Brain-Derived Neurotrophic Factor/TrkB Signaling in Memory Processes

Kiyofumi Yamada1,* and Toshitaka Nabeshima2

1Laboratory of Experimental Therapeutics, Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Kanazawa University, Kanazawa 920-0934, Japan
2Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University Graduate School of Medicine, Showa-ku, Nagoya 466-8560, Japan

Received January 7, 2003

Abstract. Activity-dependent changes in synaptic strength are considered mechanisms underlying learning and memory. Brain-derived neurotrophic factor (BDNF) plays an important role in activity-dependent synaptic plasticity such as long-term potentiation. Recent experimental evidence supports the role of BDNF in memory processes: Memory acquisition and consolidation are associated with an increase in BDNF mRNA expression and the activation of its receptor TrkB. Genetic as well as pharmacologic deprivation of BDNF or TrkB impairs learning and memory. In a positively motivated radial arm maze test, activation of the TrkB/phosphatidylinositol-3 kinase (PI3-K) signaling pathway in the hippocampus is associated with consolidation of spatial memory through an activation of translational processes. In a negatively motivated passive avoidance test, mitogen-activated protein kinase (MAPK) is activated during acquisition of fear memory. Furthermore, recent findings suggest the importance of interaction between BDNF/TrkB signaling and NMDA receptors for spatial memory. A Src-family tyrosine kinase, Fyn plays a role in this interaction by linking TrkB with NR2B. These findings suggest that BDNF/TrkB signaling in the hippocampus plays a crucial role in learning and memory.

Keywords: brain-derived neurotrophic factor, TrkB, plasticity, learning and memory, hippocampus

Introduction

Activity-dependent changes in synaptic strength are considered mechanisms underlying learning and memory. One attractive candidate for modulating synaptic plasticity in learning and memory is brain-derived neurotrophic factor (BDNF) (1, 2), a member of the neurotrophin family, including nerve growth factor (NGF), neurotrophin-3 (NT-3), and NT-4/5 (3). BDNF has been implicated in the modulation of synaptic function and plasticity (4). In this article, we review the recent findings indicating a role of BNF in memory processes and discuss the intracellular signaling pathway in BDNF-dependent learning and memory.

BDNF and synaptic plasticity

BDNF depolarizes neurons as rapidly as glutamate does by activating tyrosine kinase Trk receptors (5), enhances glutamatergic synaptic transmission (6), and increases phosphorylation of the subunits of N-methyl-D-aspartate (NMDA) receptors in the hippocampus (7). Furthermore, this neurotrophin enhances long-term potentiation (LTP) in the hippocampus (8). In BDNF mutant mice, LTP is markedly impaired, but the deficit can be rescued by exogenous BDNF (9). BDNF acts through TrkB receptors either pre- and postsynaptically to modulate LTP (10, 11). A recent study using BDNF-green fluorescent protein fusion protein has demonstrated that BDNF is released at synapses in an activity-dependent manner to act on postsynaptic neurons (12).

BDNF is involved in the modulation of the development of ocular dominance columns in the visual cortex. Monocular deprivation during restricted periods of development renders the neurons of the visual cortex, which are normally binocular, nonresponsive to stimuli.
presented to the deprived eye. The local administration of BDNF to the visual cortex during the critical period prevents the formation of ocular dominance columns and reverses the monocular deprivation-induced ocular dominance shift (13). Morphological studies indicate that BDNF modulates the growth and complexity of the dendrites in the cerebral cortex (14). These evidence suggests that the regulation of synaptic plasticity is the primary function of BDNF.

**BDNF and memory**

Accumulating evidence supports the role of BDNF in learning and memory. There is a good correlation between BDNF mRNA expression and behavioral performance in various learning and memory tests (1, 2). Thus, hippocampus-dependent learning in the Morris water maze, contextual fear, and passive avoidance tests is associated with a rapid and transient increase in BDNF mRNA expression in the hippocampus (1, 2, 15).

To examine the causal relationship between BDNF and learning, effects of pharmacologic as well as genetic deprivation of BDNF or TrkB have been investigated. Heterozygous BDNF mutant mice show a moderate but significant impairment of water maze learning without any effect on memory retention (16). The role of BDNF in learning and memory has also been investigated with function-blocking anti-BDNF antibodies. Treatment with anti-BDNF antibodies causes impairment of memory in the water maze (17) and passive avoidance tests (18). Minichiello et al. (19) have developed conditionally gene-targeted mice in which the knockout of the trkB gene is restricted to the forebrain and occurs only during postnatal development (trkB-CRE) (mutant mice). The trkB-CRE mutant mice show severe deficits in the stressful water maze test and partial impairment in the 8-arm maze test, but no changes in simple passive avoidance learning, suggesting a role for BDNF/TrkB receptor signaling in complex learning. The findings also imply that procedural long-term memory is relatively spared, whereas short-term plasticity within the hippocampus is impaired in the trkB-CRE mutant mice (19). Transgenic mice overexpressing the truncated trkB.T1 isoform, a C-terminal truncated dominant negative TrkB receptor without the tyrosine kinase domain, show a mild impairment of long-term spatial memory as assessed by a water maze task, although LTP in hippocampal slices from these mice is normal (20).

