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Regulation and function of local protein synthesis in neuronal dendrites

Changan Jiang and Erin M. Schuman

It has long been shown that protein synthesis can occur in neuronal dendrites, but its significance remained unclear until relatively recently. Studies suggest that local protein synthesis has crucial roles in synaptic plasticity, the change in neuronal communication efficiency that is probably a cellular basis of learning and memory. Induced by neuronal activity, local protein synthesis provides key factors for the modification of activated synapses. In this review, we summarize the evidence for local protein synthesis and its functions in synaptic plasticity. We also discuss the molecular mechanisms by which neuronal activity induces the synthesis of proteins that allow for changes in synaptic function.

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Synapses are the major mediators of neuronal communication in nervous systems. With thousands of them present in a single cell, they connect all the neurons in an animal into a powerful information-processing network. Far from passively relaying signals from a presynaptic neuron to a postsynaptic neuron, a synapse constantly modifies its transmission efficiency based on its recent history. This amazing ability, called synaptic plasticity, probably forms the cellular basis of learning and memory [1,2].

Electrical activation of a synapse can change its function. Two major forms of enduring plasticity are long-term potentiation (LTP) and long-term depression (LTD), which represent increases or decreases in transmission efficiency, respectively. Both LTP and LTD have different temporal phases with distinct molecular requirements. The short-lasting forms of plasticity result primarily from the modification of pre-existing proteins at the synapse, whereas the long-lasting forms require new protein synthesis in the postsynaptic neuron [3]. It has long been held that proteins are synthesized in the cell body and delivered to the activated synapses (Fig. 1a and 1b), but recent evidence suggests that proteins can also be synthesized locally near

synaptic sites [4] (Fig. 1c). In this review, we first summarize the evidence for local protein synthesis triggered by synaptic activity. Next, we focus on its functions in synaptic plasticity, as revealed by studies in mollusks and mammals. Finally, we will discuss the molecular mechanisms by which activity induces local protein synthesis.

