BDNF in Synaptic Plasticity and Memory

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Introduction

Among members of the neurotrophin family, brain-derived neurotrophic factor (BDNF) stands out for its ability to regulate synaptic plasticity and various cognitive functions of the brain. A Medline search with the terms 'BDNF' and 'synaptic' yields more than 700 research articles, mostly published in the last 7 years. Given that neurotrophins were initially defined as secretory factors that promote neuronal survival and differentiation during development, the role of BDNF in synaptic modulation was not recognized until late 1990s. A number of observations have aided in the realization that the primary function of BDNF is to regulate synaptic transmission and plasticity, rather than neuronal survival. One is that BDNF is widely distributed in many regions of the adult brain, with levels much higher than any other neurotrophins. The other is that the expression of BDNF can be rapidly enhanced by neuronal activity under conditions relevant to synaptic plasticity. Because neuronal activity is known to be crucial for synaptic plasticity, it was hypothesized that activity-dependent synaptic modulation is mediated by BDNF. Indeed, early studies demonstrated that BDNF mimics neuronal activity in altering the number and/or strength of synaptic connections. Subsequent studies revealed a much more complex and interesting picture. On the one hand, BDNF regulates various forms of synaptic plasticity, leading to changes in neuronal circuitry subserving complex behaviors. On the other hand, many aspects of BDNF cell biology, such as transcription and secretion, are tightly controlled by neuronal activity. Complex interactions between BDNF and neuronal activity may offer a plethora of means to control sophisticated cognitive functions of the mammalian brain.

Cell Biology of BDNF

All neurotrophins arise from their precursors as a result of proteolytic cleavage of the prodomain. Proneurotrophins have long been thought to be inactive precursors. However, this view was challenged a few years ago when proneurotrophins were shown to promote apoptosis via p75 neurotrophin receptor (p75NTR). This is opposite to the cell survival effect by mature neurotrophins, which act via their preferred tropomyocin-related receptor tyrosine kinase (Trk) receptors. Similarly, proBDNF and mature BDNF (mBDNF) have been shown to elicit opposite effects on synaptic plasticity (Figure 1). In recognition that proneurotrophins are biologically active, cleavage of proneurotrophins becomes an important regulatory mechanism that controls the direction of neurotrophin regulation.

Signal Transduction

The biological functions of BDNF are mediated by two receptor systems: TrkB and p75NTR. It is well established that mBDNF binds TrkB with high affinity. Upon binding, BDNF triggers TrkB dimerization resulting in tyrosine phosphorylation in its cytoplasmic domain. These autophosphorylation events recruit a series of intracellular proteins that primes subsequent activation of several signaling pathways. Three classical signaling pathways have been identified: phosphatidylinositol-3-kinase (PI3K) pathway, phospholipase C-γ (PLC-γ) pathway, and Map-Erk Kinase (MEK)-MAPK pathway (Figure 1). The majority of BDNF actions described thus far are attributed to signaling cascades activated by TrkB. In addition to cell surface signaling, BDNF induces the endocytosis of TrkB. Rather than simply inactivating TrkB, the endocytosis of BDNF-TrkB complex results in the formation of BDNF-TrkB signaling endosomes, triggering signaling cascades different from those initiated from cell surface TrkB. This process is required for translation-dependent long-term functions, and is involved in retrograde propagation of BDNF signal from axonal terminals to cell body.

All neurotrophins including proBDNF bind p75NTR, which triggers signaling events distinct from those by Trk receptors. The cytoplasmic domain of p75NTR lacks intrinsic catalytic activity. Upon ligand binding, several intracellular signal transduction cascades are activated, including nuclear factor kappa B (NF-κB), Jun kinase, and sphingomyelin hydrolysis (Figure 1). Notably, p75NTR activation is associated with the initiation of apoptosis. For many years, p75NTR was considered a 'low affinity' neurotrophin receptor. Recent studies indicate that preferred ligands for p75NTR are proneurotrophins, with binding affinities just as high as that between mature neurotrophins and Trk receptors. Current data support a model that pro- and mature neurotrophins induce very different functions through two distinct receptor-signaling systems. An added complexity is the newly discovered coreceptor sortilin. The prodomain of proneurotrophins bind sortilin, whereas the mature domain binds p75NTR. The formation of

