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Dendritic protein synthesis in the normal and diseased brain

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Abstract

Synaptic activity is a spatially-limited process that requires a precise, yet dynamic, complement of proteins within the synaptic micro-domain. The maintenance and regulation of these synaptic proteins is regulated, in part, by local mRNA translation in dendrites. Protein synthesis within the postsynaptic compartment allows neurons tight spatial and temporal control of synaptic protein expression, which is critical for proper functioning of synapses and neural circuits. In this review, we discuss the identity of proteins synthesized within dendrites, the receptor-mediated mechanisms regulating their synthesis, and the possible roles for these locally synthesized proteins. We also explore how our current understanding of dendritic protein synthesis in the hippocampus can be applied to new brain regions and to understanding the pathological mechanisms underlying varied neurological diseases.

Keywords

dendritic protein synthesis; mRNA localization; synaptic plasticity; neurological disease

1. Introduction

The brain encodes information by transducing experience-mediated neural activity into long-term modifications of synapses. These activity-dependent alterations in synapse structure and function are generally termed synaptic plasticity. A single neuron bears as many as 10^4 synapses, which can be modified independently during input-specific forms of synaptic plasticity. In many cases, the long-term synaptic modifications underlying synaptic plasticity rely upon new protein synthesis. Therefore, synaptic plasticity requires precise mechanisms to deliver newly synthesized proteins to specific synapses. One means to control the synaptic protein composite is through dendritic mRNA transport and local protein synthesis at postsynaptic sites. Local synthesis of new proteins affords the neuron tight spatial and temporal control of signal-induced gene expression. While both somatic and

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synaptic protein synthesis are critical for neuronal function, herein, we focus on the role of local protein synthesis in the normal and diseased brain.

The earliest evidence suggesting that local protein synthesis might regulate synaptic communication was the discovery of polyribosomes near postsynaptic membranes in spinal motoneurons (Bodian, 1965). Subsequently, polyribosomes were discovered at postsynaptic sites throughout the dendritic arbor of hippocampal neurons, putting forth the hypothesis that local protein synthesis may regulate hippocampal synapse development and plasticity (Steward and Levy, 1982). Dendrites also contain mRNA, ribosomal proteins, translation factors, tRNA, tRNA synthetases, and co-translational protein sorting organelles (Steward and Levy, 1982, Davis et al., 1987, Steward and Reeves, 1988, Tiedge and Brosius, 1996, Gardiol et al., 1999). Ribosomal proteins and translation factors are associated with membranous cisterns positive for endoplasmic reticulum markers near synapses (Gardiol et al., 1999), and the endoplasmic reticulum-to-Golgi secretory pathway is functional in dendrites (Horton and Ehlers, 2003). Together, these findings indicate that the molecular machinery necessary for synthesizing functional cytoplasmic and membrane-bound proteins is present within dendrites.

The quest to determine if dendritic protein synthesis occurs required novel technique development. Torre and Steward cultured neurons on a porous surface through which only neurites could extend, and transected neurites were pulsed with ^3H -leucine resulting in puromycin-sensitive labeling of proteins within dendrites (Torre and Steward, 1992). Using hippocampal slices, Feig and Lipton showed that the muscarinic receptor agonist carbachol in combination with high-frequency stimulation produced a three-fold increase in ^3H -leucine incorporation in CA1 neuron dendrites (Feig and Lipton, 1993). More recently, dendritic protein synthesis was visualized in cultured hippocampal neurons using local perfusion of a fluorescently-labeled non-canonical amino acid and brain-derived neurotrophic factor (BDNF) (Dieterich et al., 2010). These elegant studies and novel technologies demonstrated that new proteins can indeed be synthesized within the dendrites of hippocampal neurons.

In this review, we discuss the seminal studies addressing several fundamental questions: 1) what is the relationship between synaptic activity and dendritic protein synthesis, 2) what mRNAs are localized to and translated within dendrites, 3) what are the molecular mechanisms that regulate activity-induced dendritic protein synthesis, and 4) does disrupted dendritic protein synthesis contribute to brain disease? We also discuss the possibility that our increasing knowledge of the basic mechanisms regulating dendritic protein synthesis at hippocampal synapses can be applied to other brain regions and, perhaps, to developing novel therapeutics for brain diseases involving disrupted synaptic protein synthesis. Local protein synthesis in the axonal compartment is important during neuronal development and regeneration; however, these topics have been extensively summarized in recent reviews and will not be discussed here (Vuppalaanchi et al., 2009, Yoo et al., 2010, Jung and Holt, 2011, Jung et al., 2012).

2. Dendritic protein synthesis mediates some types of long-term synaptic plasticity

In 1963, Flexner and colleagues showed that protein synthesis is necessary for long-term memory in mice (Flexner et al., 1963). Since that time, protein synthesis has been shown to be required for many types of long-term synaptic plasticity and behavior. Specifically, a collection of studies showed that the late-phase of long-term potentiation (LTP) in the hippocampus requires protein synthesis (reviewed in (Silva and Giese, 1994)). Kang and Schuman showed that a protein synthesis-dependent form of LTP induced by BDNF can be generated in CA1 pyramidal neuron dendrites even when severed from their cell bodies (Kang and Schuman, 1996). Subsequently, both tetanus- and theta frequency-induced LTP were shown to be induced in severed CA1 neuron dendrites (Cracco et al., 2005, Huang and Kandel, 2005, Vickers et al., 2005). Of note, an earlier study found that tetanus-induced LTP could not be induced in severed dendrites (Frey et al., 1989); the cause of the discrepancy between these studies remains unclear. Huber and colleagues also used dendrites severed from cell bodies to show that metabotropic glutamate receptor-dependent long-term depression (mGlu-LTD) is dependent on dendritic protein synthesis (Huber et al., 2000). In addition, Sutton and colleagues demonstrated that miniature synaptic neurotransmission tonically represses dendritic protein synthesis, and dendritic protein synthesis is necessary for the homeostatic increase of GluA2-lacking AMPA receptors on the cell surface during activity blockade (Sutton et al., 2004, Sutton et al., 2006). The combination of input-specific and cell-wide control of synaptic activation is critical for the plasticity and maintenance of neural circuits, and the important studies described above have demonstrated that some forms of each plasticity type involve dendritic mRNA regulation.

3. Dendritic mRNA trafficking

Early studies suggested that dendritic mRNA localization is transcript-specific. Microtubule-associated protein 2 (MAP2) and calcium/calmodulin-dependent kinase II (α CaMKII) mRNAs are present in hippocampal dendrites, but β -tubulin and CaMKII mRNAs are restricted to the soma (Garner et al., 1988, Burgin et al., 1990, Kleiman et al., 1990). Further investigations have identified many other dendritic transcripts including mRNAs encoding the glutamate receptor subunits GluA1, GluA2, GluN1, and GluN2A (Benson, 1997, Gazzaley et al., 1997, Grooms et al., 2006, Cajigas et al., 2012, Udagawa et al., 2012), postsynaptic scaffolding proteins including postsynaptic density protein 95 (PSD95), SAP90/PSD-95-associated protein 3 (SAPAP3), and Shank1 (Kindler et al., 2004, Welch et al., 2004, Muddashetty et al., 2007, Falley et al., 2009), and other plasticity-related proteins such as β -actin, protein kinase M zeta (PKM ζ), Arc/Arg3.1, and BDNF (Miyashiro et al., 1994, Link et al., 1995, Lyford et al., 1995, Tongiorgi et al., 1997, Tiruchinapalli et al., 2003, Muslimov et al., 2004). The presence of mRNAs encoding important synaptic proteins in dendrites indicates that local protein synthesis could contribute to activity-induced changes in synapse structure and function.

Interestingly, the complement of known dendritic mRNAs also includes those encoding the translational regulators eIF4E and eEF1A as well as RNA binding proteins such as fragile X mental retardation protein (FMRP) and Pumilio2 (Antar et al., 2004, Huang et al., 2005,

Tsokas et al., 2005, Zhong et al., 2006, Moon et al., 2009). These findings suggest that proteins regulating mRNA translation can be replenished locally and, perhaps, allow for a local change in protein synthesis that extends beyond the initial synaptic activation. In addition, the mRNAs encoding transcription factors such as cAMP response element binding protein (CREB), Elk-1, Jacob, and Engrailed1 are localized to dendrites, suggesting that local protein synthesis might regulate synapse-to-nucleus signaling leading to altered transcriptional regulation (Crino et al., 1998, Barrett et al., 2006, Di Nardo et al., 2007, Kindler et al., 2009).

