

Dendritic mRNA: transport, translation and function

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Abstract | Many cellular functions require the synthesis of a specific protein or functional cohort of proteins at a specific time and place in the cell. Local protein synthesis in neuronal dendrites is essential for understanding how neural activity patterns are transduced into persistent changes in synaptic connectivity during cortical development, memory storage and other long-term adaptive brain responses. Regional and temporal changes in protein levels are commonly coordinated by an asymmetric distribution of mRNAs. This Review attempts to integrate current knowledge of dendritic mRNA transport, storage and translation, placing particular emphasis on the coordination of regulation and function during activity-dependent synaptic plasticity in the adult mammalian brain.

Postsynaptic density (PSD). An electron dense complex that is located at the synaptic membrane of a postsynaptic cell. The PSD contains transmembrane proteins, such as neurotransmitter receptors, as well as intracellular signalling molecules.

Ribonucleoprotein particle (RNP). A transport granule that contains mRNA, mRNA-binding proteins, motor proteins and small, non-coding RNA (also known as microRNA).

Lasting activity-dependent changes in synaptic strength depend on new protein synthesis and the growth or remodelling of excitatory synapses. The dendritic tree of a typical projection neuron in the adult mammalian brain contains approximately 10,000 dendritic spines, onto each of which is formed a single excitatory synapse. As a discrete structural, physiological and biochemical compartment, dendritic spines afford a necessary degree of autonomy during information processing and storage. The discovery of mRNA, ribosomes and translation factors in dendrites, and even in the dendritic spines themselves, suggested that synapses could be modified directly — and perhaps individually — through regulation of local protein synthesis^{1,2}.

Although numerous (possibly several hundred) mRNA species are distributed in the dendrites of cultured neurons, far fewer such dendritic mRNAs have been experimentally confirmed in adult non-cultured neurons. TABLE 1 lists some of the dendritic mRNAs for which key regulatory features are known. Different neurons express different sets of dendritic mRNAs, and some transcripts appear to be unique to a specific class of neuron. As the postsynaptic density (PSD) of excitatory synapses consists of more than 300 different proteins assembled into elaborate complexes, it is not surprising that dendritic mRNAs encode a diverse array of proteins, including neurotransmitter receptors, scaffolding proteins and signal transducing enzymes. More unexpectedly, dendrites also contain mRNA for secretory proteins, such as tissue plasminogen activator (tPA) and matrix metalloproteinase 9 (MMP9).

This Review highlights recent advances in our understanding of the mechanisms of mRNA transport, localization and translation in dendrites. Particular emphasis is placed on the regulation and coordination of these mechanisms, and on the function of dendritic protein synthesis in activity-dependent synaptic plasticity in the adult mammalian brain, using long-term potentiation (LTP) and long-term depression (LTD) as examples.

Transport and localization

That mRNA can distribute into both neuronal axons and dendrites is well established. However, the mechanism by which specific mRNAs are transported is still largely a mystery. What is evident is that the process of mRNA localization in neuronal dendrites is complex, and involves multiple mRNA binding proteins and at least three types of RNA-containing granules: ribonucleoprotein particles (RNPs), stress granules (SGs) and processing bodies (PBs)^{3,4} (BOX 1). A model for mRNA transport and localization in neurons is emerging (FIG. 1). Not every step in this process has been verified for any single mRNA; rather, the model is a composite of data that have been generated from multiple different mRNAs. However, our confidence in the model is bolstered by findings that show similar mechanisms acting in non-neuronal cells⁵. Indeed, much of the molecular workings of mRNA transport and translation in neurons were gleaned from findings in non-neural cells.

It is widely accepted that most mRNAs are transported into dendrites as part of large RNPs. Although not proven, it is thought that the mRNAs are

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doi:10.1038/nrn2150

Published online

12 September 2007

Table 1 | Neurotransmitter-regulated dendritic mRNAs in mammalian neurons

Dendritic mRNA	RNA binding proteins/IRES	Neurotransmitter regulation			References
		NMDAR	mGluR	BDNF	
β -Actin	ZBP1	Increased dendritic transport	NA	Increased dendritic transport	11,12
Arc	IRES	Increased dendritic transport	NA	Increased dendritic transport and increased translation	28,29,40,53,121
α CaMKII	CPEB1, FMRP, RNG105, IRES	Increased translation	Increased dendritic transport	Increased translation	35,42,45,70,73,161
eEF1A	FMRP	NA	Increased translation	NA	59
FMR1	FMRP, CPEB1, IRES	NA	Increased dendritic transport and increased translation	NA	80,90
GluR1	NA	NA	Increased translation	NA	162
GluR2	CPEB3	NA	Increased translation	NA	64,162, 163
InsP3R	Hzf	NA	NA	Increased translation	164
LIMK1	NA	NA	NA	Increased translation	96
tPA	CPEB1	NA	Increased translation	NA	74

Known RNA-binding proteins for these mRNAs are listed, but only a few studies have linked neurotransmitter regulation to specific RNA-binding proteins. Several dendritic mRNAs also contain internal ribosomal entry sites (IRES), but the use of IRES-mediated translation in dendritic protein synthesis has not been shown. α CaMKII, calcium/calmodulin-dependent protein kinase II (α -subunit); Arc, activity-regulated cytoskeleton-associated protein; BDNF, brain-derived neurotrophic factor; CPEB1, cytoplasmic-polyadenylation-element-binding protein 1; eEF1A, eukaryotic translation elongation factor 1A; FMRP, fragile-X mental retardation protein; Hzf, hematopoietic zinc finger; InsP3R, inositol 1,4,5-trisphosphate receptor; LIMK, Lim-domain kinase 1; mGluR, metabotropic glutamate receptor; NA, not applicable; NMDAR, N-methyl-D-aspartate receptor; RNG105, RNA granule protein 105; tPA, tissue plasminogen activator; ZBP1, zip-code-binding protein 1.

transported in a translationally dormant state. Therefore, in order for specific mRNAs to be dendritically targeted, they must first be sequestered from the translational machinery in the cytoplasm and organized into RNPs. The sequestration from translation is likely to start in the nucleus, with the binding of proteins that will remain bound to the mRNA on its journey out of the nucleus and into the dendrite. Consistent with this model, eukaryotic translation initiation factor 4AIII (*eIF4AIII*), a protein that is involved in pre-mRNA splicing in the nucleus, was recently shown to be associated with dendritic mRNA encoding fragile-X mental retardation protein (*FMRP*) and the activity-regulated cytoskeleton-associated protein (*Arc*; also known as *Arg3.1*) (REF. 6). Because *eIF4AIII* would be removed from the mRNA by the first ribosome to read the transcript, this suggests that these dendritic mRNAs have not been previously translated. Although the molecular mechanisms that are involved in mRNA sequestration and transport into dendrites are still largely unresolved, several steps in the regulation of β -actin mRNA by the RNA-binding protein zip-code-binding protein 1 (*ZBP1*) have been elucidated. The most extensively studied example of this process is the localization of *ASH1* mRNA in yeast⁷, however, β -actin mRNA transport into neuronal growth cones is also well established, and β -actin mRNA also localizes to synapses⁸, raising the possibility that a similar process is occurring in dendrites. *ZBP1* associates with β -actin mRNA in the nucleus at presumptive sites of transcription⁹, and this interaction is capable of inhibiting mRNA translation¹⁰. *ZBP1* protein and β -actin mRNA colocalize in individual dendritic RNPs¹¹, and either interfering with *ZBP1*'s ability to bind a 54-nucleotide *cis*-element (a zip-code) or knocking down *ZBP1* protein in neurons

reduces the localization of β -actin mRNA to the axon and dendrites^{8,12}. Together these data are consistent with a model in which *ZBP1* binding of β -actin mRNA in the nucleus induces both translational silencing of the mRNA and its incorporation into RNPs.

Given these findings, one would expect a high degree of colocalization of *ZBP1* and β -actin mRNA in dendrites. Surprisingly, only ~50% of the RNPs that contain β -actin mRNA colocalize with *ZBP1*, and only ~30% of the *ZBP1*-containing RNPs colocalize with β -actin¹¹. This clearly suggests that RNA-containing granules do not all have the same composition. Indeed, as mentioned above, there are at least two other RNA-containing granules in dendrites: SGs and PBs^{3,13}. The relationship between transport RNPs, SGs and PBs is not currently understood, but these granules are thought to be functionally distinct (BOX 1). However, in rat hippocampal neurons, few SGs or PBs are detected unless metabolic stress is induced¹³. Therefore, the vast majority of RNA-containing granules under normal conditions are likely to be transport RNPs and, thus, transport RNPs in neurons are likely to be diverse.

