Journal of Neuroscience Research 58:76–87 (1999)

Neurotrophins and Hippocampal Synaptic Transmission and Plasticity

Bai Lu* and Ana Chow
Unit on Synapse Development and Plasticity, Laboratory of Developmental Neurobiology, NICHD, NIH, Bethesda, Maryland

Neurotrophins are traditionally thought to be secretory proteins that regulate long-term survival and differentiation of neurons. Recent studies have revealed a previously unexpected role for neurotrophins in synaptic development and plasticity in diverse neuronal populations. In this review, we focus on the synaptic function of brain-derived neurotrophic factor (BDNF) in the hippocampus. Although a variety of in vitro experiments have shown the ability of BDNF to acutely modulate synaptic transmission, whether BDNF truly potentiates basal synaptic transmission in hippocampal neurons remains controversial. More consistent evidence has been obtained for the role of BDNF in long-term potentiation (LTP), a cellular model for learning and memory. BDNF also potentiates high frequency transmission by modulating the number of docked vesicles and the levels of the vesicle protein synaptobrevin and synaptophysin at the CA1 synapses. Both pre- and postsynaptic effects of BDNF have been demonstrated. Recent studies have begun to address the role of BDNF in late-phase LTP and in the development of hippocampal circuit. BDNF and other neurotrophins may represent a new class of neuromodulators that regulate neuronal connectivity and synaptic efficacy. J. Neurosci. Res. 58:76-87, 1999. **Published 1999 Wiley-Liss, Inc.**†

Key words: neurotrophins; brain-derived neurotrophic factor (BDNF); synaptic transmission; long-term potentiation (LTP); hippocampus; vesice docking; CAI synapse

INTRODUCTION

Neurotrophins are a family of structurally related proteins that include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and NT-4/5 (Lewin and Barde, 1996). The signaling and biological functions of these molecules are mediated primarily by the Trk receptor tyrosine kinases. NGF binds to TrkA; BDNF and NT-4/5 to TrkB; and NT-3 to TrkC (Chao, 1992; Barbacid, 1993). According to the classic definition, neurotrophins, and indeed all neurotrophic factors, are endogenous signaling molecules that regulate the long-term survival and differentiation of specific populations of neurons during development, and the viability of neurons in adulthood. The characteristic features of neurotrophic action are their slow-acting and long-lasting effects. However, more recent studies have challenged this traditional view, and have suggested a previously unexpected role for these factors: regulation of synaptic transmission and plasticity. The first evidence for such a novel role was the demonstration that BDNF and NT-3 rapidly enhance synaptic transmission at the developing neuromuscular synapse in culture (Lohof et al., 1993). Since then, experiments from many laboratories have demonstrated that neurotrophins indeed play important roles in synaptic development and plasticity in a variety of systems. For example, two major effects of neurotrophins have been described at the neuromuscular synapses: acute enhancement of synaptic transmission (Lohof et al., 1993; Stoop and Poo, 1995, 1996; Wang and Poo, 1997; Xie et al., 1997), and long-term regulation of synapse maturation (Wang et al., 1995, 1998; Liou and Fu, 1997; Liou et al., 1997). In the visual cortex, neurotrophins have been implicated in the activity-dependent synaptic competition and the formation of ocular dominance columns (Domenici et al., 1991; Maffei et al., 1992; Cabelli et al., 1995, 1997; Riddle et al., 1995). Neurotrophins have also been shown to be involved in complex and activity-dependent modulation of dendritic and axonal growth in the cortex (McAllister et al., 1995, 1996, 1997). Significant attention has also been directed toward the role of BDNF in synaptic transmission and plasticity in the hippocampus. These studies have brought together two intensely pursued areas in neuroscience, namely, the function of neurotrophic factors and the mechanisms for synaptic plasticity. Thus, an important new concept has emerged: neurotrophins may serve as a new class of neuromodulators that mediate activity-dependent modifications of neuronal connectiv-

*Correspondence to: Bai Lu, Ph.D., Unit on Synapse Development and Plasticity, Laboratory of Developmental Neurobiology, NICHD, NIH, Building 49, Rm. 5A38, 49 Convent Dr., MSC4480, Bethesda, MD 20892-4480. E-mail: lub@codon.nih.gov

Received 12 May 1999; Accepted 21 May 1999

ity and synaptic efficacy. Further studies in this emerging field will provide important insights into the fundamental mechanisms for synapse development and function, and how they are regulated.

In this review, we focus primarily on the role of BDNF in the cortical structures, particularly the hippocampus. We discuss in detail the physiological implications and the possible mechanism of BDNF-mediated modulation, and try to put complex and sometimes conflicting results into perspective. The readers are referred to a number of recent reviews for more complete discussion of the role of neurotrophins in other systems (Lo, 1995; Thoenen, 1995; Berninger and Poo, 1996; Bonhoeffer, 1996; Lu and Figurov, 1997; McAllister et al., 1999).

EFFECT ON BASAL SYNAPTIC TRANSMISSION

Based on the finding that BDNF and NT3 rapidly potentiate synaptic transmission at the neuromuscular synapses, it was natural to test whether similar modulation also occurs in the central nervous system (CNS). Initial experiments using primary cultures of hippocampal neurons seem to support this notion. Acute application of BDNF has been found to rapidly enhance synaptic transmission and transmitter release (Knipper et al., 1994; Lessmann et al., 1994; Levine et al., 1995; Takei et al., 1997; Li et al., 1998a). More careful analysis, however, revealed some complex effects of BDNF on cultured hippocampal neurons. Among the glutamatergic synapses, 30% were potentiated whereas 10% were inhibited by BDNF, and the remaining 60% showed no response to the neurotrophin (Lessmann and Heumann, 1998). Interestingly, whether or not BDNF potentiates excitatory synaptic transmission may depend on the intrinsic properties of the presynaptic neurons; BDNF preferentially enhances transmission in synapses with higher degree of paired pulse facilitation (PPF) (Lessmann and Heumann, 1998). In cultured cortical neurons, another neurotrophin, NT-3, also potentiates neuronal excitability and synchronizes excitatory synaptic activity, though possibly indirectly by inhibiting GABAergic transmission (Kim et al., 1994). Recent studies indicate that BDNF may mediate an activity-dependent scaling of quantal amplitude, a new form of synaptic plasticity for neural networks (Rutherford et al., 1997, 1998; Turrigiano et al., 1998). BDNF differentially regulates the quantal amplitude of the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropri-onate)-mediated synapses, depending on whether the postsynaptic cell is pyramidal or interneuron. Chronic blockade of neuronal activity by tetrodotoxin (TTX) increases the amplitude of miniature excitatory postsynaptic currents (mEPSCs) at all pyramidal–pyramidal synapses, and treatment with BDNF prevents the TTX effect. In contrast, BDNF increases the quantal amplitude of pyramidal–interneuron synapses (Rutherford et al., 1998). Whereas the exact physiological significance of the culture experiments remains to be established, these data suggest that BDNF is capable of modulating synaptic function in hippocampal neurons under certain conditions.

Whether BDNF can also enhance low frequency, basal synaptic transmission at CA1 synapses in acute hippocampal slices remains controversial. Several reports showed that BDNF can enhance basal synaptic transmission in the CA1 excitatory synapses in a time course of 5–10 min (Kang and Schuman, 1995, 1996; Kang et al., 1996). In contrast, many groups have found that BDNF has no effects on excitatory transmission (Figurov et al., 1996; Patterson et al., 1996; Tanaka et al., 1997; Frerking et al., 1998; Gottschalk et al., 1998). One possible explanation is that BDNF is a sticky molecule and its ability of BDNF to penetrate into the slices may vary depending on the perfusion rate (Kang et al., 1996). However, when using exactly the same experimental conditions, one group found that BDNF had no effect on basal, excitatory postsynaptic currents (EPSCs), but elicited a small decrease in inhibitory postsynaptic currents (IPSPs) (Frerking et al., 1998). In other areas of the hippocampus such as CA3 and the dentate gyrus, BDNF was able to potentiate excitatory synaptic transmission and neuronal excitability but in a much slower time course (30–90 min) (Scharfman, 1997; Messaoudi et al., 1998). Thus, BDNF may modulate neuronal excitability by inhibiting GABAergic transmission, but whether or not it enhances basal synaptic transmission in CA1 synapses is questionable.

