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Cell biology of BDNF and its relevance to schizophrenia

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Abstract

BDNF is a key regulator of synaptic plasticity and hence is thought to be uniquely important for various cognitive functions. While correlations of schizophrenia with polymorphisms in the BDNF gene and changes in BDNF mRNA levels have been reported, specific links remain to be established. Cell biological studies of BDNF may provide clues as to how BDNF signalling impacts schizophrenia aetiology and pathogenesis: (1) the Val-Met polymorphism in the pro-domain affects activity-dependent BDNF secretion and short-term, hippocampus-mediated episodic memory. (2) pro-BDNF and mBDNF, by interacting with their respective $p75^{NTR}$ and TrkB receptors, facilitate long-term depression (LTD) and long-term potentiation (LTP), two common forms of synaptic plasticity working in opposing directions. (3) BDNF transcription is controlled by four promoters, which drive expression of four BDNF-encoding transcripts in different brain regions, cell types and subcellular compartments (dendrites, cell body, etc.), and each is regulated by different genetic and environmental factors. A role for BDNF in early- and late- phase LTP and short-term and long-term, hippocampal-dependent memory has been firmly established. Extending these studies to synaptic plasticity in other areas of the brain may help us to better understand how altered BDNF signalling could contribute to intermediate phenotypes associated with schizophrenia.

BDNF is the most widely distributed neurotrophin in the CNS. BDNF was initially isolated and defined as a secretory molecule capable of promoting the survival of peripheral neurons through activation of its receptor TrkB. This has been show in cultured CNS neurons including hippocampal and cortical, cholinergic, dopaminergic and serotonergic neurons. However, current thinking, derived largely from genetic and behavioural studies, posits that the primary function of BDNF in the adult brain is to regulate synaptic transmission and plasticity, rather than cell survival (Lu 2003). Hypotheses that BDNF may play a potential role in the pathophysiology of schizophrenia are based on the idea that BDNF is a key regulator of synaptic plasticity, and therefore various cognitive functions (Lewis et al 2005). Data from animal models of schizophrenia in which BDNF signalling is abnormally regulated lent initial support to these hypotheses (Angelucci et al 2004). In humans, genetic studies have further bolstered a link between BDNF and schizophrenia as well as with brain dysfunction associated with the disorder (Szekeres et al 2003). In addition, changes in levels of BDNF and its receptor TrkB in the dorsal-lateral pre-frontal cortex (DF-PLC) (Hashimoto et al 2005, Weickert et al 2003) as well as in serum (Toyooka et al 2002) of patients with schizophrenia have been reported. However, complex interactions between BDNF and neuronal activity may be key components in the control of sophisticated cognitive functions in the mammalian brain that are impaired in schizophrenia. Recent progress in BDNF research revealed multiple levels at which BDNF signalling can be regulated or altered. Thus, when studying the role of BDNF in schizophrenia, it is necessary to take the full spectrum of BDNF cell biology into consideration as opposed to simply focusing on up- or down-regulation of BDNF mRNA or protein levels.

Cell biology of BDNF

The precursors of neurotrophins, proneurotrophins, were once considered functionally inactive. This view is no longer valid after the discovery that proneurotrophins can promote apoptosis via the p75 neurotrophin receptor ($p75^{NTR}$) (Lee et al 2001). Activation of pro-BDNF-$p75^{NTR}$ and mature BDNF (mBDNF)-TrkB signalling pathways also elicits completely opposite effects on synaptic plasticity (Lu et al 2005). Considering the opposing roles of pro- and mature BDNF, cleavage of proneurotrophins may serve an important regulatory mechanism in the mammalian brain. A key characteristic of BDNF cell biology is its activity dependence (Lu 2003). For example, visual input and stimulation of the vibrissae control BDNF expression in the visual and barrel cortex, respectively. In addition to regulation of BDNF gene expression, neuronal activity can control cellular processes affecting BDNF, including intracellular trafficking, secretion, and perhaps cleavage.