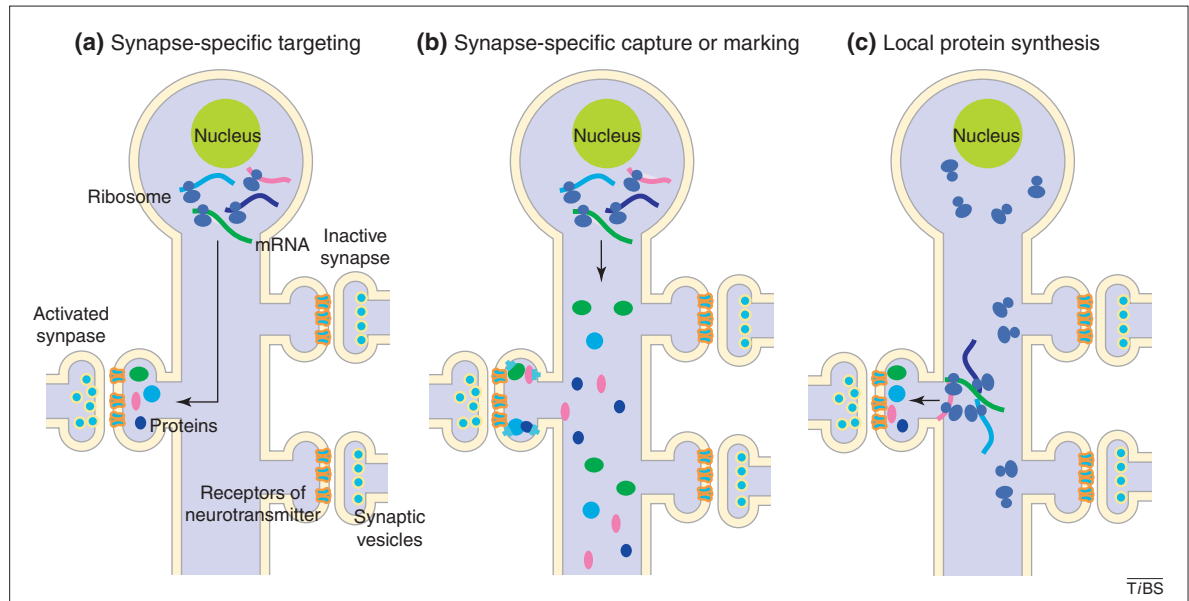
Evidence of local protein synthesis

The idea of local protein synthesis began with the observation that ribosomes are present in neuronal dendrites. This phenomenon was first studied in 1965 [5], but its significance was not fully appreciated until 1982, when Steward and Levy discovered the preferential localization of ribosomal clusters at the bases of dendritic spines in rat central nervous system (CNS) neurons [6]. As they are with membranous cisterns during membrane protein synthesis in neurons, these polyribosomes provided the first strong indication of ongoing translation in the dendrites. More importantly, the high selectivity of their location led these investigators to speculate further that the synthesized proteins might be key components of synapses and their synthesis was regulated by synaptic activity.

In past twenty years, the local protein synthesis hypothesis has received increasing experimental support. Detailed immunohistochemical analysis indicates the presence of virtually every component of translation machinery in the dendrites, including rRNAs, translational factors, endoplasmic reticulum (ER) and Golgi apparatus [7–9]. At the same time, mRNAs from the dendrites have been isolated and their identities have provided clues to the functions of local protein synthesis. *In situ* hybridization analysis has confirmed the presence of more than a dozen mRNAs in the dendrites of different rodent neurons

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Fig. 1. Models for synaptic activity-induced protein synthesis in postsynaptic neurons. (a) Synapse-specific targeting. Synaptic activity induces the translation of plasticity-related mRNAs in the cell body. The synthesized proteins are specifically trafficked to the activated synapse. (b) Synapse-specific capture or marking. Synaptic activity induces the translation of plasticity-related mRNAs in the cell body. The synthesized proteins are transferred to the dendrites and captured only by the activated synapse. (c) Local protein synthesis. Synaptic activity induces the translation of plasticity-related mRNAs locally in the dendrite and the synthesized proteins are used at the activated synapse.



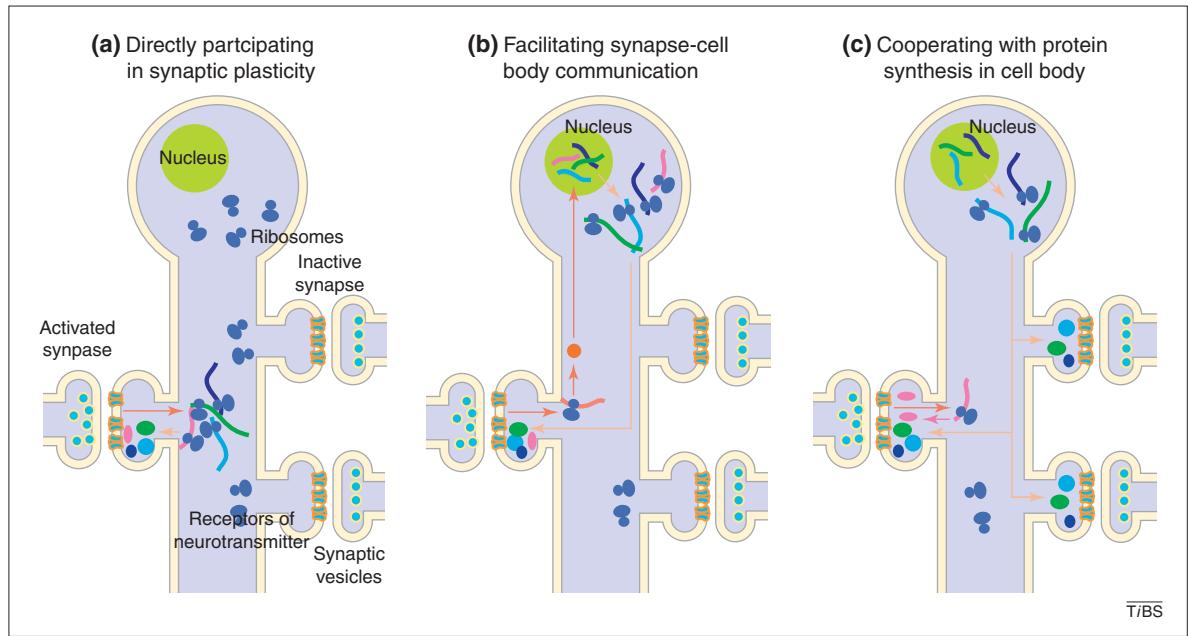
(reviewed in Ref. [10]). As predicted by Steward and Levy, some proteins encoded by these mRNAs regulate synaptic function. For example, *NR1* mRNA encodes a subunit of the *N*-methyl-D-aspartate receptor (NMDAR) [11,12], which is a receptor of the CNS neurotransmitter glutamate and is essential for the induction of major forms of LTP and LTD [13,14]. *CaMKII α* mRNA encodes the α subunit of Ca^{2+} /calmodulin-dependent protein kinase II, which has crucial roles in activity-induced LTP [15,16], partly through phosphorylating glutamate receptors [17]. *Arc* mRNA encodes a cytoskeleton-associated synaptic protein that is required for the maintenance of LTP in the hippocampus [18]. Also found in the dendrites of cultured hippocampal neurons are the mRNAs for brain-derived neurotrophic factor (BDNF) and its receptor TrkB [19]. Activation of TrkB by BDNF is a key step in the induction of LTP [20,21]. In fact, the application of BDNF can potentiate synaptic transmission in hippocampal slices [22]. Significant insights have also been gained from studies of the transport of these mRNAs to the dendrites. *Cis*-elements required for dendritic targeting have been identified in mRNAs, including *CaMKII α* , suggesting the existence of sophisticated mechanisms to selectively transport mRNAs to the dendrites for local protein synthesis [23–25].

