Neuropharmacology xxx (2013) 1–18

Contents lists available at SciVerse ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

# BDNF-induced local protein synthesis and synaptic plasticity

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ARTICLE INFO

*Article history:*
Received 2 February 2013
Received in revised form
25 March 2013
Accepted 3 April 2013

*Keywords:*
Brain-derived neurotrophic factor (BDNF)
Synaptic plasticity
Long-term potentiation (LTP)
Translation
RNA transport

ABSTRACT

Brain-derived neurotrophic factor (BDNF) is an important regulator of synaptic transmission and long-term potentiation (LTP) in the hippocampus and in other brain regions, playing a role in the formation of certain forms of memory. The effects of BDNF in LTP are mediated by TrkB (tropomyosin-related kinase B) receptors, which are known to be coupled to the activation of the Ras/ERK, phosphatidylinositol 3-kinase/Akt and phospholipase C-γ (PLC-γ) pathways. The role of BDNF in LTP is best studied in the hippocampus, where the neurotrophin is thought to act at pre- and post-synaptic levels. Recent studies have shown that BDNF regulates the transport of mRNAs along dendrites and their translation at the synapse, by modulating the initiation and elongation phases of protein synthesis, and by acting on specific miRNAs. Furthermore, the effect of BDNF on transcription regulation may further contribute to long-term changes in the synaptic proteome. In this review we discuss the recent progress in understanding the mechanisms contributing to the short- and long-term regulation of the synaptic proteome by BDNF, and the role in synaptic plasticity, which is likely to influence learning and memory formation.

This article is part of a Special Issue entitled 'BDNF'.



## 1. Introduction

In the mammalian nervous system, experience-dependent changes in synapse structure and function is thought to underlie learning and memory formation (Kandel, 2001). The long-term potentiation (LTP) of hippocampal synapses, particularly in the CA1 region, is the most studied form of plasticity, comprising three sequential steps: the short-term potentiation and the early-LTP (E-LTP), which are transcription and translation independent and last for about 1–2 h, and the late LTP (L-LTP), which may last for hours to days and depend on transcription and translation activity (Costa-Mattioli et al., 2009; Malenka and Bear, 2004; Mayford et al., 2012).

The neurotrophin brain-derived neurotrophic factor (BDNF) has been shown to play a key role as mediator of activity-induced LTP in the hippocampus as well as in other brain regions (Bramham and Messaoudi, 2005; Cowansage et al., 2010; Lu et al., 2008; Minichiello, 2009; Park and Poo, 2013; Santos et al., 2010). The early effects of BDNF result from the modification of components already available at the synapse (e.g. protein phosphorylation) while the long-term effects arise from modification of translation activity at the synapse and changes in transcription. This has been investigated to a great extent in the hippocampus, and is the main focus of this review. The contribution of BDNF to the behavioral plasticity has been reviewed elsewhere (Cowansage et al., 2010) and will not be further discussed here.

*Abbreviations:* ADF, actin-depolymerizing factor; A2RE, heterogeneous nuclear ribonucleoprotein (hnRNP) A2 response element; Arc, activity-regulated cytoskeleton-associated protein; AS, antisense; BDNF, brain-derived neurotrophic factor; CaMKII, $Ca^{2+}$- and calmodulin-dependent protein kinase II; CaMKK, $Ca^{2+}$- and calmodulin-dependent protein kinase kinase; CPE, cytoplasmic polyadenylation element; CPEB, cytoplasmic polyadenylation element-binding protein; CREB, cAMP-response element-binding protein; CYFIP1, cytoplasmic Fmr-interacting protein 1; DG, dentate gyrus; 4EBP, eIF4E-binding protein; eEF, eukaryotic elongation factor; eIF, eukaryotic initiation factor; EJC, exon junction complex; E-LTP, early-LTP; FMRP, fragile X mental retardation protein; GIPC1, PDZ (postsynaptic density-95/Discs large/zona occludens-1) domain-containing adaptor protein, type 1; GRIP1, glutamate receptor-interacting protein 1; HFS, high-frequency stimulation; hnRNP, heterogeneous nuclear ribonucleoprotein; IEG, immediate-early genes; IP3, inositol 1,4,5-trisphosphate; IRES, internal ribosomal entry site; LIMK1, LIM domain kinase 1; L-LTP, late-LTP; LTP, long-term potentiation; MAP, microtubule-associated protein; MEK1/2, MAPK and ERK kinase, type 1/2; mRNPs, messenger ribonucleoprotein complexes; MSK1, mitogen- and stress-activated kinase 1; mTOR, mammalian target of rapamycin; NT-4, neurotrophin-4; PAK, p21-activated kinase; P-bodies, RNA processing bodies; PH domain, pleckstrin homology domain; PICK1, protein interacting with C kinase 1; PI3-K, phosphatidylinositol 3-kinase; PLC-γ, phospholipase C-γ; PSD, postsynaptic density; PSD95, postsynaptic density protein 95; PSF, polypyrimidine tract binding protein-associated splicing factor; Pum2, pumilio2; Rim1α, Rab3a interacting molecular 1 α; RISC, RNA-induced silencing complex; SAM68, Src-associated in mitosis of 68 kDa; SAP97, synapse-associated protein 97; TORC, target of rapamycin (TOR) complex; TrkB, tropomyosin-related kinase B; TRPC3, transient receptor-potential cation channel subfamily C (TRPC), type 3; ZBP1, zipcode-binding protein 1.