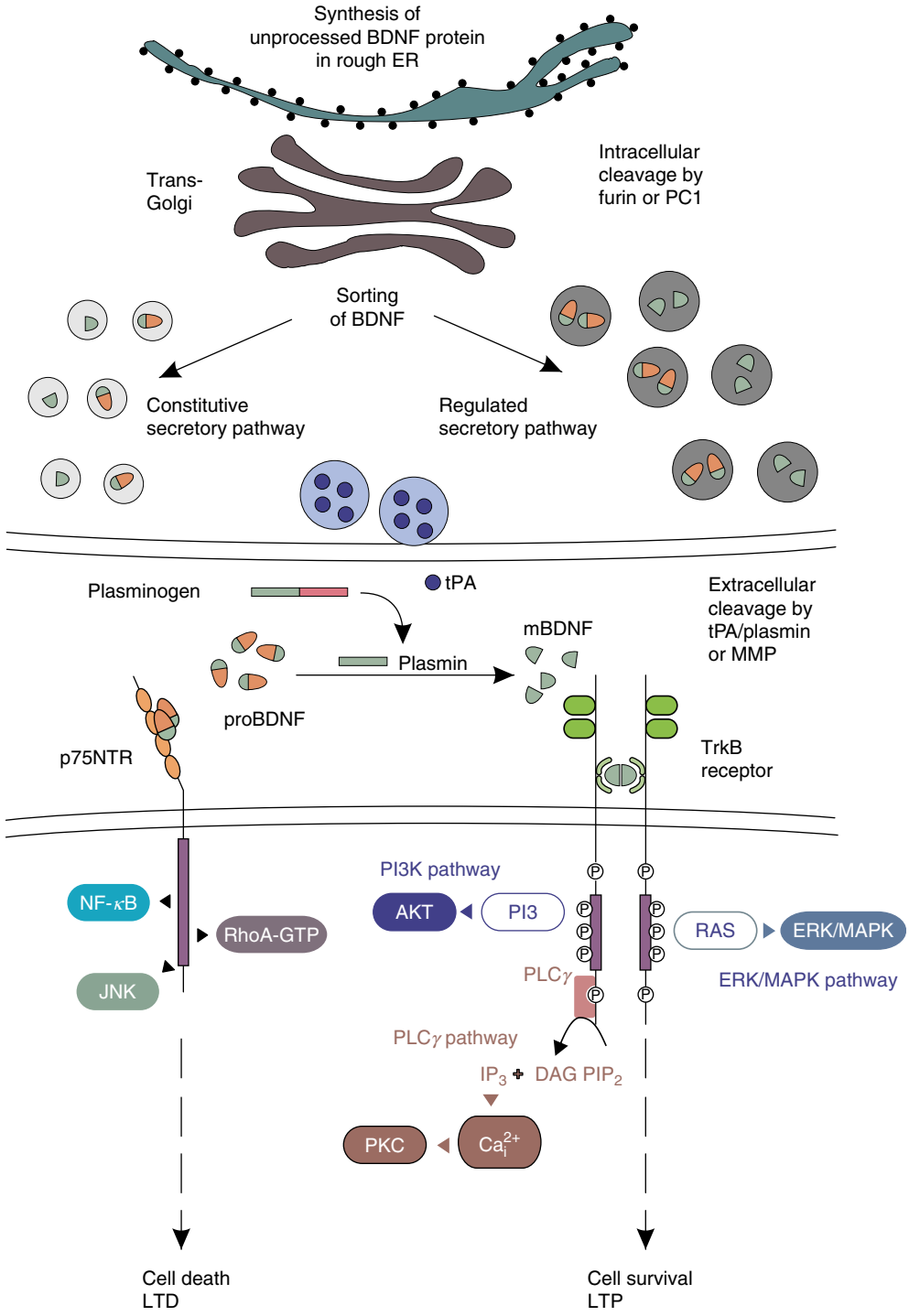

Figure 1 Synthesis, trafficking, and receptor-signaling of BDNF. Initially synthesized in the endoplasmic reticulum (ER) as a precursor protein, proBDNF is properly folded in the ER and Golgi network and packaged into secretory vesicles. Subsequently, BDNF is sorted into either the constitutive or regulated secretory pathway, and transported to the appropriate site of release. The prodomain can be cleaved intracellularly by furin or protein convertases, resulting in the secretion of mature BDNF (mBDNF). Alternatively, proBDNF can be secreted and cleaved extracellularly by the tPA/plasmin cascade or metalloproteinases to yield mBDNF. Once secreted, proBDNF and mBDNF elicit diverse and often opposing biological actions via two distinct receptor-signaling systems. mBDNF binds TrkB, leading to the autophosphorylation of tyrosine residues in the tyrosine kinase domain. Consequently, three major signaling cascades can be activated by mBDNF-TrkB, including the PI3K pathway, ERK/MAPK pathway, and PLCγ pathway. In contrast, proBDNF binds p75NTR, resulting in the activation of several signaling molecules, including NF-κB, JNK and RhoA.

the sortilin–proneurotrophin–p75NTR triplex may be necessary for p75NTR signaling.

Activity-Dependent Controls

A cardinal feature of BDNF is that its expression is regulated by neuronal activity. It is now recognized that a multitude of physiological stimuli can alter BDNF expression. For example, visual input and sensory stimulation of the whiskers control BDNF expression in the visual cortex and barrel cortex, respectively. In the superchiasmatic nucleus and amygdala, expression of BDNF is regulated by circadian rhythm and fear emotion. Remarkably, learning or exercise can also enhance BDNF expression in the hippocampus. Moreover, BDNF levels are also affected in a variety of pathological conditions associated with altered neuronal activity in the brain including seizure, Alzheimer's, depression, and stress. In addition to regulation of BDNF gene expression, a new theme emerging from recent studies is that neuronal activity also controls many cellular processes of BDNF, including intracellular trafficking, secretion of BDNF, and perhaps cleavage of proBDNF.