Local protein synthesis can be stimulated by synaptic activity. In an early experiment using hippocampal slices, Feig and Lipton used [3 H]leucine to label newly synthesized proteins and found that electrical stimulation increased translation in the dendrites but not in the cell body [26]. To monitor the synthesis of specific proteins, another experimental preparation, the synaptosomes, has been combined with western blot analysis to study local protein synthesis. Like the related preparations synaptodendrosomes and synaptoneurosome, synaptosomes are prepared by subcellular

fractionation of brain tissues. These fractions contain resealed synapses and other dendritic constituents, including ribosomes and mRNAs, thus they can be used as a reduced preparation to study local protein synthesis. Several studies have shown that synaptic stimulation can activate protein synthesis in synaptosomes. For example, depolarization of synaptosomal membranes with a high concentration of K^+ increases the synthesis of CaMKII α [27], whereas BDNF application increases the synthesis of Arc [28]. However, this system does have two drawbacks. First, synaptosomes can be easily contaminated with fragments of neuronal and glial cell bodies; thus, the protein synthesis observed might include the translation of mRNAs of non-dendritic origins. Second, given the destructive preparation process, it is probable that some signaling pathways are not well preserved in the synaptosomes; as such, the regulatory mechanisms observed in synaptosome experiments might not be identical to those *in vivo*.

Recent use of green fluorescent protein (GFP)-based protein synthesis reporters holds the promise to solve synaptosome-related problems. This approach offers at least two advantages. First, properly designed, the reporter can faithfully mimic the translation of most dendritic mRNAs. For example, Aakalu *et al.* flanked the destabilized GFP coding sequence with the 5'- and 3'-untranslated regions (UTRs) of *CaMKII α* mRNA to reproduce its dendritic targeting and translational regulation [4]. Second, it allows visualization of protein synthesis in real time by confocal or two-photon microscopy. By expressing the CaMKII α reporter in cultured hippocampal neurons, Aakalu *et al.* demonstrated that BDNF application induced protein synthesis in both physically dissected dendrites and dendrites whose cell body was photobleached. Job *et al.* used a different experimental system, which involved transfecting dissected dendrites with GFP mRNA, to

Fig. 2. Functions of local protein synthesis in synaptic plasticity. (a) Directly participating in synaptic plasticity. In response to synaptic activity, plasticity-related proteins are synthesized locally in the dendrite. They are transferred to the activated synapse and are required for the induction of long-lasting synaptic enhancement or depression. (b) Facilitating synapse-cell body communication. Synaptic activity triggers the local synthesis of retrograde signaling protein(s), which induce the transcription of plasticity-related genes in the postsynaptic neuron. The plasticity-related proteins are synthesized in the cell body and trafficked back to the activated synapse to induce long-lasting changes in synaptic transmission. (c) Cooperating with protein synthesis in cell body. Synaptic activity induces protein synthesis both in the dendrite and in the cell body. These new proteins cooperate to induce synaptic plasticity at the activated synapse.



show that activation of group I metabotropic glutamate receptors (mGluRs) induced protein synthesis in the dendrites [29].