Composition of neuronal transport RNPs. Two recent studies attempted a molecular characterization of RNPs that were isolated from neural tissue^{14,15}. The first study made use of the interaction of transport RNPs with the conventional kinesin KIF5 to isolate large RNA-containing granules from the adult mouse brain and hence restrict the characterization to only transport RNPs¹⁵. The speed of RNP movement in dendrites and the sensitivity of RNPs to microtubule depolymerizing drugs had previously implicated microtubule motor proteins in the transport of RNPs in dendrites⁴. The KIF5 granules contained at least two dendritically targeted mRNAs — one encod-

Stress granule

A dense cytosolic protein and RNA aggregation that appears under conditions of cellular stress. The RNA molecules are thought to be stalled translation pre-initiation complexes.

Processing body

A cytoplasmic structure that is thought to be the site of mRNA degradation.

Kinesins

Molecular motor proteins that transport cargoes in one direction along microtubules. For movement in the opposite direction, another motor protein, dynein, is used.

Heterogeneous nuclear ribonucleoproteins

(hnRNPs). A large family of RNA-binding proteins that are involved in RNA regulation and metabolism. Examples of hnRNPs that have been implicated in dendritic mRNA processing include ZBP1, FMRP and hnRNP A2.

Polyribosome

A functional unit of protein synthesis comprised of several ribosomes attached along the length of an mRNA molecule.

Synaptodendrosome

A biochemical fraction that is enriched in pinched-off, resealed axon terminals that are connected to pinched-off, resealed dendritic spines. They are commonly prepared by a two-step ultracentrifugation through a sucrose gradient.

ing the α -subunit of calcium/calmodulin-dependent protein kinase II (α CaMKII) and the other encoding the immediate-early gene protein Arc — as well as 42 identified proteins, including known regulators of mRNA transport (for example, purine-rich-element-binding protein- α (Pur- α) and *Staufen1*)¹⁶ and translation (for example, eukaryotic translation initiation factor 2 α (eIF2 α) and eukaryotic translation elongation factor 1A (eEF1A))¹⁷. In addition, other mRNA-binding proteins that have been implicated in mRNA stabilization (synaptotagmin-binding, cytoplasmic-RNA-interacting protein (SYNCRIP))¹⁸, translocation (TLS)¹⁹ and translation (FMRP and fragile-X mental retardation, autosomal homolog 1 (FXR1) and 2 (FXR2))²⁰ were identified¹⁵. Interestingly, cytoplasmic-polyadenylation-element-binding protein 1 (CPEB1), a protein that was previously shown to bind to α CaMKII mRNA, regulate its translation²¹ and participate in its localization into dendrites²², was not detected. In addition, neither β -actin mRNA nor ZBP1 were members of this complex, which is consistent with the idea that the pool of RNPs is heterogeneous.

The second study¹⁴ used biochemical fractionation to isolate a fraction that was enriched in RNPs from developing rat brains, and exposed this fraction to proteomic evaluation. In contrast to the KIF5 granule, the large granules obtained in this study contained mRNA encoding ZBP1 and β -actin, but not α CaMKII. However, the two RNP preparations had many common components, including several heterogeneous nuclear ribonucleoproteins (hnRNPs), SYNCRIP, FMRP, Pur- α , Pur- β , *Staufen* and *DEAD (Asp-Glu-Ala-Asp) BOX polypeptide 1*, *DEAD BOX 3* and *DEAD BOX 5* (REF. 14). This suggests that there are core components of transport RNPs, which are always required, and that additional RNA-binding proteins are added based on brain region or stage of development.

Activity-regulated transport. Several groups have examined the dynamic transport of RNPs in dendrites by fluorescently labelling either the mRNA or mRNA-binding proteins and monitoring movement in cultured neurons by live-cell imaging techniques^{8,11,23–27}. Consistently, they have found that the majority of particles are stationary, but that some display either rapid retrograde (towards the cell body) or anterograde (away from the cell body) movements that are dependent on microtubules. These movements can be altered by neuronal activity. One study showed that neuronal activity resulted in an increase in the number of dendrite-localized α CaMKII-mRNA-containing granules, probably as a result of the conversion of stationary (or oscillatory) granules into anterograde-moving granules²⁶. The movement of ZBP1-containing granules into dendrites is also stimulated by depolarization, and is dependent on NMDA (N-methyl-D-aspartate) receptor activation¹¹. Using *in situ* hybridization histochemistry, NMDA receptor-dependent localization of Arc mRNA to dendrites close to recently activated synapses in the dentate gyrus was demonstrated *in vivo*^{28,29}. Similarly, activation of metabotropic glutamate receptors (mGluRs) promotes the localization of mRNAs encoding the α -amino-3-hydroxy-5-methyl-4-isoazolepropionic acid (AMPA)

receptor subunits *GluR1* and *GluR2* into dendrites³⁰. This suggests that synaptic activity leads to a prolonged increase in dendritic protein synthesis. Supporting this idea, translocation of polyribosomes into spines was observed 2 hours after LTP induction in the CA1 region of hippocampal slices³¹, and elevated α CaMKII mRNA levels were found in synaptodendrosomes following LTP induction in the dentate gyrus of awake rats³². Detailed information on the mechanism of translocation is lacking, but recent work in cultured neurons suggests that mRNA translocation into spines involves the actin-based

Box 1 | RNA granule heterogeneity

In response to stress, eukaryotic cells reprogramme their mRNA metabolism to adapt to the changing conditions. They turn off the synthesis of most 'housekeeping' proteins by sequestering their mRNA into stress granules (SGs). Most of the components of SGs were identified in non-neuronal cells, although their presence in neurons has also been established. Ribonucleoprotein particles (RNPs) are transport granules that contain mRNA, mRNA-binding proteins, motor proteins and small non-coding RNA (also known as microRNA). Processing bodies (PBs) are the third type of RNA granule; they are thought to function in RNA degradation. However, our understanding of the relationship between RNPs, SGs and PBs in neurons is still in its infancy. In non-neuronal cells, SGs contain small ribosomal subunits only, in contrast to neuronal RNPs, which contain both small and large ribosomal subunits. However, like neuronal transport granules, SGs contain components of the translation initiation complex, such as eukaryotic translation initiation factor 2 (eIF2), eIF3, eIF4E and eIF4G^{150,151}. SGs also contain mRNA-binding proteins that regulate mRNA translation and transport, such as cytoplasmic-polyadenylation-element-binding protein 1 (CPEB1), *Staufen*, GTPase-activating-protein (SH3 domain)-binding protein 1 (G3BP) and fragile-X mental retardation protein (FMRP)^{152–155}. It is thought that SGs are temporary holding compartments where mRNA can be stored while the cell is recovering from oxidative or metabolic stress. When the stress is relieved, SGs disassemble, and the sequestered mRNAs either return to the translationally active pool or proceed to degradation in the PBs. PBs contain decapping enzymes (for example, DCP1–DCP2), exonucleases (for example, 5'–3' exoribonuclease 1 (XRN1)) and components of the nonsense-mediated decay pathway (for example, SMG5 and SMG7). In mammalian cells, PBs also contain microRNAs (miRNAs) and components of RNA-induced gene silencing complexes, for example, argonaute³. As a greater understanding of the constituents and functions of SGs and PBs in mammalian and non-mammalian cells is achieved, it is becoming clear that the definition of a PB is cell-type dependent. For example, in mammalian cells, PBs contain the machinery for miRNA-mediated translational silencing — components not found in yeast PBs. However, yeast PBs do have many of the same characteristics as mammalian SGs³. Highlighting the potential species variation, a recent study in *Drosophila* neurons suggests that in this species, one granule type acts as both transport RNP and PB¹⁵⁶.

