Available online at www.sciencedirect.com
ScienceDirect
Neurobiology of Learning and Memory 89 (2008) 312–323
Neurobiology of Learning and Memory
www.elsevier.com/locate/ynlme

BDNF: A key regulator for protein synthesis-dependent LTP and long-term memory?

Yuan Lu [a], Kimberly Christian [c], Bai Lu [a,b,*]

[a] *Gene, Cognition and Psychosis Program (GCAP), NIMH, National Institutes of Health, Bethesda, MD 20892-3714, USA*
[b] *Section on Neural Development & Plasticity, NICHD, National Institutes of Health, Bethesda, MD 20892-3714, USA*
[c] *Mood and Anxiety Program (MAP), NIMH, National Institutes of Health, Bethesda, MD 20892-3714, USA*

Received 12 August 2007; revised 23 August 2007; accepted 23 August 2007
Available online 17 October 2007

Abstract

It is generally believed that late-phase long-term potentiation (L-LTP) and long-term memory (LTM) require new protein synthesis. Although the full complement of proteins mediating the long-lasting changes in synaptic efficacy have yet to be identified, several lines of evidence point to a crucial role for activity-induced brain-derived neurotrophic factor (BDNF) expression in generating sustained structural and functional changes at hippocampal synapses thought to underlie some forms of LTM. In particular, BDNF is sufficient to induce the transformation of early to late-phase LTP in the presence of protein synthesis inhibitors, and inhibition of BDNF signaling impairs LTM. Despite solid evidence for a critical role of BDNF in L-LTP and LTM, many issues are not resolved. Given that BDNF needs to be processed in Golgi outposts localized at the branch point of one or few dendrites, a conceptually challenging problem is how locally synthesized BDNF in dendrites could ensure synapse-specific modulation of L-LTP. An interesting alternative is that BDNF–TrkB signaling is involved in synaptic tagging, a prominent hypothesis that explains how soma-derived protein could selectively modulate the tetanized (tagged) synapse. Finally, specific roles of BDNF in the acquisition, retention or extinction of LTM remain to be established.
Published by Elsevier Inc.

Keywords: Synaptic plasticity; TrkB; Presynaptic; Postsynaptic; Local translation; Dendritic; Tetanic stimulation; Synaptic tagging; Encoding; Consolidation; Extinction

1. Introduction

Synaptic plasticity describes the process by which connections between two neurons, or synapses, change in strength. By definition, it is a functional term referring to an increase or decrease in synaptic efficacy, but we now know that the physiological changes in the strength of transmission are often accompanied by structural alterations of the synapses. Since memories are believed to be stored in synapses of the brain, synaptic plasticity is thought to be the cellular mechanism for learning and memory. LTP in the hippocampus is the most studied form of synaptic plasticity. It has been widely accepted that LTP can be divided into at least two temporally distinct phases that are fundamentally different in their underlying mechanisms. A weak, high frequency tetanus (e.g. a train of 100 pulses at 100 Hz) can trigger an increase in synaptic efficacy that lasts for 1–2 h. This short-lasting form of LTP is called early phase LTP (E-LTP). E-LTP requires modification of existing proteins and their trafficking at synapses but not de novo protein synthesis (Bliss & Collingridge, 1993; Malenka & Bear, 2004). On the other hand, repeated, strong high frequency stimulations (e.g. multiple trains of 100 pulses at 100 Hz) can induce an increase in synaptic efficacy lasting over 8 h (Frey, Krug, Reymann, & Matthies, 1988) or even days (Abraham, 2003). L-LTP differs from E-LTP in its requirement for de novo mRNA and in its association with structural changes at synapses (Frey et al., 1988; Harris,

* Corresponding author. Address: Building 35, Rm. 1C1004, 35 Convent Dr., MSC 3714, Bethesda, MD 20892-3714, USA. Fax: +1 301 496 1777.
E-mail address: bailu@mail.nih.gov (B. Lu).

1074-7427/$ - see front matter Published by Elsevier Inc.
doi:10.1016/j.nlm.2007.08.018

Fiala, & Ostroff, 2003; Kandel, 2001; Krug, Lossner, & Ott, 1984; Muller, Nikonenko, Jourdain, & Alberi, 2002; Yuste & Bonhoeffer, 2001). It is generally believed that the E-LTP and L-LTP inducing stimuli trigger very different, albeit partially overlapping, biochemical pathways that lead to distinct changes at synapses. In particular, induction of L-LTP results in activation of cAMP-dependent protein kinase (PKA) and mitogen-associated protein kinase (MAPK, also known as extracellular signal-related protein kinase, ERK) (Kandel, 2001; Pang & Lu, 2004). Subsequently, several constitutively expressed transcription factors [e.g. cAPM/calcium responsive-element binding protein (CREB), and Elk-1] are phosphorylated and activated for the transcription of downstream genes that presumably mediate the changes in the structure and/or function of the synapses (Kandel, 2001; Shaywitz & Greenberg, 1999). One of the downstream genes induced by the L-LTP-inducing tetanus is BDNF.