Similar conflicting results exist in the visual cortex. Using whole-cell recordings slices, one report indicated that BDNF increases the amplitude of EPSCs as well as the frequency of spontaneous EPSCs in some layer II/III neurons of p12–17 rats (Carmignoto et al., 1997). Another report showed that BDNF had no effect on basal transmission but enhanced long-term potentiation (LTP) at a low concentration (20 ng/ml), whereas it increased basal transmission in layer II/III neurons at high concentration (200 ng/ml) (Akaneya et al., 1997). The BDNF effect on LTP in visual cortex was replicated by another group, but no effect on field EPSPs was observed in young adult rats, even at a high concentration (200 ng/ml) (Huber et al., 1998). Thus, as in hippocampus, it is unclear why different laboratories have obtained such conflicting results regarding the effect of BDNF on basal synaptic transmission. One possibility is that the ability of the synapses to respond to BDNF may vary depending on their intrinsic activity under different experimental conditions. Boulanger and Poo (1999) demonstrated recently that potentiation of synaptic efficacy by BDNF is facili-

tated greatly by presynaptic depolarization at the neuromuscular synapses. A brief depolarization in the presence of low level of BDNF resulted in a marked potentiation of synaptic activity whereas exposure to BDNF at this concentration or depolarization alone had no effect. Using the same preparation, we found recently that the neurotrophin-mediated synaptic potentiation requires intracellular calcium ($[Ca^{2+}]i$) and activation of calcium/calmodulin-dependent protein kinases (CaMKs) (He and Lu, unpublished results). At hippocampal CA1 synapses, BDNF potentiates synaptic responses to high frequency stimulation (HFS, 100 Hz), but not low frequency stimulation, under normal extracellular calcium ($[Ca^{2+}]o$) (Gottschalk et al., 1998, see below for details). HFS will undoubtedly elevate $[Ca^{2+}]i$ and activate CaMKs in hippocampal neurons, and under these conditions BDNF exerts the modulatory effects that might be difficult to see otherwise. Indeed, synaptic facilitation is increased more in BDNF-treated slices when $[Ca^{2+}]o$ is switched from 2.5 to 5 mM (Gottschalk et al., 1998). Thus, $[Ca^{2+}]i$ may determine whether or not a hippocampal neuron responds to BDNF.

REGULATION OF LTP AND LONG-TERM DEPRESSION (LTD)

Much more consistent results have been obtained for the role of BDNF in hippocampal LTP. Electrophysiological studies have demonstrated that BDNF is involved in the tetanus-induced LTP in both developing and adult hippocampus (Figurov et al., 1996). During hippocampal postnatal development, the expression of BDNF and the TrkB receptor increases gradually with age (Maisonpierre et al., 1990; Friedman et al., 1991; Dugich-Djordjevic et al., 1993; Ringstedt et al., 1993). The level of BDNF in the hippocampus appears to be important for the induction of tetanus-induced LTP. Application of exogenous BDNF facilitates LTP induced by theta burst stimulation (TBS) in neonatal hippocampal slices, in which the endogenous BDNF levels are low. In contrast, treatment with TrkB-IgG, a fusion protein that scavenges endogenous BDNF, reduces the magnitude of LTP in adult hippocampus, in which the endogenous BDNF levels are high. The effect of BDNF on LTP induction seems to be due, at least in part, to an enhanced ability of hippocampal synapses to follow tetanic stimulation, such as TBS or a train of high frequency stimulation (100 Hz, 1 sec, HFS) used to induce LTP (Figurov et al., 1996; Gottschalk et al., 1998). LTP induced by pairing of low frequency stimulation with postsynaptic depolarization was not affected by BDNF, suggesting that BDNF does not modulate the LTP-triggering mechanisms (Figurov et al., 1996, but see Korte et al., 1995). BDNF may also be involved in the maintenance of already established LTP; application of TrkB-IgG 30 min after LTP induction reverses the synaptic potentiation to baseline (Kang et al., 1997).

In addition to pharmacological approaches, the role of BDNF in hippocampal synaptic plasticity has also been studied using BDNF knockout mice. Although the homozygous ($-/-$) mice exhibit growth retardation, sensory deficits, and impairments in coordination of movement, no obvious neuronal loss in the hippocampus has been observed (Ernfors et al., 1994; Jones et al., 1994). The heterozygous ($+/-$) mice show no signs of behavioral abnormalities. Two independent lines of BDNF knockout mice have shown a severe impairment in hippocampal LTP in both $-/-$ and $+/-$ mice (Korte et al., 1995; Patterson et al., 1996). Moreover, $+/-$ mice showed the same degree of impairment as the $-/-$ mice, consistent with the idea that a critical level of BDNF in the hippocampus is important for LTP induction and/or maintenance. The impairment in hippocampal LTP can be restored after incubation with recombinant BDNF for a few hours (Patterson et al., 1996), or by virus-mediated BDNF gene transfer (Korte et al., 1996), suggesting that the mutation of BDNF gene per se, rather than cumulative developmental abnormalities, is responsible for impaired LTP in the BDNF knockout mice.

The finding that BDNF modulates hippocampal LTP implies a role in learning and memory. Injection of BDNF antisense oligonucleotides into the hippocampus reduced BDNF levels and the magnitude of LTP (Ma et al., 1998). Moreover, injection of the antisense before and during memory consolidation markedly impaired memory retention performance, whereas injection 6 hr post-training no longer affected the memory retention. Deficits in spatial learning are also found in BDNF knockout mice, using the Morris water maze test (Linnarsson et al., 1997, but see Montkowski and Holsboer, 1997). Young adult $+/-$ mice required twice the training to reach full performance, and aged $+/-$ mice did not learn at all (Linnarsson et al., 1997). Interestingly, infusion of BDNF into the hippocampus of normal animals does not seem to further improve learning or memory (Fischer et al., 1994; Pelleymounter et al., 1996).

A number of laboratories have also studied the role of BDNF in LTD and LTP in layer II/III of the visual cortex. The slices treated with BDNF showed little difference from control when maximal level of LTP was induced by TBS, but exhibited significantly greater synaptic potentiation in response to a weak (20 Hz) tetanus (Huber et al., 1998). Application of TrkB-IgG or k252a, a specific inhibitor for Trk receptor tyrosine kinases, completely prevented TBS-induced LTP (Akaneya et al., 1997). BDNF also inhibited LTD induced by a low frequency stimulation (1 Hz, 15 min) (Huber et al., 1998; Kinoshita et al., 1999). Moreover, the

Trk tyrosine kinase inhibitor k252a or an anti-BDNF antibody increased the magnitude of LTD (Akaneya et al., 1996; Kinoshita et al., 1999). Thus, LTD and LTP in the visual cortex can each be modulated by BDNF.

PRESYNAPTIC MODULATION

Studies from a number of laboratories have revealed a presynaptic mechanism for BDNF-induced synaptic potentiation in cultured hippocampal neurons. The enhancement of excitatory synaptic transmission is accompanied by changes in paired pulse facilitation (PPF) and in the frequency of miniature EPSCs (mEPSCs) (Lessmann and Heumann, 1998). Biochemical experiments indicated that application of BDNF to the cultured neurons elicited an increase in glutamate release, possibly through a non-exocytotic pathway (Takei et al., 1997, 1998). Targeting of a C-terminal truncated dominant negative TrkB into presynaptic, but not postsynaptic neurons, prevented the BDNF effects on both evoked EPSCs and mEPSCs (Li et al., 1998a). BDNF did not affect the amplitudes of glutamate-induced postsynaptic currents or mEPSCs (Li et al., 1998b). These experiments, however, do not completely rule out postsynaptic modulation by BDNF. Indeed, potent modulation of postsynaptic glutamate receptors has been reported by a number of groups (see below).

Several pieces of evidence suggest a presynaptic action of BDNF in CA1 synapses of the hippocampal slice (Gottschalk et al., 1998). First, the effect of BDNF on repetitive synaptic responses is dependent on the stimulation frequency. BDNF was found to be effective only when CA1 synapses had undergone severe synaptic fatigue elicited by HFS ($>$ 50 Hz) but not low frequency ($<$ 20 Hz). Because HFS-induced fatigue is a known presynaptic phenomenon (Zucker, 1989; Larkman et al., 1991; Dobrunz and Stevens, 1997), BDNF must act presynaptically to attenuate the fatigue. Second, treatment with BDNF alters PPF, a simple and reliable measure of presynaptic properties with very few assumptions, especially in hippocampal CA1 synapses (Foster and McNaughton, 1991; Schultz et al., 1994; Dobrunz et al., 1997). This effect of BDNF is restricted to PPF elicited with interpulse intervals shorter than 20 msec. Lowering the extracellular calcium concentrations ($[Ca^{2+}]o$) is known to increase PPF and synaptic responses to HFS. BDNF mimicked the effect of lowering $[Ca^{2+}]o$ in PPF and synaptic responses to HFS. Moreover, BDNF became much less effective when combined with lowering $[Ca^{2+}]o$, although the two manipulations did not completely occlude each other. Finally, when the desensitization of glutamate receptors was blocked by cyclothiazide or aniracetam, the BDNF potentiation of the synaptic responses to HFS remained the same, suggesting that the attenuation of synaptic fatigue by BDNF is not due to a reduction of the desensitization of postsynaptic non-*N*-methyl-D-aspartate (non-NMDA) receptor. Studies using BDNF knockout mice have also suggested the presynaptic impairments of CA1 synapses (Pozzo-Miller et al., 1999). Post-tetanic potentiation (PTP) and PPF at short ($<$ 20 msec) interpulse intervals, for example, are significantly reduced in the mutant mice.

