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Progress in Neurobiology 76 (2005) 99–125

progress in Neurobiology

www.elsevier.com/locate/pneurobio

BDNF function in adult synaptic plasticity: The synaptic consolidation hypothesis

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Received 24 February 2005; received in revised form 9 May 2005; accepted 16 June 2005

Abstract

Interest in BDNF as an activity-dependent modulator of neuronal structure and function in the adult brain has intensified in recent years. Localization of BDNF-TrkB to glutamate synapses makes this system attractive as a dynamic, activity-dependent regulator of excitatory transmission and plasticity. Despite individual breakthroughs, an integrated understanding of BDNF function in synaptic plasticity is lacking. Here, we attempt to distill current knowledge of the molecular mechanisms and function of BDNF in LTP. BDNF activates distinct mechanisms to regulate the induction, early maintenance, and late maintenance phases of LTP. Evidence from genetic and pharmacological approaches is reviewed and tabulated. The specific contribution of BDNF depends on the stimulus pattern used to induce LTP, which impacts the duration and perhaps the subcellular site of BDNF release. Particular attention is given to the role of BDNF as a trigger for protein synthesis-dependent late phase LTP—a process referred to as synaptic consolidation. Recent experiments suggest that BDNF activates synaptic consolidation through transcription and rapid dendritic trafficking of mRNA encoded by the immediate early gene, Arc. A model is proposed in which BDNF signaling at glutamate synapses drives the translation of newly transported (Arc) and locally stored (i.e., αCaMKII) mRNA in dendrites. In this model BDNF tags synapses for mRNA capture, while Arc translation defines a critical window for synaptic consolidation. The biochemical mechanisms by which BDNF regulates local translation are also discussed. Elucidation of these mechanisms should shed light on a range of adaptive brain responses including memory and mood resilience.

Contents

Abbreviations: ACD, actinomycin D; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor; Arc, activity-regulated cytoskeleton-associated protein; Arg, activity-regulated gene; BDNF, brain-derived neurotrophic factor; BDNF-LTP, brain-derived neurotrophic factor-induced long-term potentiation; CA, cornu ammonis; CaMKII, calcium/calmodulin-dependent protein kinase II; CPEB, cytoplasmic polyadenylation binding protein; CRE, calcium/cyclic AMP responsive element; Cre, cyclization recombination; CREB, calcium/cyclic AMP responsive element binding protein; eEF2, eukaryotic elongation factor-2; eIF4E, eukaryotic initiation factor 4E; 4E-BP, eIF4E binding protein; EPSP, excitatory postsynaptic potential; ERK, extracellular signal-regulated protein kinase; GFP, green fluorescent protein; HFS, high-frequency stimulation; IEG, immediate early gene; IPSP, inhibitory postsynaptic potential; LTD, long-term depression; LTP, long-term potentiation; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MEK, mitogen and extracellular signal regulated protein kinase; mGluR, metabotropic glutamate receptor; Mnk1, MAPK integrating kinase 1; mTOR, mammalian target of rapamycin; NGF, nerve growth factor; NMDAR, *N*-methyl-D-aspartate (NMDA) receptor; NT-3, neurotrophin-3; PI3K, phosphatidylinositol-3-OH kinase; PKA, cyclic AMP-dependent protein kinase; PLC, phospholipase C; PSD, postsynaptic density; Trk, tropomyosin-related receptor kinase; TRP, transient receptor potential; UTR, untranslated region

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0301-0082/$ – see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.pneurobio.2005.06.003

1. Introduction

The neurotrophin family of signaling proteins, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and NT-4/5, is crucially involved in regulating the survival and differentiation of neuronal populations during development (Levi Montalcini, 1987; Davies, 1994; Lewin and Barde, 1996). In addition to these well-established functions in development, a large body of work suggests that neurotrophins continue to shape neuronal structure and function throughout life (Castren et al., 1992; Schnell et al., 1994; Thoenen, 1995; Bonhoeffer, 1996; Prakash et al., 1996; Cabelli et al., 1997; Alsina et al., 2001; Maffei, 2002; Bolanos and Nestler, 2004; Duman, 2004; Tuszynski and Blesch, 2004). While neurotrophins traditionally were thought to operate on a time scale of days and weeks, rapid effects have now been demonstrated on a host of cellular functions including ion channel activity, neurotransmitter release, and axon pathfinding (Song and Poo, 1999; Schinder and Poo, 2000; Kovalchuk et al., 2004).

BDNF has emerged a major regulator of synaptic transmission and plasticity at adult synapses in many regions of the CNS. This unique role within the neurotrophin family fits with the widespread distribution of BDNF and the co-localization of BDNF and its receptor, TrkB, at glutamate synapses. The versatility of BDNF is emphasized by its contribution to a range of adaptive neuronal responses including long-term potentiation (LTP), long-term depression (LTD), certain forms of short-term synaptic plasticity, as well as homeostatic regulation of intrinsic neuronal excitability (Desai et al., 1999; Asztely et al., 2000; Ikegaya et al., 2002; Maffei, 2002). Here, we focus on the molecular mechanisms and functions of BDNF in LTP in the hippocampus. The hippocampus is the only structure in which these mechanisms have been explored in any detail in the adult brain. Despite individual breakthroughs in recent years, the results often appear contradictory and an integrated understanding of BDNF function in synaptic plasticity is lacking. The role of BDNF in visual cortical plasticity is covered in several recent papers and will not be discussed here (Akaneya et al., 1996, 1997; Kinoshita et al., 1999; Kumura et al., 2000; Sermasi et al., 2000; Bartoletti et al., 2002; Ikegaya et al., 2002; Maffei, 2002; Jiang et al., 2003).

The review has three goals. First, we will critically evaluate the literature, dividing the actions of BDNF into three discrete mechanisms (permissive, acute instructive, and delayed instructive). Second, we will elaborate on recent studies suggesting that BDNF drives the formation of stable, protein synthesis-dependent LTP—a process referred to as synaptic consolidation. A working model for synaptic consolidation based on induction of the immediate early gene Arc/Arg3.1 and local regulation of dendritic protein synthesis, is proposed. Third, we aim to integrate current views of BDNF function in synaptic plasticity while pointing to major gaps in the field.

2. LTP: induction switch, consolidation process

Synaptic plasticity can be defined as an experience-dependent change in synaptic strength (Bliss and Collingridge, 1993). Lasting changes in synaptic strength are almost certainly important in information storage during memory formation (Morris, 2003), yet this traditional view is changing as roles for synaptic plasticity in other adaptive responses including mood stability, drug addiction, and chronic pain are starting to unfold (Malenka and Bear, 2004). LTP is typically induced by high-frequency stimulation (HFS) of excitatory input leading to rapid elevation of calcium in postsynaptic dendritic spines. At most excitatory synapses this critical calcium influx is provided by activation of *N*-methyl-D-aspartate (NMDA) type glutamate receptors, with contributions from voltage-gated calcium channels and mobilization of calcium from