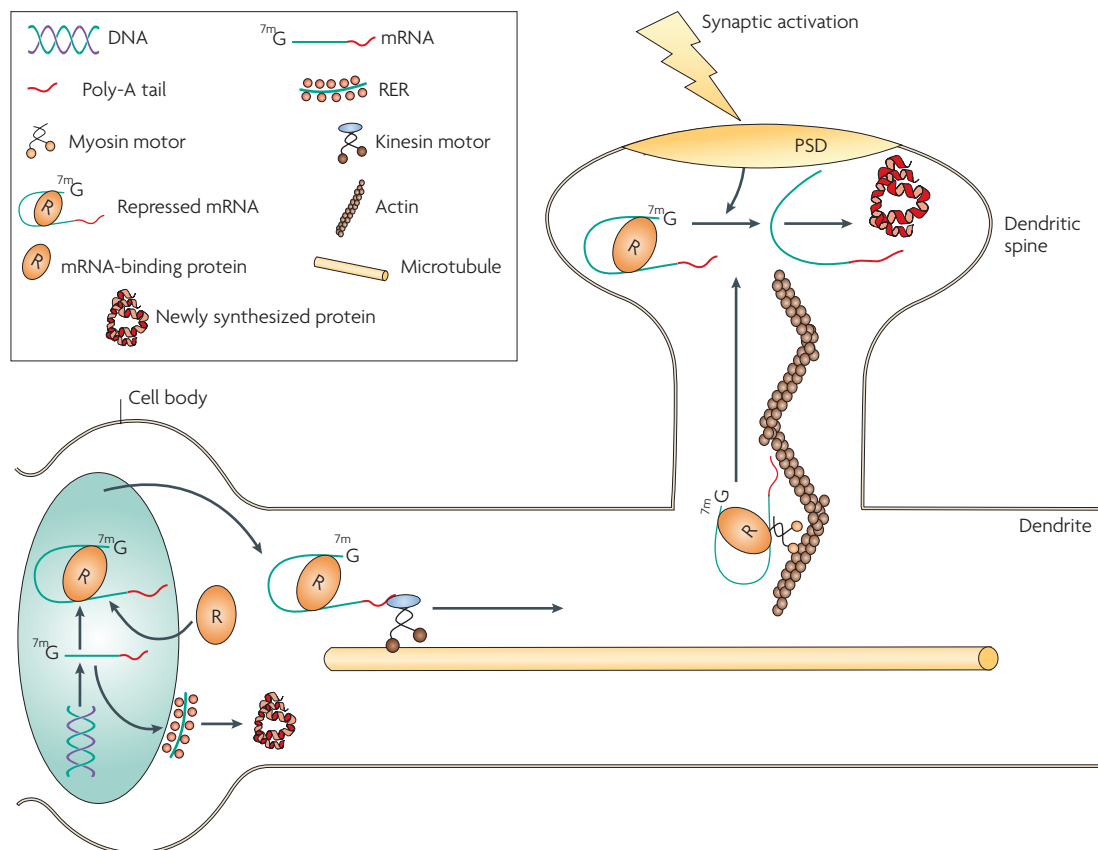


Figure 1 | Proposed model for mRNA translation in neuronal dendrites. Binding of a specific mRNA in the nucleus by an mRNA-binding protein (R) that is capable of inhibiting translation allows the mRNA to be sequestered away from the protein-synthetic apparatus in the cell body. These repressed mRNAs are then packaged into transport granules that are transported into the dendrite by kinesin motors on microtubules. Following synaptic activation, the granules are dispersed and the mRNA is localized to spines by the actin-based myosin motor proteins. Translation is activated in the synaptic compartment by neutralizing the repressive RNA-binding protein. ^{7mG}, 7-methyl-guanosine; PSD, postsynaptic density; RER, rough endoplasmic reticulum.

motor *myosin Va*³³. Making an important connection between local protein synthesis and structural changes in spines, it was shown that spines that contained polyribosomes were larger than those that did not, and had larger PSDs³¹.

Translation

LTP and LTD are rapidly induced following high-frequency stimulation and low-frequency stimulation (respectively) of excitatory synaptic inputs. The maintenance of LTP and LTD is typically divided into a transient early phase and a persistent late, protein-synthesis-dependent phase¹⁶⁵. This protein-synthesis-dependent process is sometimes referred to as synaptic consolidation, in analogy to mechanisms of long-term memory formation. In addition to mRNA transport and localization, recent research has given insight into various mechanisms that govern global translation, as well as the translation of specific mRNAs, in dendrites (FIG. 2).

Translation initiation. Phosphorylation of *eIF4E* is considered the rate-limiting step for the translation of most mRNAs (those 'capped' with a 7-methyl-guanosine residue at their 5' terminus). The phosphorylation is

correlated with enhanced rates of cap-dependent translation, whereas hypophosphorylation is associated with decreased translation^{17,34}. Cap-dependent translation in dendrites is thought to be stimulated by two receptor-coupled kinase pathways: extracellular signal-regulated kinase (ERK) signalling, which leads to phosphorylation of *eIF4E*, and mammalian target of rapamycin (mTOR) signalling, which leads to phosphorylation of *eIF4E*-binding protein (*eIF4E-BP*) and release of *eIF4E*, which then becomes available for cap binding. In many brain regions, the application of brain-derived neurotrophic factor (BDNF) induces LTP (BDNF-LTP) of excitatory synaptic transmission, whereas the application of dihydroxyphenylglycine (DHPG), an agonist of group I metabotropic glutamate receptors (mGluRs), produces LTD (DHPG-LTD). Remarkably, both of these opposing changes in synaptic efficacy require the activation of ERK, mTOR and dendritic protein synthesis^{35–46}.

In addition to cap-dependent mechanisms, mRNA translation can be initiated at internal ribosomal entry sites (IRES). Inhibition of cap-dependent translation appears to favour the use of IRES-mediated translation⁴⁷. In the marine snail *Aplysia*, neuronal activity-dependent