Transcription

BDNF's complex genomic structure is ideal for regulation and control at multiple levels. In rodents, there are at least four promoters, each driving a short 5′ exon that is alternatively spliced onto a common 3′ exon (exon V) encoding the pre-pro-BDNF protein (Timmusk et al 1993). Recent studies indicate that there are as many as seven promoters and eight exons in human and mouse (Liu et al 2005). What is the purpose of multiple BDNF transcripts if they encode the same protein? It has been shown that BDNF transcripts are distributed in different brain regions, different cell types, and even in different parts of the cell (e.g. soma versus dendrites). Importantly, a wide variety of physiological stimuli could elicit differential regulation of these transcripts.

Because it is regulated by neuronal activity in the amygdala, hippocampus and cortex, promoter III transcription has attracted much attention. Increases in promoter III-driven transcription have been associated with long-term potentiation (LTP) and learning and memory (Korte et al 1995, Minichiello et al 2002, Patterson et al 1996). BDNF gene expression relies on intracellular Ca^{2+}, which signals through three Ca^{2+}-dependent elements located in BDNF promoter III (West et al 2001). Tight regulation of BDNF exon III transcription by several mechanisms allows for the coupling of neuronal activity with gene transcription. Impairment in promoter III-driven BDNF transcription has been implicated in Rett Syndrome and depression. MeCP2, a methyl-CpG-dependent transcriptional repressor that is mutated in Rett Syndrome, binds methylated DNA in promoter III. Neuronal depolarization induces dissociation of MeCP2, resulting in derepression of exon III (Chen et al 2003, Martinowich et al 2003). Depressive-like behaviours in mice are associated with a decrease in BDNF promoter III-mediated transcription, an effect which can be counteracted by antidepressants via induction of histone acetylation (Tsankova et al 2006).

Processing and trafficking

Pro-BDNF, translated from BDNF mRNA in the endoplasmic reticulum (ER), is folded in the trans-Golgi network, packaged into secretory vesicles, and sorted into one of two principal pathways, the constitutive (i.e. spontaneous release) or regulated (i.e. release in response to stimuli) (Mowla et al 1999). BDNF-containing vesicles are trafficked to their appropriate sub-cellular compartments, including dendritic spines and axonal terminals, and secreted in response to extracellular and intracellular signals.

BDNF's pro-domain is important for dendritic trafficking and synaptic localization. A single-nucleotide polymorphism (SNP) in the pro-region of human BDNF produces a valine to methionine substitution at amino acid 66 (Val66Met). In cultured hippocampal neurons,

Val-BDNF is localized to both the cell body and dendrites with a fraction localized to the synapse, whereas Met-BDNF is largely found in the cell body and proximal dendrites. Met-BDNF is largely absent from distal dendrites and the synapse (Egan et al 2003, Chen et al 2004).

It is possible that pro-BDNF is processed to mBDNF in the secretory granules by intracellular proteases. However, a large fraction of neuronal BDNF is actually secreted in the pro-form, which is converted to mBDNF by extracellular proteases including plasmin and the matrix metalloproteinases (Lee et al 2001, Teng et al 2005). Because pro-BDNF and mBDNF elicit distinct biological effects via different receptor systems, the proteolytic step is important in influencing BDNF's functional output. An interesting candidate that could be influential in this step is tissue plasminogen activator (tPA), an extracellular protease that converts the inactive zymogen plasminogen to plasmin. Conceivably, neuronal activity could control pro-BDNF→mBDNF conversion by triggering tPA secretion from axon terminals in response to activity (Pang et al 2004).