The GFP-based CaMKII α reporter was also modified to determine the subcellular sites at which protein synthesis occurs. Conventional GFP is not an ideal reporter for these studies because it tends to diffuse away from the sites of its synthesis. To mitigate this problem, Aakalu *et al.* attached a canonical myristoylation signal to the GFP coding sequence. When expressed in neurons, the GFP was myristoylated and targeted to the membrane system nearby. Photobleaching experiments indicated that the diffusion of the myristoylated reporter was markedly reduced and thus it could faithfully represent the sites of its synthesis. In neurons expressing this modified CaMKII α reporter, GFP signals were often concentrated at spatially distinct and temporally stationary hot spots along the dendrites. To determine whether these hot spots represent the translationally active sites near the synapses, Aakalu *et al.* immunolabeled the neurons with an antibody against rRNA, the postsynaptic protein PSD95, or the presynaptic protein synapsin I. In each case, they observed a pair-wise correlation between the signals of GFP and those of the ribosomal or synaptic markers, suggesting that most reporter protein was indeed synthesized by ribosomes located in the vicinity of synapses [4].

Functions of local protein synthesis in synaptic plasticity

Theoretical speculation on the functions of local protein synthesis has been abundant. One major argument for going local is that it greatly simplifies the task of targeting newly synthesized proteins to the activated synapses, the sites that need them to induce plasticity. By keeping the protein synthesis

machineries nearby, each synapse can operate as an autonomous entity and change its transmission efficacy independent of others. Early support came from a study on rodent hippocampus, where neurotrophin-induced local protein synthesis was required for synaptic potentiation [30]. Kang and Schuman discovered that application of BDNF or neurotrophin 3 (NT-3) to hippocampal slices induced a long-lasting potentiation. Unlike electrical stimulation-induced LTP, this form of plasticity requires protein synthesis for its initiation. More interestingly, the protein-synthesis dependence persisted even after the cell bodies of presynaptic and postsynaptic neurons were severed from their dendrites, strongly arguing that neurotrophins induced synaptic potentiation by triggering protein synthesis locally in the dendrites (Fig. 2a).

Studies on long-term facilitation (LTF), a type of synaptic enhancement observed in *Aplysia* neurons, have revealed more subtle functions of local protein synthesis. Using a three-cell culture system, which consists of a bifurcated sensory neuron forming synapses with two motor neurons, Martin *et al.* examined the 'capture' of two forms of LTF [31,32]. In one set of experiments, serotonin, a modulatory neurotransmitter for sensory neurons, was applied to a first synapse to produce long-lasting LTF. This increase in synaptic strength could be 'captured' by the second synapse if the latter was treated with a single pulse of serotonin, which by itself produced only short-lasting facilitation. Formation of the synapse-specific LTF in the first neuron had an early requirement for local protein synthesis, but in contrast to neurotrophin-induced synaptic potentiation, it also required transcription in the cell body. Thus in this system, local protein synthesis itself is not sufficient to induce LTF. Instead, the newly synthesized protein(s) appears to facilitate the

interaction between the stimulated synapse and the cell body [31]. One intriguing possibility is that the locally synthesized protein(s) serves as a retrograde signal to induce transcription in the nucleus (Fig. 2b). In the second set of experiments, serotonin was repeatedly applied to the cell body of the sensory neuron to induce cell-wide LTF, which was 'captured' by each synapse and lasted 24 h. Application of a single pulse of serotonin to a synapse consolidated this 24-h LTF to 72-h LTF in a synapse-specific and local protein synthesis-dependent manner [32]. Again, in this system, local protein synthesis plays a modulatory role in long-lasting LTF. The mechanism of LTF prolongation is still a matter of speculation. A leading hypothesis is that certain plasticity-related proteins are only synthesized locally or have to be synthesized locally to be functional. If this is true, results from this study indicate that proteins made in the dendrites can cooperate with those made in the cell body to mediate long-lasting changes in synaptic transmission (Fig. 2c). A similar function of local protein synthesis has been observed in acutely dissected *Aplysia* ganglia neurons [33].