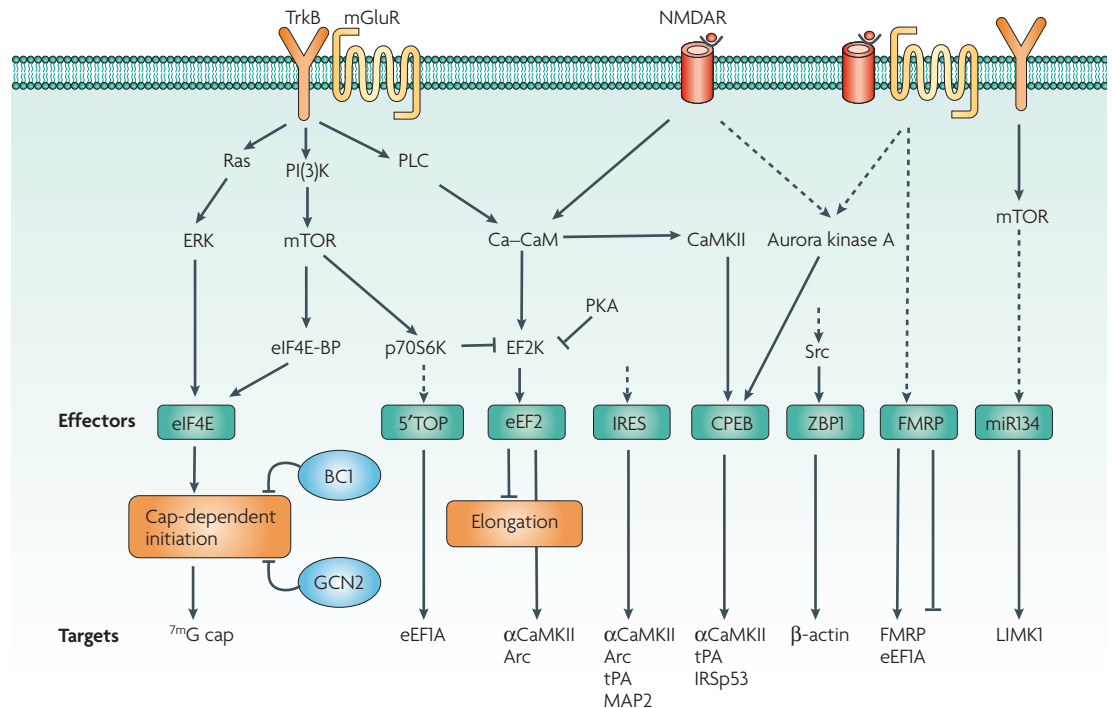


Figure 2 | Translation control in dendrites. The illustration depicts neurotransmitter receptor-coupled pathways that have been implicated in the control of dendritic protein synthesis at excitatory synapses in the mammalian brain (the dotted lines represent unknown signalling pathways). In this model, *N*-methyl-D-aspartate receptors (NMDARs), metabotropic glutamate receptors (mGluRs) and the brain-derived neurotrophic factor (BDNF) receptor, TrkB, regulate global translation and the translation of specific mRNAs through multiple effectors (depicted as green boxes). Some of the known mRNA targets are listed. Phosphorylation of eukaryotic translation initiation factor 4E (eIF4E) is rate-limiting for cap-dependent translation initiation^{17,34,41–46}. eIF4E is released from eIF4E-binding protein (eIF4E-BP) in response to activation of mammalian target of rapamycin (mTOR) and then phosphorylated by extracellular signal-regulated kinase (ERK). mTOR also facilitates the translation of mRNAs that contain a 5' terminal oligopyrimidine tract (5'TOP)^{36,58}, such as eukaryotic translation elongation factor 1A (eEF1A), which might serve to increase translational capacity. eEF2 phosphorylation is associated with the global arrest of peptide chain elongation, yet translation of the activity-regulated cytoskeleton-associated protein (Arc) and of the calcium/calmodulin-dependent protein kinase II α -subunit (α CaMKII) appears to be enhanced in this context^{45,51,52}. Several dendritic mRNAs, including Arc and α CaMKII, are capable of cap-independent translation through the use of internal ribosomal entry sites (IRES)⁴⁹. RNA-binding proteins and microRNAs are major regulators of mRNA-specific translation. Phosphorylation of cytoplasmic-polyadenylation-element-binding protein (CPEB), through either NMDAR- or mGluR-coupled activation of Aurora kinase A or α CaMKII, stimulates translation of CPE-containing mRNAs^{70–72}. Phosphorylation of zip-code-binding protein 1 (ZBP1), through activation of the cytoplasmic tyrosine kinase Src, increases β -actin translation¹⁰. Fragile-X mental retardation protein (FMRP) exerts bidirectional effects on translation, possibly through binding to microRNAs and BC1 (interaction not shown), a small untranslated RNA that represses translation by interfering with the assembly of the translation initiation complex¹⁵⁷. *FMR1* mRNA is itself a target for enhanced translation⁹⁰. The microRNA miR134 binds to Lim domain kinase 1 (LIMK1) and represses its translation⁴². BDNF signalling through mTOR relieves this repression, resulting in local synthesis of LIMK1. *GCN2* is a kinase that phosphorylates and activates the translational repressor eIF2 α ¹⁵⁸. ^{7mG}, 7-methyl-guanosine; EF2K, EF2 kinase; IRESp53, insulin receptor substrate p53; MAP2, microtubule-associated protein 2; p70S6K, ribosomal protein S6 kinase, 70kDa; PI(3)K, phosphatidylinositol 3-kinase; PKA, protein kinase A; PLC, phospholipase C; tPA, tissue plasminogen activator.

dephosphorylation of eIF4E triggers a switch to IRES-mediated translation of egg-laying hormone⁴⁸. Several dendritic mRNA species, including Arc and α CaMKII, contain IRES sequences and are capable of IRES-dependent translation *in vitro*⁴⁹, although evidence that they undergo this kind of translation *in vivo* is lacking (TABLE 1). During BDNF-LTP in the dentate gyrus, transient phosphorylation of eIF4E is outlasted by a period of sustained Arc synthesis^{40,45}. It will hence be important to determine whether IRES-mediated translation contributes to sustained translation of Arc and other dendritic mRNAs.

Elongation. Dendritic protein synthesis that affects synaptic plasticity is also controlled at the level of peptide chain elongation. eEF2 is a GTP-binding protein that mediates the translocation of peptidyl-tRNAs from the A-site to the P-site on the ribosome as amino acids are added to the peptide chain. Phosphorylation of eEF2 on Thr56 inhibits eEF2-ribosome binding and arrests elongation⁵⁰. eEF2 phosphorylation during LTP might therefore explain the decrease in synthesis of some proteins that has been observed in two-dimensional gel studies¹⁶⁶. Interestingly, Arc and α CaMKII mRNA — two dendritic mRNAs that are important in synaptic

Synaptoneurosome

A biochemical fraction that is qualitatively similar to a synaptodendrosome but which is prepared by low-speed centrifugation and filtration.

plasticity — exhibit enhanced expression in the context of eEF2 phosphorylation^{45,51,52}. BDNF-LTP in the adult rat dentate gyrus *in vivo* is associated with transient ERK-dependent eEF2 phosphorylation and enhanced Arc expression, as measured in dentate gyrus homogenates⁴⁵. Surprisingly, BDNF treatment of synaptodendrosomes does not alter the phosphorylation state of eEF2, but it does lead to rapid eIF4E phosphorylation and enhanced translation of dendritic mRNAs, such as Arc, α CaMKII and Lim domain kinase 1 (*LIMK1*)^{42,45,53}. Thus, BDNF appears to affect translation in a compartment-specific manner, enhancing initiation at synapses while promoting elongation arrest at non-synaptic sites. By contrast, NMDA treatment of synaptoneurosome enhances eEF2 phosphorylation and suppresses global protein synthesis while increasing α CaMKII expression⁵¹. Further work is therefore needed to resolve how local translation of specific transcripts is maintained in the context of eEF2 phosphorylation. It is nonetheless clear that dendritic synthesis of transcripts such as α CaMKII can be stimulated by multiple receptor-coupled pathways, including those linked to NMDA receptors, mGluR and the BDNF receptor, *TrkB*.

Although most studies of dendritic protein synthesis have focused on regulation by evoked neuronal activity, others have shown that dendritic protein synthesis in dissociated hippocampal neurons is tonically suppressed by spontaneous, action-potential-independent neurotransmitter release^{54,55}. This tonic brake on protein synthesis by spontaneous (miniature) excitatory transmission is mediated at least in part by eEF2 phosphorylation⁵⁶. Using the photoconvertible fluorescent protein Kaede as a reporter for local protein synthesis, spontaneous NMDA-receptor-activity was shown to decrease dendritic synthesis of the voltage-dependent potassium channel $K_v1.1$, through a mechanism that involves inhibition of mTOR⁵⁷. These studies highlight the role of spontaneous excitatory transmission in decreasing local protein synthesis.

TOP mRNAs. The ability to maintain translation capacity during periods of intensive protein synthesis often depends on the synthesis of ribosomal proteins and translation factors. The mRNAs that encode these components of the translation machinery typically contain a terminal oligopyrimidine tract (TOP) in their 5' untranslated region (UTR), and undergo enhanced translation through an mTOR-dependent pathway that involves activation of p70S6 kinase (ribosomal protein S6 kinase, 70kDa)⁵⁸. Stimulus paradigms that produce late LTP (but not early LTP) induce sustained mTOR and p70S6 kinase activation in dendrites and enhanced dendritic expression of several TOP-containing mRNAs, including eEF1A and eEF2 (REFS 36,58). Similar increases in dendritic expression of eEF1A are observed in hippocampal slices during DHPG-LTD⁵⁹. BDNF-LTP in the dentate gyrus is associated with enhanced ERK-dependent expression of eIF4E⁴⁵, whereas BDNF treatment of synaptoneurosome derived from cultured hippocampal neurons enhances mTOR-dependent synthesis of several translation factors and ribosomal proteins⁶⁰. Taken together, these

studies suggest that TOP translation and translation capacity is rapidly modulated in dendrites, although it remains to be shown that such modulation is required for LTP and LTD consolidation.

Translation control of specific mRNAs

Many of the factors discussed so far regulate the mRNA translational machinery and can thereby increase or decrease general dendritic translation rates. This raises the question of how (or whether) specific dendritically targeted mRNAs are regulated. For example, mRNAs that are important for LTP might be a different or overlapping population from those that are required for LTD, but both are presumably present in the same region of the dendrite. Therefore, if the translational machinery has been enhanced in dendrites, how are selective mRNAs activated while others remain dormant? The answer might reside in the presence of RNA-binding proteins that bind to specific *cis*-elements and are capable of regulating mRNA translation⁶¹. One example of this type of regulation has already been discussed — the regulation of β -actin mRNA by ZBP1. Here, ZBP1 binds to β -actin mRNA as it is being transcribed in the nucleus, probably keeping the mRNA translationally inactive. Once in the cytoplasm, ZBP1 can be dissociated from the mRNA by phosphorylation by *Src*, thus allowing β -actin to be synthesized¹⁰. Other candidate regulators of specific mRNA translation in neurons are the cytoplasmic-polyadenylation-element-binding protein (CPEB) and FMRP families of proteins.