Secretion

Unlike other growth factors, BDNF is secreted primarily through the regulated, rather than the constitutive, pathway. BDNF secretion occurs at both pre- and postsynaptic sites. In general, tetanic stimulation is more effective in inducing BDNF secretion than low frequency stimulation. The effects of the Val66Met polymorphism have drawn attention to the pro-domain's role in activity-dependent BDNF secretion. In neurons expressing Met-BDNF, depolarization-induced secretion is selectively impaired while the integrity of constitutive secretion is preserved (Egan et al 2003). Recent studies have identified a new receptor for pro-BDNF called sortilin (Nykjaer et al 2004). Sortilin specifically interacts with the pro-domain in a region encompassing Val66Met. Inhibition of the pro-domain/sortilin interaction attenuates depolarization-induced secretion of BDNF (Chen et al 2005). However, since sortilin is likely to interact with the pro-domains of neurotrophins incapable of regulated secretion, the mechanism may not be specific. Interaction between the sorting motif on mBDNF and the well-known sorting receptor, carboxypeptidase E (CPE), allows for sorting of pro-BDNF into regulated pathway vesicles for activity-dependent secretion (Lou et al 2005).

BDNF and synaptic plasticity

Accumulated evidence supports the notion that BDNF is a key regulator of several forms of synaptic plasticity in the hippocampus and cortex. These studies have led to the idea that BDNF may be involved in various cognitive brain functions.

Early phase LTP

LTP can be divided into an early phase (E-LTP, lasting ~1–2 hours) and a later phase (L-LTP, lasting days). This distinction is based not only on the duration of LTP, but also its dependence on gene transcription and protein synthesis. Early work focused on the role of BDNF in E-LTP. In the neonatal hippocampus, where endogenous BDNF levels are low, application of high frequency stimulation (HFS) induces only short-term potentiation but not LTP. In hippocampal slices treated with BDNF, LTP can be reliably induced (Figurov et al 1996). Conversely, in the adult hippocampus, where endogenous levels of BDNF are relatively high, inhibition of BDNF activity attenuates expression of E-LTP (Figurov et al 1996). Moreover, a subthreshold tetanus that normally induces only weak potentiation can elicit pronounced LTP (Figurov et al 1996). These findings are backed by studies using BDNF knockout mice. Heterozygous mice ($BDNF^{+/-}$) exhibit severe impairments in E-LTP (Korte et al 1995, Patterson et al 1996). The LTP deficit in BDNF mutant mice can be

reversed by introducing BDNF back into the system (Korte et al 1995, Patterson et al 1996). TrkB knockout mice also exhibit deficits in E-LTP (Minichiello et al 2002).

The mechanisms by which BDNF regulates E-LTP have largely been worked out (Lu & Chow 1999). Genetic and biochemical studies support a model in which BDNF facilitates the docking of synaptic vesicles to presynaptic membranes through TrkB-mediated phosphorylation of synaptic proteins such as synapsin I and synaptobrevin. An actin motor complex containing Myo6 and a Myo6-binding protein, GIPC1, might be involved in the presynaptic function of BDNF (Yano et al 2006). An increase in the number of docked vesicles would enhance the ability of hippocampal synapses to respond to HFS, resulting in the facilitation of hippocampal E-LTP. Despite overwhelming evidence for BDNF regulation of presyanptic transmitter release at excitatory synapses, a postsynaptic role of BDNF cannot be excluded. Indeed, BDNF has been show to regulate properties of NMDA channels (Levine et al 1998), and elicit both acute and long-term effects on dendritic spines (Ji et al 2005).

