BDNF and Synaptic Plasticity, Cognitive Function, and Dysfunction

B. Lu, G. Nagappan, and Y. Lu

Abstract

Among all neurotrophins, brain-derived neurotrophic factor (BDNF) stands out for its high level of expression in the brain and its potent effects on synapses. It is now widely accepted that the main function of BDNF in the adult brain is to regulate synapses, with structural and functional effects ranging from short-term to long-lasting, on excitatory or inhibitory synapses, in many brain regions. The diverse effects of BDNF on brain synapses stem from its complex downstream signaling cascades, as well as the diametrically opposing effects of the pro- and mature form through distinct receptors, TrkB and $p75^{NTR}$. Many aspects of BDNF cell biology are regulated by neuronal activity. The synergistic interactions between neuronal activity and synaptic plasticity by BDNF make it an ideal and essential regulator of cellular processes that underlie cognition and other complex behaviors. Indeed, numerous studies firmly established that BDNF plays a critical role in hippocampal long-term potentiation (LTP), a long-term enhancement of synaptic efficacy thought to underlie learning and memory. Converging evidence now strongly suggest that deficits in BDNF signaling contribute to the pathogenesis of several major diseases and disorders such as Huntington's disease, Alzheimer's disease, and depression. Thus, manipulating BDNF pathways represents a viable treatment approach to a variety of neurological and psychiatric disorders.

Keywords

Brain-derived neurotrophic factor • Synaptic plasticity • mRNA trafficking

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Abbreviations

BDNF	Brain-derived neurotrophic factor
BDNF-KIV	BDNF GFP knockin in exon IV
CA1/CA3	Cornu ammonis areas 1 and 3
E-LTP	Early phase long-term potentiation
GAD	Glutamate decarboxylase
HA	Hemagglutinin
HFS	High frequency stimulation
IgG	Immunoglobulin
KO	Knockout
L-LTP	Late phase long-term potentiation
LTD	Long-term depression
mBDNF	Mature BDNF
MMP	Matrix metalloprotease
MRI	Magnetic resonance imaging
NMDAR	*N*-methyl-D-aspartate receptor
$p75^{NTR}$	p75 neurotrophin receptor
proBDNF	Precursor BDNF
PRP	Plasticity-related protein
PV	Parvalbumin
SNP	Single nucleotide polymorphism
STDP	Spike time-dependent plasticity
TBS	Theta burst stimulation
tDCS	Transcranial direct current stimulation
tPA	Tissue plasminogen activator
TrkB	Tropomyosin-related kinase B
UTR	Untranslated region
$Val^{66}Met$	Valine 66 to methionine

1 BDNF Regulation of Early Phase-LTP

1.1 Initial Discovery

The hint that BDNF might be involved in synaptic plasticity came from the observation that the expression of BDNF in the hippocampus can be induced by high frequency stimulation (HFS) that is often used to induce LTP (Castren et al. 1993; Patterson et al. 1992). The first paper on pharmacological regulation of LTP by BDNF was the report by Figurov et al. (1996) demonstrating that treatment of hippocampal slices with BDNF facilitates early phase LTP (E-LTP) induced by theta burst stimulation (TBS). Neonatal hippocampus generally expresses a low level of BDNF, and TBS induces only short-term synaptic

potentiation (STP). Application of exogenous BDNF enhances the synaptic response to TBS, leading to LTP. In adult hippocampus, where the endogenous BDNF levels are high, inhibition of BDNF activity by the BDNF scavenger TrkB-IgG reduces the magnitude of LTP. In parallel, genetic experiments using two independent lines of BDNF knockout mice demonstrate that a reduction in BDNF expression is associated with a significant impairment in hippocampal LTP (Korte et al. 1995; Patterson et al. 1996). Moreover, heterozygous (+/−) and homozygous (−/−) BDNF-KO mice exhibit similar degrees of impairment in LTP, suggesting that a certain level of BDNF in the hippocampus is required for LTP induction and/or maintenance. Incubation with recombinant BDNF for a few hours (Patterson et al. 1996) rescues the LTP deficits seen in BDNF-KO mice, suggesting that the genetic impairment is amenable for pharmacological manipulations. Subsequent experiments using more sophisticated genetic (TrkB conditional knockout, regional or inducible BDNF knockout, chemical genetic model) and pharmacological (BDNF (Chen et al. 1999) or TrkB (Kang et al. 1997) antibody) approaches have ascertained unequivocally the obligatory role of BDNF-TrkB pathway in hippocampal LTP. BDNF regulation of LTP has also been demonstrated in other brain regions such as visual cortex (Akaneya et al. 1997; Huber et al. 1998; Jiang et al. 2001).

1.2 Acute Versus Chronic Synaptic Modulation by BDNF

In addition to its role in LTP, bath application of BDNF has also been shown to induce long-lasting increase in basal synaptic transmission at hippocampal CA1 synapses (Kang and Schuman 1995). However, similar experiments by a number of laboratories, where BDNF was slowly perfused (as opposed to bath application) acutely showed no such enhancement (Figurov et al. 1996; Patterson et al. 1996; Tanaka et al. 1997). Why would different methods of BDNF application (bath or acute application versus slow or chronic perfusion) elicit such distinct effects? Would different modes of BDNF delivery (or secretion under the physiological conditions) lead to different functional outcomes? To address this question, Ji et al. (2010) applied the same amount of BDNF (final concentration: 1 nM) either acutely as a single bath application or gradually by increasing BDNF concentration from 0.0001 to 1 nM with increments of tenfold every 30 min. Remarkably, the kinetics of TrkB activation and its downstream signaling molecules (Erk, PLCγ1, GSK-3β activation) differed dramatically depending on the mode of BDNF delivery. When BDNF was applied acutely, the activation was robust but transient and declined to baseline within 2 h of application. However, when BDNF concentration increased gradually, the kinetics of TrkB activation was slow, reached the maximal in 1 h, and persisted for up to 8 h without decline. The difference in TrkB signaling kinetics is not due to differential degradation or synthesis of TrkB. Rather, the gradual but not acute delivery of BDNF appears to allow more TrkB receptor to recycle back to the cell surface. Moreover, TrkB activation by acute BDNF application elicited transient activation of both Ras- and Rap-dependent activation

of Erk, whereas gradual BDNF increase resulted in a sustained, Rap-dependent activation of Erk. These differences in downstream signaling pathways suggest that TrkB in different compartments (plasma membrane, endocytic vesicles/signaling endosomes) activate different signaling molecules as reported earlier (Arimura et al. 2009; Heerssen and Segal 2002; Huang and Reichardt 2003; Watson et al. 1999, 2001; Zhou et al. 2007; Zweifel et al. 2005). For instance, stimulation of both Erk1/2 and PI3K/Akt signaling at the plasma membrane is important for axonal elongation. However, preventing endocytosis using genetic or pharmacological inhibitors reduce Erk1/2 phosphorylation but not PI3K/Akt activation suggesting PI3K/Akt activation precedes Trk internalization, while Erk1/2 activation follows receptor endocytosis (York et al. 2000; Zhang et al. 2000). The acute and gradual modes of BDNF signaling also lead to differential expression of TrkB-responsive genes such as Homer1 and Arc. The steady state levels of these proteins increased and lasted longer when BDNF was applied gradually as opposed to acute application, where the levels only increased transiently.