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0028-3908/$ – see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.neuropharm.2013.04.005

## 2. Dendritic transcripts

The hypothesis of local protein synthesis at neuronal sites distant from the soma was raised after to the work of Steward and Levy, who showed that polyribosomes can accumulate at the base of the dendritic spines forming a rosette-like structure (Steward and Levy, 1982), suggesting that they were bound to mRNA and involved in protein synthesis. This observation lead to the search for the mRNAs present in dendrites, and to the study of the mechanisms involved in their transport and how local protein synthesis is regulated at the synapse.

In highly polarized cells such as neurons, the transport of mRNAs coupled with local translation provides an important mechanism for spatial and temporal control of protein synthesis. Dendritic localized mRNAs are usually packaged into large messenger ribonucleoprotein complexes (mRNPs) that engage with motor proteins for the microtubule-dependent transport along dendrites. These transcripts are generally kept in a dormant state during the transport and then translated upon stimulation at or near activated synapses (Bramham and Wells, 2007) (Fig. 1). Several mRNAs were found to localize in dendritic processes under different physiological conditions. One of the major challenges of identifying dendritic mRNAs is the concentration of mRNAs in dendrites which is several times lower when compared with cell body-localized mRNAs, making somatic contamination a real issue.

The dendritic transcriptome is not yet fully characterized. The first estimations predicted that approximately 400 dendritic mRNAs could be present in the dendrites of cultured rat hippocampal neurons (Eberwine et al., 2001). A similar number of transcripts was identified in two other studies: i) in neurites of hippocampal neurons, using microarray analysis and a culture system that allows mechanical separation of axons and dendrites (129 mRNAs) (Poon et al., 2006); ii) in the *stratum radiatum* (dendritic lamina) from the rat hippocampal CA1 region (156 mRNAs) (Zhong et al., 2006). A different approach used consisted in the identification of conserved sequence elements in the transcripts that may explain their cellular localization and intracellular transport specificity (Lein et al., 2007). This strategy also predicted a low number of dendritic mRNAs (59 transcripts). A much higher number of transcripts was recently identified using deep RNA sequencing in microdissected synaptic neuropil (*stratum radiatum* and *lacunosum moleculare*) segments from the CA1 region of the adult rat hippocampus (Cajigas et al., 2012). Since the neuropil tissue is comprised of dendrites, axons, glial cells, interneurons and blood vessels, the data obtained for the full neuropil transcriptome was filtered and 2550 mRNAs were attributed to dendrites and/or axons (Cajigas et al., 2012).