Late-phase LTP

A number of early studies also implicate a role for BDNF in L-LTP. Expression of BDNF and TrkB mRNAs is selectively enhanced by tetanic stimulation that is capable of inducing L-LTP, and the time course of BDNF synthesis correlates well with that of L-LTP (Patterson et al 1992). This transcription is partially dependent on CREB, a transcription factor known to be necessary for L-LTP. In $BDNF^{+/-}$ mice, application of strong tetanic stimulation such as long theta burst stimulation (e.g., 12 sets of TBS) or forskolin failed to induce L-LTP (Korte et al 1998, Patterson et al 2001). Moreover, in conditions in which only E-LTP could occur, such as delivering weak tetanus (three sets of TBS) or strong tetanus (12TBS) in the presence of protein synthesis inhibitors, robust L-LTP can be induced after application of exogenous BDNF (Pang et al 2004). Several recent studies further reveal the importance of activity-dependent BDNF transcription, possibly through promoter III. When protein synthesis was completely blocked, perfusion of exogenous BDNF could restore L-LTP (Pang et al 2004). In VP16-CREB mice in which CREB-mediated BDNF transcription is elevated, a weak, E-LTP-inducing tetanus could induce L-LTP, and this could be reversed by application of BDNF scavenger TrkB-IgG (Barco et al 2005). Finally, we have recently generated a line of mutant mice in which activity-dependent, promoter III-mediate BDNF transcription is blocked. Remarkably, L-LTP was selectively impaired, but E-LTP remained intact (K. Sakata 2005 Society for Neuroscience, abstract). Thus, BDNF is a key protein synthesis product responsible for L-LTP expression.

In addition to activity-dependent transcription of BDNF, L-LTP is also dependent on conversion of pro-BDNF to mBDNF by extracellular proteases, particularly, the tissue plasminogen activator (tPA)/plasmin system. tPA is an enzyme that can cleave plasminogen (an inactive precursor) to plasmin. These proteases are expressed in the brain and secreted at hippocampal synapses. Plasmin has been show to cleave pro-BDNF and generate mBDNF *in vitro* (Lee et al 2001). Mice lacking tPA exhibit selective impairments in L-LTP, but not E-LTP (Baranes et al 1998). These results have led us to hypothesize that L-LTP requires an enzymatic cascade in which tPA cleaves the inactive zymogen plasminogen to plasmin, which then cleaves pro-BDNF to mBDNF. Indeed, in both tPA and plasminogen mutant mice, pro-BDNF is elevated in the hippocampus. Moreover, application of mBDNF, but not uncleavable pro-BDNF, can rescue the L-LTP deficit seen in tPA and plasmin knockout mice (Pang et al 2004). These results provide a mechanistic link between these two seemingly independent molecule systems in L-LTP expression.

Long-term depression (LTD)

LTD is defined as a persistent reduction in synaptic strength, which is induced by prolonged low frequency stimulation (LFS). Several different forms of LTD exist, each sub-served by different glutamate receptors. NMDA dependent LTD, the most well-known form of LTD, is robustly expressed in young, but not adult animals. Several recent studies have implicated the role of pro-BDNF- $p75^{NTR}$ in NMDAR-dependent form of LTD (Woo et al 2005, Zagrebelsky et al 2005). In $p75^{NTR}$ mutant mice, NMDAR-dependent LTD was absent while other forms of plasticity, including NMDAR-dependent LTP and NMDAR-independent LTD, remained intact. Furthermore, protein levels of NR2B, an NMDAR subunit implicated in LTD, as well as NR2B-mediated currents were significantly reduced in the $p75^{NTR}$ mutant hippocampus. Importantly, cleavage-resistant pro-BDNF was able to increase NR2B-mediated synaptic currents and enhance LTD in the wild type, but not the mutant, $p75^{NTR}$ hippocampus (Woo et al 2005). These results implicate pro-BDNF as an endogenous ligand of $p75^{NTR}$, which enhances expression of LTD via an NR2B-mediated mechanism.