In addition to the differences in the kinetics of TrkB activation and its downstream signaling, different modes of BDNF application also induced differential morphological changes. For instance, acute BDNF application promoted neurite elongation and spine head enlargement, whereas gradual application increased dendritic branching and filopodia-like spines. This is in parallel to changes in different downstream signaling pathways causing relevant morphological changes to establish homeostasis. Mimicking the gradual and acute increases in BDNF concentrations in neonatal rat hippocampal slices showed that slow perfusion of BDNF (slow and chronic) facilitated LTP induced by weak TBS without changing baseline synaptic strength. In contrast, fast perfusion of BDNF (acute) to adult hippocampal slices induced a rapid increase in activation of BDNF signaling that promotes synaptic growth required for establishing neuronal networks during development. It may also be beneficial for long-term, activity-induced structural and functional changes in synapses. In contrast, transient activation of TrkB as a consequence of acute BDNF secretion may rapidly potentiate synaptic transmission in the adult brain (Ji et al. 2010).

1.3 Activity-Dependent Secretion of BDNF and Its Role in Synapse Plasticity and Memory

Similar to all neurotrophins, BDNF is synthesized first as a precursor, proBDNF, which is proteolytically cleaved either inside the cells (Mowla et al. 2001) or after its secretion (Nagappan et al. 2009; Yang et al. 2009b) to form mature BDNF (mBDNF). Unlike other neurotrophins, BDNF is secreted through constitutive as well as regulated pathways. BDNF has been localized to both 200 and 400 nm diameter vesicles by electron microscopy, suggesting that BDNF is trafficked in vesicles that fuse with the plasma membrane either stochastically or in a regulated fashion. While the secretion of mBDNF has been shown to be induced by depolarization, high frequency electric stimulation (HFS), and some chemical inducers,

relatively little is known about the secretion of proBDNF until 2001. Teng et al. reported that proBDNF was detectable in neuronal culture medium, if collected in the presence of α2 anti-plasmin inhibitors and in the absence of glial cells (Lee et al. 2001; Yang et al. 2009b). In contrast, pulse-chase experiments by Matsumoto et al. (2008) detected only mBDNF but not proBDNF extracellularly in hippocampal cultures even after stimulation by the GABA antagonist bicuculline (Matsumoto et al. 2008). This finding questioned whether proBDNF is secreted by neurons at all. To resolve this discrepancy, Yang et al. (2009b) used the BDNF-HA, knockin mice, in which BDNF is tagged with HA fragment to help detection of secreted BDNF, as well as an antibody that specifically detected proBDNF but not mBDNF. Results showed that proBDNF is highly expressed, especially during postnatal development, and secreted in response to neuronal depolarization. The following key measures helped demonstrate activity-dependent secretion of proBDNF: (1) pure neuronal culture with minimum glial contamination; (2) a potent plasmin inhibitor to prevent secreted proBDNF from converting to mBDNF in the culture medium; (3) more sensitive antibodies to detect secreted proBDNF.

Nagappan et al. (2009) reported that hippocampal neurons secrete proBDNF both constitutively and also in a regulated fashion. Moreover, they showed that proBDNF isoform is the major species secreted in response to physiological stimuli such as the LTD-inducing low frequency stimulation (LFS). Interestingly, tissue plasminogen activator (tPA), the enzyme identified to be responsible for converting proBDNF to mBDNF isoform, was secreted only under LTP, but not in LTD stimulating conditions. These results further substantiate that proBDNF secreted from neurons is converted to mBDNF extracellularly in situ and is regulated by neuronal activity. Pharmacological inhibition of tPA in different phases of L-LTP suggests that extracellular conversion of proBDNF by a tPA/plasminogen mechanism may be necessary for the induction phase, whereas the intracellular production of mBDNF may be involved in the maintenance phase (Pang et al, SfN Abstract, 2007). In addition to the tPA/plasmin system, proBDNF can also be converted extracellularly by matrixmetalloprotease 2, 3, 7, and 9 and tolloid-like metalloproteinase (Hwang et al. 2005; Keifer et al. 2009; Lee et al. 2001; Yang et al. 2009a). Further studies are necessary to establish the specificities of proBDNF→mBDNF converting enzymes involved in different brain regions and their physiological functions.

An important question is how cells sort BDNF into different vesicular (constitutive and regulated) trafficking system. The discovery of the association between the single nucleotide polymorphism (SNP) in humans (Egan et al. 2003) and Val^{66}Met (dbSNP number rs6265, with nucleotide change G196A; occurrence: 20–30 % in Caucasian population) greatly facilitated the study of BDNF cell biology and functions. Remarkably, cell culture experiments demonstrate that depolarization-induced secretion of Met^{66}BDNF from hippocampal neurons is significantly reduced compared with Val^{66}BDNF (Chen et al. 2004). Subjects with this SNP exhibit lower levels of hippocampal *N*-acetyl aspartate (an indicator of cell health) as measured by MRI spectroscopy, abnormal hippocampal activation in fMRI,

poorer verbal episodic memory (Egan et al. 2003), as well as reduced hippocampal volume (Pezawas et al. 2004; Szeszko et al. 2005). Interestingly, the Val^{66}Met polymorphism resides in the pro-domain of BDNF and not in mBDNF. How does a SNP in the pro-domain affect activity-dependent BDNF secretion? In vitro experiments using the Val^{66} and Met^{66} forms of BDNF indicate that Met^{66}BDNF protein tends to be clustered in neuronal cell bodies and the proximal regions of the dendritic compartment, whereas the Val^{66} BDNF is distributed as punctates throughout neuronal cell bodies and can travel to the distal dendrites. It is important to note that the functional properties of Met^{66} derived mBDNF were not altered. However, Val^{66}BDNF, but not Met^{66}BDNF, is co-localized with *SecII*, a regulated secretory granule marker (Egan et al. 2003). Moreover, a large fraction of Val^{66}BDNF, but not Met^{66}BDNF, is co-localized with synaptic markers such as synapsin I and PSD95. Taken together, these results suggest that the majority of BDNF is normally sorted into regulated secretory vesicles from Golgi compartments. These vesicles are capable of being transported to distal dendrites or axons, localized to synapses, and released in an activity-dependent manner.

Identification of Val^{66}Met in BDNF trafficking and therefore its consequential function in human episodic memory opened a new area for research in BDNF biology. To further understand the impact of Val^{66}Met substitution, Chen et al. (2006) generated a genetic knockin line of mice in which the Val^{66}BDNF is replaced by Met^{66}BDNF. Similar to the human results reported by Egan et al., neurons derived from the transgenic mice also exhibited reduced BDNF secretion (~30 %), and Met^{66}BDNF mice showed reduced hippocampal volume, due to changes in dendritic complexity, as well as deficits in hippocampal-dependent contextual memory. Moreover, these mice exhibit anxiety-like behaviors, and treatment with antidepressants such as fluoxetine did not alleviate the anxiety phenotype, suggesting that this antidepressant may achieve its anxiolytic effects through activity-dependent BDNF secretion. Consistent with reduction in regulated secretion of BDNF, synaptic plasticity in Met^{66}BDNF mice was significantly altered (Ninan et al. 2010). While the basal glutamatergic transmission remained unaltered in the Met^{66}BDNF animals (no changes in input/output curve, paired pulse facilitation), both NMDAR-dependent LTP and LTD were significantly reduced. Interestingly, mGluR-dependent LTD remained intact. These results suggest that activity-dependent BDNF secretion is selectively involved in the NMDA-dependent forms of synaptic plasticity. Future detailed studies should investigate the specific mechanisms by which Val^{66}MetBDNF alters NMDA receptor function. Considering the rarity of the Met/Met allele frequency in humans (<0.3 %), the Met^{66}BDNF knockin line could serve as a good model to study synaptic dysfunction and effects of pharmacological interventions.