Large-scale microarray studies have profiled the population of localized mRNAs in the hippocampal CA1 stratum radiatum and in cultured hippocampal neurons (Poon et al., 2006, Zhong et al., 2006). The most abundant and consistently detected mRNA transcripts belong to families encoding cell surface receptors, cytoskeletal proteins, synaptic signaling molecules, translational machinery, and cell adhesion molecules. Recently, deep sequencing of the CA1 stratum radiatum revealed that as many as 2,550 mRNA transcripts might be localized to dendrites and axons (Cajigas et al., 2012). In this study, fluorescence in situ hybridization was used to validate the dendritic localization of 74 mRNAs in cultured neurons and 19 mRNAs in hippocampal sections. The wide variety of transcripts identified speaks to the potential importance of local protein synthesis in many neuronal functions and reveals an intriguing panel of newly identified mRNAs that warrant further investigation.

3.1. Activity-induced dendritic mRNA transport

Synaptic activity regulates dendritic mRNA localization, which further suggests that mRNA regulation at synapses is important for neuron function. Notably, LTP in anaesthetized rats increases dendritic localization of α CaMKII and MAP2 mRNAs suggesting that neural activity regulates dendritic mRNA localization *in vivo* (Roberts et al., 1998). LTP induction in the hippocampus of awake, behaving rats increases α CaMKII and Arc/Arg3.1 mRNA levels in synaptic fractions isolated from the dentate gyrus (Havik et al., 2003). Interestingly, the increased synaptic localization of Arc/Arg3.1 mRNA was dependent upon NMDA receptor activity, whereas α CaMKII mRNA synaptic localization was not. Taken together, these findings indicate that mRNA transport is regulated by activity *in vivo* and, perhaps, in a transcript-specific manner.

In cultured neurons, several activity-dependent mechanisms have been shown to regulate dendritic mRNA localization. For example, depolarization-induced increases in dendritic BDNF and tyrosine kinase B (TrkB) mRNAs are dependent upon L-type calcium channels and ionotropic glutamate receptor activation (Tongiorgi et al., 1997), whereas depolarization-induced localization of GluA1 and Fmr1 (fragile X mental retardation 1) mRNAs is mediated by mGlu receptor activation (Antar et al., 2004, Grooms et al., 2006). In addition, BDNF application increases the dendritic localization of β -actin, BDNF, and TrkB mRNAs (Tongiorgi et al., 1997, Eom et al., 2003). The differential regulation of specific mRNAs by particular receptor-mediated pathways indicates that parallel and/or convergent signaling pathways might activate mRNA transport machinery in neurons.

Notably, some mRNAs are targeted to dendrites in a region-specific manner. Newly synthesized Arc/Arg3.1 mRNA is targeted specifically to activated synapses in the dentate

gyrus following high frequency stimulation of a particular dendritic layer (Steward et al., 1998). Similar to Arc/Arg3.1 mRNA localization, Tongiorgi et al. found that epileptogenic stimuli localizes BDNF mRNA to specific synaptic fields in the CA3 region of the hippocampus (Tongiorgi et al., 2004). Both forms of region-specific mRNA localization are dependent on *N*-methyl-*D*-aspartate (NMDA) receptor signaling (Steward and Worley, 2001, Tongiorgi et al., 2004). In addition, the 3' UTR of Arc/Arg3.1 mRNA is sufficient to localize mRNA to individual dendritic spines of cultured hippocampal neurons (Dynes and Steward, 2012). The region- and/or synapse-specific localization of other mRNAs has not been well-studied, but these data regarding Arc/Arg3.1 and BDNF mRNA localization suggest that mRNA transport, as well as local protein synthesis, might mediate input specificity during synaptic plasticity.

Dendritic mRNA levels may also be regulated through activity-dependent mRNA degradation. Specifically, NMDA receptor activation has been shown to decrease dendritic levels of GluA1 and GluA2 mRNAs in a calcium-dependent manner (Grooms et al., 2006). While this study showed that NMDA receptor activation reduces GluA2 mRNA transcription, the rapid decrease suggests use-dependent decay in dendrites. In this regard, one study has indicated a role for eIF4AIII in activity-induced translation-dependent decay of Arc/Arg3.1 mRNA in dendrites (Giorgi et al., 2007). Interestingly, eIF4AIII is localized to dendrites, and its expression is increased during spatial learning *in vivo* (Giorgi et al., 2007, Barker-Haliski et al., 2012). While the mechanisms underlying localized mRNA degradation are just beginning to be explored, these studies indicate that mRNA degradation is likely an important regulatory step controlling local protein synthesis.

3.2. *Cis*-acting RNA elements and cognate *trans*-acting RNA binding proteins mediate dendritic mRNA transport

Messenger RNAs are transcribed, processed, and assembled into ribonucleoprotein particles (RNPs) in the nucleus and then exported to the cytoplasm (Farina and Singer, 2002). In dendrites, RNPs are actively transported on microtubules (Knowles et al., 1996, Rook et al., 2000), and several lines of evidence support a role for RNA binding proteins in microtubule-based dendritic mRNA transport. Neuronal RNPs isolated by immunoprecipitation of the kinesin protein KIF5 contain RNA binding proteins such as Staufen1 and 2, FMRP, and zipcode binding protein 1 (ZBP1) (Kanai et al., 2004). Staufen2, FMRP, and another RNA binding protein cytoplasmic polyadenylation element binding protein (CPEB) interact with kinesin proteins, and deletion of the kinesin binding domain or disruption of kinesin function restricts the dendritic localization of these RNA binding proteins as well as specific target mRNAs (Huang et al., 2003, Goetze et al., 2006, Davidovic et al., 2007, Jeong et al., 2007, Dictenberg et al., 2008, Zivraj et al., 2012). Live imaging studies have shown that Staufen2, FMRP, ZBP1, and CPEB exhibit bidirectional and microtubule-dependent movements, suggesting that they might shuttle from the soma to dendrites and back to repetitively capture and deliver mRNA transcripts (Kohrmann et al., 1999, Huang et al., 2003, Tiruchinapalli et al., 2003, Antar et al., 2005, Dictenberg et al., 2008).

Cis-acting dendritic targeting elements have been identified in the 3' UTR of many dendritic mRNAs, and, in some cases, the cognate *trans*-acting RNA binding protein has been

identified. The dendritic localization of β -actin mRNA is mediated through a 54 nucleotide sequence that ZBP1 binds, and this interaction regulates the constitutive and neurotrophin-induced dendritic localization of both ZBP1 and β -actin mRNA (Ross et al., 1997, Zhang et al., 2001, Eom et al., 2003). In the 3' UTR of MAP2 mRNA, a 640 nucleotide sequence is necessary and sufficient for dendritic localization in both hippocampal and sympathetic neurons (Blichenberg et al., 1999). The RNA binding proteins MARTA1 and MARTA2 interact with this dendritic targeting element, and MARTA2 regulates the dendritic transport of MAP2 mRNA (Rehbein et al., 2000, Rehbein et al., 2002, Zivraj et al., 2012). The 3' UTR of MAP2 also contains cytoplasmic polyadenylation element (CPE) sequences, which are bound by CPEB, and both the CPE sequences and CPEB regulate MAP2 mRNA localization (Huang et al., 2003). Several other dendritic mRNAs also contain CPE sequences, such as GluN2A, α CaMKII, inositol-phosphate-3 receptor (IP3R), BDNF, and DSCAM (down syndrome cell adhesion molecule); specifically, the CPEs in BDNF and α CaMKII mRNA have been shown to mediate dendritic mRNA localization (Wu et al., 1998, Wells et al., 2001, Huang et al., 2003, Du and Richter, 2005, Oe and Yoneda, 2010, Udagawa et al., 2012). Thus, the CPEB-CPE interaction is likely a critical regulator of dendritic transport for at least a subset of localized mRNAs. The mRNAs encoding two critical plasticity-related proteins, PKM ζ and Arc/Arg3.1, contain A2RE sequences in their 3' UTRs, and these sequences interact with hnRNP A2 to mediate dendritic mRNA localization (Shan et al., 2003, Muslimov et al., 2004, Kobayashi et al., 2005). hnRNP A2 also interacts with and regulates the dendritic localization of α CaMKII and neurogranin mRNAs (Muslimov et al., 2011, Raju et al., 2011), suggesting that hnRNP A2 also regulates dendritic transport for a subset of mRNAs.