CPEB. CPEB was first identified in *Xenopus* oocytes, where it regulates mRNA polyadenylation and translation⁶². Three additional proteins were identified in mice that contained similar RNA-binding domains, and were thus called CPEB2–4 (REF. 63). It now appears that CPEB2–4 do not bind to the same *cis*-element as CPEB1 and, although they might regulate mRNA translation, they do not do so by regulating polyadenylation⁶⁴. Therefore, CPEB2–4 might represent a separate class of RNA-binding proteins. A great deal more is known about how CPEB1 regulates translation. CPEB1 is present in many regions of the brain, including the hippocampus, the cerebellum and the cortex, where it localizes to synapses and is a component of the PSD²¹. The binding of CPEB1 near the end of the 3' UTR anchors a complex of proteins that include an eIF4E binding protein (*maskin*), a poly(A)-polymerase (*Gld2*), a scaffolding protein (*symplekin*) and a deadenylase (poly(A)-specific ribonuclease (*PARN*))^{65–67}. Binding of CPEB1 to the mRNA initially inhibits mRNA translation through the interaction of *maskin* and eIF4E, however, CPEB1 phosphorylation leads to the dissociation of *PARN* from the complex and subsequent polyadenylation of the 3' tail by *Gld-2* (REF. 67). This polyadenylation results in the dissociation of *maskin* from eIF4E and the activation of translation⁶⁸.

CPEB1-mediated translation is activated when CPEB1 is phosphorylated at two crucial residues (Thr171 and Ser177 in mouse)⁶⁹. In hippocampal neurons, both *Aurora kinase A* and α CaMKII have been implicated in the phosphorylation of this site^{70,71}, and *Aurora kinase A*

RNA interference complex (RISC). A complex of proteins that is involved in silencing target mRNAs.

is thought to phosphorylate CPEB in cerebellar Purkinje neurons⁷². Furthermore, CPEB1-mediated translation can be activated following glutamate stimulation, and both NMDA-receptor- and mGluR-involvement have been described^{70,72–74}. Interestingly, NMDA receptor and mGluR appear to activate CPEB1-mediated translation of different mRNAs in hippocampal neurons, suggesting that CPEB1 works in concert with other regulatory mechanisms to control protein synthesis in dendrites. Consistent with this idea, knockout of CPEB1 produces a modest effect on hippocampal LTP and LTD that can be overcome by increasing the stimulus intensity⁷⁵. Indeed, both CPEB1 and FMRP associate with α CaMKII mRNA in neurons^{21,76}, and the *Drosophila* homologues of these proteins (*orb* and *dFMR1*, respectively) are located in the same RNP in the developing oocyte⁷⁷. However, the loss of CPEB1 does have demonstrable effects on some forms of learning and memory^{72,78}.

FMRP. Mutations in the gene that encodes FMRP are associated with a form of mental retardation called *fragile-X syndrome* (FXS)⁷⁹. FMRP is a member of the hnRNP family of mRNA-binding proteins, and is likely to be involved in mRNA metabolism in many cell types. In neurons, FMRP is localized to dendrites, and the loss of FMRP results in altered synaptic morphology and plasticity.

The regulation of mRNA translation by FMRP is a complicated and poorly defined process, although several recent reviews have examined the current understanding of FMRP regulation and function^{20,79}. We will not recapitulate this excellent work here, however, a fundamental understanding of FMRP function is germane to our current topic. FMRP is localized to synapses, where evidence suggests that it regulates mRNA translation following the activation of type I mGluRs, although this has not been formally proved^{176,80,81}. Following LTD induction by mGluR activation in the hippocampus, there is an immediate increase in FMRP levels, followed by a ubiquitin-mediated proteosomal degradation⁸². Both the synthesis of new FMRP and its subsequent degradation appear to be required for LTD⁸². The binding of FMRP to mRNA is thought to inhibit translation^{83,84}. Surprisingly, however, mice that lack FMRP exhibit both up- and downregulation of putative FMRP targets^{85,86}. Consistent with this multifaceted role in mRNA translation, FMRP can associate with multiple types of RNA granules that contain both actively translating polysomes^{87,88} and non-translating RNPs^{76,89}. These data highlight both the complexity of the process of mRNA translation in the dendrites and the uncertainty that is still present in the field with regards to the exact mechanisms that are at play.

At the synapse, a model for FMRP function has been proposed whereby mGluR activation results in a disinhibition of FMRP-bound mRNA. Interestingly, the best characterized mRNA target is *FMR1*, which encodes the FMRP protein itself. FMRP and FMRP mRNA colocalize to the same RNPs in hippocampal neurons in culture, and their localization into dendrites is enhanced following synaptic activity⁹⁰. Activation of mGluRs induces an increase in the synthesis of FMRP in the

synaptic region, which might in turn limit the response by turning off dendritic synthesis^{91,92}. Consistent with this idea, loss of FMRP results in an enhancement of LTD amplitude^{93,94}.

microRNAs. microRNAs (miRNAs) are small, noncoding RNAs that bind to the 3' UTR of target mRNAs and either block their translation or induce transcript degradation⁹⁵. Because miRNAs generally bind to numerous target mRNAs, and because many mRNAs are regulated by more than one species of miRNA, the possibilities for fine regulation of translation are enormous. miR-134, a brain-specific miRNA that is found in the synaptodendritic compartment, negatively regulates dendritic spine morphogenesis in cultured hippocampal neurons by repressing translation of LIMK1 mRNA⁹⁶. Application of BDNF relieves miR134-mediated repression of LIMK1 translation and promotes spine morphogenesis. Interestingly, the RNA interference complex (RISC) proteins that mediate the effects of miRNA are themselves subject to regulation. A recent study demonstrated that RISC pathway proteins regulate dendritic mRNA transport and local protein synthesis during the acquisition of long-term memory in flies⁹⁷. According to this model, training in an olfactory/electric shock paradigm triggers proteosomal degradation of the SDE3 helicase *Armitage*, which leads to the relief of RISC-mediated suppression of several mRNAs, including α CaMKII, the kinesin heavy chain and Staufen. Adding to this complexity, regulation of miRNA transcription might be coupled to specific physiological effects. cyclic AMP-responsive-element-binding protein (CREB)-dependent transcription of miR-132 promotes neuronal morphogenesis by decreasing synthesis of the GTPase-activating protein p250GAP⁹⁸. Like many CREB-dependent effects in neurons, this mechanism is activated by BDNF. Furthermore, recent experiments that used microarray expression profiling and PCR analysis revealed bidirectional regulation of miRNA expression following LTP induction in the dentate gyrus *in vivo*⁹⁹.

Function

Studies that used pharmacological inhibitors of global translation demonstrated the general requirement for dendritic protein synthesis in stable forms of synaptic plasticity^{2,38,39,100–102}. However, causal roles for specific dendritically synthesized proteins have been hard to define. Here we highlight recent advances in this area, using Arc function in LTP in the dentate gyrus and CPEB1 function in LTD in the cerebellum as examples. These examples underscore the diversity of the mechanisms that are involved and highlight some common themes.

LTP. In addition to the requirement for new gene expression and protein synthesis, there is now strong evidence that LTP consolidation requires actin polymerization in spines. Actin polymerization is associated with expansion of the PSD and conversion of small, stubby dendritic spines to large mushroom-shaped spines^{103–105}. A number of F-actin functions might contribute to this growth process, including the tethering of receptors and

signalling complexes, the trafficking of receptors, and the positioning of polyribosomes and other components of the translation machinery^{106,107}. LTP of medial perforant path–granule cell synapses in the dentate gyrus is associated with enhanced F-actin formation in spines and phosphorylation of cofilin, a major regulator of actin dynamics¹⁰⁴. Phosphorylation of cofilin on Ser3 inhibits its F-actin-severing activity, and thus promotes F-actin formation and stabilization. Following LTP induction, cofilin phosphorylation is observed in enlarged spines that have enhanced F-actin content^{108,109}. The expression of stable LTP in the CA1 region and in the dentate gyrus is crucially dependent on the atypical protein kinase C (PKC) isoform, protein kinase M ζ (PKM ζ). Constitutive activity of this enzyme is thought to maintain LTP by increasing the number of active postsynaptic AMPA receptors^{110,111}.

LTP is associated with the induction of various immediate-early genes, including the zinc-finger transcription factor early growth response 1 (*egr1*; also known as *zif268*), *tPA* and *Arc*. Mice in which these genes have been knocked out have defects in LTP maintenance and/or memory consolidation^{112–114}. A specialized role for *Arc* in synaptic plasticity is implied by the fact that newly expressed *Arc* mRNA is rapidly transported to the dendritic processes of granule cells, suggesting that it undergoes local translation at activated synapses^{24,28,29}. *Arc* also co-sediments with crude F-actin and localizes to the PSD of excitatory synapses^{112,115–117}, whereas injection of *Arc* antisense oligodeoxynucleotides before LTP induction impairs the maintenance of LTP in the dentate gyrus¹¹⁸. A more recent study explored the dynamics of *Arc* synthesis during LTP maintenance by injecting *Arc* antisense oligodeoxynucleotides at multiple time points after high-frequency stimulation of medial perforant path–granule cell synapses⁴⁰. The study identified a stringent requirement for *Arc* synthesis that commences immediately after synaptic activation and lasts between 2 and 4 hours. At 2 hours after LTP induction, antisense oligodeoxynucleotide administration results in rapid knockdown of newly induced dendritic *Arc* mRNA and protein, dephosphorylation of hyperphosphorylated cofilin and loss of nascent F-actin at medial perforant path–granule cell synapses. Furthermore, infusion of an F-actin-stabilizing drug prevented antisense oligodeoxynucleotide-induced reversal of LTP. Taken together, current evidence suggests that sustained *Arc* synthesis promotes LTP consolidation and allows stable expansion of F-actin at synapses. As such, *Arc* provides a compelling link between two central tenets of LTP consolidation: gene expression and F-actin expansion.