1.4 Effect of tDCS on LTP and Motor Learning

The genetics of BDNF polymorphism offers an opportunity to study the functional consequences of alteration of activity-dependent BDNF secretion in human. It is

conceivable that a reduction in BDNF secretion throughout development may lead to structural alterations in neuronal circuits. It is therefore important to determine whether some of the changes observed in Met^{66}BDNF carriers could be reversed through acute manipulations. Unfortunately, studies of synaptic plasticity have been limited to animal models. Among the few available approaches for use in man, transcranial direct current stimulation (tDCs) has emerged as a safe, simple, noninvasive, and effective manipulation of cortical activity in humans (Antal et al. 2004; Fregni et al. 2005; Gandiga et al. 2006; Iyer et al. 2005; Nitsche et al. 2003). It has been shown that when the anode electrode is placed over the target cortical area on a subject's head and a weak direct current (mA) is applied, stimulation can enhance cortical excitability and function (Webster et al. 2006). In a simple experimental design, Reis et al. (2009) demonstrated that anodal tDCS applied over the human motor cortex (M1) during training facilitates motor skill learning, resulting in substantial improvements in long-term retention of motor memories. In line with these findings, BDNF levels are reported to be elevated in rat motor cortex following motor learning (Klintsova et al. 2004). Moreover, training-induced potentiation of motor-evoked potentials is reduced in human Met^{66}BDNF carriers (Kleim et al. 2006). Thus, one could speculate that motor learning is facilitated by tDCS-induced BDNF secretion in M1 cortex.

To test this hypothesis, Fritsch et al. (2010) developed a method that allows direct application of DCS to mouse slices from M1 cortex, mimicking tDCS in humans (Fritsch et al. 2010). Using this approach, they have identified a novel, long-lasting synaptic potentiation induced by DCS (DCS-LTP), which is polarity (anodal)-specific, NMDA-receptor dependent, and requires coupling of DCS with simultaneous low frequency (0.1 Hz) synaptic activation (mimicking training). Several lines of evidence suggest that DCS-LTP is mediated by DCS-induced secretion of BDNF. First, DCS-LTP is completely blocked in M1 slices derived from BDNF or TrkB knockout mice. Second, combined DCS and low frequency stimulation results in TrkB phosphorylation suggesting BDNF secretion. Finally, scavenging secreted BDNF by TrkB-IgG eliminated DCS-LTP. Thus, activity-dependent BDNF secretion appears to mediate this novel DCS-induced synaptic plasticity in mouse M1 motor cortex.

How activity-dependent secretion of BDNF could alter motor learning in vivo (mouse and humans) was further examined using BDNF Val66Met allele careers (Reis et al. 2009) and $BDNF^{Met/Met}$ knockin mice (Fritsch et al. 2010). Interestingly, acquisition of a fine motor skill over multiple days was found to be significantly impaired in human Met allele careers as well as in $BDNF^{Met/Met}$ knockin mice. Furthermore, Met allele careers exhibited an attenuated response to combined anodal tDCS and training. Taken together, these findings suggest that BDNF is an important player in human motor learning, likely through its contribution to synaptic plasticity at M1, and therefore may have implications in the treatment of motor deficits in neurological and psychiatric conditions.

1.5 Role of TrkB Trafficking

As a diffusible factor, how does BDNF achieve synapse-specific modulation? In addition to local synthesis and/or secretion of BDNF at the active synapse, it is likely that active synapses may also respond better to BDNF compared to less active ones. Therefore, neuronal/synaptic activity may enhance TrkB signaling selectively at active synapses, without affecting the neighboring less active ones. Indeed, multiple studies have revealed several mechanisms conferring activity-dependent regulation of TrkB signaling. First, TrkB mRNA is localized at synapses, especially in the dendritic regions and in synaptosomal fractions, suggesting that similar to BDNF, TrkB mRNA may be locally translated (Righi et al. 2000; Simonato et al. 2002; Tongiorgi et al. 1997). Tongiorgi et al. (1997) have shown that neuronal activity induces translocation of TrkB mRNA into dendrites in vitro. BDNF also induce dendritic translocation of TrkB mRNA, suggesting that activity-dependent local secretion of BDNF may mobilize TrkB mRNA into the dendrites (Tongiorgi and Baj 2008; Tongiorgi et al. 1997). Second, contrary to TrkB mRNA transport into the dendrites, which occur in hours, dendritic TrkB protein levels increased within minutes (~10 min) following neuronal activity. TrkB mRNA local translation may serve as the first node of regulation by neuronal activity. Third, in addition to local translation, BDNF regulation of active synapses may also be mediated through selective insertion of TrkB receptors, providing a positive feed forward regulation (Meyer-Franke et al. 1998). Corroborating this notion are the results from Du et al., demonstrating that the physiologically relevant tetanic stimulation, but not the low frequency stimulation, increase the number of surface TrkB receptors (Du et al. 2000). Neuronal activity or BDNF stimulation led to rapid insertion of TrkB receptors (<30 min) and was dependent on intracellular increase in Ca^{2+} and activation of CaMKII. However, surface expression of TrkB is tightly regulated depending on how TrkB is exposed to BDNF. For instance, acute exposure to BDNF rapidly increases surface expression (Du et al. 2000), whereas chronic exposure results in decrease in surface TrkB levels (Frank et al. 1996; Haapasalo et al. 2002; Sommerfeld et al. 2000), possibly due to TrkB endocytosis and proteasome-mediated degradation. However, if neuronal activity significantly elevates the surface levels of TrkB rapidly in a random fashion, then how does BDNF-TrkB signaling provide synapse-specific regulation?

One mechanism that could potentially constrain BDNF regulation to highly active synapses is through the lateral movement of surface TrkB receptors that are inserted at extrasynaptic sites to move into active synapses (spines/active zones). Presence of lipid rafts (cholesterol and sphingolipid-rich microdomains) at the synapses does offer specialized signaling platform for TrkB regulation (Assaife-Lopes et al. 2010; Suzuki et al. 2004; Wu et al. 1997). Interestingly, translocation of TrkB into lipid rafts selectively activates the Ras/MAPK/Erk pathway, but not PI3K/Akt pathway, suggesting that lipid rafts could compartmentalize downstream signaling events of TrkB (Suzuki et al. 2004). Moreover, blocking TrkB translocation into lipid rafts abolished the potentiating effects of BDNF on evoked synaptic transmission in culture and blocked evoked synaptic

responses in hippocampal slices in response to tetanic stimulation (Suzuki et al. 2004). Finally, alternate mechanisms do exist that can specifically regulate the responsiveness of TrkB receptors at synapses. Along with BDNF secretion, neuronal activity also increases the intracellular concentration of cAMP ([cAMP]i) in situ (spines and active zones), which has been shown to be responsible for regulating BDNF-induced TrkB phosphorylation as well as facilitating the movement of TrkB into the postsynaptic density in dendritic spines (Ji et al. 2005). Together, multiple mechanisms have been discovered that can regulate BDNF actions in a synapse-specific manner by modulating its receptor, TrkB.