Local protein synthesis also has an important role in some forms of LTD. Bath application of a group I mGluR agonist, 3,5-dihydroxyphenylglycine (DHPG), to rodent hippocampal slices reliably induces LTD [34]. This 'chemical LTD' requires new protein synthesis, and removal of cell bodies does not perturb its formation, suggesting that it is dependent on proteins made in the dendrites but not those from the cell bodies. A similar form of LTD can be induced by activating mGluRs with electrical stimulation in a synapse-specific fashion, arguing that LTD-related proteins were synthesized locally, near the activated synapses [34]. A different study showed that DHPG treatment can also change an electrically-induced weak and decaying LTP into a long-lasting form of potentiation. This 'priming' effect was also group I mGluR- and protein synthesis-dependent [35]. Future work will determine whether it is achieved through local protein synthesis.

Regulation of local protein synthesis

The functional diversity of local protein synthesis suggests that different types of synaptic stimulation might induce the synthesis of unique sets of proteins. This requires a precise control of translation in the dendrites. Three features of translational regulation by synaptic activity are emerging from recent studies. First, translation activation is achieved through a combination of different mechanisms, including the mRNA-specific mechanisms, which affect the availability or translatability of individual mRNAs, and non-specific mechanisms, which affect the efficiency of the translation machinery. Second, translation of at least some mRNAs is regulated by multiple mechanisms. Finally, a given synaptic stimulation can induce translation through multiple mechanisms. While the molecular details

underlying these features remain largely unclear, the examples discussed below illustrate the precision and complexity of translational regulation in the dendrites.

Studies on *Aplysia* neurons suggest that synaptic activity could induce local protein synthesis through a rapamycin-sensitive signaling pathway [32]. The key player in this pathway is a protein kinase called target of rapamycin (TOR), whose activities can be blocked by rapamycin [36]. Activation of TOR by neurotransmitters increases protein synthesis by two mechanisms (Fig. 3a). First, it facilitates translation initiation by releasing the inhibition of eukaryotic initiation factor 4E (eIF4E), a crucial initiation factor in cap-dependent translation. Second, it activates p70 S6 kinase and promotes the translation of mRNAs containing a 5' terminal oligopyrimidine tract (5'TOP). In *Aplysia* sensory neurons, the rapamycin-sensitive pathway is required for serotonin-induced stabilization of cell-wide LTF in individual synapses. Metabolic labeling shows that ~60% of serotonin-induced local protein synthesis is rapamycin-sensitive, indicating that this pathway regulates the translation of a subset of dendritic mRNAs [32]. Recently, Tang *et al.* showed the presence of a similar pathway in the dendrites of hippocampal neurons [37]. Its significance in mammalian synaptic plasticity is supported by the fact that both electrical stimulation- and BDNF-induced long-lasting potentiation were rapamycin-sensitive [37]. However, it remains to be determined whether this rapamycin-sensitive pathway-dependent protein synthesis occurs in the dendrites or in the cell bodies.

Translation elongation has also been proposed as a regulatory target for local protein synthesis. Using synaptosomes prepared from rat superior colliculus, Scheetz *et al.* found that activation of NMDAR rapidly increased the phosphorylation of eukaryotic elongation factor 2 (eEF2), a process known to reduce the speed of peptide chain elongation. As in other cell types, eEF2 phosphorylation appears to have paradoxical effects on protein synthesis in synaptosomes. Three minutes after NMDAR activation, the rate of total protein synthesis decreased by 35% while that of CaMKII α synthesis increased by more than 50%. This effect is mimicked by the addition of low concentrations of cycloheximide, which partially inhibits the elongation step of translation, suggesting that the increased CaMKII α synthesis was a result of translation pausing following eEF2 phosphorylation [38] (Fig. 3b). Although direct evidence supporting this hypothesis is still lacking, these results provide a tentative explanation for the stimulation-induced shifts in protein expression observed in neurons [39]. Interestingly, it has long been known that sub-maximal inhibition levels of cycloheximide activate TOR [40], which potentially induces the translation of 5'TOP-containing transcripts. Given the highly similar effects of NMDAR activation and cycloheximide treatment on