MODULATION OF HIGH FREQUENCY TRANSMISSION AND SYNAPTIC VESICLE DOCKING

Substantial evidence supports the notion that BDNF enhances high-frequency transmission in the hippocampus. Treatment of neonatal slices with BDNF elicited a marked increase in synaptic responses to HFS and attenuated synaptic fatigue in the CA1 synapses (Figurov et al., 1996; Gottschalk et al., 1998). Conversely, inhibition of endogenous BDNF activity by gene knockout or by TrkB-IgG elicited a more pronounced fatigue at these synapses (Figurov et al., 1996; Pozzo-Miller et al., 1999). Similar modulation has been observed in the visual cortex (Huber et al., 1998). BDNF knockout mice have been used to further elucidate the cellular and molecular mechanisms for BDNF modulation of high frequency transmission (Pozzo-Miller et al., 1999). Electron microscopic studies have revealed a significant reduction in the number of vesicles docked at presynaptic active zones in both +/− and −/− BDNF mutant mice. In contrast, the number of reserve pool vesicles, active zone length, and presynaptic terminal area remained unchanged in the mutant mice. Quantitative analysis has indicated that there are approximately 10.3 docked vesicles per active zone in +/+ CA1 synapses, but only 3–5 docked vesicles in the +/− and −/− synapses (Schikorski and Stevens, 1997; Pozzo-Miller et al., 1999). A selective reduction in the number of docked vesicles explains why the BDNF knockout mice exhibited more pronounced fatigue with no change in basal synaptic transmission. Biochemical experiments have demonstrated that hippocampal synaptosomes prepared from mutant mice exhibit a marked decrease in the levels of synaptophysin and synaptobrevin (VAMP-2), a protein known to be involved in vesicle docking and fusion (Pozzo-Miller et al., 1999). Other synaptic proteins, including synaptotagmin, syntaxin-1, and SNAP-25, were unaffected. Treatment of the mutant slices with BDNF for a few hours can reverse the electrophysiological and biochemical deficits at the hippocampal synapses. Thus, the synaptic defects in these mice

do not simply reflect developmental consequence of BDNF gene knockout, but rather reflect an acute requirement for BDNF in high frequency transmission. Taken together, these results reveal a role of BDNF in the mobilization and/or docking of synaptic vesicles to presynaptic active zones.

Figure 1 shows a tentative model that integrates currently available experimental results. A BDNF-induced increase in the vesicle proteins synaptophysin and synaptobrevin at nerve terminals may facilitate vesicle docking. Synapses with more docked vesicles in the presynaptic active zone will undoubtedly respond better to high frequency, tetanic stimulation. An enhancement of synaptic responses to tetanus may contribute, at least in part, to BDNF modulation of LTP.

Preferential potentiation of high frequency transmission by BDNF may have important physiological implications in activity-dependent synaptic modification, such as synaptic competition during development and synaptic plasticity in the adult. As a general principle, synaptic efficacy may be potentiated and synaptic connections stabilized by the synchronization of electric activities between pre- and postsynaptic neurons. Conversely, asynchronized activities cause synaptic weakening and elimination (Stent, 1973; Goodman and Shatz, 1993; Katz and Shatz, 1996). Thus, more active synapses are favored during synaptic competition. The essence of synaptic competition is the local action and specificity (Constantine-Paton et al., 1990). How are active inputs selected among very adjacent, less active inputs to the same postsynaptic targets? There are two possible mechanisms if diffusable molecules such as BDNF are considered to mediate the activity-dependent synaptic competition. One is the activity-dependent, localized secretion of the molecules (Fig. 2A). In the hippocampus, activity-dependent secretion of neurotrophins including BDNF has been demonstrated (Blochl and Thoenen, 1995; Thoenen, 1995; Goodman et al., 1996; Canossa et al., 1997). Although BDNF is a sticky molecule and truncated TrkB molecules may limit its diffusion (Fryer et al., 1996; McAllister et al., 1999), it is difficult to imagine that locally secreted BDNF would not spread at all to the neighboring, less active synapses. An alternative mechanism is that highly active presynaptic neurons/terminals respond to BDNF better than less active ones (Fig. 2B). Indeed, depolarization (which presumably increases neuronal activity) has been shown to rapidly increase the levels of TrkB receptors on the cell surface of CNS neurons (Meyer-Franke et al., 1998). The effect of BDNF in potentiating synaptic efficacy is greatly enhanced by presynaptic depolarization at the neuromuscular synapses (Boulanger and Poo, 1999). We have demonstrated that BDNF preferentially enhances synapses that are stimulated at high frequency (Gottschalk et al., 1998). The physiological consequence of the BDNF regulation of the responses to tetanic stimulation (i.e., LTP) is relatively confined and does not spread to distant synapses (Gottschalk et al., 1998). Thus, even if the secretion of BDNF is not restricted to the active synapses, it could still favor the more active synapses. Moreover, the selective pairing of high-frequency neuronal activity and BDNF concentration could potentially provide the signal for coincidence detection, analogous to presynaptic activity and postsynaptic membrane depolarization leading to NMDA receptor activation in LTP induction.

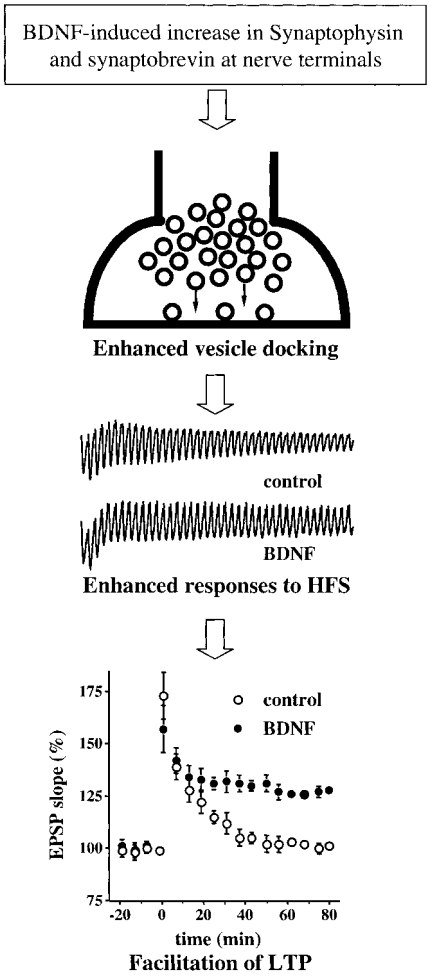

Fig. 1. A schematic presentation of brain-derived neurotrophic factor (BDNF) modulation of synaptic plasticity in hippocampal CA1 synapses. A BDNF-induced increase in the vesicle proteins synaptophysin and synaptobrevin at nerve terminals may facilitate vesicle docking. Synapses with more docked vesicles in the presynaptic active zone will undoubtedly respond better to high frequency, tetanic stimulation (HFS). An enhancement of synaptic responses to tetanus may contribute, at least in part, to BDNF modulation of long-term potentiation (LTP).