Several lines of evidence suggest that BDNF stimulates LTP consolidation¹¹⁹. BDNF is released from or near glutamatergic synapses following synaptic stimulation and activates TrkB receptor tyrosine kinases pre- and postsynaptically. In the dentate gyrus, BDNF-induced LTP is transcription-dependent, occludes with late LTP and is associated with upregulation and dendritic transport of *Arc* mRNA^{120,121}. Moreover, injection of *Arc* antisense

oligodeoxynucleotides abolishes BDNF-LTP induction and reverses ongoing potentiation while inhibiting cofilin phosphorylation⁴⁰. Furthermore, BDNF application, like high-frequency stimulation, activates cofilin phosphorylation in dendritic spines¹⁰⁹. Thus, BDNF appears to directly activate the *Arc*-dependent expression and consolidation of LTP.

In the model of *Arc*-dependent consolidation of LTP that is shown in FIG. 3, postsynaptic BDNF signalling through TrkB receptors is vital for initial translation activation. This involves the liberation of mRNA from storage granules, the fine-positioning of the translation apparatus (mRNA, ribosomes and translation factors) and the biochemical activation of translation through hyperphosphorylation of eIF4E and (probably) mRNA-specific derepression, as discussed earlier. Spines or dendritic branches activated in this way might effectively capture and translate local mRNA pools. A sequential mechanism is envisioned whereby the translation of pre-existing transcripts such as α CaMKII mRNA is followed by the translation of dendritically transported mRNAs such as *Arc*. During *Arc*-dependent consolidation, sustained translation of *Arc* is necessary for cofilin phosphorylation, local F-actin expansion and the formation of stable LTP⁴⁰.

Electron microscopic studies have shown increased *Arc* expression and F-actin formation in the spines of synapses that have undergone long-term potentiation^{104,122,123}. It is nonetheless evident from many studies that *Arc* is upregulated throughout the dendritic arbor of granule cells, yet the significance of this widespread increase is unknown. Recently, *Arc* was found to mediate homeostatic synaptic scaling of AMPA receptor transmission through its ability to activate a specific AMPA receptor endocytic pathway^{124–126}. These *in vitro* studies in dissociated hippocampal neurons and slice cultures suggested that *Arc* scales down (depresses) AMPA receptor transmission as a means of stabilizing overall neuronal excitability. Attempting to reconcile these seemingly opposing effects of *Arc* in different preparations, it is perfectly conceivable that *Arc*-dependent LTP consolidation is followed by delayed homeostatic scaling. A major challenge for future research is to determine the fate and function of *Arc* that is synthesized in different subcellular locales.

LTD. The two mRNA-binding proteins for which the neural functions are best known are CPEB1 and FMRP. In both cases, loss of function results in an alteration in LTD^{72,93,94}.

The cerebellum controls coordinated movement and has a well-established neural circuitry¹²⁷. The sole output of the cerebellum comes from neurons in the deep cerebellar nucleus (DCN). These DCN neurons are driven by direct excitatory inputs from pre-cerebellar nuclei (which they receive through mossy fibres) and inhibitory inputs from Purkinje neurons that are located in the cerebellar cortex. Each Purkinje neuron receives excitatory inputs from granule cells in the cerebellum (there are ~200,000 such synapses on each Purkinje neuron) and from the brain stem (through climbing fibres). Purkinje neurons receive inputs from only one

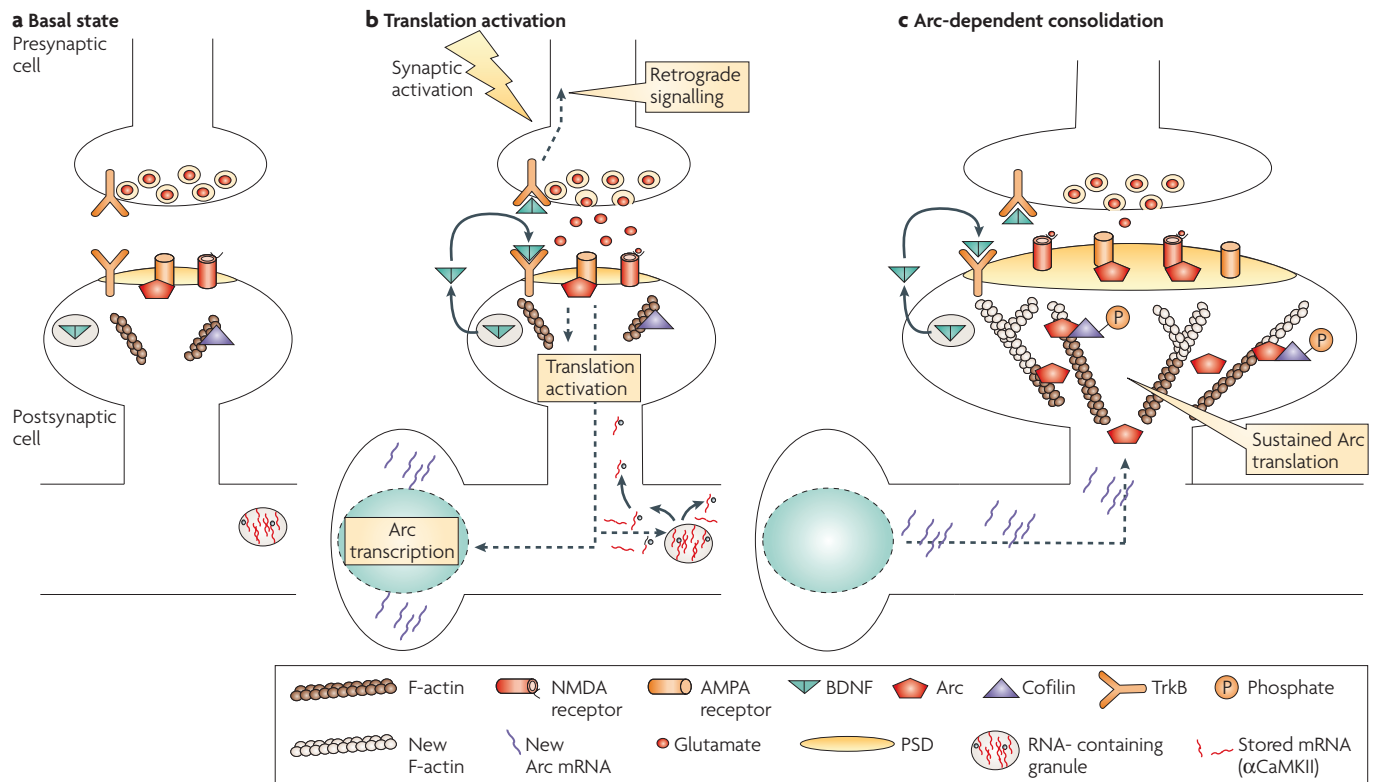


Figure 3 | A model of Arc-dependent LTP consolidation in the dentate gyrus. In this two-stage model, translation activation is followed by Arc-dependent consolidation. The model is based on current evidence, but many of the details require further experimental validation. **a** | A neuron in the resting (basal) state, showing mRNA sequestered in an RNA-containing granule. **b** | High-frequency stimulation (HFS) causes the activation of postsynaptic NMDA (N-methyl-D-aspartate) receptors and TrkB receptors, leading to rapid postsynaptic translation activation and induction of Arc transcription in the nucleus. Translation activation is achieved through biochemical regulation of the translation machinery (FIG. 2), liberation of mRNA (for example, the mRNA that encodes the α -subunit of calcium/calmodulin-dependent protein kinase II (α CaMKII)) from RNA granules and fine-positioning of the translation machinery, including the translocation of polyribosomes into spines (not shown). Spines activated in this way might effectively capture and translate local mRNA pools. The site of brain-derived neurotrophic factor (BDNF) release in the adult dentate gyrus is uncertain, but HFS-induced release of BDNF from dendrites has been observed in primary hippocampal cell culture¹⁵⁹. Activation of presynaptic TrkB receptors might contribute to long-term potentiation (LTP) through retrograde nuclear signalling¹³⁸. **c** | Arc-dependent consolidation. Arc mRNA is transported to dendrites and locally captured. Sustained translation of dendritically transported Arc is necessary for cofilin phosphorylation and local F-actin expansion. Through unknown mechanisms, F-actin formation promotes growth of the postsynaptic density (PSD) and the spine head and formation of stable LTP. This model applies to late stabilization of F-actin⁴⁰; early actin polymerization might use distinct mechanisms. AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; Arc, activity-regulated cytoskeleton-associated protein. Modified, with permission, from REF. 160 © (2006) Portland Press.

climbing fibre, but that one axon makes approximately 1,400 synapses onto the Purkinje neuron cell body and proximal dendrites. Purkinje neurons undergo a well-studied form of LTD that is dependent on mGluR1 activation. Cerebellar LTD is also protein-synthesis-dependent, and if LTD-inducing stimuli are given in the presence of a protein synthesis inhibitor, synaptic depression is not maintained^{72,128}.