2 BDNF Regulation of Late Phase-LTP and Long-Term Memory

2.1 proBDNF Cleavage by tPA/Plasmin System Regulates Late Phase-LTP

In addition to its role in E-LTP, substantial evidence suggests that BDNF is also critical for late phase LTP (L-LTP). Reduction of BDNF levels either genetically by BDNF gene knockout (BDNF+/− mice) (Patterson et al. 1996) or pharmacologically by the application of a BDNF scavenger (Chen et al. 1999) (TrkB-IgG) results in impairment in L-LTP in rat hippocampal slices. Moreover, application of BDNF after hippocampal slices were stimulated with a weak TBS (three sets of four pulses at 100 Hz), which normally only induce E-LTP, resulted in sustained L-LTP. These results suggest that BDNF is necessary and sufficient for L-LTP. In addition, tPA has also been implicated in L-LTP (Frey et al. 1996; Huang et al. 1996). The biochemical function of tPA is to cleave and convert the inactive zymogen plasminogen into active protease plasmin. The finding by Lee et al. (2001) that plasmin can convert proBDNF into mBDNF in vitro (Lee et al. 2001) prompted Pang et al. (2004) to hypothesize that if proBDNF is produced and secreted in the brain, then conversion of proBDNF to mBDNF by the tPA/plasmin system may be involved in L-LTP. Using different transgenic knockout animals (tPA, plasmin, BDNF), this hypothesis was tested systematically to establish the functional relationship between tPA/plasmin and BDNF. First, L-LTP was severely impaired in both tPA and plasminogen knockout mice, and this impairment was completely rescued by perfusing cleaved mBDNF (Pang et al. 2004). Remarkably, perfusion of cleavage-resistant proBDNF (mutated at furin cleavage site) was unable to rescue the L-LTP deficit in tPA (−/−) and plasminogen (−/−) mice, suggesting that conversion of proBDNF to mBDNF is essential for expressing L-LTP. Second, in vitro biochemical experiments showed that tPA together with plasmin was necessary for the conversion of proBDNF to mBDNF, and proBDNF is not a direct substrate of tPA (Pang et al. 2004). Consistent with this finding, tPA knockout animals showed elevated levels of proBDNF. Third, perfusion of tPA failed to rescue the L-LTP deficit in plasminogen (−/−) or BDNF (+/−) mice, whereas perfusion of plasmin rescued the L-LTP deficit in tPA (−/−) mice but not in BDNF

(+/−) mice. These results, together with the finding that mBDNF rescued the L-LTP deficit in both tPA (−/−) and plasminogen (−/−) mice, suggest that tPA, by activating the extracellular protease plasmin, converts the precursor proBDNF to mBDNF in the hippocampus, and such conversion is required for L-LTP (Pang et al. 2004).

An even more remarkable finding is that application of mBDNF after tetanus is sufficient to allow L-LTP to occur even when all protein synthesis is blocked (Pang et al. 2004). It is well established that both long-term memory and L-LTP require new protein synthesis (Govindarajan et al. 2011; Klann and Sweatt 2008). An essential and yet unresolved question is what is (are) the specific product (s) mediating the long-term changes at synapses. The results by Pang et al. (2004) suggest that mBDNF is likely to be the key (or only) protein synthesis product that is essential to convert E-LTP to L-LTP. This is truly a provocative idea that surprised many in the field.

2.2 BDNF Regulation of Long-Term Memory

L-LTP is considered as a cellular basis for long-term memory (LTM). Substantial evidence supports a critical role of BDNF in LTM. An elevation in BDNF mRNA level in the hippocampus has been observed following acquisition of spatial tasks such as Morris water maze and radial arm maze (Kesslak et al. 1998; Mizuno et al. 2000); inhibitory avoidance (Alonso et al. 2002a; Ma et al. 1998); contextual fear conditioning (Hall et al. 2000); olfactory recognition (Broad et al. 2002); and conditioned taste aversion memory (Ma et al. 2011). In addition, the retrieval of spatial memories increases the level of BDNF mRNA in hippocampus following contextual fear conditioning and Morris water maze training (Hall et al. 2000; Kesslak et al. 1998). Moreover, significant increase of BDNF expression is observed to accompany a new form of learning, the extinction of previously acquired memories (e.g., conditioned fear) in the prefrontal cortex (Bredy et al. 2007) and amygdale (Chhatwal et al. 2006).

On the other hand, LTM is impaired by disrupting BDNF signaling. Morris water maze acquisition (Linnarsson et al. 1997) and contextual fear conditioning (Liu et al. 2004) are impaired in BDNF (+/−) mice. Intraventricular injection of anti-BDNF neutralizing antibody into rat brain prior to training also impaired LTM in the Morris water maze task (Mu et al. 1999). In addition, over-expression of truncated TrkB impaired long-term spatial memory (Saarelainen et al. 2000), while over-expression of TrkB resulted in improved learning and memory in the water maze, contextual fear conditioning, and conditioned taste aversion tests (Koponen et al. 2004). Surprisingly, over-expression of BDNF also resulted in modest learning deficits in spatial memory tasks, potentially due to precocious effects of BDNF on the development of multiple circuits, leading to abnormal wiring in the CNS (Cunha et al. 2009).

Region-specific genetic and pharmacological manipulations have helped delineate the role of BDNF signaling in specific brain regions. Inhibition of BDNF

mRNA expression via hippocampal infusion of BDNF antisense oligonucleotides or anti-BDNF antibody before training also blocks acquisition in inhibitory avoidance and radial arm maze tasks (Alonso et al. 2002a; Ma et al. 1998; Mizuno et al. 2000). Gorski et al. (2003) deleted BDNF gene from the forebrain using site-specific Cre recombinase and found that such mice failed to learn Morris water maze task. Prelimbic cortical-specific deletion of BDNF resulted in robust deficits in consolidation of cued fear (Choi et al. 2010). In addition, decreased BDNF mRNA expression in the hippocampus by targeted deletion of BDNF gene using lentiviral vector engineered to express Cre recombinase led to impairments in spatial learning in Morris water maze and the extinction of fear-potentiated startle (Heldt et al. 2007). A recent study using post-training CA1 intrahippocampal infusion of anti-BDNF antibody also revealed a critical role of BDNF in object recognition LTM retention (Furini et al. 2009). Moreover, deletion of TrkB gene in forebrain results in severe behavioral deficits in a spatial water maze task and moderate deficits in a radial arm maze task (Minichiello et al. 1999), while expression of a dominant-negative TrkB in amygdala specifically impaired consolidation of conditioned fear extinction (Chhatwal et al. 2006).

Unfortunately, due to the lack of temporally restricted and reversible manipulation of BDNF signaling, it is very difficult to discriminate the role of BDNF signaling in specific processes of LTM such as formation (acquisition or encoding), retention, retrieval, and extinction. However, using intra-hippocampal infusion of BDNF antibodies or antisense oligonucleotide, recent studies demonstrated the existence of two-time windows in LTM that requires BDNF: one at 1–4 h after encoding, which is critical for LTM lasting for 1–2 days (Alonso et al. 2002a, b) and the other at 12 h after memory formation that is essential for LTM 7 days later (Bekinschtein et al. 2007). It remains unclear whether the second wave of BDNF is induced by initial memory acquisition or it is the result of subsequent signaling cascades initiated post-acquisition.