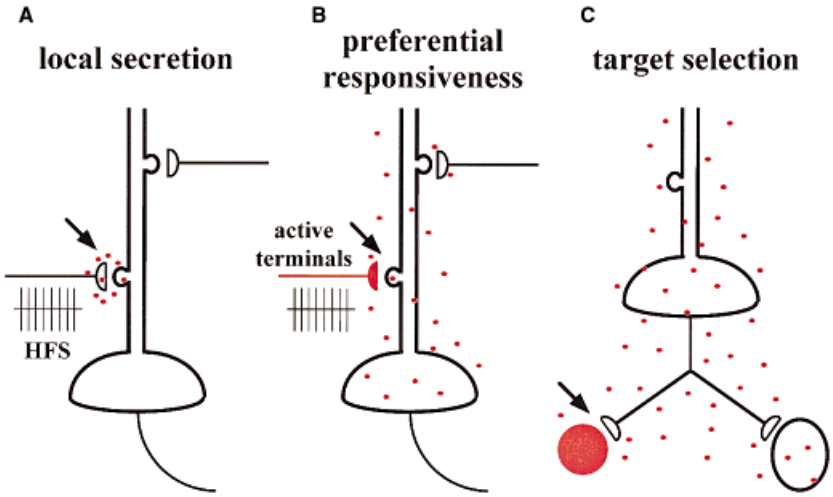

Fig. 2. Three possible mechanisms to ensure synapse specificity of brain-derived neurotrophic factor (BDNF) modulation. **A:** Local secretion model. BDNF is secreted only at or near active synapses. **B:** Preferential responsiveness model. Active presynaptic neurons/terminals respond better to widely diffused BDNF. **C:** Target selection model. Responses to BDNF are determined by the nature or status of postsynaptic cells. Arrows indicate the specific synapses modulated BDNF. Red dots represent BDNF molecules.

POSTSYNAPTIC MODULATORY EFFECT

Although ample evidence supports presynaptic actions of BDNF, several studies have demonstrated that BDNF also exerts its effects postsynaptically. In cultured hippocampal neurons, the acute effect of BDNF on synaptic transmission has been attributed, at least in part, to an increase in postsynaptic responsiveness (Levine et al., 1995). The effect appears to be mediated specifically by the TrkB receptor. NT-4, another TrkB ligand, has similar effects, whereas NGF and NT-3 have no effect (Levine et al., 1996). Application of the Trk receptor inhibitor k252a into the intracellular recording pipette significantly decreased the amplitude EPSCs. In addition, application of okadaic acid, a phosphatase inhibitor, enhanced the BDNF effect, suggesting the role of protein phosphorylation downstream of TrkB activation (Levine et al., 1995). Moreover, BDNF increased the amplitude of EPSCs in the presence of the non-NMDA receptor antagonist CNQX, and the response to iontophoretically applied NMDA, but not AMPA or acetylcholine. These results suggest that NMDA receptor responses are selectively enhanced by BDNF (Levine et al., 1998; Song et al., 1998). Consistent with this finding, TrkB is localized to the postsynaptic density (Wu et al., 1996), and activation of the TrkB receptor leads to phosphorylation of the NMDA receptor subunits I and 2B (Lin et al., 1998; Suen et al., 1998).

Exactly how BDNF modulates NMDA receptors remains controversial. Single channel recording demonstrated that BDNF increases the probability of opening the NMDA channels on hippocampal neurons (Jarvis et al., 1997; Levine et al., 1998). Jarvis et al. showed that the kinase inhibitors genistein or H7 cannot block the BDNF effect on whole-cell NMDA currents, and all other neurotrophins have similar effect as BDNF. Further, BDNF modulation of NMDA currents occurs only when the extracellular glycine concentration is low, and other unrelated peptides with *N*-terminus glycine also cause a glycine-dependent enhancement of NMDA currents (Jarvis et al., 1997). Thus, these authors argued that BDNF enhanced NMDA currents by interacting nonspecifically with the glycine-binding site of the NMDA receptor. In contrast, Levine et al. (1998) found that the BDNF effect on NMDA channels can be blocked by the Trk-specific tyrosine kinase inhibitor k252a, and NGF and NT-3 have no effect on NMDA currents. Thus, further investigations are required to elucidate the exact mechanisms by which BDNF enhances NMDA receptor function.

Whereas acute application of BDNF may enhance the activity of NMDA-type glutamate receptors in the hippocampus, long-term BDNF treatment of cultured cerebellar neurons has been shown to regulate the expression and function of NMDA receptors (Muzet and Dupont, 1996; Brandoli et al., 1998). Moreover, long-term BDNF treatment of cortical neurons also modulates synaptic currents mediated by AMPA-type glutamate receptors (Rutherford et al., 1998). Blockade of activity-dependent expression/secretion of BDNF by TTX for 2 days resulted in a marked increase in the amplitude of AMPA currents recorded from pyramidal–pyramidal synapses. BDNF prevented whereas TrkB-IgG mimicked the TTX effect. In contrast, BDNF increased the quantal amplitude of pyramidal–interneuron synapses (Rutherford et al., 1998). Thus, BDNF differentially regulates the quantal amplitude of the AMPA-mediated synapses, depending on whether the postsynaptic cell is pyramidal or interneuron. Dependence on postsynaptic target cells represents another way to ensure the specificity of BDNF action (Fig. 2C).

SIGNALING MECHANISMS

Rapid advances have been made in our understanding of the signal transduction mechanisms that mediate

BDNF actions. Studies using primarily PC12 cells have identified a number of important signaling pathways that are activated by neurotrophins (Segal and Greenberg, 1996). This activation is initiated by binding of neurotrophins with specific Trk receptors (Barbacid, 1994; Kaplan and Stephens, 1994). Once activated, the Trk receptors autophosphorylate specific tyrosine residues within the intracellular domains (Kaplan et al., 1991; Lamballe et al., 1991; Soppet et al., 1991). The phosphorylated tyrosines serve as protein interaction sites for Shc (SH2-containing adapter protein), phospholipase C-γ (PLC-γ), and phosphatidylinositol 3-kinase (PI3K), the intracellular molecules that lead to the activation of three major signaling pathways (Vetter et al., 1991; Ohmichi et al., 1992; Obermeier et al., 1993; Stephens et al., 1994). Tyrosine phosphorylation of SHC subsequently triggers SHC/Grb2/Sos interaction, Ras activation, and a series of phosphorylation reactions that include Raf, MEK, and mitogen-associated protein kinase (MAPK) (reviewed in Segal and Greenberg, 1996). The active PLC-γ cleaves phosphatidylinositol 4, 5-biphosphate to generate inositol-trisphosphate (IP3) and diacylglycerol (DAG), which in turn induces the release of Ca^{2+} from internal stores and activates protein kinase C (PKC), respectively (Kaplan and Stephens, 1994). The putative effector of PI3K is the serine and threonine kinase Akt (Burgering and Coffer, 1995; Franke et al., 1995). The cyclic AMP response element-binding protein (CREB), a transcription factor known for its role in synaptic plasticity, appears to be an important downstream mediator for BDNF function, at least in cortical neurons (Finkbeiner et al., 1997).

Although it has been shown that acute potentiation of synaptic efficacy is accompanied by an increase in $[Ca^{2+}]i$ in cultured hippocampal neurons, the downstream signaling events remain unidentified (Li et al., 1998b). Further investigation is also needed to establish the signaling pathways that mediate BDNF modulation of LTP. Recently, we have examined the signaling mechanisms for BDNF-induced modulation of high frequency transmission at the CA1 synapses in hippocampal slices (Gottschalk et al., 1999). Application of BDNF rapidly activated MAPK and PI3K, but not PLC-γ. Inhibition of MAPK and PI3K, but not PLC-γ, prevented the BDNF modulation of high frequency synaptic transmission. NT-3 did not activate MAPK or PI3K, and had no effect on synaptic fatigue in the neonatal hippocampus. Neither forskolin, which activated MAPK but not PI3 kinase, nor ciliary neurotrophic factor (CNTF), which activated PI3K but not MAPK, affected HFS-induced synaptic fatigue. Treatment of the slices with forskolin together with CNTF still had no effect on synaptic fatigue. Thus, activation of MAPK and PI3K is required but the two together are not sufficient to mediate the BDNF modulation of high frequency transmission.

ROLE OF BDNF IN LATE PHASE OF LTP

LTP can be separated into an early phase (E-LTP) and a later phase (L-LTP). E-LTP is short lasting (1–3 hr) and is independent of new protein synthesis, whereas L-LTP requires activation of cAMP and new protein synthesis (Frey et al., 1988; Nguyen et al., 1994). In addition to the role of BDNF in E-LTP discussed above, several lines of evidence suggest that BDNF may also be involved in hippocampal L-LTP. Tetanic stimulation used to induce L-LTP rapidly and selectively increased BDNF mRNA levels, with little or no effects on other neurotrophins (Patterson et al., 1992; Castren et al., 1993; Dragunow et al., 1993; Kesslak et al., 1998; Morimoto et al., 1998). The delayed and sustained enhancement in BDNF synthesis in the hippocampus correlated well with the time course of the late, protein synthesis-dependent phase of LTP. TrkB receptor expression was also increased by LTP-inducing stimuli (Bramham et al., 1996; Dragunow et al., 1997). The transcription of BDNF appears to be mediated, in part, by CREB, a cAMP-induced transcription factor required for L-LTP (Shieh et al., 1998; Tao et al., 1998). Taken together, these results suggest that enhanced BDNF production and secretion may contribute to the maintenance of L-LTP, which is dependent on both transcription and protein synthesis.