BDNF, cognition and schizophrenia

The profound effects of BDNF on hippocampal plasticity, particularly LTP, strongly suggest a role for BDNF in hippocampal-dependent forms of memory. In rodents, disruption of BDNF or TrkB signalling markedly impairs two hippocampal-dependent form of memory. In humans, studies of the BDNF Val66Met polymorphism, where the Met allele was shown to be associated with abnormal hippocampal structure and function provided the first evidence for direct involvement of BDNF (Hariri et al 2003, Egan et al 2003, Pezawas et al 2004). Direct tests of memory function show that human subjects with two copies of the Met allele exhibit selective impairment in short-term episodic memory, but not in hippocampal-independent working memory or semantic memory tasks (Egan et al 2003). The high frequency of the BDNF Val66Met SNP in the population also facilitated the ability to run association analyses between this polymorphism and other cognitive tasks. In one report, elderly carriers of two BDNF Met alleles score higher in non-verbal reasoning, verbal fluency and logical memory (Harris et al 2006), whereas in another report, young Chinese that are homozygous for the Val allele score higher on IQ tests (Tsai et al 2004). In addition, the BDNF Met allele has been associated with decreased hippocampal volumes (Pezawas et al 2004).

The BDNF gene is one of just a few genes that are prominently implicated in cognitive functions. This, coupled with the impairments in hippocampal structure and memory functions that have been associated with the BDNF Val66Met polymorphism, have generated a great deal of interest in linking deficits in BDNF signalling/function with schizophrenia and/or its intermediate phenotypes. It is believed that inappropriate or inadequate neurotrophic support during brain development could underlie structural and functional disorganization of neural and synaptic networks, leading to the decreased ability of the brain to make necessary adaptive changes seen in schizophrenia. The studies so far fall into three categories. (1) Numerous studies have reported association between BDNF Val66Met and other single nucleotide polymorphisms (SNPs) and schizophrenia (Craddock et al 2006). However, these associations have not been replicated in some recent studies (Craddock et al 2006). (2) A more consistent finding is the decrease in the serum (or plasma) BDNF levels in schizophrenic patients (Toyooka et al 2002). However, in drug-naïve first-episode schizophrenic patients, serum BDNF levels are increased (Jockers-Scherubl et al 2004). Thus, it is unclear whether the reduction in serum BDNF is truly associated with the illness or antipsychotic drug administration. (3) A more relevant study might be to examine BDNF expression levels in relevant brain regions from animal models of schizophrenia or postmortem schizophrenic brains. Neonatal lesion of rodent ventral hippocampus

recapitulates many schizophrenia-like phenotypes. In this model, BDNF mRNA levels were reduced in the hippocampus, prefrontal cortex (PFC), and cingulate cortex (Ashe et al 2002, Lipska et al 2001, Molteni et al 2001). In postmortem brains from schizophrenia patients, there is a significant decrease in BDNF mRNA in dorsal lateral PFC and hippocampus (Hashimoto et al 2005, Weickert et al 2003). In parallel, expression of TrkB and calbindin-D, a marker for GABAergic neurons, were significantly reduced in the hippocampus or PFC (Hashimoto et al 2005, Weickert et al 2003, Takahashi et al 2000). Again, it is unclear whether the changes in BDNF or TrkB expression are direct consequences of the illness or secondary to antipsychotic drug treatment. Rodents could be used to directly test the effect of antipsychotics. Chronic treatment of rodents with typical antipsychotic drugs generally suppresses BDNF expression in the brain, whereas atypical antipsychotics increase BDNF expression (Lipska et al 2001, Chlan-Fourney et al 2002).