2.3 BDNF-TrkB Signaling in Synaptic and Behavior Tagging

Like LTM, L-LTP requires gene transcription and de novo protein synthesis. Since gene expression occurs at the neuronal soma, how can the newly synthesized proteins (known as "plasticity-related proteins" or PRPs) specifically modify the stimulated or activated synapses but not the nearby, less active ones? The "synaptic tagging hypothesis," proposed by Frey and Morris (1997), states that local synaptic activity generates a tag, which "captures" the soma-derived PRPs. Several lines of evidence strongly suggest BDNF as a PRP.

First, BDNF mRNA levels are significantly increased 1–3 h after the induction of L-LTP in hippocampal CA1 neurons (Castren et al. 1993; Dragunow et al. 1993; Morimoto et al. 1998; Patterson et al. 1992). Such an increase is probably mediated by enhanced BDNF transcription through activity-dependent transcription. Second, application of mBDNF can rescue the impaired L-LTP in mice with reduced BDNF expression (Pang et al. 2004; Patterson et al. 2001). Third, in mice with elevated

levels of BDNF, a weak TBS, which can create a "synaptic tag" but not PRP, can induce L-LTP (Barco et al. 2005). Moreover, application of BDNF to wild-type mouse hippocampal slices also converts E-LTP induced by weak TBS to L-LTP. Finally, BDNF application completely rescued L-LTP blocked by protein synthesis inhibition.

In an insightful review, Tonegawa and colleagues proposed several criteria for molecules to function as a synaptic tags (Kelleher et al. 2004): (1) a tag can be generated by weak stimulation that induces only E-LTP, which is protein synthesis-independent; (2) the lifetime of a tag must be about 1–2 h; (3) the activation of a tag must not require protein synthesis; (4) a tag must be induced in an input-specific manner and should be spatially restricted; and (5) a tag must interact with (and therefore capture) PRP to facilitate L-LTP. If BDNF is a PRP, TrkB is an obvious candidate for a synaptic tag. Using combined biochemical, genetic, electrophysiological, and cell biological approaches, Lu and colleagues have recently demonstrated that TrkB satisfies four of the five criteria (Lu et al. 2011). For example, TrkB phosphorylation (and therefore activation) was induced in hippocampal slices by weak TBS that only induces E-LTP, and this TrkB activation is transient (about 1 h) and protein synthesis-independent. To demonstrate that TrkB activation is input-specific and spatially restricted, BDNF-conjugated beads were locally applied to cultured hippocampal neurons to mimic BDNF release at synapses upon local stimulation. Imaging studies demonstrated that TrkB activation is confined to stimulated synapses (Lu et al. 2011). A litmus test for TrkB to act as a synaptic tag is the two-pathway experiment in which induction of L-LTP by strong stimulation (12 sets of TBS) in one pathway converts E-LTP induced by weak stimulation (four sets of TBS) to L-LTP in a second, independent pathway. Taking advantages of the pharmacologically regulatable $TrkB^{F616A}$ transgenic mice (Chen et al. 2005), in which the ATP binding site of TrkB is genetically modified to be reversibly inhibited by the compound 1NMPP1, it was shown that application of 1NMPP1 at the time of stimulation with a weak stimulus in the second pathway diminished L-LTP in that pathway but had no effect on the first one. Since TrkB is the natural receptor for BDNF, there is no conceptual difficulty for TrkB to capture the potential PRP: BDNF (the fifth criterion).

Since L-LTP is considered as the cellular model for LTM, "synaptic tagging" may serve as a cellular mechanism underlying "behavioral tagging"—a conversion of short-term memory (STP) provided by weak training to LTM, if a PRP could be induced by strong training of completely different modality. Specifically, it was found in rats that are exposed to a strong stimulation such as a novel environment or a novel taste before or after a weak training could provide the PRPs necessary to convert STM to LTM (Ballarini et al. 2009; Moncada and Viola 2007). This behavioral paradigm was adapted to mice: weak inhibitory avoidance conditioning (IA) normally results in a STM detectable at 1 h but not 24 h after training. However, exposure to a novel environment at 1 h before the IA training results in LTM lasting for 24 h after training. Remarkably, inhibition of TrkB activation by 1NMPP1 in $TrkB^{F616A}$ mice prior to IA training blocked the conversion of STM to LTM by novelty (Lu et al. 2011). These findings demonstrate that BDNF/TrkB has

the strongest potential to serve as a PRP/tag for L-LTP and LTM both in vitro and in vivo, respectively.

2.4 Role of Untranslated Region (UTR) of BDNF mRNA

Various isoforms of BDNF mRNAs are detected in neuronal dendrites, and such dendritic localization of BDNF mRNAs has been shown to be regulated by neuronal activity (Chiaruttini et al. 2009; Tongiorgi et al. 1997). A remarkable feature of the BDNF transcripts is that they are processed at two alternative polyadenylation sites, giving rise to two pools of BDNF mRNAs that harbor either a short or a long 3′UTR of 0.35 kb and 2.85 kb in length, respectively (Liu et al. 2005, 2006). These two pools of BDNF mRNA isoforms encode the same BDNF protein. Recently, a study by An et al. (2008) showed that short 3′UTR BDNF mRNA is restricted to somata while the long 3′UTR BDNF mRNA can be localized to dendrites of cultured hippocampal neurons. A line of transgenic mice that express only the short 3′UTR but not the long 3′UTR BDNF mRNA ($BDNF^{klox/klox}$) was used to investigate the functional role of long 3′UTR in vivo. Truncation of the long 3′UTR disrupts dendritic localization of BDNF mRNA in the brain, leading to pruning and enlargement of dendritic spines, and selective impairment in LTP at apical dendrites but not in somata, of hippocampal neurons. In addition, lack of dendritic BDNF ($BDNF^{klox/klox}$) in layer 2/3 pyramidal neurons of the visual cortex also showed altered spine pruning, late phase spine maturation, and recovery of cortical responsiveness following monocular deprivation (Kaneko et al. 2012). These results reveal a critical role for local BDNF synthesis in the structural and functional plasticity in dendrites of hippocampal neurons. Furthermore, this study provides an example that mRNAs containing the same coding sequence but distinct 3′UTRs can have distinct physiological functions due to their selective subcellular localization and translation. Interestingly, dendritically localized BDNF mRNAs remain translationally silent and are made competent in response to neuronal activity (Lau et al. 2010). Pilocarpine, a muscarinic cholinergic receptor agonist known to exacerbate excitatory neuronal activity leading to seizures, specifically mobilized long 3′UTR BDNF transcripts into the polyribosomal fractions in neurites. Further investigations are required to reveal how the long 3′UTR silences BDNF mRNA translation, and how neuronal stimulation removes the silencing.

The above data suggest that activity-dependent regulation of BDNF expression could be achieved at the levels of trafficking and/or translation. These could be mediated by one or more *trans*-acting factors, including but not limited to RNA binding proteins and microRNAs that may be associated with short or long 3′UTR transcripts. Clues to the *cis*-elements in the BDNF transcripts and the *trans*-acting factors involved in this process are beginning to emerge. Chiaruttini et al. (2009) proposed G196A (rs6265) as a critical *cis* element in the 5′UTR for BDNF mRNA trafficking into dendrites. Evidence for additional *cis* elements in BDNF mRNA also came from genetic association studies of the human SNP C270T (rs56164415) in the 5′UTR in idiopathic temporal lobe epilepsy (Kanemoto et al. 2003).