The well-studied mRNA binding protein FMRP has been shown to interact with a multitude of mRNAs through several different RNA binding domains and *cis*-acting elements (Bassell and Warren, 2008, Darnell et al., 2011). However, there is only convincing evidence to support a role for FMRP in α CaMKII mRNA transport; the interaction of FMRP with kinesin and the 3' UTR of α CaMKII mRNA regulates α CaMKII mRNA transport (Dictenberg et al., 2008, Kao et al., 2010). Interestingly, these reports show that the motility and regulated dynamics of α CaMKII mRNA-containing granules is impaired in FMRP-deficient neurons, although total dendritic levels of α CaMKII mRNA are unaltered (Muddashetty et al., 2007). In *Drosophila* neurons lacking dFMRP, mRNAs are less dynamic and have reduced directional transport (Estes et al., 2008). Thus, it is possible that FMRP has a key role in regulating the quality of mRNA dynamics or transport, whereas other mechanisms might regulate the constitutive transport of FMRP targets to dendrites.

The discovery of several dendritic targeting elements in a single 3' UTR highlights the complexity inherent in dendritic mRNA trafficking and suggests that there may be redundant or stimulation-specific mechanisms mediating dendritic mRNA transport. In this regard, the RNA binding protein translin mediates depolarization-induced dendritic localization of BDNF mRNA; however, seizure- and BDNF-induced mRNA localization are not affected by reduced translin expression (Chiaruttini et al., 2009, Wu et al., 2011). In addition to the RNA binding proteins mentioned previously, the following are also localized to dendrites: Pumilio2, RNG105, HuD, TDP-43, hnRNP Q1, and hnRNP K, (Bannai et al.,

2004, Bolognani et al., 2004, Shiina et al., 2005, Wang et al., 2008a, Lu et al., 2009, Shiina et al., 2010, Proepper et al., 2011, Xing et al., 2012). However, it remains unclear whether these proteins regulate dendritic mRNA transport. Given that many dendritic mRNAs interact with multiple RNA binding proteins (see Table 1), it is critical that we understand how different RNA binding protein-mediated mechanisms cooperate in the transport of specific mRNAs. A few of these RNA binding proteins e.g. ZBP1 and CPEB have been shown to bind directly to *cis*-acting elements and play direct roles in mRNA localization, translation and/or stability, whereas the precise molecular interactions for other RNA binding proteins are less clear.

3.3. Signaling mechanisms regulating mRNA transport to dendrites and synapses

While several synaptic stimulation paradigms induce dendritic mRNA transport, the intracellular signaling mechanisms that recruit new mRNAs to dendrites have not been well-studied. One report showed that the lamina-specific targeting of Arc/Arg3.1 mRNA depends upon Rho kinase activity, actin polymerization, and ERK phosphorylation (Huang et al., 2007). Interestingly, ERK interacts with Staufen2 and regulates depolarization-induced dendritic transport of both Staufen2 and α CaMKII mRNA (Jeong et al., 2007, Nam et al., 2008). These few studies suggest that the MAP kinase pathway might be one mechanism that regulates mRNA transcription and/or mRNA transport. However, further work aimed at discovering how synapses signal to the soma to transcribe or ship more mRNA will be critical for understanding the regulation of dendritic protein synthesis.

Dendritic spines form the postsynaptic compartment at most glutamatergic synapses. While several mRNA transcripts and RNA binding proteins are localized to spines, the signaling mechanisms and structural proteins required for mRNA trafficking into spines remain poorly understood (Tiruchinapalli et al., 2003, Antar et al., 2005, Kao et al., 2010, Swanger et al., 2011, Udagawa et al., 2012). In one study, myosin Va was shown to mediate transport of the RNA binding protein TLS (translocated in liposarcoma) into spines (Yoshimura et al., 2006), but how RNPs are targeted into specific dendritic spines was not addressed. Recently, Martin and colleagues showed that in *Aplysia* neurons dendritic targeting of sensorin mRNA is regulated by a 3' UTR *cis*-acting element, whereas targeting to synapses is regulated by a 5' UTR element (Meer et al., 2012); these intriguing data suggest that a multistep mechanism regulates mRNA transport to dendrites and docking at synaptic sites. The lack of data regarding mechanisms targeting mRNAs and translation machinery to synapses and into spines is a critical gap in the field, and uncovering these mechanisms will greatly enhance our understanding of how synaptic activation mediates local protein synthesis.

3.4. Composition of individual dendritic RNPs

Investigations into the composition and assembly of individual dendritic RNPs have recently begun. One study demonstrated that Arc/Arg3.1, neurogranin, and α CaMKII mRNA assemble into the same RNPs through the action of hnRNP A2; whereas, β -actin mRNA, a non-A2RE containing mRNA, does not co-assemble with these mRNAs (Gao et al., 2008). Interestingly, this study reported that overexpression of Arc/Arg3.1 mRNA specifically decreases the dendritic transport of α CaMKII and neurogranin, suggesting that these three mRNAs use similar mechanisms for dendritic transport. Kiebler and colleagues reported that

dendritic RNPs contain very few mRNA transcripts, and that MAP2, β -actin, and α CaMKII mRNAs are not co-transported (Tubing et al., 2010, Mikl et al., 2011). Furthermore, Stauf2 regulates the inclusion of MAP2 mRNA in dendritic RNPs, but not β -actin or α CaMKII mRNAs, and neuronal activity alters the amount of MAP2 mRNA in distinct RNPs (Mikl et al., 2011). Interestingly, another study showed that mGlu_{1/5} receptor activation reduces the levels of Map1b mRNA in dendritic Stauf2-containing granules, but does not affect MAP2 mRNA levels (Lebeau et al., 2011). These important studies imply that RNA binding proteins and synaptic activity regulate not only RNP transport, but also RNP assembly. The development of single molecule labeling and detection has enabled investigations of individual RNPs. The continued application of these technologies will be key to further understanding the composition of distinct dendritic RNPs, an aspect of mRNA transport that is critical for determining how different synaptic stimulations regulate the translation of particular localized mRNAs.

4. Dendritic synthesis of specific proteins

A key element of local protein synthesis that remains unclear is the exact function of the locally synthesized contingent of synaptic proteins (Figure 1). In recent years, several classes of proteins have been found to be synthesized in dendrites, including neurotransmitter receptors, signaling proteins, and cytoskeletal proteins. Much of this recent work was based upon a study by Erin Schuman and colleagues wherein dendritic translation was visualized by fusing a diffusion-restricted GFP reporter to the α CaMKII 3' UTR (Aakalu et al., 2001). While GFP fluorescence in the soma was photobleached, BDNF application induced a protein synthesis-dependent increase in dendritic GFP fluorescence. Subsequent studies showed that activation of NMDA, mGlu_{1/5}, and estrogen receptors also induce local GFP synthesis using 3'UTR reporters (Gong et al., 2006, Sarkar et al., 2010). A similar approach was used to demonstrate that the 3' UTR of GluA1 mRNA can mediate dendritic protein synthesis during retinoic acid-induced homeostatic plasticity (Aoto et al., 2008). In *Aplysia* neurons, Martin and colleagues used a photoconvertible protein appended with the sensorin mRNA UTRs to show that local protein synthesis can be regulated by specific synaptic stimuli and at particular types of synapses (Wang et al., 2009). While these methods do not investigate the synthesis of actual synaptic proteins, they have provided seminal evidence for the occurrence of protein synthesis in dendrites and at synapses and will be important assays for continued investigation of the *cis*-acting elements mediating dendritic mRNA translation.

4.1. Local synthesis of signaling molecules

To address the role of dendritic α CaMKII synthesis *in vivo*, Miller et al. generated mice expressing α CaMKII mRNA lacking most of the 3' UTR, which restricted α CaMKII mRNA to the proximal dendrites and reduced α CaMKII protein by more than 80% in postsynaptic densities (Miller et al., 2002). These mice exhibited deficits in LTP, spatial memory, and fear conditioning suggesting that dendritic localization, and most likely the local translation, of α CaMKII mRNA contributes to hippocampal function and plasticity. Similarly, mice lacking the long form of the BDNF mRNA 3' UTR, the form that mediates dendritic mRNA localization, demonstrated reduced BDNF levels in dendrites, altered dendritic spine

pruning, and impaired LTP in the hippocampus (An et al., 2008). Importantly, these studies evaluated the loss of mRNA localization *in vivo*, however it remains unknown whether the defects seen in these mouse models were due specifically to the loss of dendritic protein synthesis or reduced total protein levels. Nevertheless, these studies are the first to establish a role for the 3' UTR of mRNAs encoding synaptic proteins *in vivo*, and they clearly demonstrate that dendritic mRNA localization contributes to normal functioning of the brain.