Transcription The genomic structure of BDNF is quite complex. In rats, there are at least four promoters controlling four short 5′ exons. Each 5′ exon is alternatively spliced onto a common 3′ exon (exon V) encoding the pre-proBDNF protein. In humans, the latest study reported seven promoters and eight exons, with exon VIII being the common exon coding for pre-proBDNF. It has long been a puzzle why nature has designed multiple BDNF transcripts that encode exactly the same protein. Cumulative evidence now indicates that these transcripts are distributed in different brain regions, different cell types, and even different parts of the cells (soma vs. dendrites). Importantly, their expression can be altered in response to different physiological stimuli. For instance, exon III transcript is detected only in cell bodies, whereas exon IV transcript is present both in cell bodies and dendritic processes of neurons in the visual cortex. During cerebellar development, thyroid hormone treatment selectively primarily enhances the expression of exon II mRNA.

Emerging evidence indicates that BDNF promoters are differentially involved in various neurological and psychiatric disorders. Promoter II-drive transcription can be suppressed by a neuronal silencer, and such suppression is removed by huntingtin, which binds and sequesters the silencer in the cytosol of cortical neurons. This is important for the survival of cortical neurons that projects to the striatum. In Huntington's disease, the mutant huntingtin can no longer bind the silencer, resulting in the translocation of the silencer into the nucleus and suppression of BDNF promoter II. Another striking example of BDNF promoter specific regulation involves MeCP2, which is a methyl-CpG-dependent transcriptional repressor that binds methylated DNA BDNF promoter III. Neuronal depolarization dissociates MeCP2 from promoter III, leading to the expression of exon III transcript in hippocampal neurons. Mutation in MeCP2, which occurs in 80% of Rett syndrome patients, abolishes this activity-dependent form of regulation. Promoter IV has been implicated in stress and is the major target of glucocortical and mineralocortical receptors. In clinical studies, a human single nucleotide polymorphism (SNP) in the exon IV has been associated with epilepsy and late-onset Alzheimer's.

Among all the promoters, promoter III has received much attention because it is by far the most effectively regulated by neuronal activity in the amygdala, hippocampus, and cortex. An increase in promoter III-driven transcription has been associated with long-term potentiation (LTP) and memory. Early work showed that BDNF gene expression was dependent on a rise in intracellular calcium and that application of high K^+ to cultured cortical neurons selectively enhanced exon III expression. Based on these observations, three elements in promoter III were characterized to be involved in Ca^{2+}-dependent expression of BDNF: the Ca^{2+} responsive sequence 1 (CaRE1) that binds Ca^{2+} responsive transcription factor (CaRF), the E-Box that binds upstream stimulatory factor (USF), and the classic cAMP responsive element (CRE) that binds cAMP responsive element binding (CREB). In addition, the transcription through promoter III is regulated by NF-κB and MeCP2. Taken together, transcription of BDNF exon III is tightly regulated by several mechanisms that couple neuronal activity with gene transcription.

Processing and trafficking Like all neurotrophins, BDNF mRNA is translated into a precursor protein, pre-proBDNF, which enters into the endoplasmic reticulum (ER) lumen through its N-terminal 'pre' sequence (signal peptide). After the removal of the pre-sequence by signal peptidases in the rough ER, the protein is folded in the trans-Golgi network and then packaged into secretory vesicles. Once folded correctly, BDNF is sorted into one of two principal pathways, the constitutive (i.e., spontaneous release) or regulated (i.e., release in response to stimuli) secretory pathway (**Figure 2**). The BDNF-containing vesicles are trafficked to the appropriate subcellular compartment. In neuronal dendrites and spines, BDNF appears to be stored in a special type of