A number of electrophysiological experiments have directly examined the role of BDNF in hippocampal L-LTP. BDNF knockout mice exhibit severe impairments in E-LTP, although some animals still show E-LTP with reduced magnitudes (Korte et al., 1995; Patterson et al., 1996; Pozzo-Miller et al., 1999). L-LTP can never be induced in the BDNF mutant mice, even in those that do exhibit E-LTP (Korte et al., 1998). Moreover, application of the BDNF scavenger TrkB-IgG 30–70 min after induction of LTP reverses the already established E-LTP, and prevents the occurrence of L-LTP (Kang et al., 1997; Korte et al., 1998). Conceivably, tetanic stimulation could induce a Ca^{2+}- and CREB-mediated transcription and translation of BDNF, which in turn elicits structural and functional changes in the hippocampal synapses.

BDNF IN HIPPOCAMPAL SYNAPSE DEVELOPMENT

In addition to the modulation of synaptic transmission and plasticity, BDNF may also be involved in hippocampal synaptogenesis. Neurons obtained from embryonic day 18 (E18), but not E16, hippocampus and cultured for 2 weeks exhibited extensive spontaneous synaptic activity. Application of BDNF or NT3 to the E16 cultures elicited a marked increase in the number of functional synapses (Vicario-Abejon et al., 1998). Low levels of endogenous BDNF expression in the neonatal hippocampus in vivo (Maisonpierre et al., 1990; Fried-

man et al., 1991; Dugich-Djordjevic et al., 1993; Ringstedt et al., 1993) correlated with the poor response to HFS and the inability to exhibit LTP at CA1 synapses (Figurov et al., 1996). Application of exogenous BDNF to the developing hippocampus attenuated the tetanus-induced synaptic fatigue, and promoted tetanus-induced LTP at the CA1 synapses (Figurov et al., 1996; Gottschalk et al., 1998). Thus, BDNF may play a role in the maturation of hippocampal CA1 synapses. Martinez and colleagues (1998) recently used the TrkB or TrkC knockout mice to assess the developmental function of neurotrophins in the hippocampus. They demonstrated a significant reduction in the number of axonal collaterals, the densities of axonal varicosities, and the number of synaptic contacts in both TrkB$-/-$ and TrkC$-/-$ mice. These mice also exhibited a decrease in many synaptic proteins and in the total number of synaptic vesicles per nerve terminal at different regions within the hippocampus. Although these data suggest a role of neurotrophins in hippocampal synaptogenesis, the underlying mechanisms remain unclear.

OTHER NEUROTROPHIC FACTORS AND HIPPOCAMPAL PLASTICITY

Recent studies have suggested roles for several novel neurotrophic factors, in addition to the neurotrophins, in the regulation of synaptic plasticity. The amyloid precursor protein (APP), which is a 695–770-amino acid transmembrane protein with a single membrane-spanning domain, is axonally transported. Activity in neuronal circuits induces an enzymatic cleavage of APP resulting in the release of the secreted form of APP (sAPPα) (see Mattson, 1997, for review). Whole-cell and single-channel patch clamp recordings from cultured embryonic hippocampal neurons have shown that sAPPα activates a signaling pathway linked to cyclic GMP production and activation of high-conductance, charybdotoxin-sensitive potassium channels (Furukawa et al., 1996). Analyses of synaptic plasticity at the CA3–CA1 synapse in hippocampal slices have indicated that sAPPα can shift the frequency-dependence for induction of LTD, and enhance LTP (Ishida et al., 1997). sAPPα induced cGMP production in hippocampal slices, and pretreatment of slices with 8-bromo-cyclic GMP mimicked the effect of sAPPα on LTD, suggesting a role for cyclic GMP in modulation of LTD. The data suggest an important role for sAPPα in modulation of synaptic plasticity in the hippocampus.

The cytokine tumor necrosis factor-α (TNF), best known for its roles in cellular responses to tissue injury, has recently been shown to be produced in response to physiological activity in neuronal circuits (Bruce et al., 1996). An early study of the effects of TNF on hippocampal synaptic physiology demonstrated that treatment with TNF enhanced basal synaptic transmission, but interfered with LTP in a dose-dependent manner (Tancredi et al., 1992). More recent studies have used TNF receptor knockout mice to address the roles of endogenous TNF in synaptic plasticity. Whereas stimulation at a frequency of 1 Hz normally induces LTD at CA3–CA1 synapses in wild-type mice, this stimulation frequency did not induce LTD in mice lacking TNF receptors (Albensi and Mattson, 1999). Stimulation at 100 Hz induced LTP in slices from both wild-type mice and mice lacking TNF receptors. TNF activates receptors linked to stimulation of the transcription factor NF-κB (nuclear factor kappa B) (Barger et al., 1995). Pretreatment of hippocampal slices from wild-type mice with κB decoy DNA prevented induction of LTD and significantly reduced the magnitude of LTP (Albensi and Mattson, 1999). Although the mechanisms whereby TNF and NF-κB modulate synaptic plasticity have not been established, whole-cell patch clamp analyses have shown that treatment of cultured hippocampal neurons with TNF results in increased current through voltage-dependent calcium channels and reduced NMDA-induced current (Furukawa and Mattson, 1998). The latter study showed that NF-κB activation was required for the effects of TNF, suggesting the possibility that NF-κB regulates expression of calcium channel and NMDA receptor subunits. TNF and signaling pathways that modulate NF-κB activity therefore appear to play important roles in the regulation of hippocampal synaptic plasticity.

CONCLUSIONS AND PERSPECTIVES

Numerous experiments have established that BDNF plays a role in hippocampal synaptic transmission and plasticity. In the hippocampus and other CNS areas, BDNF may act locally to modulate activity-dependent synaptic plasticity (Gottschalk et al., 1998), and globally in activity-dependent quantal scaling (Rutherford et al., 1998). Conflicting results exist regarding the effects of BDNF on basal synaptic transmission, as well as its pre- and postsynaptic mechanisms. Further experiments are needed to resolve these issues. Although the acute effects of neurotrophins have been studied in some detail, the long-term regulatory effects of neurotrophins on synaptic function and synapse development are less explored. An important area that deserves further investigation is the role of BDNF in the late, protein synthesis-dependent phase of LTP. Moreover, careful studies should be carried out to elucidate the underlying mechanisms as well as the physiological significance of the neurotrophic regulation of synaptic plasticity in vivo. For example, how does BDNF, or neurotrophins in general, achieve synapse-specific modulation? What is the relationship between neurotrophins and neuronal activity in various forms of

synaptic plasticity? Activity-dependent regulation of neurotrophin secretion and neurotrophic responsiveness represent exciting areas for future research.

ACKNOWLEDGMENTS

The authors thank Drs. Serena Dudek, Dan Feldman, and members of the Lu laboratory for helpful discussions and critical comments on the manuscript.

REFERENCES

Akaneya Y, Tsumoto T, Hatanaka H. 1996. Brain-derived neurotrophic factor blocks long-term depression in rat visual cortex. J Neurophysiol 76:4198–4201.

Akaneya Y, Tsumoto T, Kinoshita S, Hatanaka H. 1997. Brain-derived neurotrophic factor enhances long-term potentiation in rat visual cortex. J Neurosci 17:6707–6716.

Albensi BC, Mattson MP. 1999. Involvement of tumor necrosis factor and NF-κB in synaptic plasticity in the hippocampus. Synapse. In press.

Barbacid M. 1993. Nerve growth factor: a tale of two receptors. Oncogene 8:2033–2042.

Barbacid M. 1994. The Trk family of neurotrophin receptors. J Neurobiol 25:1386–1403.

Barger SW, Horster D, Furukawa K, Goodman Y, Krieglstein J, Mattson MP. 1995. Tumor necrosis factors α and β protect neurons against amyloid β-peptide toxicity: evidence for involvement of a κB-binding factor and attenuation of peroxide and Ca^{2+} accumulation. Proc Natl Acad Sci USA 92:9328–9332.

Berninger B, Poo M-M. 1996. Fast actions of neurotrophic factors. Curr Opin Neurobiol 6:324–330.

Blochl A, Thoenen H. 1995. Characterization of nerve growth factor (NGF) release from hippocampal neurons: evidence for a constitutive and an unconventional sodium-dependent regulated pathway. Eur J Neurosci 7:1220–1228.

Bonhoeffer T. 1996. Neurotrophins and activity-dependent development of the neocortex. Curr Opin Neurobiol 6:119–126.