The local synthesis of BDNF was also studied in an *in vitro* system wherein local perfusion of an AMPA receptor blocker led to a localized increase in BDNF protein, which was inhibited by a protein synthesis inhibitor (Jakawich et al., 2010). While *in vivo* studies are of utmost importance, this *in vitro* approach is much more amenable to molecular and pharmacological manipulations and will be of great use for determining the mechanisms regulating dendritic protein synthesis. Moreover, local perfusion experiments could allow for dissecting the differential roles of synaptic proteins synthesized within a localized area versus those synthesized in the soma.

PKM ζ is a critical molecule for long-term potentiation in the hippocampus, and its sustained kinase activity has been proposed to, in part, mediate the long-term modifications that take place at synapses (Sacktor, 2008). Indeed, PKM ζ is synthesized in the hippocampus during long-term potentiation, and PKM ζ mRNA is localized to hippocampal neuron dendrites (Osten et al., 1996, Hernandez et al., 2003, Muslimov et al., 2004). Given its autonomous and persistent activity, the local synthesis of PKM ζ is a potential mechanism for mediating protein synthesis-dependent and input-specific synaptic plasticity. In addition, PKM ζ expression is increased in synaptic fractions following glutamate stimulation (Westmark et al., 2010). In the future, it will be important to determine whether PKM ζ is definitively translated within dendrites and what mechanisms might regulate its local synthesis; one possible regulator might be hnRNP A2, which regulates PKM ζ mRNA localization.

4.2. Dendritic synthesis of receptors and ion channels

A key molecular mechanism mediating long-term synaptic plasticity is alterations in AMPA receptor surface expression. To investigate dendritic synthesis of AMPA receptor subunits, two laboratories used transected dendrites of hippocampal neurons and studied synthesis of exogenous GluA1 or GluA2 subunits fused to their 3' UTRs (Kacharina et al., 2000, Ju et al., 2004). In both cases, mGlu_{1/5} receptor activation increased dendritic synthesis and membrane insertion of the AMPA receptor subunits (Kacharina et al., 2000, Ju et al., 2004). Although the machinery necessary for synthesis and transport of a membrane protein had been previously visualized in dendrites, these were the first studies to demonstrate that a membrane protein could be translated within the dendrite and trafficked to its functional location. Interestingly, Arc/Arg3.1, a critical regulator of AMPA receptor endocytosis, is translated within dendrites during mGlu-LTD (Waung et al., 2008). In another study, a single molecule imaging method showed that dendritic Arc/Arg3.1 translation is increased by mGlu receptor activation and decreased by action potential blockade (Tatavarty et al., 2012). These data suggest that regulating AMPA receptor expression might be one key function for local protein synthesis in dendrites.

The dendritic synthesis of two potassium channels has been shown using photoconvertible proteins. The coding region and 3' UTR of Kv1.1 mRNA were fused to the photoconvertible protein Kaede, while the coding region and 3' UTR of Kv4.2 mRNA were fused to Dendra2 (Raab-Graham et al., 2006, Lee et al., 2011). In these studies, NMDA receptor activation inhibited dendritic translation of Kv1.1, whereas it stimulated the local translation of Kv4.2. The expression of potassium channels is regulated during many forms of synaptic plasticity, and these findings suggest that dendritic protein synthesis could mediate plasticity-induced changes in dendritic excitability.

4.3. Dendritic synthesis of translational machinery and regulators

Increasing the translational capacity of a synapse might be another mechanism that mediates long-term alterations in synaptic activation. Interestingly, one study showed that the elongation factor eEF1a is rapidly synthesized within severed CA1 neuron dendrites during high frequency stimulation (Tsokas et al., 2005). However, a concurrent study showed that eEF1a is synthesized during LTD, and that the increase in dendritic eEF1a levels during high frequency stimulation in the dentate gyrus is not due to protein synthesis (Huang et al., 2005). While the results of these studies differed, it is clear that eEF1a is a dendritically regulated mRNA, and it will be interesting to determine whether altered levels of eEF1a affect local protein synthesis. The mRNA binding protein FMRP is also synthesized within dendrites, thus it is possible that its synthesis alters local mRNA translation and/or stability (Weiler et al., 1997, Tatavarty et al., 2012). Alternatively, locally synthesized RNA binding proteins could return to the nucleus or soma to bind new mRNA transcripts and transport them to dendrites. The function of this locally synthesized contingent of RNA binding proteins remains entirely unclear and will be an important topic of future study.

In addition, the local synthesis of signaling proteins regulating localized protein synthesis has also been shown. For example, the mRNA encoding p110 β , a catalytic subunit of PI3-kinase, is localized to hippocampal neuron dendrites and synthesized in synaptic fractions (Gross et al., 2010). This key signaling molecule regulates local protein synthesis as part of the Akt/PI3K/mTOR pathway (Gong et al., 2006, Gross et al., 2010). Also, PKM ζ activity has been shown to increase synaptic protein synthesis through phosphorylation-mediated inhibition of Pin1, a proline isomerase that interacts with eIF4E and 4EBP1/2 and inhibits synaptic translation (Westmark et al., 2010). These findings warrant further investigation of the function of locally synthesized p110 β and PKM ζ to determine whether a local increase of these proteins alters neuronal signaling and protein synthesis at particular synapses.

5. Translational regulation in dendrites and at synapses

Protein synthesis can be regulated through general mechanisms or through mRNA-specific mechanisms mediated by *trans*-acting factors and *cis*-acting elements. While general mechanisms can affect all mRNA transcripts, their activation can be spatially restricted through localized signaling, and, as such, these mechanisms can regulate local protein synthesis. Several receptor-mediated signaling pathways regulate local protein synthesis in dendrites, including TrkB, NMDA, and mGlu receptors (see Table 2). Interestingly, these receptors signal to both general translational mechanisms as well as mRNA-specific translational mechanisms.

5.1. Synaptic regulation of the translation machinery

Two common general translational control mechanisms are regulation of eIF2 phosphorylation and the association between eIF4E and eIF4G. eIF2 is part of the tRNA ternary complex, and eIF2 phosphorylation decreases translation by reducing the levels of functional ternary complexes (Rowlands et al., 1988). The interaction between eIF4E and eIF4G is critical for cap-dependent translation initiation as it forms part of the bridge connecting the 43S pre-initiation complex to the mRNA. A family of proteins termed eIF4E inhibitory proteins regulate this interaction by binding eIF4E and preventing its binding to eIF4G (Pause et al., 1994, Gingras et al., 1998, Richter and Sonenberg, 2005). One key signaling mechanism regulating a subset of eIF4E inhibitory proteins, called eIF4E binding proteins (4E-BPs), is the mammalian target of rapamycin (mTOR) pathway. mTOR-mediated phosphorylation of 4E-BPs disrupts their interaction with eIF4E, which allows eIF4E to bind eIF4G and facilitates translation initiation. mTOR also enhances protein synthesis through activating S6 kinase, which phosphorylates ribosomal protein S6 (Hay and Sonenberg, 2004). Importantly, eIF2, eIF4E, eIF4G, 4E-BPs, S6, and components of the mTOR signaling pathway are localized to synapses and regulated by synaptic activity (Tang et al., 2002, Asaki et al., 2003, Smart et al., 2003, Menon et al., 2004, Carroll et al., 2006, Kanhema et al., 2006, Moon et al., 2009, Takei et al., 2009). Long-term synaptic plasticity, learning, and memory are regulated by eIF2 phosphorylation as well as mTOR signaling (Tang et al., 2002, Banko et al., 2005, Costa-Mattioli et al., 2007, Antion et al., 2008a, Antion et al., 2008b, Hoeffler et al., 2008, Slipczuk et al., 2009). Moreover, mTOR signaling can be locally activated in dendrites and can regulate dendritic synthesis of an α CaMKII 3' UTR reporter protein through both Akt/PI3K and ERK signaling (Takei et al., 2004, Gong et al., 2006). A recent study also showed that BDNF-induced local dendritic protein synthesis is mediated by calcium signaling to calmodulin and PI3K, which leads to mTOR-mediated phosphorylation of S6 kinase (Zhou et al., 2010). Both mGlu and NMDA receptors have also been shown to be key regulators of translation initiation at glutamatergic synapses. mGlu receptors signal through the PI3K/mTOR pathway as well as the ERK1/2 pathway to regulate protein synthesis and synaptic plasticity (Gallagher et al., 2004, Hou and Klann, 2004, Banko et al., 2006, Ronesi and Huber, 2008, Waung and Huber, 2009). NMDA receptor activation also has been shown to elevate ERK1/2 signaling and increase eIF4E phosphorylation in the hippocampus, perhaps through activating the mTOR pathway. Interestingly, one report indicates that GluN2A-containing NMDA receptors mediate dendritic protein synthesis, whereas GluN2B-containing receptors do not (Tran et al., 2007), and the GluN2A and GluN2B subunits have shown to differentially regulate the mTOR and ERK signaling pathways (Kim et al., 2005, Wang et al., 2011). Thus, it is possible that NMDA receptor subunit expression might, in part, determine the signaling mechanism regulating dendritic protein synthesis. Together, these findings suggest that synaptic mTOR signaling to the general translation initiation machinery regulates local protein synthesis and is critical for synapse function.