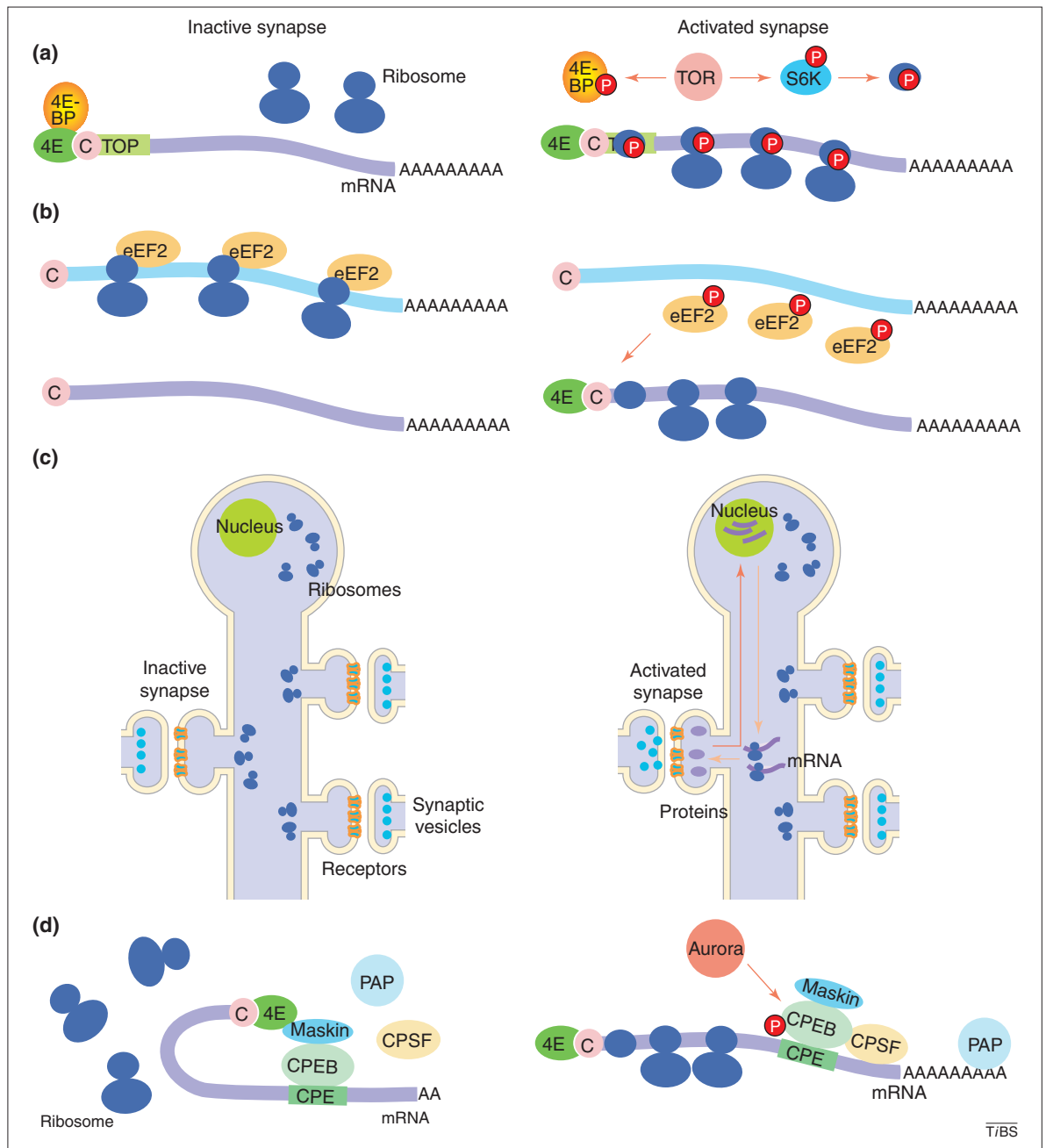


Fig. 3. Mechanisms by which synaptic activity induces local protein synthesis. (a) Induction of local protein synthesis through rapamycin-sensitive signaling pathway. Synaptic stimulation activates target of rapamycin protein (TOR), which leads to the phosphorylation of eukaryotic translation initiation factor 4E (eIF4E)-binding protein (4E-BP) and the activation of P70 S6 kinase (S6K). Phosphorylated 4E-BP releases eIF4E for translation initiation. The activated S6K phosphorylates S6 protein in the ribosome and facilitates the translation of 5'TOP-containing mRNAs. (b) Induction of local protein synthesis through the phosphorylation of eukaryotic elongation factor (eEF2). Synaptic stimulation triggers the phosphorylation of eEF2. The phosphorylated eEF2 dissociates from the translating ribosomes and causes a pausing of ongoing translation. Through unknown mechanisms, this induces the translation of plasticity-related mRNAs.

