AAUAAA, a near-ubiquitous sequence that also functions in nuclear pre-mRNA cleavage and polyadenylation. The second is the cytoplasmic polyadenylation element (CPE), whose sequence is UUUUUAU (consensus) and which is found only in select mRNAs. In most mRNAs, the CPE is 10–20 nucleotides upstream of the AAUAAA sequence, which, in turn, is ~20 nucleotides from the beginning of the poly(A) tail. However, the CPE can function when it is immediately adjacent to the AAUAAA sequence, and even when it is up to 100 nucleotides away [43,47,48].

The CPE is bound by CPEB, which is a 62 kDa protein containing two RNA recognition motifs (RRMs), and a zinc finger — all of which are essential for CPE-dependent RNA binding [49]. CPEB, which is constitutively bound to RNA even before the onset of oocyte maturation, is activated by a single phosphorylation event at a time nearly commensurate with the onset of polyadenylation [50]. In *Xenopus*, this phosphorylation is catalyzed by the serine/threonine kinase Eg2. This enzyme, which is homologous to Aurora in *Drosophila*, is the earliest known kinase activated upon the initiation of oocyte maturation [50,51]. The function of this Eg2 phosphorylation is still unclear. One possibility is that it could recruit or stabilize the binding of CPSF (cleavage and polyadenylation specificity factor) to the AAUAAA sequence [52]. CPSF could, in turn, recruit poly(A) polymerase to the end of the mRNA [53,54]. It is the process of polyadenylation that

Figure 1



Model for the CPEB-dependent masking and activation of mRNA translation in oocytes. CPE-containing mRNAs are constitutively bound by CPEB in a complex with maskin, which in turn binds eIF-4E. CPSF may or may not be associated with the hexanucleotide sequence (HEX) prior to activation. In this configuration, mRNA translation is repressed or masked. When oocyte maturation is induced by progesterone, CPEB is phosphorylated and might stabilize the association of CPSF with the hexanucleotide sequence, thus enabling the recruitment of polyadenylation polymerase (PAP) and elongation of poly(A) tails. Polyadenylation may sever the association between maskin and eIF-4E, allowing eIF-4G and eIF-4E to interact. eIF-4G is bound by eIF-3 which directs the small ribosomal subunit on the mRNA. Polyadenylation also triggers 5′ cap methylation, which is another critical step for translation initiation.

initiates mRNA translation. The activation of translation may be the result of ribose methylation of the 5′ cap and the liberation of a sequestered translation initiation factor, eIF-4E (see below).

In a surprising development, the CPE and CPEB have also been shown to participate in the repression of mRNA translation. Although this observation may superficially seem paradoxical, a coherent molecular explanation for the role of this system in both activation and the repression of protein synthesis has emerged. A short poly(A) tail is not sufficient to keep an mRNA in a dormant state in the ooplasm: an intact CPE and associated CPEB is also necessary [55•]. CPEB binds the protein maskin, which, in turn, sequesters the translation initiation factor eIF-4E in such a way that it cannot bind eIF-4G [56]. Because eIF-4E can initiate translation only when it is bound to eIF-4G, the association of CPEB, maskin, and eIF-4E constitutes a 'masking complex' that inhibits mRNA translation. Notably, this repression is restricted to CPE-containing mRNAs. The mechanism of de-repression is not fully understood, but one hypothesis is that polyadenylation liberates eIF-4E and thus allows it to bind to eIF-4G and participate in the initiation of mRNA translation (Figure 1).