Translation elongation is also a prominent step of regulation; one key regulatory mechanism is the phosphorylation of eEF2. Translocation of the ternary complex to the ribosome P-(peptidyl-) site is regulated by eEF2-mediated GTP hydrolysis, and phosphorylation of eEF2 by CaMKIII inhibits its activity, thus repressing translation elongation (Mathews et al.,

2007; Merrick and Nyborg, 2000). Interestingly, eEF2 and CaMKIII are localized at synapses and activation of ionotropic glutamate receptors leads to eEF2 phosphorylation (Marin et al., 1997, Scheetz et al., 2000, Asaki et al., 2003, Chotiner et al., 2003, Carroll et al., 2006, Kanhema et al., 2006). Sutton et al. showed that increasing miniature synaptic events at glutamatergic synapses enhances eEF2 phosphorylation, whereas blocking miniature neurotransmission decreases eEF2 phosphorylation in dendrites; this work suggests that eEF2 could regulate local protein synthesis in a manner dependent on neuronal activity level (Sutton et al., 2007).

5.2. mRNA-specific mechanisms of translation control

Subsets of mRNAs can be controlled through regulation of *trans*-acting factors that associate with specific mRNA sequences or structures. These regulatory mechanisms can be activated within particular subcellular compartments and, thus, are important in the precise temporal and spatial regulation of translation (Jackson et al., 2010). Here, the focus of discussion will be on regulatory mechanisms mediated by *trans*-acting factors that interact with 3' UTR *cis*-acting elements including RNA binding proteins, mRNA-specific eIF4E inhibitory proteins, cytoplasmic polyadenylation, and micro-RNAs. It is important to note that specific elements within the 5' UTR are also key regulators of translation; these include IRESs, complex secondary structure, and upstream open reading frames (Morris and Geballe, 2000, Hellen and Sarnow, 2001, Pickering and Willis, 2005).

5.2.1. mRNA binding proteins and bidirectional translational regulation—

Dendritic protein synthesis has two distinct phases: translational repression during transport and activation beneath distinct synaptic sites. Importantly, RNA binding proteins can reversibly repress and activate translation through stimulus-induced post-translational modifications. RNP transport granules are considered to be translationally silenced because they contain components of RNA processing bodies, which are sites of translational repression, and do not incorporate radio-labeled amino acids (Krichevsky and Kosik, 2001, Barbee et al., 2006, Eulalio et al., 2007, Cougot et al., 2008). In neurons, both depolarization and BDNF application induce several mRNAs to shift from the cellular fractions containing transport RNP markers to the fractions containing polyribosomes (Krichevsky and Kosik, 2001, Shiina et al., 2005). Indeed, these studies indicate that synaptic activity can redistribute mRNAs from a repressed state to a translation-ready state.

The RNA binding protein FMRP regulates the translation of many synaptic mRNAs and does so through different mechanisms. In many cases, FMRP represses the translation of target mRNAs, such as PSD-95, α CaMKII, GluA1, Map1b, p110 β , and Arc/Arg3.1 (Zalfa et al., 2003, Dolen et al., 2007, Muddashetty et al., 2007, Westmark and Malter, 2007, Gross et al., 2010, Kao et al., 2010), but there is also evidence that FMRP enhances translation of some mRNAs (Bechara et al., 2009, Fahling et al., 2009, Gross et al., 2011). FMRP can inhibit mRNA translation through ribosome stalling, the non-coding RNA BC1, and microRNAs (Bassell and Warren, 2008). FMRP was shown to stall ribosomes on several mRNA targets, and it has been proposed that the large majority of translational regulation by FMRP is due to ribosome stalling as FMRP is primarily associated with polyribosomes (Darnell et al., 2011). In addition, FMRP was shown to restrict the synaptic synthesis of Arc/

Arg3.1 and Map1b by interacting with the non-coding RNA, BC1 (Zalfa et al., 2003); however, there are contradicting reports regarding the interaction between FMRP and BC1 (Iacoangeli et al., 2008). A recent study suggests convergent regulation of FMRP and BC1 in neuronal function and excitability (Zhong et al., 2010). The association between FMRP and components of the microRNA pathway have encouraged studies of how FMRP and microRNAs work together to control translation (Ishizuka et al., 2002, Jin et al., 2004). In the case of PSD-95 mRNA, FMRP interacts with the dendritic microRNA miR-125a and the argonaute protein Ago2 in order to repress translation (Muddashetty et al., 2011). The phosphorylation of FMRP recruits Ago2 and miR-125a to repress PSD-95 mRNA translation, and FMRP de-phosphorylation releases Ago2 from the mRNA. GluN2A mRNA has also been proposed to be regulated by a microRNA and FMRP (Edbauer et al., 2010), suggesting that FMRP might regulate a subset of target mRNAs through microRNAs. Understanding how the different FMRP-mediated regulatory mechanisms function to control synaptic structure and function is a critical unanswered question.

The ZBP1-mediated mechanism regulating localized β -actin mRNA translation is well-studied in many cell types, and if one synthesizes work from different systems a coherent mechanism can be constructed. ZBP1 represses β -actin mRNA translation through binding the zipcode sequence and blocking 80S ribosome formation, and ZBP1 phosphorylation removes translational repression by release of ZBP1 from β -actin mRNA (Huttelmaier et al., 2005). Recently, RACK1 was identified as a scaffolding protein that facilitates the interaction between ribosomes and the ZBP1/ β -actin complex and the stimulus-induced translation of β -actin mRNA (Ceci et al., 2012). In axonal growth cones, BDNF application induces local β -actin synthesis that is dependent upon Src-mediated phosphorylation of ZBP1 (Sasaki et al., 2010). In dendrites, ZBP1 and the β -actin mRNA zipcode regulate the trafficking of β -actin mRNA, and can influence BDNF-mediated regulation of dendritic filopodia (Eom et al., 2003), suggesting that ZBP1-mediated translational regulation is necessary for normal actin distribution in dendrites. Recently, ZBP1 was shown to regulate dendrite arborization, and ZBP1 deficiency or expression of a non-phosphorylatable mutant altered dendritic morphology (Perycz et al., 2011). Since ZBP1 expression and phosphorylation were similarly required for β -actin mRNA localization and actin expression in dendrites, these data are consistent with local translation playing a critical role in dendrites, as it does in axons.

5.2.2. Cytoplasmic polyadenylation—The poly(A) tail length of some mRNAs is regulated in the cytoplasm, and this process is mediated by 3' UTR CPE sequences and the associated RNA binding protein CPEB (Richter, 2007). In neurons, activity induces the polyadenylation of several CPE-containing mRNAs such as α CaMKII, tissue plasminogen activator, and GluN2A mRNA (Wu et al., 1998, Huang et al., 2002, Shin et al., 2004, Udagawa et al., 2012). CPEB regulates activity-induced mRNA polyadenylation in neurons by interacting with a complex of translation factors that is localized to dendrites; these factors include (1) cleavage and polyadenylation specificity factor (CPSF), which binds the polyadenylation hexanucleotide AAUAAA, (2) Gld2, a poly(A) polymerase, (3) PARN, a deadenylating enzyme, and (4) symplekin, a scaffold protein upon which the ribonucleoprotein (RNP) complex is assembled (Udagawa et al., 2012). Upon NMDA

receptor activation, CPEB is rapidly phosphorylated in dendrites, which leads to the expulsion of PARN from the RNP complex and mRNA polyadenylation (Huang et al., 2002, Udagawa et al., 2012). Interestingly, in Purkinje neurons of the cerebellum, CPEB phosphorylation regulates LTD, dendritic spine morphology, and motor learning (McEvoy et al., 2007). In the hippocampus, CPEB phosphorylation is increased during LTP induction and decreased during LTD (Atkins et al., 2005), and constitutive protein phosphatase 1 activity keeps CPEB phosphorylation low in hippocampal neurons (Atkins et al., 2004). Together, these studies indicate that opposing kinase and phosphatase activities function to reversibly regulate CPEB phosphorylation in neurons, which leads to the bidirectional regulation of mRNA polyadenylation in dendrites. The GluN2A subunit of the NMDA receptor is one dendritic mRNA transcript that is regulated by the CPEB-associated complex, but several other mRNAs were recently identified as being regulated by Gld2 polymerase activity (Udagawa et al., 2012). The continued investigation of these mRNA transcripts will be critical for understanding exactly how the CPEB-associated translation factors modulate synaptic function.