When thinking about future research on the role of BDNF in schizophrenia, several points warrant further discussion. First, given BDNF's complex genomic structure, it may be helpful to examine expression of specific BDNF transcripts in the schizophrenic brain, particularly in relevant regions such as hippocampus and sub-regions of prefrontal cortex (PFC). Second, BDNF gene expression is subject to strong epigenetic regulation. Thus, lack of genetic association does not automatically suggest that BDNF is not involved. A recent precedent was the demonstration that social defeat stress induced long-lasting down-regulation of BDNF transcripts III and IV, and chronic antidepressants reversed this down-regulation by increasing histone acetylation at these promoters (Tsankova et al 2006). Third, studies of BDNF Val66Met polymorphism suggest that the mode of BDNF secretion (regulated versus constitutive), rather than the levels of BDNF per se, might be more important in cognitive functions and behaviours. Indeed, BDNF (Met/Met) knock-in mice, which exhibit increased anxiogenic behaviours, have normal BDNF levels in the brain, but show significantly impaired activity-dependent secretion of BDNF (Chen et al 2006). Third, all studies thus far have used methods that cannot distinguish pro-BDNF from mBDNF. Since pro-BDNF and mBDNF elicit opposing actions on synaptic plasticity, their distinction is paramount to determining the role of pro-BDNF and mBDNF in specific aspects of cognitive behaviours relevant to schizophrenia. Finally, given that the majority of negative symptoms in schizophrenia are associated with PFC deficits such as impairments in working memory and executive functions, future efforts should be directed towards studying the regulation of PFC function by BDNF. Since synchronized firings in the PFC last only a few seconds, LTP-like mechanisms may not be involved. It is more likely that BDNF controls the development of underlying cortical networks. A major target is the parvalbumin (PV)-positive GABAergic interneurons, which coordinate sustained firing of pyramidal neurons within a PFC network. Among all interneurons, TrkB is preferentially expressed in PV interneurons. Accumulated data suggest that TrkB signaling is disrupted in the PV interneurons in schizophrenics, leading to decreased expression of GABA-related genes (Lewis et al 2005). Multidisciplinary approaches, particularly network recording and behavioural assays relevant to PFC functions, should be used to study BDNF regulation of the development of GABAergic interneurons, and its functional consequences. How impairments in cortical network are linked to the pathophysiology of schizophrenia is fascinating subject worthy of future studies.

References

Angelucci F, Mathe AA, Aloe L. Neurotrophic factors and CNS disorders: findings in rodent models of depression and schizophrenia. Prog Brain Res. 2004; 146:151–165. [PubMed: 14699963]

Ashe PC, Chlan-Fourney J, Juorio AV, Li XM. Brain-derived neurotrophic factor (BDNF) mRNA in rats with neonatal ibotenic acid lesions of the ventral hippocampus. Brain Res. 2002; 956:126–135. [PubMed: 12426055]

Baranes D, Lederfein D, Huang YY, Chen M, Bailey CH, Kandel ER. Tissue plasminogen activator contributes to the late phase of LTP and to synaptic growth in the hippocampal mossy fiber pathway. Neuron. 1998; 21:813–825. [PubMed: 9808467]

Barco A, Patterson S, Alarcon JM, et al. Gene expression profiling of facilitated L-LTP in VP16-CREB mice reveals that BDNF is critical for the maintenance of LTP and its synaptic capture. Neuron. 2005; 48:123–137. [PubMed: 16202713]

Chen WG, Chang Q, Lin Y, et al. Derepression of BDNF transcription involves calcium-dependent phosphorylation of MeCP2. Science. 2003; 302:885–889. [PubMed: 14593183]

Chen ZY, Patel PD, Sant G, et al. Variant brain-derived neurotrophic factor (BDNF) (Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons. J Neurosci. 2004; 24:4401–4411. [PubMed: 15128854]

Chen ZY, Ieraci A, Teng H, et al. Sortilin controls intracellular sorting of brain-derived neurotrophic factor to the regulated secretory pathway. J Neurosci. 2005; 25:6156–6166. [PubMed: 15987945]

Chen ZY, Jing D, Bath KG, et al. Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. Science. 2006; 314:140–143. [PubMed: 17023662]

Chlan-Fourney J, Ashe P, Nylen K, Juorio AV, Li XM. Differential regulation of hippocampal BDNF mRNA by typical and atypical antipsychotic administration. Brain Res. 2002; 954:11–20. [PubMed: 12393228]

Craddock N, O'Donovan MC, Owen MJ. Genes for schizophrenia and bipolar disorder? Implications for psychiatric nosology. Schizophr Bull. 2006; 32:9–16. [PubMed: 16319375]