The 5′UTRs encoded by human BDNF gene exons V and VIII are proposed to contain putative internal ribosome entry sequence (IRES), which may serve as alternate sites for ribosomal binding and translation. In addition to the *cis* elements, Chiaruttini et al. (2009) also proposed the role for the *trans*-acting complex translin/trax in transporting BDNF mRNA into the dendrites. However, recent studies using translin knockout mice showed that translin/trax complex-independent mechanisms may also be involved in dendritic trafficking of BDNF mRNA (Wu et al. 2011). Corroborating this idea, CArG box binding factor A or A2RE/RTS binding factor (CBF-A) was shown to be a *trans* factor (other than staufen-1, DDX3 translin) responsible for facilitating dendritic transport of different mRNAs including BDNF, Arc, CaMKIIα (Raju et al. 2011). Similarly, fragile X mental retardation protein (FMRP) has been suggested as a *trans* factor for dendritic BDNF mRNA transport (Louhivuori et al. 2010). More interestingly, the mutant protein huntingtin (htt), in which the change in the CAG repeat length is responsible for causing Huntington's disease, has also been shown to be associated with BDNF mRNA granules (Ma et al. 2010). Other non-proteinaceous *trans*-acting factors, like microRNAs 134, 381, and 495 that regulate BDNF mRNA translation, are beginning to emerge (Wu et al. 2010).

While these findings unveiled multiple mechanisms of BDNF regulation by the 3′UTRs, it is important to emphasize that BDNF transcripts also contain different 5′UTRs and may impart additional regulatory mechanisms. BDNF mRNA trafficking into different neuronal compartments, their local regulation of translation, and association with factors that play a causal role in different neurological diseases have opened up a new area in BDNF biology, which will be one of the key areas for research focus in near future.

3 BDNF Regulation of Long-Term Depression

3.1 proBDNF Effect on LTD

Compared with the vast literature supporting the role of mBDNF in LTP, relatively few studies have focused on BDNF regulation of other forms of plasticity such as long-term depression (LTD). A clue came from outside of the synaptic plasticity field. Hempstead and colleagues elegantly demonstrated that proNGF (also proBDNF) induced neuronal apoptosis through the pan-neurotrophin receptor, $p75^{NTR}$, along with the co-receptor, sortilin (Lee et al. 2001). This result suggested that proneurotrophins through a distinct receptor ($p75^{NTR}$) may elicit effects opposite to mature neurotrophins. However, although there was no obvious cellular phenotype, $p75^{NTR}$ homozygous (−/−) mice (Lee et al. 1992) did show impairments in several learning and memory tasks (in C57Bl/6 background) (Peterson et al. 1999; Wright et al. 2004). These results remain controversial, as a recent study demonstrated that spatial memory and hippocampal LTP are significantly enhanced in the $p75^{NTR}$-knockout mice (in 129/Sv background) (Barrett et al. 2009). These data strongly suggest that proBDNF-$p75^{NTR}$ interaction may

regulate synaptic function, rather than apoptosis, in adult mice. Given that a significant proportion of BDNF secreted in the brain is proBDNF (Mowla et al. 2001; Nagappan et al. 2009) and that cleavage of proBDNF facilitates L-LTP, it was hypothesized that uncleaved proBDNF might have an opposite role—regulation of long-term depression (LTD). Indeed, Korte and colleagues reported that LTD could not be induced in two lines (exon III and exon IV) of $p75^{NTR}$ transgenic mice (Rosch et al. 2005). A systematic analysis by Woo et al. (2005) showed that $p75^{NTR}$ (−/−) mice indeed exhibit selective impairment in the NMDA-dependent LTD (called NR-LTD), without affecting basal synaptic transmission or other forms of synaptic plasticity. LTD could be reliably induced either by application of a train of low frequency stimulation (LFS) or perfusion of NMDA to the hippocampal slices from wild-type juvenile mice but not the $p75^{NTR}$−/− mice of the same age. This effect is very specific since NMDA-dependent LTP and NMDA-independent LTD are completely normal in p75−/− mice (Woo et al. 2005).

More direct evidence for the role of proBDNF in LTD came from pharmacological studies (Woo et al. 2005). Uncleavable proBDNF facilitated NR-LTD, but not LTP, not only in young mice (3–4 weeks when LTD is normally measurable) but also in older mice (7–8 weeks old). Moreover, proBDNF promotes NR-LTD through $p75^{NTR}$, as deletion of the $p75^{NTR}$ gene or inhibition of $p75^{NTR}$ by functionally blocking $p75^{NTR}$ (REX) antibody completely inhibited the potentiating effect of proBDNF on NR-LTD. These results, together with the electron microscopic evidence that $p75^{NTR}$ is localized in the dendritic spines of CA1 pyramidal neurons, suggest that proBDNF is the endogenous ligand acting on postsynaptic $p75^{NTR}$ in the CA1 neurons to control NR-LTD. This conclusion was unexpected, since the traditional thinking was that $p75^{NTR}$ is only expressed at the cholinergic afferents projecting from the basal forebrain neurons into the hippocampus. Further experimentation revealed that NR2B, but not NR2A, is responsible for $p75^{NTR}$/NR-LTD. In hippocampal CA1 synapses from the $p75^{NTR}$ mutant mice, synaptic currents mediated by NR2B, but not those by NR2A, were selectively eliminated. Further, activation of $p75^{NTR}$ by proBDNF enhanced NR2B-mediated synaptic currents. A selective impairment in NR2B expression could therefore explain the specific failure of NR-LTD, but not LTP or NR-independent LTD, in $p75^{NTR}$−/− mice. Together, these findings revealed a novel role of proBDNF-$p75^{NTR}$ signaling in LTD in hippocampal slices and its potential mechanism of action (Woo et al. 2005).

In vivo studies in awake and behaving rats suggest a possible role for endogenous proBDNF in regulating memory. During recall, a fully consolidated memory can undergo either reconsolidation or be subject to extinction, depending on whether the memory is enforced or not. Extinction memory competes with consolidated memory to control behavior. Memories encoded in rats that are conditioned in two different contexts can be retrieved and manipulated without interference from each other. In one such experiment, Barnes et al. established an extinction protocol in rats that were fear conditioned by foot shock in two different contexts (Barnes and Thomas 2008). Interestingly, proBDNF levels in the

hippocampal CA1 region were found to increase by ~2.5-fold only during extinction but not in acquisition or recall. Moreover, when proBDNF levels increased by inhibiting the proBDNF processing enzymes tPA/plasmin using tPA-STOP (a small molecule inhibitor), the extinction of conditioned fear memory was potentiated. In parallel, tPA-STOP attenuated consolidation of memory during recall testing. Together these studies suggest that the extent of proBDNF cleavage may be precisely controlled by neuronal activity induced during memory recall: higher levels of proBDNF may promote extinction while suppressing consolidation. This study provides a mechanistic link from molecular events (proBDNF conversion by tPA/plasmin cascade) to circuits (LTD facilitated by proBDNF) and behavior (extinction memory).