Boulanger L, Poo MM. 1999. Presynaptic depolarization facilitates neurotrophin-induced synaptic potentiation. Nat Neurosci 2:346–351.

Bramham CR, Southard T, Sarvey J, Herkenham M, Brady LS. 1996. Unilateral LTP triggers bilateral increases in hippocampal neurotrophin and trk receptor mRNA expression in behaving rats: evidence for interhemispheric communication. J Comp Neurol 368:371–382.

Brandoli C, Sanna A, De Bernardi MA, Follesa P, Brooker G, Mocchetti I. 1998. Brain-derived neurotrophic factor and basic fibroblast growth factor downregulate NMDA receptor function in cerebellar granule cells. J Neurosci 18:7953–7961.

Bruce AJ, Boling W, Kindy MS, Peschon J, Kraemer PJ, Carpenter MK, Holtsberg FW, Mattson MP. 1996. Altered neuronal and microglial responses to brain injury in mice lacking TNF receptors. Nature Med. 2:788–794.

Burgering BM, Coffer PJ. 1995. Protein kinase B (c-Akt) in phosphatidylinositol-3-OH kinase signal transduction. Nature 376:599–602.

Cabelli RJ, Horn A, Shatz CJ. 1995. Inhibition of ocular dominance column formation by infusion of NT-4/5 or BDNF. Science 267:1662–1666.

Cabelli RJ, Shelton DL, Segal RA, Shatz CJ. 1997. Blockade of endogenous ligands of trkB inhibits formation of ocular dominance columns. Neuron 19:63–76.

Canossa M, Griesbeck O, Berninger B, Campana G, Kolbeck R, Thoenen H. 1997. Neurotrophin release by neurotrophins: implications for activity-dependent neuronal plasticity. Proc Natl Acad Sci USA 94:13279–13286.

Carmignoto G, Pizzorusso T, Tia S, Vicini S. 1997. Brain-derived neurotrophic factor and nerve growth factor potentiate excitatory synaptic transmission in the rat visual cortex. J Physiol (Lond) 498:153–164.

Castren E, Pitkanen M, Sirvio J, Parsadanian A, Lindholm D, Thoenen H, Riekkinen PJ. 1993. The induction of LTP increases BDNF and NGF mRNA but decreases NT-3 mRNA in the dentate gyrus. NeuroReport 4:895–898.

Chao MV. 1992. Neurotrophin receptors: a window into neuronal differentiation. Neuron 9:583–593.

Constantine-Paton M, Cline HT, Debski E. 1990. Patterned activity, synaptic convergence, and the NMDA receptor in developing visual pathways. Ann Rev Neurosci 13:129–154.

Dobrunz LE, Huang EP, Stevens CF. 1997. Very short-term plasticity in hippocampal synapses. Proc Natl Acad Sci USA 94:14843–14847.

Dobrunz LE, Stevens CF. 1997. Heterogeneity of release probability, facilitation and depletion at central synapses. Neuron 18:995–1018.

Domenici L, Berardi N, Carmignoto G, Vantini G, Maffei L. 1991. Nerve growth factor prevents the amblyopic effects of monocular deprivation. Proc Natl Acad Sci 88:8811–8815.

Dragunow M, Beilharz E, Mason B, Lawlor P, Abraham W, Gluckman P. 1993. Brain-derived neurotrophic factor expression after long-term potentiation. Neurosci Lett 160:232–236.

Dragunow M, Hughes P, Mason-Parker SE, Lawlor P, Abraham WC. 1997. TrkB expression in dentate granule cells is associated with a late phase of long-term potentiation. Brain Res Mol Brain Res 46:274–280.

Dugich-Djordjevic MM, Ohsawa F, Hefti F. 1993. Transient elevation in catalytic trkB mRNA during postnatal development of the rat brain. Neuroreport 4:1091–1094.

Ernfors P, Lee K-F, Jaenisch R. 1994. Mice lacking brain-derived neurotrophic factor develop with sensory deficits. Nature 368: 147–150.

Figurov A, Pozzo-Miller L, Olafsson P, Wang T, Lu B. 1996. Regulation of synaptic responses to high-frequency stimulation and LTP by neurotrophins in the hippocampus. Nature 381:706–709.

Finkbeiner S, Tavazoie SF, Maloratsky A, Jacobs KM, Harris KM, Greenberg ME. 1997. CREB: a major mediator of neuronal neurotrophin responses. Neuron 19:1031–1047.

Fischer W, Sirevaag A, Wiegand SJ, Lindsay RM, Björklund A. 1994. Reversal of spatial memory impairments in aged rats by nerve growth factor and neurotrophins 3 and 4/5 but not by brain-derived neurotrophic factor. Proc Natl Acad Sci USA 91:8607–8611.

Foster TC, McNaughton BL. 1991. Long-term synaptic enhancement in CA1 is due to increased quantal size, not quantal content. Hippocampus 1:79–91.

Franke TF, Yang SI, Chan TO, Datta K, Kazlauskas A, Morrison DK, Kaplan DR, Tsichlis PN. 1995. The protein kinase encoded by the Akt proto-oncogene is a target of the PDGF-activated phosphatidylinositol 3-kinase. Cell 81:727–736.

Frerking M, Malenka RC, Nicoll RA. 1998. Brain-derived neurotrophic factor (BDNF) modulates inhibitory, but not excitatory, transmission in the CA1 region of the hippocampus. J Neurophysiol 80:3383–3386.

Frey U, Krug M, Reymann KG, Matthies H. 1988. Anisomycin, an inhibitor of protein synthesis, blocks late phases of LTP phenomena in the hippocampal CA1 region in vitro. Brain Res 452:57–65.

Friedman WJ, Olson L, Persson H. 1991. Cells that express brain-derived neurotrophic factor mRNA in the developing postnatal rat brain. Eur J Neurosci 3:688–697.

Fryer RH, Kaplan DR, Feinstein SC, Radeke MJ, Grayson DR, Kromer LF. 1996. Developmental and mature expression of full-length and truncated TrkB receptors in the rat forebrain. J Comp Neurol 374:1.21–40.

Furukawa K, Barger SW, Blalock E, Mattson MP. 1996. Activation of K+ channels and suppression of neuronal activity by secreted β-amyloid precursor protein. Nature 379:74–78.

Furukawa K, Mattson MP. 1998. The transcription factor NF-κB mediates increases in calcium currents and decreases in NMDA and AMPA/kainate-induced currents in response to TNFα in hippocampal neurons. J Neurochem 70:1876–1886.

Goodman LJ, Valverde J, Lim F, Geschwind MD, Federoff HJ, Geller AI, Hefti F. 1996. Regulated release and polarized localization of brain-derived neurotrophic factor in hippocampal neurons. Mol Cell Neurosci 7:223–228.

Goodman CS, Shatz CJ. 1993. Developmental mechanisms that generate precise patterns of neuronal connectivity. Cell 10: 77–98.

Gottschalk W, Pozzo-Miller LD, Figurov A, Lu B. 1998. Presynaptic modulation of synaptic transmission and plasticity by brain-derived neurotrophic factor in the developing hippocampus. J Neurosci 18:6830–6839.

Gottschalk WA, Jiang H, Tartaglia N, Feng L, Figurov A, Lu B. 1999. Signaling mechanisms mediating BDNF modulation of synaptic plasticity in the hippocampus. Learning and Memory. In press.

Huber KM, Sawtell NB, Bear MF. 1998. Brain-derived neurotrophic factor alters the synaptic modification threshold in visual cortex. Neuropharmacology 37:571–579.

Ishida A, Furukawa K, Keller JN, Mattson MP. 1997. Secreted form of β-amyloid precursor protein shifts the frequency dependence for induction of LTD, and enhances LTP in hippocampal slices. Neuroreport 8:2133–2137.

Jarvis CR, Xiong ZG, Plant JR, Churchill D, Lu WY, MacVicar BA, MacDonald JF. 1997. Neurotrophin modulation of NMDA receptors in cultured murine and isolated rat neurons. J Neurophysiol 78:2363–2371.

Jones KR, Farinas I, Backus C, Reichardt LF. 1994. Targeted disruption of the BDNF gene perturbs brain and sensory neuron development but not motor neuron development. Cell 76:989–999.

Kang H, Schuman EM. 1995. Long-lasting neurotrophin-induced enhancement of synaptic transmission in the adult hippocampus. Science 267:1658–1662.

Kang H, Schuman EM. 1996. A requirement for local protein synthesis in neurotrophin-induced hippocampal synaptic plasticity. Science 273:1402–1406.