To determine the role of CPEB1-mediated protein synthesis in cerebellar LTD, a mutant CPEB1 protein (CPEB-AA) that contained two point mutations at the phosphorylation sites that are crucial for activation was expressed in Purkinje neurons only⁷². CPEB-AA can bind CPE-containing mRNA and inhibit its translation, but it is incapable of activating translation following cellular stimulation^{129,130}. CPEB-AA-expressing

Purkinje neurons showed a loss of cerebellar LTD that was indistinguishable from that recorded in the presence of a protein synthesis inhibitor⁷². In addition, the degree to which the cerebellar LTD was inhibited was dependent on the level of CPEB-AA that was expressed. This result is in contrast to that seen when FMRP function is altered in Purkinje neurons: in FMRP knockout mice, and when FMRP is specifically deleted from Purkinje neurons, LTD is enhanced⁹⁴. This suggests that CPEB1-mediated protein synthesis is required for the initial stages of cerebellar LTD maintenance and that subsequent FMRP-mediated effects limit the change in synaptic strength.

In addition to these changes in LTD, altering FMRP and CPEB1 function also results in changes in spine morphology. In CPEB-AA mice and FMRP-deficient

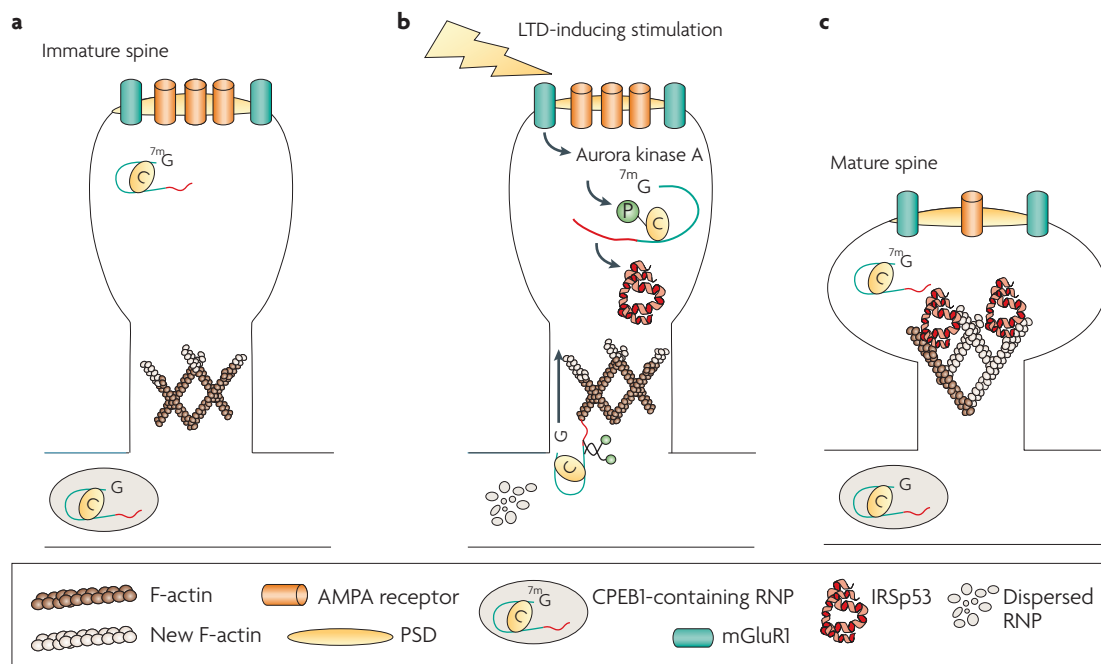


Figure 4 | A proposed model for the role of CPEB1-mediated protein synthesis in cerebellar LTD. **a** | Cytoplasmic-polyadenylation-element-binding protein 1 (CPEB1) is bound to mRNAs in an unphosphorylated state, and it thereby holds the mRNA in a state of translational dormancy. This complex is localized to dendrites in a ribonucleoprotein particle (RNP). **b** | Following synaptic induction of long-term depression (LTD), CPEB1 is phosphorylated by Aurora kinase A, and translation of insulin receptor substrate p53 (IRSp53) is induced (along with the translation of other CPE-containing dendritic mRNAs). In this model, CPEB1-containing RNPs would then be dispersed in the shaft of the dendrite, and CPEB1-bound mRNA would be translocated into the spine head. **c** | IRSp53 promotes a remodelling of F-actin in the spine and a change in spine morphology. This change in spine morphology is thought to occur during the development from immature to mature spines, and CPEB1-mediated long-term differentiation is thought to contribute to this process⁷². Synaptic strength is reduced by the phosphorylation and removal of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors from the synaptic membrane by clathrin-mediated endocytosis. Although the removal of these AMPA receptors is not dependent on new protein synthesis, if protein synthesis or CPEB1 function is disrupted, then synaptic strength returns to baseline levels⁷². 7mG, 7-methyl-guanosine; mGluR1, metabotropic glutamate receptor 1; PSD, postsynaptic density.

Purkinje neurons, synaptic spine morphology was altered, resulting in longer spine profiles^{72,94}. This change in spine shape is thought to represent a failure in spine maturation, and could be one of the underlying causes of the cognitive alterations in FXS^{20,131}. These results indicate that alterations in synaptic strength are accompanied by changes in morphology; however, the morphological changes do not predict the type of synaptic deficit that is involved (whether an LTD block or LTD enhancement).

These changes in spine shape are likely to be due to alterations in the actin cytoskeleton. For example, insulin receptor substrate p53 (IRSp53) is an adaptor protein that contains many functional domains, including an amino-terminal Rac-binding domain (RCB), a partial Cdc42 and Rac1-interacting binding (CRIB) domain, a Src homology 3 (SH3) domain and a carboxy-terminal PDZ domain^{94,132}. In non-neural cells, IRSp53 is activated by Rho, Rac1 and Cdc42, and forms a complex with WAVE2 and Mena to nucleate actin filament assembly¹³³. The mRNA that encodes IRSp53 contains a CPEB binding sequence, and IRSp53 protein synthesis is induced following motor learning in the cerebellum. Interestingly, in CPEB-AA mice, the

basal level of IRSp53 protein is unchanged; however, the motor-learning-induced increase in IRSp53 is inhibited. This suggests that CPEB1-mediated synthesis has little effect on the constitutive synthesis of IRSp53, but that it controls synaptically driven IRSp53 synthesis that probably contributes to spine morphological changes and maturation (FIG. 4).

Emerging concepts

Functional synergy of dendritically synthesized proteins. A major goal of current research into dendritic protein synthesis is to determine how dendritically synthesized proteins cooperate to regulate synaptic efficacy. To date, no studies have examined interactions between dendritically synthesized proteins in the same cell type and preparation. Nevertheless, by looking at a short-list of established dendritic mRNAs and their putative functions, a number of cooperative effects in synaptic plasticity can be predicted (FIG. 5). Arc and LIMK1 are both implicated in the local regulation of actin dynamics that underlies the remodelling of spines, whereas α CaMKII and PKM ζ are key regulators of AMPA-receptor-trafficking and activity^{111,134}. The secreted proteases tPA and MMP9 regulate the extracellular

matrix, which is likely to be important for coordinated pre- and postsynaptic modification. Recent evidence suggests that MMP9 modulates synaptic efficacy in the CA1 region of adult hippocampal slices through the activation of integrin receptors¹³⁵. Interestingly, β 1-family integrins are implicated in actin polymerization that underlies LTP consolidation¹³⁶.