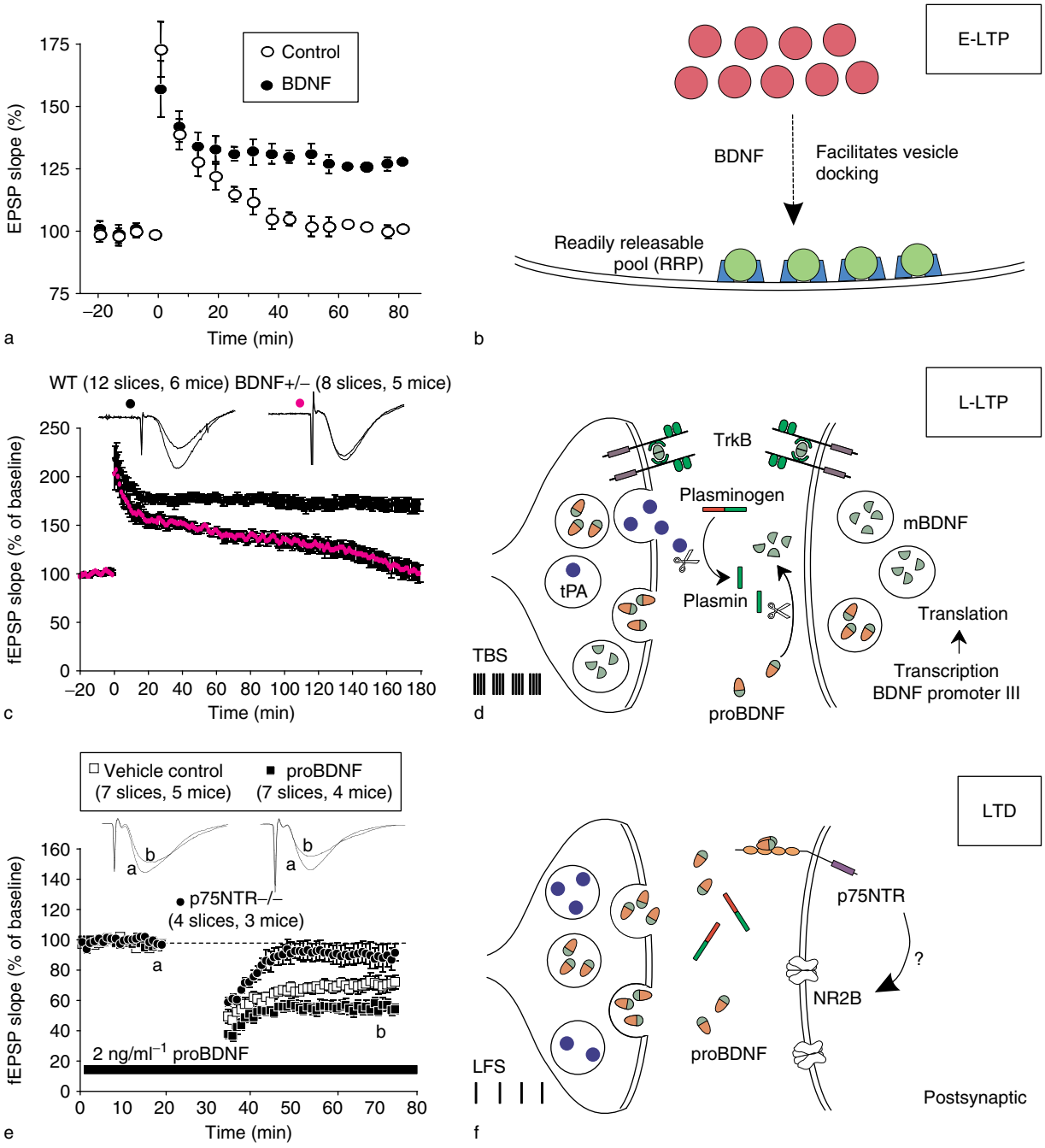

Figure 2 Regulation of distinct forms of hippocampal synaptic plasticity by BDNF. (a) mBDNF facilitates E-LTP in neonatal hippocampus in which BDNF level is low. Application of tetanic stimulation to neonatal slices (p12-p13) induces only short-term potentiation (STP), which can be converted to E-LTP by exposure to exogenous BDNF. (b) mBDNF facilitates E-LTP by promoting vesicle docking. (c) mBDNF is also involved in L-LTP. Strong theta-burst stimulation (TBS) induces robust L-LTP in wild-type (WT), but not in BDNF +/– mice hippocampal slices. (d) ProBDNF → mBDNF conversion by tPA/plasmin is required for L-LTP. Strong TBS triggers the secretion of tPA, which cleaves plasminogen to form plasmin. Plasmin subsequently cleaves proBDNF to yield mBDNF, which binds TrkB and permits L-LTP expression. (e) proBDNF promotes hippocampal LTD. Slices from p75NTR–/– mice fail to exhibit NMDA receptor-dependent LTD, whereas treatment with cleavage-resistant proBDNF enhances LTD in wild-type slice. (f) proBDNF binds to p75NTR to facilitate LTD, possibly through the regulation of NR2B, a distinct NMDA receptor subunit implicated in hippocampal LTD. EPSP, excitatory postsynaptic potential; fEPSP, field excitatory postsynaptic potential; LFS, low-frequency stimulation. (a) Reproduced from Figurov A, Pozzo-Miller L, Olafsson P, Wang T, and Lu B (1996) Regulation of synaptic responses to high-frequency stimulation and LTP by neurotrophins in the hippocampus. *Nature* 381: 706–709, with permission. (c) Reprinted with permission from Pang PT, Teng HK, Zaitsev E, et al. (2004) Cleavage of proBDNF by tPA/plasmin is essential for long-term hippocampal plasticity. *Science* 306: 487–491. Copyright 2004 AAAS. (e) Reproduced from NH Woo, Teng HK, Ciao C, et al. (2005) Activation of p75NTR by proBNF facilitates hippocampal long-term depression. *Nature Neuroscience* 8: 1069–1077, with permission.

secretory granules that lack chromogranin A (CGA), a marker for large dense core vesicles (LDCV). In contrast, conventional BDNF-containing LDCVs have been found in axons and terminals, possibly through anterograde axonal transport. Nonneuronal cells such as fibroblasts and Schwann cell secrete neurotrophins constitutively, whereas principal neurons and neuroendocrine cells secrete neurotrophins in response to depolarization and a rise in intracellular calcium.