Egan MF, Kojima M, Callicott JH, et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell. 2003; 112:257–269. [PubMed: 12553913]

Figurov A, Pozzo-Miller LD, Olafsson P, Wang T, Lu B. Regulation of synaptic responses to high-frequency stimulation and LTP by neurotrophins in the hippocampus. Nature. 1996; 381:706–709. [PubMed: 8649517]

Hariri AR, Goldberg TE, Mattay VS, et al. Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance. J Neurosci. 2003; 23:6690–6694. [PubMed: 12890761]

Harris SE, Fox H, Wright AF, et al. The brain-derived neurotrophic factor Val66Met polymorphism is associated with age-related change in reasoning skills. Mol Psychiatry. 2006; 11:505–513. [PubMed: 16446742]

Hashimoto T, Bergen SE, Nguyen QL, et al. Relationship of brain-derived neurotrophic factor and its receptor TrkB to altered inhibitory prefrontal circuitry in schizophrenia. J Neurosci. 2005; 25:372–383. [PubMed: 15647480]

Ji Y, Pang PT, Feng L, Lu B. Cyclic AMP controls BDNF-induced TrkB phosphorylation and dendritic spine formation in mature hippocampal neurons. Nat Neurosci. 2005; 8:164–172. [PubMed: 15665879]

Jockers-Scherubl MC, Danker-Hopfe H, Mahlberg R, et al. Brain-derived neurotrophic factor serum concentrations are increased in drug-naive schizophrenic patients with chronic cannabis abuse and multiple substance abuse. Neurosci Lett. 2004; 371:79–83. [PubMed: 15500971]

Korte M, Carroll P, Wolf E, Brem G, Thoenen H, Bonhoeffer T. Hippocampal long-term potentiation is impaired in mice lacking brain-derived neurotrophic factor. Proc Natl Acad Sci USA. 1995; 92:8856–8860. [PubMed: 7568031]

Korte M, Kang H, Bonhoeffer T, Schuman E. A role for BDNF in the late-phase of hippocampal long-term potentiation. Neuropharmacology. 1998; 37:553–559. [PubMed: 9704996]

Lee R, Kermani P, Teng KK, Hempstead BL. Regulation of cell survival by secreted proneurotrophins. Science. 2001; 294:1945–1948. [PubMed: 11729324]

Levine ES, Crozier RA, Black IB, Plummer MR. Brain-derived neurotrophic factor modulates hippocampal synaptic transmission by increasing N-methyl-D-aspartic acid receptor activity. Proc Natl Acad Sci USA. 1998; 95:10235–10239. [PubMed: 9707630]

Lewis DA, Hashimoto T, Volk DW. Cortical inhibitory neurons and schizophrenia. Nat Rev Neurosci. 2005; 6:312–324. [PubMed: 15803162]

Lipska BK, Khaing ZZ, Weickert CS, Weinberger DR. BDNF mRNA expression in rat hippocampus and prefrontal cortex: effects of neonatal ventral hippocampal damage and antipsychotic drugs. Eur J Neurosci. 2001; 14:135–144. [PubMed: 11488957]

Liu QR, Walther D, Drgon T, et al. Human brain derived neurotrophic factor (BDNF) genes, splicing patterns, and assessments of associations with substance abuse and Parkinson's Disease. Am J Med Genet B Neuropsychiatr Genet. 2005; 134:93–103. [PubMed: 15666411]

Lou H, Kim SK, Zaitsev E, Snell CR, Lu B, Loh YP. Sorting and activity-dependent secretion of BDNF require interaction of a specific motif with the sorting receptor carboxy-peptidase e. Neuron. 2005; 45:245–255. [PubMed: 15664176]

Lu B. BDNF and activity-dependent synaptic modulation. Learn Mem. 2003; 10:86–98. [PubMed: 12663747]