Comparison of the axodendritic transcriptome in hippocampal neurons with the whole rat genome clearly shows that certain functional categories are preferentially targeted to the neurite

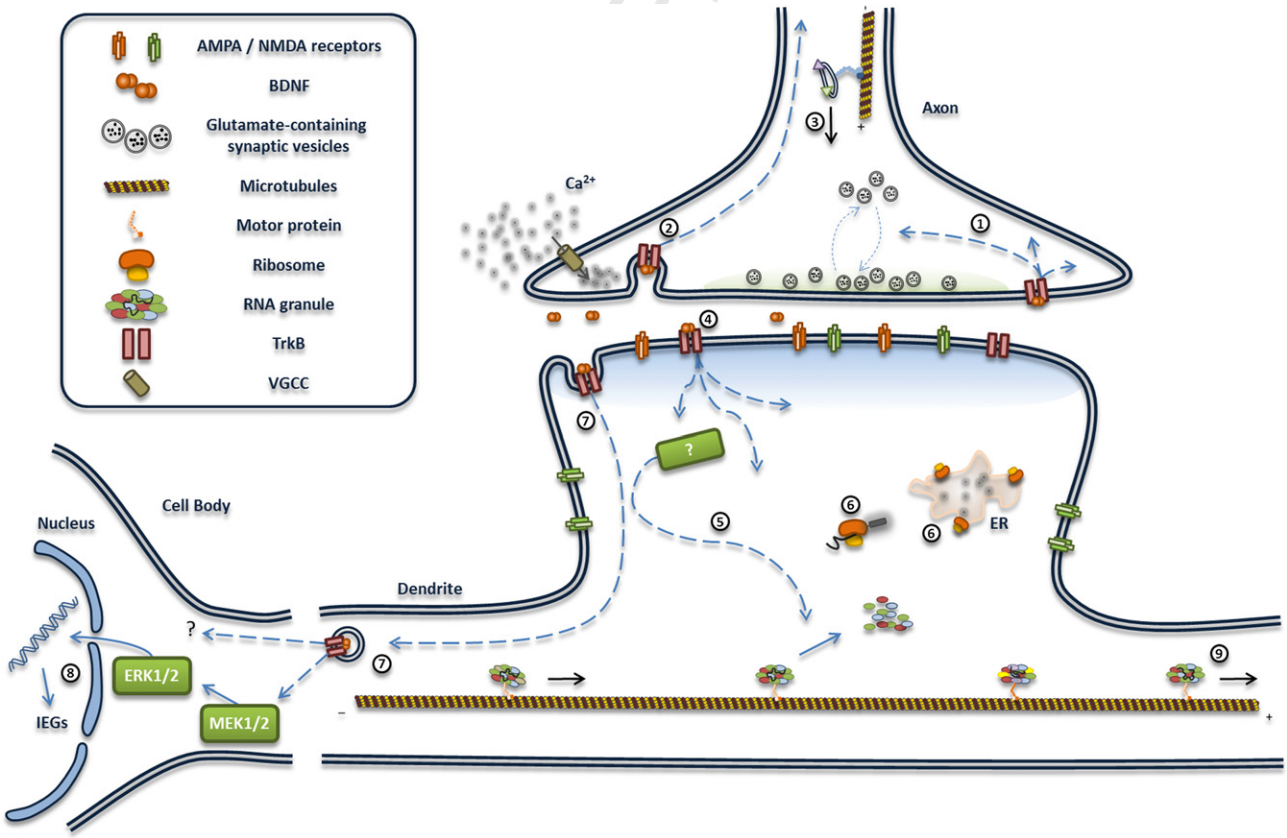


**Fig. 1.** BDNF-induced local translation at the synapse and upregulation of gene expression. TrkB receptor activation upon BDNF binding increases the accumulation of synaptic vesicles at the active zone in the presynaptic region, thereby potentiating synaptic transmission (1). BDNF-TrkB complex can be internalized and retrogradely transported toward the cell body (2). Once in the soma the active receptors may change gene expression and mRNA translation, and newly synthesized proteins may be then transported along the axon together with preexisting proteins (3). The BDNF-TrkB complex may also induce postsynaptic responses (4), including the disassembly of the RNA granules (5), through activation of different signaling pathways. RBPs-associated mRNAs become therefore available for translation, either at free polysomes or at the ER-associated ribosomes (6). BDNF-TrkB "signaling endosomes" are also transported from the dendritic spine to the cell body (7), where it leads to the transcription of IEGs in a MEK1/2 and ERK1/2 dependent manner (8). In dendrites, RNA granules containing mRNAs are transported along microtubules and can be "recruited" by an active dendritic spine or they may continue the movement toward more distal sites (9).

Please cite this article in press as: Leal, G., et al., BDNF-induced local protein synthesis and synaptic plasticity, Neuropharmacology (2013), http://dx.doi.org/10.1016/j.neuropharm.2013.04.005