The dendritic trafficking and synaptic localization of BDNF appear to be influenced by its own prodomain. This was implicated in a study that examined a SNP in the pro-region of the human BDNF gene. This SNP, located at nucleotide 196, produces a valine-to-methionine substitution at amino acid 66 (Val66Met). In cultured hippocampal neurons, fluorescence-tagged val-BDNF is distributed in cell body, as well as dendrites. A fraction of val-BDNF is also located at synapses, as revealed by their co-localization with synaptic markers. In marked contrast, met-BDNF is largely located in cell body and proximal dendrites. Met-BDNF was rarely localized at distal dendrites and was absent at synapses. These results suggest that the prodomain, particularly the region containing Val66, is critical for dendritic trafficking and synaptic localization of BDNF.

A long-held view is that proneurotrophins, particularly proNGF and proBDNF, are processed by intracellular proteases including the serine protease furin in the trans-Golgi network and the prohormone convertases (PC1/3) in the secretory granules. Recent studies have shown that a large fraction of BDNF in the brain is secreted in the proform, which is converted to mBDNF by extracellular proteases including plasmin or metalloproteinases (MMP3 or MMP7). Because proBDNF and mBDNF elicit distinct and often opposing biological actions through different receptors, proteolytic cleavage has now emerged as a new mechanism that determines the function of BDNF. Of particular interest is tissue plasminogen activator (tPA), an extracellular protease that converts the inactive zymogen plasminogen to plasmin. tPA is secreted from axonal terminals in response to neuronal activity. It is conceivable that neuronal activity could control proBDNF → mBDNF conversion by triggering tPA secretion.

Secretion BDNF is perhaps the only neurotrophin indisputably secreted in response to neuronal activity. In fact, majority of BDNF is sorted into the regulated, rather than the constitutive, secretory pathway. Experiments using green fluorescent protein (GFP)-tagged BDNF revealed that BDNF can be secreted from either pre- or postsynaptic sites. The amount of BDNF secretion depends on the pattern of neuronal activity. Generally, tetanus such as those used to induce LTP is more effective in inducing BDNF secretion than low-frequency stimulation. This has been demonstrated in cultured neurons as well as in slices that underwent different forms of plasticity.

Studies of Val66Met SNP have drawn attention to the role of prodomain in activity-dependent BDNF secretion. In neurons transfected with met-BDNF, depolarization-induced secretion was selectively impaired while constitutive secretion remained normal. Subsequent studies demonstrate that proBDNF is co-localized with the neurotrophin coreceptor sortilin intracellularly in secretory granules, and that sortilin interacts specifically with the prodomain in a region encompassing Val66Met. Remarkably, inhibition of the interaction between the prodomain and intracellular sortilin attenuates secretion of BDNF induced by depolarization, suggesting that this interaction is critical for regulated secretion. However, sortilin could interact with the prodomain of other neurotrophins incapable of regulated secretion, making it less likely to be a specific mechanism for sorting. On the other hand, a sorting motif was recently identified in the mature domain of BDNF, but not nerve growth factor (NGF), that interacts with a well-known sorting receptor, carboxypeptidase E (CPE). Such an interaction was deemed essential for sorting proBDNF into regulated pathway vesicles for activity-dependent secretion. Given that the prodomain promotes proper folding of neurotrophins, it is conceivable that interaction between the prodomain and sortilin may hold proBDNF in a correct configuration, exposing the mature domain to the sorting receptor CPE, which sorts proBDNF into the regulated secretory pathway.

Roles of BDNF in Synaptic Plasticity

The ability of the mammalian brain to adapt or modify itself in response to experience and/or environment depends on the plasticity of synaptic connections. Substantial evidence indicates that the number and strength of synapses is readily altered by neuronal activity. This process, known as synaptic plasticity, displays several physiological properties that substantiate its role as a cellular correlate for multiple cognitive processes, including learning and memory. These include the activity dependence and associative nature of induction as well as the input specificity of expression, all of which endow the vast storage and processing capacity of the mammalian brain. Remarkably, BDNF is involved in many of these features. An emerging theme is that BDNF plays a

critical role in regulating several forms of synaptic plasticity in distinct regions of the brain, including the hippocampus and visual cortex.

Input Specificity

Most activity-dependent forms of synaptic plasticity expressed in the brain are input specific, namely modifications at one synapse are not spread to synapses nearby. Experiments have shown that BDNF elicits its actions in a local and synapse-specific manner, with particular preference to active synapses. This unique property may be attributed to several key characteristics of BDNF signaling.

First, secretion of BDNF is activity dependent and is likely to occur at synaptic sites. The control of BDNF secretion occurs relatively fast, usually in a timescale of seconds. Imaging studies demonstrate that BDNF is often co-localized with pre- and postsynaptic markers in hippocampal neurons, suggesting the synaptic localization of BDNF. Application of high-frequency stimulation (HFS) induces a rapid decay of GFP-tagged BDNF, indicating BDNF is secreted in an activity-dependent manner at synapses. Due to its negative charge, BDNF is thought to have a limited capacity for diffusion, and therefore constrains the actions of BDNF at or near its site of secretion.