An important question that remains unclear is how CPEB, or any local translation factor, might contribute to long-lasting synaptic plasticity. Synaptic modifications are made rapidly but must also be maintained in order to support long-term alterations in synaptic efficacy. α CaMKII mRNA is one established CPEB target that undergoes polyadenylation and is critical for long-term synaptic plasticity. One proposed model for long-term synaptic modification by CPEB is through a positive-feedback mechanism whereby activation of CPEB-mediated polyadenylation leads to increased translation of α CaMKII molecules, which are then incorporated into active CaMKII holoenzymes; thus, leading to further CPEB phosphorylation and translation of α CaMKII (Aslam et al., 2009). One could imagine a similar positive feedback mechanism for any plasticity-related protein that would increase NMDA receptor signaling to the CPEB-associated polyadenylation machinery. Thus, further understanding the regulation and function of CPEB-mediated local protein synthesis will provide insight regarding, not only the importance of mRNA polyadenylation at synapses, but also the newly synthesized proteins necessary for the long-term synaptic modifications underlying synaptic plasticity, learning, and memory.

5.2.3. eIF4E binding proteins—An additional mRNA-specific mechanism for regulating translation is inhibiting 43S initiation complex formation by mRNA-specific eIF4E inhibitory proteins (Abaza and Gebauer, 2008). In neurons, FMRP interacts with the eIF4E binding protein called cytoplasmic FMRP interacting protein (CYFIP, also known as Sra-1) to mediate translational repression (Napoli et al., 2008). In addition, Pumilio2 is an RNA binding protein that binds a specific 3' UTR sequence present in some mRNAs, and it inhibits translation initiation by interacting directly with the 5' cap and preventing eIF4E binding (Wharton et al., 1998, Cao et al., 2010). Finally, neuroguidin is an eIF4E binding protein that represses CPE-mediated translation and interacts with CPEB (Jung et al., 2006, Udagawa et al., 2012). Pumilio2, CYFIP, FMRP, neuroguidin, and CPEB are all localized to dendrites and have been shown to regulate synapse structure and/or function. Future work is necessary to elucidate the molecular mechanisms mediating these interactions and to determine the subset of target mRNAs regulated by these eIF4E inhibitory proteins.

5.2.4. microRNAs—Synaptic stimulation regulates the composition and levels of miRNA-containing P-body structures in dendrites (Cougot et al., 2008, Zeitelhofer et al., 2008, Banerjee et al., 2009, Huang et al., 2012). In one report, the RISC component MOV10 was shown to be rapidly released from dendritic RNA granules and degraded following NMDA receptor activation, thus leading to increased translation of CaMKII and Limk1 mRNAs (Banerjee et al., 2009). Interestingly, Schratt et al. showed that BDNF-induced translation of Limk1 mRNA is regulated by miR-134 in dendrites (Schratt et al., 2006). It will be interesting to determine if MOV10 and miR-134 work together to regulate Limk1 mRNA translation as FMRP, Ago2, and miR-125a were shown to regulate PSD-95 translation.

In addition, three studies have used large-scale approaches to determine the repertoire of synaptic microRNAs. Using laser capture and multiplex PCR, Kosik and colleagues found 5 microRNAs that were enriched in dendrites; these include miR-26, which regulates the expression of MAP2, a dendritic mRNA (Kye et al., 2007). Two other studies evaluated the enrichment of microRNAs in biochemically isolated synaptic fractions and collectively found that as many as 20 different microRNAs might be enriched at synapses (Lugli et al., 2008, Siegel et al., 2009); however, the dendritic localization was validated for only 3 microRNAs: miR-9, miR-138, and miR-218 (Siegel et al., 2009). Thus, these specific microRNAs might also have an important role for mRNA-specific translational control at synapses. These recent studies suggest that microRNAs might play a key role in modulating activity-induced translation at synapses and understanding the physiological roles for individual microRNAs at synapses is an important area for continued study.

6. Local protein synthesis throughout the brain

The overwhelming majority of studies on dendritic protein synthesis have been completed using hippocampal neurons or slices. Indeed, the hippocampus is critical for long-term memory formation, but protein synthesis-dependent synaptic plasticity occurs in many other brain regions as well (see Table 3). Collectively, these studies have established that protein synthesis-dependent plasticity controls a variety of animal behaviors including spatial memory, motor learning, drug addiction, social and reproductive behaviors, appetitive learning, and fear conditioning. Moreover, this collection of findings underscores the critical function of protein synthesis during synaptic plasticity throughout the brain and the importance for understanding how protein synthesis controls synapse structure and function. So far, a few studies have indicated that dendritic protein synthesis might play a role in brain regions other than the hippocampus (Table 3). In particular, two studies have hinted at a role for dendritic protein synthesis in the amygdala. First, polyribosomes are present within the dendrites and spines of lateral amygdala neurons, and fear conditioning increases the number of polyribosomes within dendrites (Ostroff et al., 2010). Secondly, mice lacking the 3' UTR of α CaMKII showed altered fear learning in an amygdala-dependent (hippocampus-independent) conditioning paradigm, suggesting that the dendritic localization of α CaMKII in amygdala neurons is necessary for this type of learning (Miller et al., 2002). However, as stated above, a caveat with this study is that it is unclear whether the severe reduction in α CaMKII protein caused the observed deficit in fear learning or whether it is truly a lack of dendritic translation. Nevertheless, the role of dendritic protein synthesis in the amygdala has been implicated by both of these studies, and these findings warrant future work

investigating what transcripts are localized and translated in dendrites as well as the mechanisms regulating local protein synthesis in the amygdala.

An exciting recent study has also indicated a role for dendritic protein synthesis in the hypothalamus. BDNF mRNA is localized to dendrites of hypothalamic neurons, and this localization is mediated by the long form of the BDNF mRNA 3' UTR (Liao et al., 2012). Mice lacking the long 3' UTR of BDNF mRNA show hyperphagia, severe obesity, and dysregulated leptin-induced neural activation in the hypothalamus. Each of these phenotypes can be fully rescued by viral expression of BDNF with the long 3' UTR in the hypothalamus. Whereas, overexpression of BDNF with the short 3' UTR rescues BDNF protein levels, but only partially rescues the dysregulated energy balance phenotypes. This study clearly demonstrates that the post-transcriptional regulation of BDNF mRNA through the long 3' UTR is required for appropriate metabolic regulation mediated by the hypothalamus. These studies highlight the beginning of a new focus in the field of local protein synthesis: to investigate the function of local protein synthesis beyond its role in hippocampal-dependent plasticity.

In addition to focusing on the hippocampus as a primary site of local protein synthesis, the field has also mainly focused on glutamate receptor-mediated regulation of dendritic protein synthesis. However, many neuromodulatory inputs to the hippocampus and cerebral cortex regulate protein synthesis-dependent plasticity. These afferents include dopaminergic inputs from the ventral tegmental area (Huang and Kandel, 1995, Kudoh et al., 2002, Tischmeyer et al., 2003, Huang et al., 2004, Smith et al., 2005, Nagai et al., 2007, Navakkode et al., 2007, Bloomer et al., 2008, Schicknick et al., 2008, Wang et al., 2010a), cholinergic inputs from the medial septal nucleus and the nucleus basalis magnocellularis (Frey et al., 2001, Massey et al., 2001, Frey et al., 2003, Bergado et al., 2007, McCoy and McMahon, 2007, Volk et al., 2007), and noradrenergic inputs from the locus coeruleus (Straube et al., 2003, Walling and Harley, 2004, Gelinas and Nguyen, 2005, Gelinas et al., 2007, Bloomer et al., 2008).