3.2 Opposing Effects of proBDNF and Mature BDNF: Yin-Yang Hypothesis

The studies highlighted above not only established a bidirectional regulation of hippocampal plasticity by proBDNF and mBDNF but also helped formulate a "yin-yang hypothesis": the uncleaved proBDNF (pro-neurotrophins) leads to negative effects such as apoptosis and LTD through $p75^{NTR}$, while mBDNF (mature neurotrophins) elicit positive functions such as cell survival and LTP through TrkB. This hypothesis is based on several major findings that are now well validated. First, pro-neurotrophins are secreted, and they could serve as signaling molecules, rather than inactive precursors (Lee et al. 2001; Yang et al. 2009b). It is now clear that the pro and mature neurotrophins elicit distinct signal transduction pathways (Koshimizu et al. 2010; Koshimizu et al. 2009; Sun et al. 2012). Second, in contrast to mature neurotrophins which preferentially bind Trk receptors, pro-neurotrophins bind with high affinity to $p75^{NTR}$, which previously was considered a low affinity pan neurotrophin receptor (Nykjaer et al. 2004). Third, pro and mature neurotrophins often elicit opposite effects. Under this simple model, the binary actions of neurotrophins depend on *both* the forms of the neurotrophin (pro vs. mature) and the class of receptors activated ($p75^{NTR}$ vs. Trk's). In addition to cell survival and synaptic plasticity, recent studies have also shown that proBDNF elicits axonal retraction (Sun et al. 2012; Yang et al. 2009a), inhibits neuronal migration (Xu et al. 2011), and reduces dendritic growth and spines (Koshimizu et al. 2009), through $p75^{NTR}$. Finally, proNGF and proBDNF can be cleaved by extracellular proteases such as MMP7 and plasmin (Lee et al. 2001; Pang et al. 2004). An important concept emerged from the Yin-yang hypothesis is that cleavage of pro-neurotrophins (or not) by extracellular proteases becomes a critical control mechanism for bidirectional neurotrophin regulation. These results may have implications in neural development, synaptic plasticity, and even nervous system diseases. It remains to be established whether the yin and yang actions of neurotrophins are equally prevalent.

3.3 Role of p75 and LTD in Stress Coping and Anxiety

The unexpected discovery that proBDNF promotes NR-LTD in the juvenile hippocampus through $p75^{NTR}$ raised more questions. Since in adults $p75^{NTR}$ is primarily expressed in basal forebrain cholinergic neurons but rarely in other brain regions, what is the role of $p75^{NTR}$ in the adult brain? Given that NR-LTD is also restricted to the juvenile brain, one may also ask can LTD ever be induced in the adult, and if so, what is its physiological function? Further, what role does $p75^{NTR}$ play in pathological conditions such as during stress?

Martinowich and colleagues have performed a series of experiments to address these questions using the $p75^{NTR}$ (−/−) mice (Martinowich et al. 2011b). First, acute stress (placing the mice on a small elevated platform) could enhance NMDA-dependent LTD in hippocampus with weak low frequency stimulation (LFS), which by itself will not enhance LTD in adult wild-type mice. Remarkably, this "stress-enabled" NR-LTD was completely absent in the $p75^{NTR}$ (−/−) mice. The effect of $p75^{NTR}$ gene deletion on LTD is very specific: there was no change in LTP, basal synaptic transmission, or even LTD induced by a perfusion of NMDA or muscarinic receptor agonist carbachol in adult $p75^{NTR}$ (−/−) slices. These results identified a new form of LTD in the adult hippocampus that is dependent on NMDA receptor, $p75^{NTR}$, as well as cholinergic inputs to the hippocampus.

Second, upon stress, the $p75^{NTR}$ mutants exhibit a selective increase in anxiety-like, but not depressive-like, behaviors, as well as a decreased stress resiliency (Martinowich et al. 2011b). These mice mount a normal stress-induced glucocorticoid surge and hyperthermia (a transient increase in body temperature, which recovers upon removal of stress), but their ability to recover from this stress is impaired, suggesting their inability to cope with stressful conditions. The muscarinic receptor antagonist scopolamine also blocked stress-enabled LTD, leading to anxiety. In contrast, an increase in cholinergic transmission by the acetylcholinesterase inhibitor (−)-phenserine resulted in anxiolytic effects. Taken together, these results support a hypothetical pathway for stress coping (Martinowich et al. 2011b): $p75^{NTR}$ → cholinergic transmission → stress-enabled hippocampal LTD → control of stress-induced anxiety.

Finally, to test this hypothesis, a membrane permeable and brain-penetrating peptide, Tat-$GluA2_{3Y}$, was used to block GluR2 endocytosis. Remarkably, systemic administration of the peptide attenuated the recovery of wild-type animals from stress-induced hyperthermia and exacerbated anxiety-like behavior after exposure to an acute stressor. Thus, LTD is a coping mechanism for stress-induced anxiety, which is regulated by $p75^{NTR}$-mediated cholinergic transmission in the hippocampus. Piecing together these results suggest that acute stress leads to acetylcholine release, which can be modulated by $p75^{NTR}$ in the basal forebrain cholinergic afferents, and these cholinergic inputs facilitate hippocampal LTD, which in turn suppresses the development of anxiety-like behaviors in response to stress.

4 BDNF Regulation of GABAergic Network

4.1 Activity-Dependent Transcription and GABAergic Interneurons

While a majority of the studies have focused on BDNF regulation of excitatory synapses, evidence for the role of BDNF in GABAergic inhibitory synapses is in fact quite substantial (Holm et al. 2009; Huang et al. 2011; Olofsdotter et al. 2000). For example, pharmacological treatment of brain slices with mature BDNF, but not proBDNF, has been shown to decrease inhibitory synaptic transmission (Frerking et al. 1998; Holm et al. 2009; Tanaka et al. 1997). A series of recent studies have now pointed to a major role of activity-dependent BDNF transcription in the development and function of GABAergic synapses.

BDNF gene is transcribed through multiple discrete promoters (I–VIII); each drives a unique 5′exon (exons I–VIII) that is spliced on to the common 3′ coding exon (exon IX). Thus, a total of nine BDNF transcripts are synthesized in rodents (Aid et al. 2007; Timmusk et al. 1993) and ~17 transcripts in humans (Pruunsild et al. 2007). Why are there so many different BDNF mRNAs that code for exactly the same BDNF protein? Different transcripts are expressed in different brain regions, cell types, and even different subcellular loci. They are also expressed during different developmental stages and regulated by different environmental factors. An emerging concept is that some promoters control the basal levels of *bdnf* expression necessary for neuronal survival and differentiation, whereas others drive activity-dependent *bdnf* expression, which may be involved in experience-dependent circuit maturation and plasticity in vivo (Hong et al. 2008; Sakata et al. 2009). Two groups have used sophisticated mouse genetics to address the role of activity-dependent *bdnf* expression, which is mediated largely by promoter IV. In one study, Hong et al. generated a mouse line in which the CaRE3/CRE (CREm) in endogenous promoter IV was mutated. CREm mice exhibit reduced spontaneous inhibitory postsynaptic currents (sIPSCs) in cortical culture and fewer GABAergic synapses in the cortex (Hong et al. 2008). In another study, Sakata and colleagues disrupted the promoter IV-mediated *bdnf* gene expression completely by a GFP-STOP cassette after *bdnf* exon IV (the BDNF-KIV line) (Sakata et al. 2009). These mice exhibit fewer parvalbumin (PV)-expressing, fast-spiking GABAergic interneurons in the prefrontal cortex (PFC), reduced frequency and amplitude of sIPSCs in cortical culture, as well as an altered spike-time dependent synaptic potentiation (STDP) in PFC slices. Interestingly, the structure and function of cortical glutamatergic synapses appear to be normal in both lines. These studies demonstrate specific requirements for activity-dependent *bdnf* expression in the development of inhibitory circuits in cortex.