Second, there is good evidence that BDNF exon II and IV transcripts can be targeted into the dendrites of hippocampal neurons, and neuronal activity enhances such targeting. Recent studies have shown that dendritic BDNF mRNA can be translated locally into BDNF protein. Taken together, a possible scenario is that local synaptic activity triggers dendritic translation of BDNF and may serve as an alternative mechanism to ensure synapse-specific modulation by BDNF.

Finally, local synaptic activity may ensure a better response of target synapses to BDNF by regulating TrkB trafficking. High-frequency neuronal activity has been shown to promote the insertion of TrkB into the surface membrane of hippocampal neurons. This process appears to be ligand independent and requires calcium influx and activation of Ca^{2+}/calmodulin-dependent kinase II (CaMKII). BDNF secreted from active synapses/neurons recruits TrkB from extrasynaptic sites into lipid rafts, microdomains of membrane enriched at synapses. This lateral movement requires TrkB tyrosine kinase activity. Synaptic activity often induces a rise of postsynaptic cAMP. This local increase in cAMP concentration at active synapses facilitates translocation of TrkB into the postsynaptic density, and functions to gate synapse-specific effects of BDNF by controlling TrkB tyrosine phosphorylation locally. Finally, neuronal activity promotes BDNF-induced TrkB endocytosis, a signaling event important for many long-term BDNF functions. All of these could contribute to a more efficient response to BDNF at active synapses.

Early Phase Long-Term Potentiation

It is well established that BDNF plays a key role in LTP, a persistent enhancement of synaptic strength. LTP can be divided into an early phase (E-LTP) and a later phase (L-LTP). E-LTP is relatively short-lasting (1 h) and depends on protein phosphorylation, while L-LTP lasts many hours and requires new protein synthesis. Early work has focused on BDNF regulation of E-LTP in the hippocampus. In neonatal hippocampus in which BDNF levels are low, exogenous BDNF facilitates E-LTP induced by HFS (**Figure 2(a)**). In addition, exogenous BDNF facilitates LTP induced by subthreshold tetanus that normally induces weak potentiation. Conversely, in the adult hippocampus, a stage where endogenous levels of BDNF are relatively high, inhibition of BDNF activity either by function-blocking BDNF antibody or BDNF scavengers, TrkB immunoglobulin G (IgG), attenuates the expression of E-LTP.

In agreement with pharmacological studies, genetically modified mice with mutation of either BDNF or TrkB gene exhibit severe impairments in E-LTP. Interestingly, heterozygous mice (BDNF+/−) with only half of the BDNF gene dosage show a similar degree of impairment as homozygous mice (BDNF−/−), arguing that a critical level of BDNF is important for hippocampal LTP. The impairment of LTP in BDNF-mutant mice is reversed by acute application of recombinant BDNF or by virus-mediated BDNF gene transfer. Deletion of BDNF gene selectively in the adult forebrain by inducible knockout approaches confirms that the effects of BDNF on E-LTP are not due to developmental abnormalities.

The effects of BDNF on hippocampal E-LTP result primarily from alterations of presynaptic function (**Figure 2(b)**). Exogenous BDNF enhances synaptic response to HFS and paired pulse facilitation (PPF), two indicators of presynaptic function. In mice lacking BDNF, posttetanic potentiation (PTP) and PPF are significantly reduced. Electron microscopy reveals a reduction in the number of vesicles docked at presynaptic active zones in these mutant mice. Moreover, biochemical experiments using hippocampal synaptosomes indicate that BDNF modulates the levels or phosphorylation of synaptic proteins involved in vesicle docking and fusion, such as synapsin, synaptophysin, and synaptobrevin. Taken together, the presynaptic role of BDNF for the mobilization and/or docking of synaptic vesicles to presynaptic active

zones may allow hippocampal synapses to follow tetanic stimulation more effectively, resulting in the facilitation of hippocampal LTP.

It is important to note that the biological effects of BDNF are not exclusively the result of its presynaptic actions. In the dentate gyrus, the induction of LTP requires postsynaptic BDNF signaling. A series of studies have demonstrated that BDNF can exert postsynaptic modulatory effects by modulating α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)-type and *N*-methyl-D-aspartate (NMDA)-type glutamate receptors in neuronal cultures, and some potassium channels in hippocampal slices. In this respect, TrkB receptors have been observed to localize in the postsynaptic density of isolated synaptosomes prepared from cortical neurons. However, whether these postsynaptic modulatory effects of BDNF directly participate in LTP remains to be established.

Late Phase Long-Term Potentiation

Several early studies suggest that BDNF may also play a role in late phase long-term potentiation (L-LTP). L-LTP-inducing tetanic stimulation selectively enhances the expression of BDNF and TrkB mRNAs in the hippocampus. BDNF transcription is regulated in part by CREB, a transcription factor required for L-LTP expression. The delayed and sustained enhancement of BDNF synthesis correlates well with the time course of L-LTP, which increases 2–4 h after L-LTP induction. More direct evidence comes from electrophysiology experiments showing a significant reduction in L-LTP recorded from slices treated with TrkB-blocking antibody, or those from BDNF +/− mice (Figure 2(c)). However, BDNF only regulates L-LTP induced by theta-burst stimulation (TBS) or application of the adenylate cyclase activator forskolin, but not by four spaced trains of HFS, a more standard protocol used to induce L-LTP. These results suggest that strong tetanic stimulation may induce signaling downstream of BDNF, bypassing the requirement of BDNF in L-LTP.