We have been employing the reference and working memory test in an 8-arm radial maze, wherein 4 out of 8 arms are baited during the training, to test the BDNF hypothesis in learning and memory processes. In this positively motivated less stressful learning and memory test, rats use a spatial search strategy, and a spatial reference memory is firmly acquired by approximately 20 training trials. Activation of the CA3 subfield of the hippocampus is essential for spatial learning in this test (21) and cyclic AMP response element binding protein (CREB) is activated in the hippocampus during the learning process (22). In well-taught animals, phosphorylation of TrkB in the hippocampus, which is extremely low in control animals, is selectively and transiently increased immediately after maze training without any changes in TrkA or TrkC phosphorylation (23). BDNF mRNA levels in the hippocampus of well-taught rats are increased 15 and 30 min after the training trial, while there are no changes immediately after the training (24). Accordingly, the BDNF/TrkB system is activated in the hippocampus of well-taught animals that have previously acquired spatial memory in the radial arm maze test (23, 24). By using antisense BDNF oligonucleotide, we have demonstrated that BDNF is necessary for not only spatial memory acquisition, but also memory retention and/or recall because intracerebroventricular infusion of the antisense in well-taught rats impairs spatial memory (24). Collectively, these findings suggest that BDNF is released in the hippocampus of well-taught rats during maze performance, and thereby TrkB activation is seen immediately after the maze training. The BDNF/TrkB system in the hippocampus plays a crucial role not only in the acquisition, but also in the retention and/or recall of spatial memory.

**BDNF/TrkB signaling pathway in memory processes**

The binding of BDNF to its receptor tyrosine kinase, TrkB, leads to the dimerization and autophosphorylation of tyrosine residues in the intracellular domain of the receptor and subsequent activation of cytoplasmic signaling pathways including mitogen-activated protein kinase (MAPK), phospholipase C-γ (PLC-γ), and phosphatidylinositol-3 kinase (PI3-K) (25). Akt, a serine-threonine protein kinase which is a downstream target of PI3-K, is activated in the hippocampus during the learning process (21) and cyclic AMP responsive element binding protein (CREB) is activated in the hippocampus during the learning process (22). In well-taught animals, phosphorylation of TrkB in the hippocampus, which is extremely low in control animals, is selectively and transiently increased immediately after maze training without any changes in TrkA or TrkC phosphorylation (23). BDNF mRNA levels in the hippocampus of well-taught rats are increased 15 and 30 min after the training trial, while there are no changes immediately after the training (24). Accordingly, the BDNF/TrkB system is activated in the hippocampus of well-taught animals that have previously acquired spatial memory in the radial arm maze test (23, 24). By using antisense BDNF oligonucleotide, we have demonstrated that BDNF is necessary for not only spatial memory acquisition, but also memory retention and/or recall because intracerebroventricular infusion of the antisense in well-taught rats impairs spatial memory (24). Collectively, these findings suggest that BDNF is released in the hippocampus of well-taught rats during maze performance, and thereby TrkB activation is seen immediately after the maze training. The BDNF/TrkB system in the hippocampus plays a crucial role not only in the acquisition, but also in the retention and/or recall of spatial memory.

The binding of BDNF to its receptor tyrosine kinase, TrkB, leads to the dimerization and autophosphorylation of tyrosine residues in the intracellular domain of the receptor and subsequent activation of cytoplasmic signaling pathways including mitogen-activated protein kinase (MAPK), phospholipase C-γ (PLC-γ), and phosphatidylinositol-3 kinase (PI3-K) (25). Akt, a serine-threonine protein kinase which is a downstream target of PI3-K, is activated in the hippocampus during the learning process (21) and cyclic AMP responsive element binding protein (CREB) is activated in the hippocampus during the learning process (22). In well-taught animals, phosphorylation of TrkB in the hippocampus, which is extremely low in control animals, is selectively and transiently increased immediately after maze training without any changes in TrkA or TrkC phosphorylation (23). BDNF mRNA levels in the hippocampus of well-taught rats are increased 15 and 30 min after the training trial, while there are no changes immediately after the training (24). Accordingly, the BDNF/TrkB system is activated in the hippocampus of well-taught animals that have previously acquired spatial memory in the radial arm maze test (23, 24). By using antisense BDNF oligonucleotide, we have demonstrated that BDNF is necessary for not only spatial memory acquisition, but also memory retention and/or recall because intracerebroventricular infusion of the antisense in well-taught rats impairs spatial memory (24). Collectively, these findings suggest that BDNF is released in the hippocampus of well-taught rats during maze performance, and thereby TrkB activation is seen immediately after the maze training. The BDNF/TrkB system in the hippocampus plays a crucial role not only in the acquisition, but also in the retention and/or recall of spatial memory.
dependent facilitation of glutamate release from brain synaptosomes is mediated by synapsin phosphorylation via the BDNF/TrkB/MAPK signaling cascade (1). More recently, it was demonstrated that BDNF triggers LTP in the hippocampus in vivo through MAPK and selective induction of the dendritic mRNA species Arc (28).