To determine how activity-driven *bdnf* gene expression shapes the GABAergic network in specific cortical circuits in vivo, Jiao et al. (2011) crossed the BDNF-KIV line with the GAD67–GFP mouse line, in which all GABAergic neurons are genetically labeled with GFP. Two interesting observations were made. First, BDNF immunoreactivity in the barrel cortex was found to be distributed in an

orderly barrel shape in the control, wild-type mice, but this barrel pattern of BDNF distribution was completely abolished in the BDNF-KIV. This implies that it is the activity-driven, not the constitutive, *bdnf* transcription that is responsible for the barrel-shaped BDNF distribution in somatosensory cortex. Whisker trimming markedly reduced BDNF expression in the barrel cortex of control mice, but not in BDNF-KIV, suggesting that whisker sensory activities drive activity-dependent BDNF expression at local barrel cortical circuits in an input-specific manner. Second, whisker trimming deprived sensory inputs to the barrel cortex, leading to fewer perisomatic GABAergic boutons on the pyramidal neurons, as well as barrel-specific attenuation of GABAergic transmission. All these occur only in wild-type mice, but not in BDNF-KIV. It is remarkable that a relatively mild manipulation on activity-dependent but not basal BDNF expression machinery could completely abolish whisker-trimming-induced plasticity of GABAergic circuit in the barrel cortex in vivo.

While the BDNF-KIV was initially generated with the intent to block the promoter IV driven *bdnf* transcription, detailed characterization indicates that the activities of promoters I and III, which also contribute to activity-dependent *bdnf* transcription, were also reduced in this line. Further analyses revealed that activity-driven increase in BDNF protein is completely blocked while baseline BDNF level has only a mild reduction in the BDNF-KIV brain (Jiao et al. 2011; Martinowich et al. 2011a; Sakata et al. 2009). Thus, the BDNF-KIV line should serve as a tool to study the function of activity-dependent BDNF expression, rather than that of promoter-IV. To begin addressing the functional role of activity-dependent BDNF expression in the adult, Martinowich et al. (2011a) found that in wild-type animals, sleep deprivation dramatically increased BDNF transcription (primarily promoter I) as well as cortistatin, a neuropeptide expressed in a subset of cortical GABAergic interneurons implicated in sleep homeostasis. Such increases were not observed in BDNF-KIV. Moreover, BDNF-KIV animals exhibited a substantial decrease in the amount of sleeping time, compared to WT animals. Thus, activity-dependent BDNF expression regulates sleep homeostasis possibly through cortistatin-expressing interneurons.

4.2 BDNF-TrkB Controls Network Oscillations Through Regulation of PV Interneurons

Compared with the vast knowledge of BDNF regulation at the cellular (synaptic transmission and plasticity) and behavioral (cognitive functions) levels, only few studies have been conducted to address the role of BDNF in neuronal networks. Neuronal rhythmic activity, particularly γ-oscillations, is thought to be important for neuronal assemblies underlying temporal encoding, binding of sensory features, and memory storage and retrieval (Freeman 1975; Fries 2005; Rodriguez et al. 1999; Singer and Gray 1995; Tallon-Baudry and Bertrand 1999). Several studies have demonstrated that the parvalbumin-expressing, fast-spiking GABAergic interneurons (PV interneuron) are essential for the γ-frequency

synchronization in cortical and hippocampal networks. PV interneuron is a major cell population in the forebrain that expresses the BDNF receptor, TrkB.

To explore the role of BDNF-TrkB signaling in network function in neuronal circuits, a line of mutant mice in which the *TrkB* gene is specifically deleted in PV interneurons (TrkB-PV$^{-/-}$) was generated (Zheng et al. 2011). These mice showed two interesting electrophysiological phenotypes: (1) The inputs and outputs of the PV interneurons, which are reflected by the amplitude of glutamatergic synaptic currents recorded in the PV interneurons and the frequency of GABAergic inputs to the pyramidal cells, respectively, were reduced in the TrkB-PV$^{-/-}$ mice. These results suggest that cortical BDNF-TrkB signaling is critical for the function of PV interneurons. (2) In parallel, the rhythmic network activity in the gamma-frequency range (30–80 Hz) recorded in the CA1 area was found to be dramatically reduced. Further characterization demonstrated that this was due to a reduction as well as desynchronization of action potentials generated in PV interneurons. Taken together, these results demonstrate for the first time a role for BDNF-TrkB signaling in network synchrony. This is another emerging area of BDNF biology that may have significant impact not only in the understanding of network oscillations during memory processes but may also help to understand abnormal or dysfunctional network activities under pathophysiological conditions such as neurological diseases and psychiatric disorders.

Conclusions

With important discoveries continually emerging one after another over the last 2 decades, BDNF regulation of synapses has been one of the most exciting areas in the neurotrophin field. BDNF elicits a wide range of effects: during development and in the adult, on excitatory and inhibitory synapses, regulating synaptic transmission or plasticity, structure or function, with either acute or long-term effects, etc. How does BDNF elicit such an array of pleiotrophic properties? One of the key discoveries was that proBDNF, acting through its preferred receptor p75^{NTR}/sortilin, elicits biologically different and often opposing effects to mBDNF. Thus, conversion of proBDNF to mBDNF through proteolytic cleavage has emerged as an important regulatory mechanism. Indeed, pharmacological and genetic studies have revealed that tPA/plasmin-mediated, extracellular conversion of proBDNF to mBDNF is necessary and sufficient for late-phase LTP. Moreover, proBDNF-p75^{NTR} signaling has been shown to facilitate LTD in young hippocampal slices in vitro and perhaps during stress in adults in vivo. Activity-dependent proBDNF→mBDNF conversion appears to play an important role in synaptic competition/elimination during development. These findings form the foundation for the "Yin-yang" hypothesis. Second major breakthrough is identification of the human val/met polymorphism that impacts selectively on activity-dependent but not constitutive BDNF secretion. This provides an unprecedented opportunity to study the function of BDNF in cognitive function and dysfunction in human. Third, the discovery that BDNF mRNA with short 3′UTR is located in neuronal soma whereas that with long 3′UTR is targeted to distal dendrites has unveiled yet another level of

complexity: compartmentalized regulation of BDNF expression in different parts of the same neurons. Indeed, initial investigations suggest that dendritically localized long 3′UTR BDNF mRNA is quiescent, and its translation is induced by local synaptic activity. Functional study of BDNF mRNA trafficking and its activity-dependent translation has been an emerging area of research likely to generate some new surprises. Fourth, neuronal activity has been shown to regulate BDNF-TrkB signaling through a wide range of mechanisms: insertion and endocytosis of TrkB receptor, translocation into lipid rafts, cAMP gating, and differential signaling kinetics. Fifth, BDNF gene is transcribed through nine different promoters in rodents, giving rise to nine mRNAs coding for the same BDNF protein. Differential regulation of BDNF promoters and its functional consequences represent an exciting area of research with profound implications in both basic neuroscience and various neurological and psychiatric disorders. Finally, BDNF also has been shown to play a significant role in brain network development and in synchronization of network activities resulting in different frequencies of oscillations. This is likely to be an intense area of investigation, especially because it will help bridge the gap between neurophysiological mechanisms to cognitive functions in the whole organism, as well as pave the way for understanding pathophysiological conditions in nervous system disorders.

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