Recent experiments have provided more in-depth insights as to the role of BDNF in L-LTP. In the presence of BDNF, weak tetanus that normally induces only E-LTP resulted in robust L-LTP. Moreover, perfusion of BDNF to hippocampal slices rescued L-LTP that is normally absent when protein synthesis is inhibited. It appears that BDNF is secreted largely in its precursor form (proBDNF), which is converted to mBDNF by extracellular proteases. Biochemical and genetic experiments indicate that this conversion is mediated by an enzymatic cascade that involves tPA and plasmin, two secreted proteases found at hippocampal synapses. tPA has long been implicated in L-LTP, but the precise downstream effector(s) of tPA was not established. The current data support the notion that tPA cleaves the inactive zymogen plasminogen to form plasmin, which in turn cleaves proBDNF to generate mBDNF. Application of mBDNF, but not cleavage-resistant proBDNF, completely reversed the L-LTP deficit observed in tPA and plasmin knockout mice. Thus, conversion of proBDNF to mBDNF by the tPA/plasmin system is critical for L-LTP expression (Figure 2(d)).

Two key cellular events associated with long-term synaptic plasticity are synaptic growth and *de novo* protein synthesis, both of which are regulated by BDNF. In addition to stimulating axonal growth, chronic application of BDNF to hippocampal slices increases the dendritic spine density of CA1 pyramidal neurons. This is particularly relevant since dendritic spines and protrusions are enhanced during L-LTP. In cell cultures, BDNF has been shown to increase mammalian target of rapamycin (mTOR)-dependent translation of a panel of synaptically expressed transcripts including GluR1 and homer2 mRNAs in the dendrites of hippocampal neurons. However, exogenous BDNF applied immediately after strong TBS rescues L-LTP in hippocampal slices in which protein synthesis was blocked for the entire course of the experiments. This provocative result, together with the finding that gene expression of BDNF is stimulated by L-LTP-inducing tetanic stimulation, implies BDNF is a key protein synthesis product required for long-term modifications necessary for L-LTP expression.

Long-Term Depression

In addition to its role in LTP, BDNF regulates long-term depression (LTD), a persistent reduction in synaptic strength induced by prolonged low-frequency stimulation. Expression of LTD is developmentally regulated and exists in several forms mediated by different glutamate receptors. The best-known form of LTD is the NMDA receptor (NMDAR)-dependent form, which is robustly expressed in young animals. mBDNF inhibits LTD in the visual cortex and hippocampus. Collectively, these observations point to a general theme that BDNF facilitates synaptic strengthening, but attenuates synaptic depression.

Analogous to the survival and apoptosis effects of mBDNF and proBDNF, respectively, in the periphery, an important advance is that proBDNF, if uncleaved, enhances NMDAR-dependent LTD via p75NTR in the CNS. Compared to TrkB, the role of p75NTR in synaptic plasticity has not been studied until

recently. In p75NTR mutant mice (p75NTR−/−), NMDAR-dependent LTD was completely absent while other forms of plasticity including NMDAR-dependent LTP and NMDAR-independent LTD were intact. Biochemical experiments indicate that NR2B, a specific NMDAR subunit uniquely implicated in LTD, was significantly reduced in the mutant hippocampus. Whole-cell recordings revealed a severe reduction in NR2B-mediated synaptic currents in CA1 neurons of p75NTR−/− mice. More importantly, application of cleavage-resistant proBDNF increased NR2B-mediated synaptic currents and enhanced LTD in hippocampal slices derived from wild-type mice but not in p75NTR−/− mice (Figure 2(e)). These findings suggest that proBDNF is an endogenous ligand of p75NTR during development, which acts to enhance LTD via modulating NR2B function (Figure 2(f)).

Learning, Memory, and Other Cognitive Functions

Given its central role in synaptic plasticity, numerous studies have examined how BDNF regulates the acquisition (learning) and retention (memory) of new information. Thus far, the strongest correlation is observed between BDNF and hippocampal-dependent forms of memory, which include declarative or episodic and spatial memory. During contextual learning, BDNF expression is rapidly and selectively upregulated in the hippocampus. When BDNF signaling is disrupted either by inhibitors or by genetic knockout, spatial learning is significantly impaired, as reflected by poor performance in the Morris water maze. In many cases impairments in memory were also mirrored with LTP deficits. For instance, deletion of BDNF or TrkB gene in the adult forebrain results in a significant attenuation of contextual fear or spatial memories, as well as hippocampal LTP.