(c) Induction of local protein synthesis through synapse-specific targeting of plasticity-related mRNAs. Synaptic stimulation induces the transcription of plasticity-related mRNAs. These mRNAs are specifically targeted to the activated synapse and locally translated. (d) Induction of local protein synthesis through polyadenylation of plasticity-related mRNAs. In unstimulated synapses, translation of mRNAs containing cytoplasmic polyadenylation elements (CPEs) is indirectly repressed by CPE-binding protein (CPEB). Synaptic stimulation activates the protein kinase Aurora, which phosphorylates CPEB. By interacting with the cleavage and polyadenylation specific factor (CPSF), the phosphorylated CPEB recruits poly(A) polymerase (PAP) to the mRNA it binds. Elongation of the poly(A) tail by PAP might facilitate the dissociation of maskin, a CPEB-associated translation inhibitor, from eIF4E and result in translation initiation.

synaptosomal protein synthesis, it is tempting to hypothesize that eEF2 phosphorylation increases the translation of *CaMKII α* mRNA through the rapamycin-sensitive pathway.

Local protein synthesis can also be regulated in an mRNA-specific manner. An effective way to confine the synthesis of an individual protein to a subcellular domain is to control the availability of its mRNA.

Steward *et al.* found that the mRNA of *Arc*, whose transcription was induced by synaptic stimulation, was selectively targeted to the activated postsynaptic regions of dendrites [41] (Fig. 3c). This was followed by an increase of Arc protein in the same dendritic sites, suggesting that the protein was synthesized through local translation of the targeted mRNA [41,42]. Consistent with this interpretation, a recent study showed that BDNF treatment increased the synthesis of Arc protein in synaptosomes [28]. As elegant as it is, mRNA targeting does not seem to be a major mechanism for controlling local protein synthesis, at least during the early stages of plasticity. Among the mRNAs identified in the dendrites, *Arc* represents an exception rather than a general rule. However, it should be noted that the dendritic mRNAs identified so far might be the abundant ones. It is possible that mRNA targeting serves as an efficient regulatory mechanism to control the translation of less abundant mRNA species in the dendrites.

Another widely used mechanism for controlling the translation of individual mRNAs is cytoplasmic polyadenylation. The length of the poly(A) tail on an mRNA often affects its translatability, with a long tail promoting its translation and a short one suppressing its translation [43]. A common feature among the mRNAs that are regulated by polyadenylation is short sequences at their 3'UTRs called cytoplasmic polyadenylation elements (CPEs) [44]. In dormant CPE-containing mRNAs, these elements are occupied by CPE-binding protein (CPEB), which represses the function of eIF4E through another protein, maskin [45]. The induction of polyadenylation is controlled by Aurora, a protein kinase that phosphorylates CPEB. The phosphorylation converts CPEB into a translation activator [46]. Through interacting with cleavage and polyadenylation specificity factor (CPSF), phosphorylated CPEB recruits poly(A) polymerase (PAP) and thereby elongates the poly(A) tail of the mRNA it binds [47]. At the same time, maskin dissociates from eIF4E, allowing translation initiation (Fig. 3d). Two putative CPEs have been identified in the 3'UTR of *CaMKII α* mRNA [48]. They are required for activity-induced *CaMKII α* synthesis in cultured hippocampal neurons [49]. Recently, in a more detailed study, Huang *et al.* showed the presence of CPEB, Aurora, maskin, CPSF and PAP in synapses. In synaptosomes prepared from cultured hippocampal neurons, activation of NMDAR significantly increased Aurora activity and led to the phosphorylation of CPEB and the polyadenylation of *CaMKII α* mRNA. Surprisingly, synaptosomes prepared directly from rodent hippocampi often contained *CaMKII α* mRNA molecules with long poly(A) tails and NMDAR activation did not trigger further elongation [50]. This high basal polyadenylation level might simply reflect the high NMDAR activity *in vivo*, but it has

raised an important question about the function of polyadenylation in local protein synthesis. As a significant fraction of dendritically localized mRNA molecules are kept in a translationally dormant state inside RNA granules [39], this result suggests that a long poly(A) tail by itself might not be sufficient to induce translation. Therefore, cytoplasmic polyadenylation might only play a permissive role in activity-induced *CaMKII α* synthesis in living animals.