We have recently demonstrated that the radial arm maze training for spatial reference and working memory activates the BDNF/TrkB/PI3-K/Akt signal pathway in the hippocampus of well-taught rats (23). Chronic infusion of PI3-K inhibitor wortmannin delays spatial learning. Activation of the BDNF/TrkB/PI3-K/Akt signal pathway in the hippocampus of well-taught animals is associated with an increase in phosphorylated 4E-BP1 and a decrease in phosphorylated eEF-2, indicating an increase in activity to translate mRNA into protein. These findings suggest that activation of TrkB/PI3-K and protein synthesis signaling pathway by BDNF in the hippocampus is important for spatial memory (23). In contract to the activation of TrkB/PI3-K signaling for spatial memory in the positively motivated radial arm maze test, the distinct signaling molecule MAPK appears to be activated by BDNF in the hippocampus for acquisition of fear memory in the negatively motivated passive avoidance test (2, 18). Although the reasons why distinct signaling pathways are activated are unclear, it is likely that diverse signaling molecules are involved in BDNF-dependent memory formation.

**Interaction of BDNF/TrkB signaling with NMDA receptors in memory processes**

Glutamate receptors, including NMDA and non-NMDA receptors, play a critical role in synaptic plasticity. BDNF phosphorylates NR1 and NR2B subunits of NMDA receptors and upregulates the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunit GR1 and GluR2/3 proteins. Furthermore, BDNF-induced enhancement of glutamate-evoked inward current in cultured hippocampal neurons is diminished by coexposure to ifenprodil, an NR2B subunit antagonist, suggesting that BDNF primarily enhances the activity of NR2B-containing NMDA receptors (1, 7, 29).

Spatial memory formation in the radial maze test is associated with an increase in phosphorylated TrkB, Fyn, and NR2B, but not NR2A, levels in the hippocampus (30). Fyn, a Src-family tyrosine kinase involved in the BDNF signal transduction pathways downstream of TrkB, is coimmunoprecipitated with TrkB and NR2B, and this association is markedly increased in well-taught rats compared with control animals. Continuous intracerebroventricular infusion of a tyrosine kinase inhibitor PP2 in rats impairs memory acquisition in the radial arm maze test, which is accompanied by the decrease of phosphorylated protein levels of Fyn and NR2B but not TrkB (30). These findings suggest the importance of interaction between BDNF/TrkB signaling and NMDA receptors for spatial memory. Fyn may play a crucial role in this interaction by linking TrkB with NR2B.

**Conclusions**

In addition to neurotrophic effects, regulation of synaptic plasticity is the primary function of BDNF. BDNF induces several forms of synaptic plasticity in various brain areas including the hippocampus. Thus, BDNF is an attractive candidate molecule mediating learning and memory. Behavioral evidence supports that BDNF is essential for at least certain forms of learning and memory. Although further studies are needed, both PI3-K and MAPK are attributable to BDNF-dependent learning and memory. The NMDA and non-NMDA receptors, as well as presynaptic proteins associated with exocytosis may be the targets of BDNF/TrkB signaling for learning and memory (1) (Fig. 1). Further experiments are needed to clarify the cellular mechanism of activity-dependent BDNF release for learning and memory. It is also important to address whether BDNF is involved in structural modification associated with long-term memory.

![Fig. 1. A model for the role of BDNF in learning and memory.](image)
Acknowledgments

This study was supported in part by Grants-in-Aid for Science Research (No. 14370031 and 14658249) and by Special Coordination Funds for Promoting Science and Technology, Target-Oriented Brain Science Research Program from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References

1 Yamada K, Mizuno M and Nabeshima T: Role for Brain-derived neurotrophic factor in learning and memory. Life Sci 70, 735 – 744 (2002)
13 Cabelli R, Hohn A and Shatz CJ: Inhibition of ocular dominance column formation by infusion of NT-4/5 or BDNF. Science 267, 1662 – 1666 (1995)
30 Mizuno M, Yamada K, He J, Nakajima A and Nabeshima T: Involvement of BDNF receptor TrkB in spatial memory forma tion. Learn Mem (in press)