A major advance came from a study on a SNP, which converts a valine (val) to a methionine (met) in the prodomain of the human BDNF gene. This SNP occurs with a frequency of approximately 19–25% in the Caucasian. Human subjects with the met allele exhibit lower hippocampal *N*-acetylaspartate (NAA), a putative measure of neuronal integrity and synaptic abundance. Functional imaging reveals an association of the met allele with abnormal hippocampal activation (Figure 3(a)). Most remarkably, subjects with the met-BDNF allele performed poorer in a hippocampal-dependent episodic memory task, but not in hippocampal-independent working memory and semantic memory tasks. In cultured neurons derived from rodent hippocampus, BDNF (val-BDNF) is packaged in secretory granules that are distributed as puncta throughout cell body and dendrites, with some localized at synapses. In contrast, significantly less met-BDNF-containing granules are localized to dendrites and synapses. Moreover, regulated secretion of met-BDNF induced by neuronal depolarization, but not constitutive secretion, is significantly reduced. Thus, impairments in trafficking, synaptic targeting, and/or regulated secretion may explain the specific memory deficits seen in human subjects with the met allele (Figure 3(b)). These results represent the first demonstration of a role for BDNF in human hippocampal function and of a single gene affecting human episodic memory.

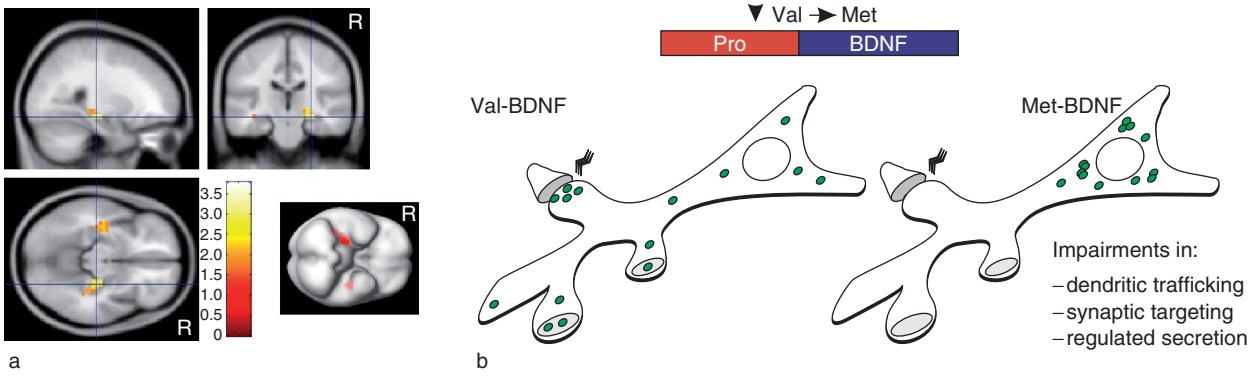

Figure 3 Impact of a SNP in the BDNF gene on cognitive brain function and intracellular trafficking of BDNF. The SNP converts a valine to a methionine in amino acid 66 located in the prodomain of BDNF (val66met). (a) Differences in fMRI responses between val/val and val/met subjects during a memory task. Subjects with val/met genotype exhibit abnormal hippocampal activation (shown in red). The met/met subjects also exhibit deficits in hippocampus-dependent episodic memory. (b) Cellular phenotypes associated with the BDNF val66met SNP. Val-BDNF is distributed throughout a typical hippocampal neuron including distal dendrites and synapses. In contrast, met-BDNF is rarely localized at distal dendrites or synapses and fails to undergo depolarization-induced secretion. Failure of intracellular trafficking and activity-dependent secretion of BDNF may underlie the cognitive deficits observed in subjects with the met allele. (a) Reproduced from Egan MF, Kojima M, Callicott JH, et al. (2003) The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* 112: 257–269, with permission from Elsevier.

Genetic analyses in mice show that genes affecting memory performance often impact other cognitive functions. It is now recognized that deficits in BDNF may contribute to neurological and psychiatric disorders. In studies of drug addiction, LTP and LTD have emerged as candidate mechanisms for drug-induced alterations in the nucleus accumbens and ventral tegmental area. Several reports have demonstrated that BDNF modulates behavioral sensitization to cocaine. Substantial evidence also points to its role in depression. There is reduced BDNF expression in the hippocampus of animal models for depression; chronic treatment with antidepressants increases its levels. However, it is unclear whether antidepressants achieve their clinical effects on depression by upregulation of BDNF.

Conclusion

Stemming from the multidisciplinary approaches used in present-day research ranging from cellular systems to behavior, BDNF is now recognized as a key regulator for synaptic circuits underlying many cognitive functions. New and unidentified role(s) of BDNF in plasticity and cognition will undoubtedly continue to surface and will provide abundant intellectual stimulation to drive future advances. Ultimately, understanding the actions of BDNF will aid in the development of therapeutic interventions that will alleviate a wide spectrum of neurological and psychiatric disorders derived from BDNF dysfunction.

See also: Enteric Nervous System: Neurotrophic Factors; Long-Term Depression: Cerebellum; Long-Term Depression (LTD): Metabotropic Glutamate Receptor (mGluR) and NMDAR-Dependent Forms; Long-Term Potentiation (LTP): NMDA Receptor Role; Synaptic Plasticity and Place Cell Formation.

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