Kang H, Jia L, Suh K, Tang L, Schuman E. 1996. Determinants of BDNF-induced hippocampal synaptic plasticity: role of the TrkB receptor and the kinetics of neurotrophin delivery. Learning and Memory 3:188–196.

Kang H, Welcher AA, Shelton D, Schuman EM. 1997. Neurotrophins and time: different roles for TrkB signaling in hippocampal long-term potentiation. Neuron 19:653–664.

Kaplan DR, Hempstead BL, Martin-Zanca D, Chao MV, Parada LF. 1991. The trk proto-oncogene product: a signal transducing receptor for nerve growth factor. Science 252:554–558.

Kaplan DR, Stephens RM. 1994. Neurotrophin signal transduction by the Trk receptor. J Neurobiol 25:1404–1417.

Katz LC, Shatz CJ. 1996. Synaptic activity and the construction of cortical circuits. Science 274:1133–1138.

Kesslak JP, So V, Choi J, Cotman CW, Gomez-Pinilla F. 1998. Learning upregulates brain-derived neurotrophic factor messenger ribonucleic acid: a mechanism to facilitate encoding and circuit maintenance? Behav Neurosci 112:1012–1019.

Kim HG, Wang T, Olafsson P, Lu B. 1994. Neurotrophin 3 potentiates neuronal activity and inhibits γ-aminobutyratergic synaptic transmission in cortical neurons. Proc Natl Acad Sci USA 91:12341–12345.

Kinoshita S, Yasuda H, Taniguchi N, Katoh-Semba R, Hatanaka H, Tsumoto T. 1999. Brain-derived neurotrophic factor prevents low-frequency inputs from inducing long-term depression in the developing visual cortex. J Neurosci 19:2122–2130.

Knipper M, da Penha Berzaghi M, Blochl A, Breer H, Thoenen H, Lindholm D. 1994. Positive feedback between acetylcholine and the neurotrophins nerve growth factor and brain-derived neurotrophic factor in the rat hippocampus. Eur J Neurosci 6:668–671.

Korte M, Carroll P, Wolf E, Brem G, Thoenen H, Bonhoeffer T. 1995. Hippocampal long-term potentiation is impaired in mice lacking brain-derived neurotrophic factor. Proc Natl Acad Sci USA 92:8856–8860.

Korte M, Griesbeck O, Gravel C, Carroll P, Staiger V, Thoenen H, Bonhoeffer T. 1996. Virus-mediated gene transfer into hippocampal CA1 region restores long-term potentiation in brain-derived neurotrophic factor mutant mice. Proc Natl Acad Sci USA 93:12547–12552.

Korte M, Kang H, Bonhoeffer T, Schuman E. 1998. A role for BDNF in the late-phase of hippocampal long-term potentiation. Neuropharmacology 37:553–559.

Lamballe F, Klein R, Barbacid M. 1991. trkC, a new member of the trk family of tyrosine protein kinases, is a receptor for neurotrophin-3. Cell 66:967–979.

Larkman A, Stratford K, Jack J. 1991. Quantal analysis of excitatory synaptic action and depression in hippocampal slices. Nature 350:344–347.

Lessmann V, Gottmann K, Heumann R. 1994. BDNF and NT-4/5 enhance glutamatergic synaptic transmission in cultured hippocampal neurons. Neuroreport 6:21–25.

Lessmann V, Heumann R. 1998. Modulation of unitary glutamatergic synapses by neurotrophin-4/5 or brain-derived neurotrophic factor in hippocampal microcultures: presynaptic enhancement depends on pre-established paired-pulse facilitation. Neuroscience 86:399–413.

Levine ES, Dreyfus CF, Black IB, Plummer MR. 1995. Brain-derived neurotrophic factor rapidly enhances synaptic transmission in hippocampal neurons via postsynaptic tyrosine kinase receptors. Proc Natl Acad Sci USA 92:8074–8077.

Levine ES, Dreyfus CF, Black IB, Plummer MR. 1996. Selective role for trkB neurotrophin receptors in rapid modulation of hippocampal synaptic transmission. Brain Res Mol Brain Res 38:300–303.

Levine ES, Crozier RA, Black IB, Plummer MR. 1998. Brain-derived neurotrophic factor modulates hippocampal synaptic transmission by increasing *N*-methyl-D-aspartic acid receptor activity. Proc Natl Acad Sci USA 95:10235–10239.

Lewin GR, Barde Y-A. 1996. Physiology of the neurotrophins. Annu Rev Neurosci 19:289–317.

Li YX, Xu Y, Ju D, Lester HA, Davidson N, Schuman EM. 1998a. Expression of a dominant negative TrkB receptor, T1, reveals a requirement for presynaptic signaling in BDNF-induced synaptic potentiation in cultured hippocampal neurons. Proc Natl Acad Sci USA 95:10884–10889.

Li YX, Zhang Y, Lester HA, Schuman EM, Davidson N. 1998b. Enhancement of neurotransmitter release induced by brain-derived neurotrophic factor in cultured hippocampal neurons. J Neurosci 18:10231–10240.

Lin SY, Wu K, Levine ES, Mount HT, Suen PC, Black IB. 1998. BDNF acutely increases tyrosine phosphorylation of the NMDA receptor subunit 2B in cortical and hippocampal postsynaptic densities. Brain Res Mol Brain Res 55:20–27.

Linnarsson S, Bjorklund A, Ernfors P. 1997. Learning deficit in BDNF mutant mice. Eur J Neurosci 9:2581–2587.

Liou JC, Fu WM. 1997. Regulation of quantal secretion from developing motoneurons by postsynaptic activity-dependent release of NT-3. J Neurosci 17:2459–2468.

Liou JC, Yang RS, Fu WM. 1997. Regulation of quantal secretion by neurotrophic factors at developing motoneurons in *Xenopus* cell cultures. J Physiol (Lond) 503:129–139.

Lo DC. 1995. Neurotrophic factors and synaptic plasticity. Neuron 15:979–981.

Lohof AM, Ip NY, Poo MM. 1993. Potentiation of developing neuromuscular synapses by the neurotrophins NT-3 and BDNF. Nature 363:350–353.

Lu B, Figurov A. 1997. Role of neurotrophins in synapse development and plasticity. Rev Neurosci 8:1–12.

Ma YL, Wang HL, Wu HC, Wei CL, Lee EH. 1998. Brain-derived neurotrophic factor antisense oligonucleotide impairs memory retention and inhibits long-term potentiation in rats. Neuroscience 82:957–967.

Maffei L, Berardi N, Domenici L, Parisi V, Pizzorusso T. 1992. Nerve growth factor (NGF) prevents the shift in ocular dominance distribution of visual cortical neurons in monocularly deprived rats. J Neurosci 12:4651–4662.

Maisonpierre PC, Belluscio L, Friedman B, Alderson RF, Wiegand SJ, Furth ME, Lindsay RM, Yancopoulos GD. 1990. NT-3, BDNF, and NGF in the developing rat nervous system: parallel as well as reciprocal patterns of expression. Neuron 5:501–509.

Martinez A, Alcantara S, Borrell V, Del Rio JA, Blasi J, Otal R, Campos N, Boronat A, Barbacid M, Silos-Santiago I, Soriano E. 1998. TrkB and TrkC signaling are required for maturation and synaptogenesis of hippocampal connections. J Neurosci 18: 7336–7350.

Mattson MP. 1997. Cellular actions of β-amyloid precursor protein, and its soluble and fibrillogenic peptide derivatives. Physiol Rev 77:1081–1132.

McAllister AK, Lo DC, Katz LC. 1995. Neurotrophins regulate dendritic growth in developing visual cortex. Neuron 15:791–803.

McAllister AK, Katz LC, Lo DC. 1996. Neurotrophin regulation of cortical dendritic growth requires activity. Neuron 17:1057–1064.

McAllister AK, Katz LC, Lo DC. 1997. Opposing roles for endogenous BDNF and NT-3 in regulating cortical dendritic growth. Neuron 18:767–778.

McAllister AM, Katz LC, Lo DC. 1999. Neurotrophins and synaptic plasticity. Annu Rev Neurosci 22:295–318.

Messaoudi E, Bardsen K, Srebro B, Bramham CR. 1998. Acute intrahippocampal infusion of BDNF induces lasting potentiation of synaptic transmission in the rat dentate gyrus. J Neurophysiol 79:496–499.

Meyer-Franke A, Wilkinson GA, Kruttgen A, Hu M, Munro E, Hanson MG Jr., Reichardt LF, Barres BA. 1998. Depolarization and cAMP elevation rapidly recruit TrkB to the plasma membrane of CNS neurons. Neuron 21:681–693.

