Translational control of synaptic plasticity

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Abstract

Synapses, points of contact between axons and dendrites, are conduits for the flow of information in the circuitry of the central nervous system. The strength of synaptic transmission reflects the interconnectedness of the axons and dendrites at synapses; synaptic strength in turn is modified by the frequency with which the synapses are stimulated. This modulation of synaptic strength, or synaptic plasticity, probably forms the cellular basis for learning and memory. RNA metabolism, particularly translational control at or near the synapse, is one process that controls long-lasting synaptic plasticity and, by extension, memory formation and consolidation. In the present paper, I review some salient features of translational control of synaptic plasticity.

Introduction

Long-lasting changes in synaptic strength, usually referred to as synaptic plasticity, pertain to the ability of neurons to alter communication with each other via synaptic connections in response to electrical and/or neurotrophin-mediated stimulation, and is generally considered to underlie LTM (long-term memory) [1]. The most studied forms of long-lasting synaptic plasticity in mammals are LTP (long-term potentiation) and LTD (long-term depression), which correspond to long-lasting increases or decreases respectively in synaptic strength [2]. Most of the work on LTP and LTD has been conducted in the hippocampus, a part of the brain required for memory formation and storage. Similar to memory, LTP can be defined temporally with respect to the requirement for new gene expression. E-LTP (early-phase LTP), like STM (short-term memory), does not require new gene expression, whereas L-LTP (late-phase LTP) does. Whereas many earlier molecular studies of gene expression control of LTM and L-LTP focused almost exclusively on transcription, particularly the transcription factor CREB (cAMP-response-element-binding protein) [3], experiments in the last 5–10 years have demonstrated the importance of translational control of both LTM and L-LTP. For extensive reviews of translational control of synaptic plasticity, the reader is referred to Richter and Klann [4], Waung and Huber [5], Costa-Mattioli et al. [6], Sutton and Schuman [7,8], and Steward and Schuman [9]. In the present paper, I focus on two specific proteins, FMRP (fragile X mental retardation protein) and CPEB (cytoplasmic polyadenylation element-binding protein), that mediate mRNA translation in neurons.

Translational control by FMRP

FXS (fragile X syndrome) is most often caused by CGG repeat expansion in the promoter of the FMR1 gene, leading to DNA methylation and transcriptional silencing. FMRP is the protein product of the FMR1 gene; it is an RNA-binding protein with two KH [hnRNP (heterogeneous nuclear ribonucleoprotein) K homology] domains and an RGG (arginine-glycine-glycine) box, which are both RNA-binding domains [10,11]. FMRP is expressed in many tissues and cell types; in neurons, it is present in the cell body, dendrites and even axons [12]. Although FMRP almost certainly represses translation, the mechanism by which it does so is not clear. For example, a number of laboratories have found that it sediments with polyribosomes [11,13–15], which has lead to the hypothesis that it represses translation at the elongation step [14,16]. Indeed, the phosphorylation state of FMRP is at least one determinant that controls its association with polysomes [16]. Moreover, FMRP interacts with the eEF2 (eukaryotic translation elongation factor 2)–eEF2K (eEF2 kinase) complex to modulate the translation of Arc (activity-regulated cytoskeleton-associated protein)/Arg3.1 mRNA [17], again indicating that FMRP controls translation at the elongation phase (for a brief review of the three phases of translation, initiation, elongation and termination, see [18]).

In contrast with the studies noted above, others have observed that FMRP sediments in the non-translating RNP (ribonucleoprotein) portion of polysome sucrose gradients, which is generally considered to be lighter than the 80S monosome [19,20]. Also sedimenting in the RNP fractions is CYFIP (cytoplasmic FMRP-interacting protein), a factor that also binds the cap-binding protein eIF (eukaryotic translation initiation factor) 4E. In an alternative model for how FMRP represses translation, CYFIP would be tethered to FMRP, which is thought to bind specific mRNAs, as well as to eIF4E [20]. By binding eIF4E, CYFIP would exclude eIF4G and hence indirectly the 40S ribosomal subunit from associating with mRNA. (Note that, for initiation to occur, eIF4E anchored to the cap structure on the mRNA 5’-end
binds the initiation factor eIF4G. eIF4G in turn binds yet another initiation factor, eIF3, which in turn positions the 40S ribosomal subunit on the 5′-end of the mRNA. The interaction between eIF4E and eIF4G is often regulated by other factors, thereby controlling initiation.) Napoli et al. [20] suggest that synaptic activity releases CYFIP from eIF4E to allow the initiation of translation.

Irrespective of how FMRP regulates translation, in its absence, protein synthesis in the hippocampus (and perhaps elsewhere as well) is elevated by approx. 20% [21,22]. This correlation suggests that in FXS (and perhaps other neurological diseases as well), aberrantly elevated protein synthesis is causative for many of the characteristics associated with the syndrome [23]. Because FXS is accompanied by aberrant synaptic function, one major question is does FMRP respond to synaptic signals to control translation? Perhaps the most prevalent hypothesis is ‘the mGluR (metabotropic glutamate receptor) theory of FXS’ [5,24–26]. Here, FMRP is downstream of the group I mGluRs, G-protein-coupled receptors that respond to certain chemical and electrical stimuli. In particular, application of an agonist of the mGluRs, DHPG ([S]-3,5-dihydroxyphenylglycine), elicits protein-synthesis-dependent LTD. In FMRP-knockout mice, the LTD is enhanced and is maintained in a protein-synthesis-independent manner [27–29]. One interpretation of these data is that FMRP represses the translation of mRNAs that encode ‘LTD proteins’, in the absence of FMRP, the LTD proteins are already made and are available in dendrites, which enhance the LTD character of FMRP-knockout mice. What are the identities of the LTD proteins? Stay tuned!