One important function of extracellular tPA is the proteolytic conversion of proBDNF to mature BDNF, which preferentially activates TrkB receptors. The generation of mature BDNF from released pro-BDNF is considered crucial for LTP consolidation¹³⁷. Because tPA mRNA is present in dendrites, and translation is induced by neuronal activity, it is tempting to speculate that local tPA synthesis and release could spatially restrict BDNF actions. As previously mentioned, BDNF can stimulate the postsynaptic translation of several plasticity-associated mRNAs (Arc, LIMK1 and α CaMKII). Activation of presynaptic TrkB enhances glutamate release, and a study of BDNF-LTP in the perforant path-granule cell system suggests that BDNF activates a retrograde signalling pathway, leading to transcriptional activation in presynaptic cell bodies¹³⁸. BDNF might therefore have a role in coordinating pre- and postsynaptic changes in protein synthesis.

Local translation and regulation of actin dynamics: a reciprocal interaction model. A central emerging theme in the field of dendritic regulation is the possibility of reciprocal interactions between actin dynamics and dendritic protein synthesis in the control of synaptic plasticity. A large percentage of ribosomes associate with F-actin in neurons, and microfilament association is necessary for translation from some RNA granules. It has been shown that BDNF application induces a redistribution of eIF4E to an RNA-granule-rich actin fraction in synaptoneurosome and trafficking of eIF4E into the spines of cultured hippocampal neurons¹³⁹. These effects were blocked by peptide inhibitors of integrin-matrix interactions or by treatment with the F-actin-destabilizing drug latrunculin A. Many initiation and elongation factors are also actin-binding proteins. The elongation factor eEF1A, which undergoes enhanced dendritic translation in LTP and DHPG-LTD, is known to promote actin bundling independently from its function in elongation. A recent study in yeast shows that mutations of the actin-interaction region of eEF1A lead to improper organization of the actin cytoskeleton and reductions in total translation due to impairments in translation initiation (not elongation)^{140,141}. These findings strongly support a role for the actin cytoskeleton in controlling the localization and activity of the protein synthesis machinery. In turn, actin dynamics and neuronal structure are modulated by local translation in dendrites (of Arc, LIMK1 and β -actin mRNAs)^{12,40,96,142,143}.

One implication from the reciprocal interaction model is that actin polymerization that is triggered by dendritic mRNA translation will promote further local protein synthesis through translocation and activation of the translation machinery. In other words, consolidation

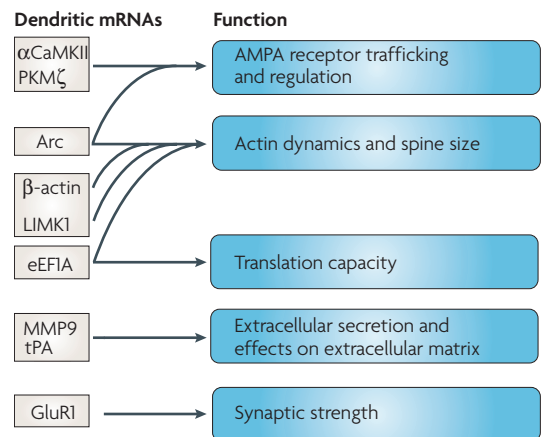


Figure 5 | Predicted functional synergy of dendritically synthesized proteins. Several dendritically synthesized proteins are implicated in long-term potentiation maintenance in the hippocampus. The known functions of these proteins suggest that they have diverse, yet overlapping roles in α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor trafficking, actin dynamics, protein synthesis and regulation of extracellular proteases. α CaMKII, calcium/calmodulin-dependent protein kinase II (α -subunit); Arc, activity-regulated cytoskeleton-associated protein; eEF1A, eukaryotic translation elongation factor 1A; LIMK1, lim domain kinase 1; MMP9, matrix metalloproteinase 9; PKM ζ , protein kinase M ζ ; tPA, tissue plasminogen activator.

might be a sequential process whereby a primary translation event generates a 'platform' for further translation. Although this idea is speculative at the moment, such a mechanism might serve as a means by which specific synapses are tagged for protein-synthesis-dependent LTP consolidation. To illustrate the point, we suggest that the translation of Arc and PKM ζ could be examples of primary and secondary translation, respectively. LTP is associated with rapid increases in Arc translation, which is necessary for stable F-actin formation. By contrast, pharmacological inhibition of PKM ζ activity reverses 1-day-old LTP in the dentate gyrus¹¹⁰. A recent report shows that treatment with an F-actin destabilizing drug blocks PKM ζ synthesis (which occurs at least partly in dendrites) and attenuates LTP maintenance^{144,145}. Taken together, these results suggest the possibility of a sequential mechanism of LTP maintenance in which Arc-dependent stabilization of F-actin facilitates PKM ζ synthesis and the maintenance of lasting LTP.

Balancing synthesis and degradation. Translation inhibitors cause LTP to decay slowly to baseline levels. However, recent data suggests that the demand for *de novo* protein synthesis varies with the level of synaptic activity after LTP induction^{146,147}. Thus, LTP decays faster when the test pulse frequency used to monitor LTP is increased from 0.017 Hz to 0.1 Hz¹⁴⁶. In addition, recent studies have shown that drugs that block the proteasome-dependent degradation of proteins prevent the formation of stable LTP^{148,149} and DHPG-LTD⁸². These surprising observations suggest that LTP and LTD

Synaptic tagging

A process by which synaptic activity evokes a transient synapse-specific change that allows the synapse to capture proteins or mRNAs that are needed for stable LTP and LTD.

consolidation involve the simultaneous rapid synthesis and degradation of proteins. One possibility is that the newly synthesized proteins are those that are being degraded, as has been demonstrated for FMRP function in DHPG-LTD⁸², and suggested for IRSp53 in cerebellar LTD⁷². During LTP consolidation in the dentate gyrus, the requirement for sustained Arc synthesis suggests that replenishment of rapidly degraded Arc could be key to its function⁴⁰.

Closing remarks

One of the major outstanding issues in this field is how dendritic protein synthesis mediates both LTP and LTD. Are these physiological changes a result of the synthesis of the same, different or overlapping sets of proteins? A definitive answer to this question awaits studies of LTP and LTD in the same neuron. However, we know

that both LTP and LTD in CA1 pyramidal neurons activate global mechanisms of translation enhancement, resulting in the synthesis of at least some of the same proteins (such as eEF1A). The specific examples of Arc and IRSp53 translation presented in this Review further suggest that the regulation of actin dynamics, through modulation of local protein synthesis, could be a common mechanism in LTP and LTD. It is likely that the direction of the efficacy change is controlled by mRNA-specific translation, combined with mechanisms for specific protein ubiquitination and proteosomal degradation. As tools for manipulating dendritic protein synthesis improve, research on the control of synaptic consolidation is likely to intensify. Such research holds promise for the development of new drugs for the management of memory disorders and other conditions linked to aberrant synaptic plasticity.

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Acknowledgements

We thank members of the Bramham and Wells laboratories for discussions. C.R.B. is supported by the Norwegian Research Council, the EU Biotechnology Program (BIO4-CT98-0333) and the Helse-Bergen Health Organization. D.G.W. is supported by the Ellison Medical Foundation and the National Institute of Mental Health. We apologize for the fact that, owing to space constraints, not all relevant papers could be cited.

Competing interests statement

The authors declare no competing financial interests.

DATABASES

Entrez Gene:

<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene>
4E-BP | α CaMKII | β -actin | Arc | Armitage | ASH1 | Aurora kinase A | BDNF | Cdc42 | CPEB1 | CREB | DCP1 | DCP2 | DEAD (Asp-Glu-Ala-Asp) BOX polypeptide 1 | DEAD BOX 3 | DEAD BOX 5 | dFMR1 | eEF1A | egr1 | eIF2 α | eIF4AIII | eIF4E | ERK1 | FMRP | FXR1 | FXR2 | G3BP | GCN2 | GluR1 | GluR2 | IIRSp53 | K1.1 | LIMK1 | Mena | MMP9 | mTOR | myosin Va | orb | P38MAP kinase | p250GAP | PARN | Pur- α | Pur- β | Rac1 | SMG5 | SMG7 | Src | Staufen | symplekin | SYNCRIP | TLS | tPA | TrkB | WAVE2 | XRN1 | ZBP1

OMIM:

<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM>

Fragile-X Syndrome

FURTHER INFORMATION

Clive R. Bramham's homepage:

<http://www.uib.no/med/biomed/research/bramham>

David G. Wells' homepage:

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