Progress has also been made in our understanding of how synaptic stimulation activate translational regulation mechanisms. Using pharmacological approaches, Takei *et al.* examined the roles of BDNF-activated signaling pathways in protein synthesis [51]. In neurons, BDNF promotes translation initiation through phosphorylation of eIF4E and its inhibitor, eIF4E-binding protein (4E-BP). Two signaling pathways, the phosphoinositide 3-kinase (PtdIns 3-kinase) pathway and the mitogen-activated protein kinase (MAPK) pathway, are required for this process. Inhibition of the PtdIns 3-kinase pathway blocks BDNF-induced activation of TOR and thus the phosphorylation of 4E-BP, while inhibition of the MAPK pathway blocks the phosphorylation of eIF4E. These results exemplify the cooperation of multiple signaling pathways in inducing protein synthesis. As BDNF activates MAPK, and possibly PtdIns 3-kinase, in the dendrites [52], it might induce local protein synthesis by a similar mechanism.

Conclusions and perspectives

Studies in *Aplysia* and rodent neurons have provided strong evidence that synaptic activity can induce protein synthesis locally in the dendrites. In synaptic plasticity, local protein synthesis has been proposed to have at least three different roles: directly participating in long-term synaptic enhancement and depression, facilitating synapse-cell body communication, and consolidating long-term synaptic changes, possibly through cooperating with protein synthesis in the cell body (Fig. 2). To selectively synthesize the proteins needed to perform these functions, synaptic activity probably induces the translation of dendritic mRNAs through a combination of regulatory mechanisms.

Despite these rapid advances, some key questions have not been addressed because of technical difficulties. For example, the induction of local protein synthesis, as well as its functions in learning and memory, has not been demonstrated convincingly in living animals. Furthermore, although there are hints about the physiological functions of local protein synthesis, the proteins that perform these functions have not been identified. Lastly, the signaling pathways that mediate activity-induced local protein synthesis have not been fully characterized. Undoubtedly,

progress in this field will greatly benefit from new technological developments, as it has in past twenty years. A few innovations will be especially useful because they address the special difficulties encountered in studying local protein synthesis. First, to identify dendritically located mRNAs, an efficient method is needed for the mass isolation of pure dendrites. Significant progress has been made by Poon and Martin (*Soc. Neurosci. Abstr.* 2001). Second, a technique to inhibit protein synthesis in a selected subcellular area would be valuable for studying the functions of local protein synthesis. Third, a method to specifically isolate the actively translating mRNA species would allow the identification of proteins synthesized locally in response to different synaptic stimulations. Combined with tools currently available, these innovations could potentially provide a technical foundation for comparative analysis of local protein synthesis in different organisms. Such studies would reveal whether the distinct physiological functions and regulatory mechanisms we currently see in mollusks and mammals represent evolutionary divergence or simply reflect our limited knowledge in this field.

An area that has not had much attention is the basal protein synthesis in neuronal dendrites. Translation has been observed in unstimulated synaptosomes and dendrites, but it has not been carefully studied. One potential function of basal translation is the maintenance of synaptic plasticity. Activity-induced local protein synthesis is often transient. Alterations in dendritic basal protein synthesis could allow enduring changes in synaptic strength. Interestingly, synaptic activity has been shown to induce the local synthesis of translational regulators, which might affect the efficiency or mRNA-selectivity of subsequent basal translation in the same synapse. For example, activation of group I mGluRs in synaptosomes leads to the synthesis of fragile X mental retardation protein (FMRP) [53], a RNA-binding protein that regulates translation in both cell body and dendrites [54,55]. If this also occurs *in vivo*, an increase in local FMRP concentration might significantly alter the profile of basal translation and contribute to the maintenance of mGluR-dependent LTD. We expect that identification of more locally synthesized translational regulators, as well as their target dendritic mRNAs, will greatly advance our understanding of basal protein synthesis in neuronal dendrites.

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