CPEB-dependent mRNA translation in the brain

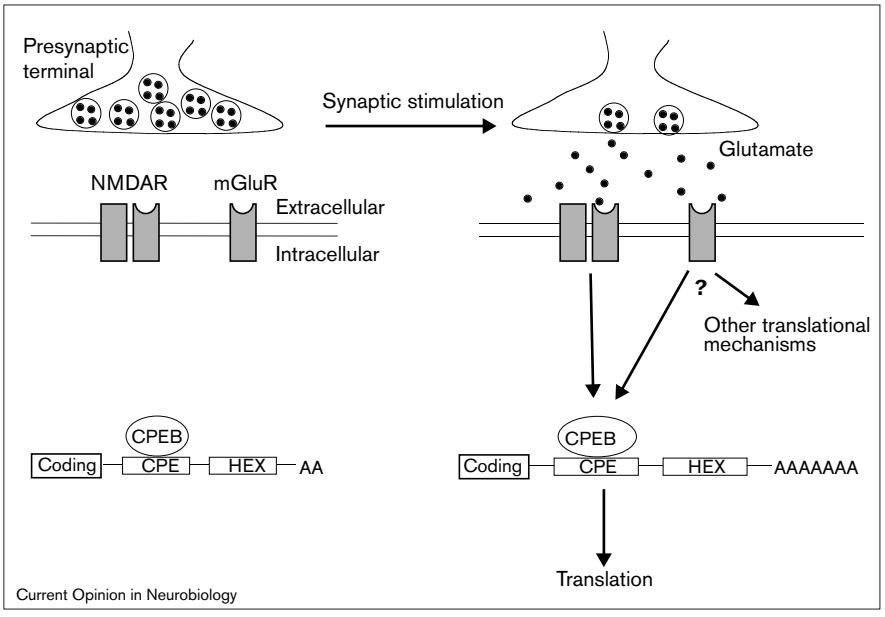
CPEB is highly expressed in the brain [38••], where it is found in the cell body and dendritic layers of the hippocampus, as well in the cerebral cortex and other regions. This sequence-specific mRNA-binding protein is localized at synapses in cultured hippocampal pyramidal neurons and is a component of the postsynaptic density (PSD) fractions isolated from adult CNS [38••]. The 3′UTR of α-CaMKII mRNA contains two CPEs within 100 nucleotides of the hexanucleotide sequence. CPEB binds this 3′UTR in a CPE-dependent manner, and the 3′UTR can regulate protein translation in a CPE-dependent manner in a heterologous system (*Xenopus* oocyte [38••]). α-CaMKII plays a central role in synaptic plasticity, and its mRNA is localized to dendrites [17,57,58]. Taken together, these observations suggest that CPEB-mediated mRNA translation could be important for synaptic modification. Moreover, the association of CPEB with the PSD raises the possibility that it plays a role in the localization of specific mRNAs to synapses.

Experiments using dark-reared rats [59] provide strong evidence that cytoplasmic polyadenylation is important for experience-dependent synaptic plasticity. α-CaMKII mRNA in the visual cortex of dark-reared rats has a relatively short poly(A) tail. Remarkably, these poly(A) tails elongate when the animals are exposed to light for as little as 30 min. This polyadenylation is accompanied by an increase in α-CaMKII protein in synaptic fractions, which is not observed when protein translation is inhibited with cycloheximide [38••]. Moreover, this synthesis of α-CaMKII is reduced in the presence of NMDA receptor antagonists, indicating that synaptic activation is also required for this process [60] (Figure 2).

The mechanism by which synaptic activation leads to the initiation of translation is still unknown. A neurally expressed homologue of Eg2 has yet to be identified. However, a kinase involved in rapamycin-sensitive translation (RAFT1, also known as target of rapamycin [TOR] in yeast) has recently been shown to bind to gephyrin [61••] — a widely expressed protein required for $GABA_A$ and glycine receptor clustering in the spinal cord [62,63].

Figure 2

Synaptic activity induces protein synthesis. In the brain, CPEB is localized to synapses and is enriched in the postsynaptic density fraction. Thus, CPEB could function to localize CPE-containing mRNAs to the synapse. Exposure of dark-reared animals to light induces polyadenylation of α-CaMKII mRNA (which contains two CPEs) and new synthesis of CaMKII protein in the visual cortex. NMDA receptor (NMDAR) antagonists and inhibitors of polyadenylation block this increase. The neural expression of maskin and the molecular mechanism by which mGluR activation leads to protein synthesis have yet to be determined (as indicated by '?').



Both gephyrin and RAFT1 are widely expressed in the brain, as well as most other bodily tissues. Interestingly, RAFT1 and gephyrin are enriched in the synaptosomal (but not the PSD) fraction [61••], indicating that RAFT1 kinase activity could play a role in the signal transduction pathway leading to synapto-dendritic mRNA translation in the brain.

It seems likely that the brain uses other, additional mechanisms to regulate local protein synthesis. One such pathway has been recently proposed for the translational regulation of α-CaMKII in synaptic fractions taken from the superior colliculus. Scheetz and Constantine-Paton [64] have demonstrated an increase in the synthesis of α-CaMKII following glutamate stimulation. The increase in α-CaMKII synthesis is temporally correlated with an increase in the phosphorylation of eukaryotic translation elongation factor 2 (eEF2). One may speculate that the combination of eEF2 phosphorylation with CPEB-mediated polyadenylation allows neurons to rapidly alter synapto-dendritic protein synthesis while regulating translation of specific mRNA species in an activity-dependent fashion.

Conclusions

After a long period of anticipation, a role for local mRNA translation in synaptic plasticity has recently been established. Several pathways have now been shown to trigger such translation, including mGluR-, NMDAR-, and neurotrophin-mediated stimulation. One molecular mechanism that is likely to regulate at least some dendritic protein synthesis is CPEB-mediated cytoplasmic polyadenylation. The task for the future will be to illuminate the links between specific kinds of synaptic activation and translational activation of identified messages, and to then determine the role of these newly synthesized proteins in creating long-lasting modifications in synaptic efficacy.

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