Interestingly, one of the first studies on dendritic protein synthesis implicated muscarinic receptors in regulating local protein synthesis in the hippocampus: carbachol treatment combined with tetanic stimulation leads to a rapid increase in protein synthesis within CA1 neuron dendrites (Feig and Lipton, 1993). Yet, since that time only one study has addressed a role for muscarinic receptors in dendritic protein synthesis. Huber and colleagues demonstrated that muscarinic receptor-dependent LTD is protein synthesis-dependent and dysregulated in the absence of the synaptic RNA binding protein FMRP (Volk et al., 2007). While this study does not definitively show that activation of muscarinic receptors regulates localized protein synthesis, it does imply a potential synaptic FMRP-mediated translational mechanism. Mice lacking FMRP also display deficits in endocannabinoid signaling and gabaergic synaptic transmission, though the mechanisms mediating these deficits remain unclear (D'Antuono et al., 2003, Centonze et al., 2008, Curia et al., 2009, Maccarrone et al., 2010). In addition, dopaminergic signaling has been shown to regulate dendritic protein synthesis in cultured hippocampal neurons using a GFP reporter and in hippocampal slices using a biotin-labeled non-canonical amino acid (Smith et al., 2005, Hodas et al., 2012). In fact, more than 300 different proteins were synthesized in the CA1 stratum radiatum

following dopamine receptor activation (Hodas et al., 2012). These studies suggest that there might be many types of neurotransmitter-mediated signaling pathways that modulate dendritic protein synthesis. Determining how these different synapses and signaling pathways are affected by newly synthesized proteins will be critical for understanding the role of local protein synthesis throughout the brain.

7. Dysregulated synaptic protein synthesis in brain disease

The evidence presented above regarding the basic mechanisms regulating dendritic protein synthesis has the potential to allow great progress in understanding the pathology of many neurological disorders. The novel technologies discussed can be applied to disease models to aid investigations of the molecular mechanisms underlying deficits in synaptic protein synthesis. Currently, basic and translational science are together fostering new therapeutic directions for some diseases associated with altered protein synthesis, such as intellectual disabilities and autism. However, there are many other types of neurological disorders potentially involving disrupted dendritic protein synthesis that have not been well-examined, and studies of these diseases might also benefit from our increasing knowledge regarding the regulation and function of dendritic protein synthesis.

7.1. Disorders associated with intellectual disability, autism, or seizures

Perhaps the best studied neurological disorder involving altered synaptic protein synthesis is fragile X syndrome (FXS), which is caused by loss of the RNA binding protein FMRP and is characterized by intellectual disability, autistic features, seizures, anxiety, and hyperactivity (Santoro et al., 2012). Mice lacking FMRP show exaggerated and dysregulated synaptic protein synthesis, enhanced mGlu-LTD, excess internalization of AMPA receptors, and increased seizure susceptibility (Bassell and Warren, 2008). Moreover, it has been hypothesized that the loss of FMRP-mediated translation regulation activated by mGlu5 receptors contributes to these synaptic deficits (Bear et al., 2004). Reducing mGlu5 receptor signaling has been shown to rescue the exaggerated synaptic protein synthesis in the mouse model and has produced promising results in clinical trials (Dolen et al., 2007, Berry-Kravis et al., 2009, Jacquemont et al., 2011, Michalon et al., 2012). In addition, further work has suggested that synaptic signaling molecules activated downstream of mGlu5 receptors such as mTOR, ERK, and PI3K might be potential therapeutic targets for fragile X syndrome (Gross et al., 2012, Santoro et al., 2012).

The wealth of research on fragile X syndrome and the basic mechanisms regulating synaptic translation has helped to elucidate a role for the mTOR pathway in regulating dendritic protein synthesis. Interestingly, dysregulated mTOR-mediated synaptic protein synthesis has been implicated in other disorders associated with intellectual disability, autism, and seizures; these include tuberous sclerosis, Down syndrome, and Rett's syndrome (Hagerman et al., 2010, Wang et al., 2010b, Troca-Marin et al., 2012). In addition, many cases of autism spectrum disorders are associated with mutations in genes encoding components of the Akt/PI3K/mTOR pathway (Lee et al., 2012). These findings collectively imply that mTOR-mediated protein synthesis is an important regulator of synaptic function and that this pathway is a potential therapeutic target for patients with varied neurological disorders.

Down syndrome has also recently been linked to dysregulated local translation of CPEB-associated dendritic mRNAs. DSCAM mRNA contains several CPE sequences and is localized to dendrites, and NMDA receptor-mediated translation of DSCAM is elevated in a mouse model of Down syndrome (Alves-Sampaio et al., 2010). In addition, BDNF protein levels and BDNF-induced local translation are elevated in this mouse model; interestingly, BDNF is also a CPE-containing mRNA that is locally translated (An et al., 2008, Oe and Yoneda, 2010, Troca-Marin et al., 2011). Moving forward it will be important to investigate whether these mRNAs are indeed locally regulated by CPEB and its associated translational regulators, and whether dysregulation of this mechanism might contribute to the altered protein expression observed in the disease model.

7.2. Neurodegenerative diseases

The dendritic RNA binding protein TDP-43 is a component of intracellular inclusions found in patients with neurodegenerative diseases such as frontotemporal lobe dementia and Alzheimer's disease (Galimberti and Scarpini, 2010, Wilson et al., 2011). While it has been suggested that TDP-43 regulates mRNA translation and is localized to dendrites in an activity-dependent manner (Wang et al., 2008a), it is unclear whether dendritic mRNA localization or local translation are dysregulated by altered TDP-43 function. In *Drosophila*, TDP-43 regulates dendrite branching suggesting it might have an important role in the maintenance or development of neural circuits (Lu et al., 2009). If indeed TDP-43 regulates mRNAs in dendrites, as is suggested by its presence within RNA granules within this compartment, it is possible that dysregulated local protein synthesis might contribute to the synapse loss associated with these diseases (Wang et al., 2008b). The continued investigation of TDP-43 in dendritic mRNA regulation will be important for understanding the pathological mechanisms underlying dementia.

Dysregulated RNA processing by TDP-43 and TLS/FUS have been implicated in amyotrophic lateral sclerosis (ALS) as well. Mutations in TDP-43 and TLS/FUS are linked to familial ALS, and both RNA binding proteins are found in the hallmark intracellular inclusions (Lagier-Tourenne et al., 2010, Strong and Volkening, 2011). TDP-43 and TLS/FUS have identified nuclear roles in mRNA splicing, but their presence in RNA transport granules in dendrites and spines suggests that altered local mRNA regulation could contribute to ALS pathogenesis (Belly et al., 2005, Fujii et al., 2005, Fujii and Takumi, 2005, Yoshimura et al., 2006, Wang et al., 2008a). TDP-43 and TLS/FUS may regulate axonal mRNA transport and local mRNA translation as well (Fallini et al., 2012, Pokrishevsky et al., 2012); thus, it will be important to determine the pre- and post-synaptic roles of these RNA binding proteins in order to understand their potential contribution to neurodegeneration.

Huntington's disease is caused by a polyglutamine expansion in the gene encoding huntingtin protein, and the primary pathological manifestation is striatal medium spiny neuron degeneration (Cowan and Raymond, 2006). The specific function of huntingtin is unclear but it has been implicated in many types of intracellular transport, and recent studies indicate that huntingtin might be involved in dendritic RNA transport and regulation. Huntingtin interacts with Ago2 and represses the translation of a reporter protein, and it co-

localizes with Ago2, P-body proteins, and Staufen in rat cortical neuron dendrites (Savas et al., 2008, Savas et al., 2010). Huntingtin was also shown to co-localize with the 3' UTR of IP3R1, -actin, and BDNF mRNAs in dendrites (Ma et al., 2010, Savas et al., 2010). Furthermore, huntingtin knockdown reduced dendritic levels of -actin mRNA, Ago2 protein, and P-bodies (Savas et al., 2010, Ma et al., 2011). These studies reveal a potentially exciting advance in understanding the basic biology of dendritic mRNA regulation and identify a new putative role for dysregulation of dendritic RNA processing in Huntington's disease. If indeed huntingtin does play a role in regulating mRNA transport and local translation, then an important next step will be to decipher why striatal neurons are specifically affected in this disease.