Montkowski A, Holsboer F. 1997. Intact spatial learning and memory in transgenic mice with reduced BDNF. Neuroreport 8:779–782.

Morimoto K, Sato K, Sato S, Yamada N, Hayabara T. 1998. Time-dependent changes in neurotrophic factor mRNA expression after kindling and long-term potentiation in rats. Brain Res Bull 45:599–605.

Muzet M, Dupont JL. 1996. Enhancement of NMDA receptor maturation by BDNF in cultured mouse cerebellar granule cells. NeuroReport 7:548–552.

Nguyen PT, Abel T, Kendal ER. 1994. Requirement of a critical period of transcription for induction of a later phase of LTP. Science 265:1104–1107.

Obermeier A, Lammers R, Wiesmuller KH, Jung G, Schlessinger J, Ullrich A. 1993. Identification of Trk binding sites for SHC and phosphatidylinositol 3′-kinase and formation of a multimeric signaling complex. J Biol Chem 268:22963–22966.

Ohmichi M, Decker SJ, Saltiel AR. 1992. Activation of phosphatidylinositol-3 kinase by nerve growth factor involves indirect coupling of the trk proto-oncogene with src homology 2 domains. Neuron 9:769–777.

Patterson S, Grover LM, Schwartzkroin PA, Bothwell M. 1992. Neurotrophin expression in rat hippocampal slices: a stimulus paradigm inducing LTP in CA1 evokes increases in BDNF and NT-3 mRNAs. Neuron 9:1081–1088.

Patterson SL, Abel T, Deuel TA, Martin KC, Rose JC, Kandel ER. 1996. Recombinant BDNF rescues deficits in basal synaptic transmission and hippocampal LTP in BDNF knockout mice. Neuron 16:1137–1145.

Pelleymounter MA, Cullen MJ, Baker MB, Gollub M, Wellman C. 1996. The effects of intrahippocampal BDNF and NGF on spatial learning in aged Long Evans rats. Mol Chem Neuropathol 29:211–226.

Pozzo-Miller L, Gottschalk WA, Zhang L, McDermott K, Du J, Gopalakrishnan R, Oho C, Shen Z, Lu B. 1999. Impairments in high frequency transmission, synaptic vesicle docking and synaptic protein distribution in the hippocampus of BDNF knockout mice. J Neurosci 19:4972–4983.

Riddle DR, Lo DC, Katz LC. 1995. NT-4-mediated rescue of lateral geniculate neurons from effects of monocular deprivation. Nature 378:189–191.

Ringstedt T, Kagercrabtz H, Persson H. 1993. Expression of members of the trk family in the developing postnatal rat brain. Dev Brain Res 72:119–131.

Rutherford LC, DeWan A, Lauer HM, Turrigiano GG. 1997. Brain-derived neurotrophic factor mediates the activity-dependent regulation of inhibition in neocortical cultures. J Neurosci 17:4527–4535.

Rutherford LC, Nelson SB, Turrigiano GG. 1998. BDNF has opposite effects on the quantal amplitude of pyramidal neuron and interneuron excitatory synapses. Neuron 21:521–530.

Scharfman HE. 1997. Hyperexcitability in combined entorhinal/hippocampal slices of adult rat after exposure to brain-derived neurotrophic factor. J Neurophysiol 78:1082–1095.

Schikorski T, Stevens CF. 1997. Quantitative ultrastructural analysis of hippocampal excitatory synapses. J Neurosci 17:5858–5867.

Schultz PE, Cook EP, Johnston D. 1994. Changes in paired-pulse facilitation suggest presynaptic involvement in long-term potentiation. J Neurosci 14:5325–5337.

Segal RA, Greenberg ME. 1996. Intracellular signaling pathways activated by neurotrophic factors. Annu Rev Neurosci 19:463–489.

Shieh PB, Hu SC, Bobb K, Timmusk T, Ghosh A. 1998. Identification of a signaling pathway involved in calcium regulation of BDNF expression. Neuron 20:727–740.

Song DK, Choe B, Bae JH, Park WK, Han IS, Ho WK, Earm YE. 1998. Brain-derived neurotrophic factor rapidly potentiates synaptic transmission through NMDA, but suppresses it through non-NMDA receptors in rat hippocampal neuron. Brain Res 799:176–179.

Soppet D, Escandon E, Maragos J, Middlemas DS, Reid SW, Blair J, Burton LE, Stanton BR, Kaplan DR, Hunter T, et al. 1991. The neurotrophic factors brain-derived neurotrophic factor and neurotrophin-3 are ligands for the trkB tyrosine kinase receptor. Cell 65:895–903.

Stent G. 1973. A physiological mechanism for Hebb's postulate of learning. Proc Natl Acad Sci USA 70:997–1001.

Stephens RM, Loeb DM, Copeland TD, Pawson T, Greene LA, Kaplan DR. 1994. Trk receptors use redundant signal transduction pathways involving SHC and PLC-gamma 1 to mediate NGF responses. Neuron 12:691–705.

Stoop R, Poo MM. 1995. Potentiation of transmitter release by ciliary neurotrophic factor requires somatic signaling. Science 267:695–699.

Stoop R, Poo MM. 1996. Synaptic modulation by neurotrophic factors: differential and synergistic effects of brain-derived neurotrophic factor and ciliary neurotrophic factor. J Neurosci 16:3256–3264.

Suen PC, Wu K, Xu JL, Lin SY, Levine ES, Black IB. 1998. NMDA receptor subunits in the postsynaptic density of rat brain: expression and phosphorylation by endogenous protein kinases. Brain Res Mol Brain Res 59:215–228.

Takei N, Sasaoka K, Inoue K, Takahashi M, Endo Y, Hatanaka H. 1997. Brain-derived neurotrophic factor increases the stimulation-evoked release of glutamate and the levels of exocytosis-associated proteins in cultured cortical neurons from embryonic rats. J Neurochem 68:370–375.

Takei N, Numakawa T, Kozaki S, Sakai N, Endo Y, Takahashi M, Hatanaka H. 1998. Brain-derived neurotrophic factor induces rapid and transient release of glutamate through the non-exocytotic pathway from cortical neurons. J Biol Chem 273: 27620–27624.

Tanaka T, Saito H, Matsuki N. 1997. Inhibition of GABAa synaptic responses by brain-derived neurotrophic factor (BDNF) in rat hippocampus. J Neurosci 17:2959–2966.

Tancredi V, D'Aracangelo G, Grassi F, Tarroni P, Palmieri G, Santoni A, Eusebi F. 1992. Tumor necrosis factor alters synaptic transmission in rat hippocampal slices. Neurosci Lett 146:176–178.

Tao X, Finkbeiner S, Arnold DB, Shaywitz AJ, Greenberg ME. 1998. Ca2+ influx regulates BDNF transcription by a CREB family transcription factor-dependent mechanism. Neuron 20:709–726.

Thoenen H. 1995. Neurotrophins and neuronal plasticity. Science 270:593–596.

Turrigiano GG, Leslie KR, Desai NS, Rutherford LC, Nelson SB. 1998. Activity-dependent scaling of quantal amplitude in neocortical neurons. Nature 391:892–896.

Vetter ML, Martin-Zanca D, Parada LF, Bishop JM, Kaplan DR. 1991. Nerve growth factor rapidly stimulates tyrosine phosphorylation of phospholipase C-gamma 1 by a kinase activity associated with the product of the trk protooncogene. Proc Natl Acad Sci USA 88:5650–5654.

Vicario-Abejon C, Collin C, McKay RD, Segal M. 1998. Neurotrophins induce formation of functional excitatory and inhibitory synapses between cultured hippocampal neurons. J Neurosci 18:7256–7271.

Wang T, Xie KW, Lu B. 1995. Neurotrophins promote maturation of developing neuromuscular synapses. J Neurosci 15:4796–4805.

Wang X, Berninger B, Poo M. 1998. Localized synaptic actions of neurotrophin-4. J Neurosci 18:4985–4992.

Wang XH, Poo MM. 1997. Potentiation of developing synapses by postsynaptic release of neurotrophin-4. Neuron 19:825–835.

Wu K, Xu JL, Suen PC, Levine E, Huang YY, Mount HT, Lin SY, Black IB. 1996. Functional trkB neurotrophin receptors are intrinsic components of the adult brain postsynaptic density. Brain Res Mol Brain Res 43:286–290.

Xie K, Wang T, Olafsson P, Mizuno K, Lu B. 1997. Activity-dependent expression of NT-3 in muscle cells in culture: implication in the development of neuromuscular junctions. J Neurosci 17:2947–2958.

Zucker RS. 1989. Short-term synaptic plasticity. Ann Rev Neurosci 12:13–31.