Translational control by CPEB

CPEB is a sequence-specific RNA-binding protein that regulates translation by modulating cytoplasmic poly(A) tail elongation [30]. In neurons, CPEB is detected at postsynaptic sites and in the cell body; in response to synaptic activity (via the ionotropic N-methyl-d-aspartate receptors), CPEB induces polyadenylation and translation of several mRNAs [31–34]. The importance of CPEB for translation in the brain was demonstrated in a CPEB-knockout mouse where θ burst-induced LTP was reduced in hippocampal Schaffer CA-1 neurons (θ burst is a type of induction protocol that resembles physiological synaptic stimulation) [35]. In addition, CPEB-knockout mice have a deficit in extinction, a type of memory where behavioural responses diminish and eventually become extinct when there is no reinforcement of the memory [36]. Although extinction requires the formation of new memories, the underlying mechanisms by which it occurs are probably separate from those of memory acquisition and consolidation [37]. One key to understanding how CPEB might influence these complex phenotypes lies in the identification of target mRNAs. Zearfoss et al. [38] have identified GH (growth hormone) as one protein whose level is reduced approx. 10-fold in the hippocampus of CPEB-knockout mice. GH mRNA contains no 3′-UTR (untranslated region) CPEs (cytoplasmic polyadenylation elements), the binding sites for CPEB, and both GH mRNA and nuclear pre-mRNA are reduced in the knockout compared with wild-type hippocampus. This suggests that an mRNA encoding a transcription factor that regulates GH gene expression might be regulated directly by CPEB. Indeed, the transcription factor c-Jun is reduced in CPEB-knockout hippocampus. The c-Jun 3′-UTR contains CPEs, and c-Jun protein co-immunoprecipitates the promoter of the GH gene in wild-type, but not CPEB-knockout, mice. Unexpectedly, GH induces LTP in hippocampal slices that, like electrical stimulation, is reduced in the CPEB-knockout mouse. In addition, the LTP induced by GH and by θ burst stimulation is reduced when slices are incubated with cordycepin (3′-deoxyadenosine), an agent that inhibits polyadenylation. These and other results suggest that GH acts as an autocrine and paracrine factor to regulate plasticity via CPEB control of c-Jun mRNA polyadenylation and translation.

Invertebrates also contain CPEB: in Aplysia sensory neurons, ablation of CPEB by antisense oligonucleotides disrupts the maintenance of LTF (long-term facilitation), a form of plasticity [39]. However, the neuronal Aplysia CPEB isoform is different from that in mammals because it contains a nearly homopolymeric stretch of glutamine residues. Polyglutamine is found in some proteins that behave as a prion, an infectious agent consisting entirely of self-reproducing protein. This observation suggested to Si et al. [39,40] that Aplysia neuronal CPEB might form a prion-like structure following synaptic stimulation, thus providing a long-lasting and self-sustaining substance to mark stimulated synapses. If this were the case, then CPEB itself, and not proteins derived from CPEB-stimulated translation, might comprise the tag that distinguishes experienced from naive synapses. Indeed, Si et al. [40] suggest that Aplysia CPEB has some features reminiscent of a prion, such as resistance to protease and a high sedimentation rate in sucrose gradients. Moreover, when introduced into yeast, Aplysia CPEB seems to have two forms: aggregated (i.e. prion-like) and non-aggregated (soluble) [40]. Surprisingly, not only did the aggregated form of CPEB bind RNA in vitro, in a yeast-based assay, it converted the non-aggregated form into an aggregated form. Such epigenetic inheritance is a primary characteristic of a prion. Si et al. [40] suggested that synaptic activation might induce the neuronal Aplysia CPEB isoform to assume a prion-like state, which in turn could induce the translation of some RNAs, cause it to alter its substrate specificity or release some mRNAs from an inhibited state. These authors hypothesized further that, once it became a prion, CPEB would be able to maintain its activity indefinitely. Although polyglutamine-containing CPEB has been hypothesized to form a prion in invertebrate neurons, vertebrate neurons do not contain a polyglutamine-rich CPEB. However, vertebrates contain three other genes that encode CPEB-like proteins (i.e. they contain similar RNA-binding regions), all of which are detected in the brain [41]. Two of these CPEB-like proteins contain some oligoglutamine, but they are not nearly as long as that in invertebrate CPEB. In addition, the other CPEB-like
proteins do not have a strong affinity for the CPE and do not support cytoplasmic polyadenylation [42]. Thus the relationship between vertebrate CPEB proteins and prions, if any, remains to be demonstrated. Even so, it is worth noting that Orb2, a *Drosophila* CPEB isoform in a head structure known as the mushroom body, is important for LTM and contains polyglutamine. Interestingly, deletion of the polyglutamine region impairs LTM, but not STM [43]. Although these data do not address prion formation or even mRNA translation, they do suggest the importance of the polyglutamine in CPEB for memory formation.

In summary, translational control in the neurons regulates many neurological activities such as synaptic plasticity and learning and memory. Although I have focused on FMRP and CPEB to illustrate general principles, it should be borne in mind that many factors regulate translation in the brain, which undoubtedly modulate additional higher-order functions in health and disease.

References


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