7.3. Psychiatric disorders

An identified human mutation in BDNF (G694A) is associated with increased susceptibility to major depressive disorder and bipolar disorder (Pezawas et al., 2004, Bath and Lee, 2006, Krishnan et al., 2007, Soliman et al., 2010, Bath et al., 2011, Bath et al., 2012). When introduced into a mouse model, this mutation disrupts the dendritic targeting of BDNF mRNA in hippocampal neurons and the interaction between BDNF mRNA and the RNA binding protein translin (Chiaruttini et al., 2009). Indeed, translin has been shown to regulate dendritic targeting of BDNF mRNA through a sequence within the coding region of BDNF (Chiaruttini et al., 2009). Translin is associated with regulation of local protein synthesis as well as learning and memory (Kobayashi et al., 1998, Muramatsu et al., 1998, Finkenshtadt et al., 2000, Li et al., 2008), and translin knockout mice have altered spatial memory, fear learning, and anxiety behaviors (Stein et al., 2006). These data suggest that altered local BDNF production could contribute to synaptic dysfunction in patients and warrant further investigations into the connection between altered BDNF synthesis at synapses and psychiatric disorders.

Recent evidence suggests that altered synaptic protein synthesis might be the mechanism underlying the rapid therapeutic effects of ketamine in patients with major depression. In one study, it was shown that the NMDA receptor antagonist ketamine rapidly activates the mTOR pathway leading to synaptic synthesis of PSD95 and GluA1 (Li et al., 2010). Indeed, postmortem studies of patients with major depressive disorder show defects in NMDA receptor levels and activation of the mTOR pathway in the prefrontal cortex, suggesting that mTOR-mediated translation might be dysregulated during major depression (Jernigan et al., 2011). Another study reported that ketamine administration does not rapidly enhance translation through the mTOR pathway, but rather through the deactivation of eEF2 kinase and rapid translation of BDNF mRNA in the cortex (Autry et al., 2011). These studies both point towards NMDA-receptor mediated protein synthesis as a possible mechanism underlying the rapid antidepressant effects of ketamine. Understanding how to rapidly relieve depressive symptoms is of utmost importance as all pharmaceutical therapies for depression take days to weeks to effect behavior. Further research is necessary to understand the specific signaling pathways and NMDA receptor subunits involved in the rapid effects of ketamine in order to develop safer and more effective treatments for major depressive disorder.

8. Concluding remarks

While recent studies have begun to reveal the contingent of localized mRNAs and the mechanisms mediating their local regulation, much work is still necessary in order to understand the function of locally synthesized proteins and the distinct physiological conditions during which specific proteins are locally synthesized. The use of novel technologies including non-canonical amino acids, local perfusion assays, and microfluidic chambers will be of the utmost importance in such studies. In addition, more work is needed to understand the multistep mechanisms involved in dendritic mRNA localization and translational regulation at synapses. Protein synthesis-dependent plasticity clearly involves multiple levels of spatio-temporal regulation, which likely proceed first by the translational de-repression of mRNAs that are already present in spines. These early responses appear to be followed by changes in the localization and dynamics of mRNAs in the nucleus, soma and dendrite. These mechanisms likely differ between mRNAs, and there appear to be a collection of important *trans*-acting mRNA binding proteins that regulate these steps. As discussed, a promising new direction for the local protein synthesis field is the expansion of studies to include brain regions beyond the hippocampus and cerebral cortex. Exciting new studies suggest that localized protein synthesis might occur in the amygdala, striatum, and hypothalamus, and it will be intriguing to see how widespread the role of dendritic protein synthesis is in modulating brain function and behavior. Finally, it is becoming evident that many neurological disorders might involve dysregulated protein synthesis. While intellectual disabilities and autism spectrum disorders have received some focus recently, additional studies indicate that neurodegenerative and psychiatric disorders could also involve altered synaptic proteins synthesis. Clinical research on fragile X syndrome that is based, in part, on basic studies of FMRP-mediated synaptic protein synthesis has already emerged, and this suggests that the continued study of basic mechanisms regulating localized protein synthesis is a promising means for understanding and identifying therapeutic strategies to treat neurological disorders.

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Highlights

Locally synthesized proteins have diverse functions at the synapse.

RNA binding proteins cooperatively regulate dendritic protein synthesis.

Local protein synthesis regulates neuronal function outside the hippocampus.

Varied neurological disorders may involve dysregulated local protein synthesis.

Figure 1. Model for maintenance of altered synaptic function through locally synthesized proteins

During neural activity leading to long-term synaptic modifications, cell surface proteins such as NMDA, receptors signal to dendritic protein synthesis machinery to regulate levels of specific TrkB, and mGlu_{1/5} synaptic proteins. The synthesis of synaptic signaling molecules, translation factors, potassium channels, and glutamate receptor subunits/regulators modulates synaptic signaling, translation, or surface receptor/channel expression, which leads to altered intracellular signaling, dendritic excitability, and receptor-mediated signaling. The nature of this system is that it feeds back to allow for persistent changes in signaling and activation at synapses.

Table 1

Combinatorial regulation of mRNA transcripts by RNA binding proteins.

		RNA binding protein							
		CPEB	FMRP	Htt ^a	hnRNP A2	MARTA1	Staufen2	Translin	ZBP1
mRNA	MAP2	+			+	+	+		
	CaMKII	+	+		+		+	+	
	-actin			+			+		+
	BDNF	+						+	
	Arc/Arg3.1		+		+				
	MAP1b		+				+		
	GluN2A	+	+						

^a Htt: huntingtin

Table 2

Specific receptor-mediated effects on RNA binding protein-controlled mRNA translation or trafficking

RNA binding protein	Extracellular signal or receptor	RNA binding protein phosphorylation/intracellular effect	References
CPEB	NMDA receptors	Aurora kinase/translation	(Wells et al., 2001, Huang et al., 2002, Udagawa et al., 2012)
	NMDA receptors	CaMKII, PP1/translation	(Atkins et al., 2004, Atkins et al., 2005)
	mGlu _{1/5} receptors	Aurora/translation	(Shin et al., 2004, McEvoy et al., 2007)
FMRP	DHPG/mGlu _{1/5} receptors	PP2A, S6 kinase/translation	(Narayanan et al., 2007, 2008)
	DHPG/mGlu _{1/5} receptors	transport	(Antar et al, 2004, Dictenberg et 2008)
	D ₁ receptors	PP2A, S6 kinase/translation	(Wang et al., 2010)
Staufen2	depolarization	MAP kinase/transport	(Jeong et al., 2007)
TLS/FUS	mGlu ₅ receptors	transport	(Fujii et al., 2005)
TDP-43	depolarization	transport	(Wang et al., 2008)
Translin	BDNF, depolarization	transport	(Chiaruttini et al., 2009, Wu et al., 2011)
ZBP1	BDNF	Src kinase/translation	(Eom et al., 2003, Sasaki et al., 2010, Welshhans et al., 2011, Perycz et al., 2011)
	NMDA receptors	transport	(Tiruchinapalli et al., 2003)

Table 3

Evidence for dendritic protein synthesis outside the hippocampus.

Brain region	Localized RNA or translation machinery	Regulation	Dendritic protein synthesis (References)	Protein synthesis-dependent plasticity (References)
Amygdala	polyribosomes	fear learning	(Ostroff et al., 2010)	reviewed in (Helmstetter et al., 2008)
	CaMKII mRNA	-	(Miller et al., 2002)	
Cerebellum	IP3R mRNA	BDNF, Hzf ^a	(Iijima et al., 2005)	(Linden, 1996, Karachot et al., 2001)
	Shank1 and Shank2 mRNAs	-	(Bockers et al., 2004)	
	L7/PCP-2 mRNA	KCl, GABA	(Wanner et al., 1997, Wanner et al., 2000, Zhang et al., 2008)	
Dorsal raphe nucleus	-	-	-	(Baker-Herman and Mitchell, 2002)
Nucleus accumbens	miR-181a	dopamine	(Saba et al., 2012)	(Hernandez and Kelley, 2004, Kuo et al., 2007, Pedroza-Llinas et al., 2009, Sun and Wolf, 2009, Ferretti et al., 2010, Neasta et al., 2010, Wang et al., 2010c)
Hypothalamus	BDNF mRNA	-	(Liao et al., 2012)	-
Striatum	PSD-95 mRNA	-	(Muddashetty et al., 2007)	(Mao et al., 2008, Maccarrone et al., 2010)
	BC1 RNA	-	(Centonze et al., 2007)	
Thalamus	-	-	-	(Parsons et al., 2006)
Ventral tegmental area	-	-	-	(Sorg and Ulibarri, 1995, Schilstrom et al., 2006, Mameli et al., 2007, Argilli et al., 2008)

^a Hzf: hematopoietic zinc finger protein