BDNF is a small dimeric protein that works through high affinity binding with the receptor tyrosine kinase, tropomyosin-related kinase B (TrkB). BDNF and TrkB are widely distributed across subregions of the hippocampus and the adult forebrain (Bramham & Messaoudi, 2005). BDNF-containing secretory vesicles are present in both axon terminals (presynaptic site) and dendrites (postsynaptic site) of glutamatergic principal neurons (granule cells and pyramidal cells) (Fawcett et al., 1997; Haubensak, Narz, Heumann, & Lessmann, 1998; Kohara, Kitamura, Morishima, & Tsumoto, 2001; Kojima et al., 2001; Lessmann, Gottmann, & Malcangio, 2003; Lu, 2003). BDNF stands out among all neurotrophins in the activity-dependent regulation of its expression and secretion. Upon high frequency stimulation, BDNF is secreted in a manner dependent on Ca^{2+} influx through NMDA subtype glutamate receptors or voltage-gated Ca^{2+} channels (Aicardi et al., 2004; Balkowiec & Katz, 2002; Gartner & Staiger, 2002; Hartmann, Heumann, & Lessmann, 2001; Lever et al., 2001). BDNF can also be secreted from either postsynaptic spines or presynaptic terminals. Possible mechanisms to trigger secretion include activation of N-type Ca^{2+} channels and mobilization of Ca^{2+} from intracellular stores (Balkowiec & Katz, 2002). Once secreted into the synaptic cleft, BDNF can bind to TrkB localized at both pre- and postsynaptic sites of glutamatergic synapses (Drake, Milner, & Patterson, 1999). In the postsynaptic density (PSD), TrkB is associated with PSD95 and NMDA receptors (Aoki et al., 2000; Husi, Ward, Choudhary, Blackstock, & Grant, 2000; Ji, Pang, Feng, & Lu, 2005; Yoshii & Constantine-Paton, 2007). In addition, the expression of BDNF, particularly transcription of the BDNF gene through promoter III, is tightly controlled by neuronal activity (Chen et al., 2003).

Given the synaptic localization of TrkB and activity-dependent secretion of BDNF protein and transcription of BDNF mRNA, it is not surprising that BDNF has emerged as a key regulator of synaptic plasticity and memory (Lu, 2003; Pang & Lu, 2004; Poo, 2001). Significant progress has been made in understanding the role of BDNF in E-LTP and short-term memory. BDNF facilitates the induction of E-LTP by enhancing synaptic responses to tetanus stimulation (Figurov, Pozzo-Miller, Olafsson, Wang, & Lu, 1996; Gottschalk, Pozzo-Miller, Figurov, & Lu, 1998; Rex et al., 2006; Yano et al., 2006). This is most likely due to BDNF regulation of synaptic vesicle mobilization and docking, possibly by regulating the distribution and phosphorylation of synaptic proteins (Jovanovic, Czernik, Fienberg, Greengard, & Sihra, 2000; Pozzo-Miller et al., 1999). BDNF also plays a role in the maintenance (or expression) of E-LTP, possibly by activating "silent synapses" (Shen et al., 2006) and/or by regulating actin motor complex (Rex et al., 2007; Yano et al., 2006). Moreover, studies of the well-known val66met polymorphism in the human BDNF gene (Egan et al., 2003) suggest that activity-dependent secretion of BDNF is critical for short-term, hippocampal-dependent episodic memory that is largely dependent on E-LTP. In contrast, progress on the studies of BDNF in L-LTP and LTM is lagging behind. Nevertheless, numerous reports have demonstrated that BDNF is critical for the induction and maintenance of L-LTP. This review will focus on our current knowledge with respect to action sites, sufficiency, and expression of BDNF in hippocampal L-LTP and LTM.

2. Role of BDNF in hippocampal L-LTP

2.1. Is activity-dependent expression of endogenous BDNF sufficient to mediate L-LTP?

A variety of genetic and pharmacological studies suggest that BDNF is necessary for L-LTP to occur. In heterozygous BDNF (+/−) knockout mice, there is a significant deficit in L-LTP induced by several different protocols including theta burst stimulation or forskolin application (Korte et al., 1995; Pang et al., 2004; Patterson et al., 2001). Treatment of hippocampal slices by the BDNF scavenger TrkB-Fc or antibodies against BDNF or TrkB also inhibits L-LTP (Kang, Welcher, Shelton, & Schuman, 1997). Similarly, L-LTP is impaired in TrkB knockout mice (Minichiello et al., 1999), as well as in mice with a targeted mutation in the phospholipase C-γ (PLC-γ) docking site (but not in the Shc site) on TrkB (Minichiello et al., 2002). Curiously, the classic L-LTP induced by multiple tetani is normal in BDNF+/− mice, suggesting that BDNF is not involved in all forms of long-term synaptic plasticity (Chen, Kolbeck, Barde, Bonhoeffer, & Kossel, 1999; Kang et al., 1997; Patterson et al., 2001).

While these findings suggest that endogenous BDNF is required for the maintenance of L-LTP, a critical question is whether an activity-dependent increase in endogenous BDNF is responsible for the maintenance of L-LTP. Converging experimental results strongly suggest that this is the case. First, BDNF transcription is enhanced by L-LTP-inducing stimuli. With in situ hybridization, BDNF mRNA level is found to increase in the hippocampal