Lu B, Chow A. Neurotrophins and hippocampal synaptic transmission and plasticity. J Neurosci Res. 1999; 58:76–87. [PubMed: 10491573]

Lu B, Pang PT, Woo NH. The yin and yang of neurotrophin action. Nat Rev Neurosci. 2005; 6:603–614. [PubMed: 16062169]

Martinowich K, Hattori D, Wu H, et al. DNA methylation-related chromatin remodeling in activity-dependent BDNF gene regulation. Science. 2003; 302:890–893. [PubMed: 14593184]

Minichiello L, Calella AM, Medina DL, Bonhoeffer T, Klein R, Korte M. Mechanism of TrkB-mediated hippocampal long-term potentiation. Neuron. 2002; 36:121–137. [PubMed: 12367511]

Molteni R, Lipska BK, Weinberger DR, Racagni G, Riva MA. Developmental and stress-related changes of neurotrophic factor gene expression in an animal model of schizophrenia. Mol Psychiatry. 2001; 6:285–292. [PubMed: 11326296]

Mowla SJ, Pareek S, Farhadi HF, et al. Differential sorting of nerve growth factor and brain-derived neurotrophic factor in hippocampal neurons. J Neurosci. 1999; 19:2069–80. [PubMed: 10066260]

Nykjaer A, Lee R, Teng KK, et al. Sortilin is essential for proNGF-induced neuronal cell death. Nature. 2004; 427:843–848. [PubMed: 14985763]

Pang PT, Teng HK, Zaitsev E, et al. Cleavage of proBDNF by tPA/plasmin is essential for long-term hippocampal plasticity. Science. 2004; 306:487–491. [PubMed: 15486301]

Patterson SL, Grover LM, Schwartzkroin PA, Bothwell M. Neurotrophin expression in rat hippocampal slices: a stimulus paradigm inducing LTP in CA1 evokes increases in BDNF and NT-3 mRNAs. Neuron. 1992; 9:1081–1088. [PubMed: 1463608]

Patterson SL, Abel T, Deuel TA, Martin KC, Rose JC, Kandel ER. Recombinant BDNF rescues deficits in basal synaptic transmission and hippocampal LTP in BDNF knockout mice. Neuron. 1996; 16:1137–1145. [PubMed: 8663990]

Patterson SL, Pittenger C, Morozov A, et al. Some forms of cAMP-mediated long-lasting potentiation are associated with release of BDNF and nuclear translocation of phospho-MAP kinase. Neuron. 2001; 32:123–140. [PubMed: 11604144]

Pezawas L, Verchinski BA, Mattay VS, et al. The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. J Neurosci. 2004; 24:10099–10102. [PubMed: 15537879]

Szekeres G, Juhasz A, Rimanoczy A, Keri S, Janka Z. The C270T polymorphism of the brain-derived neurotrophic factor gene is associated with schizophrenia. Schizophr Res. 2003; 65:15–18. [PubMed: 14623369]

Takahashi M, Shirakawa O, Toyooka K, et al. Abnormal expression of brain-derived neurotrophic factor and its receptor in the corticolimbic system of schizophrenic patients. Mol Psychiatry. 2000; 5:293–300. [PubMed: 10889532]

Teng HK, Teng KK, Lee R, et al. ProBDNF induces neuronal apoptosis via activation of a receptor complex of p75NTR and sortilin. J Neurosci. 2005; 25:5455–5463. [PubMed: 15930396]

Timmusk T, Palm K, Metsis M, et al. Multiple promoters direct tissue-specific expression of the rat BDNF gene. Neuron. 1993; 10:475–489. [PubMed: 8461137]

Toyooka K, Asama K, Watanabe Y, et al. Decreased levels of brain-derived neurotrophic factor in serum of chronic schizophrenic patients. Psychiatry Res. 2002; 110:249–257. [PubMed: 12127475]

Tsai SJ, Hong CJ, Yu YW, Chen TJ. Association study of a brain-derived neurotrophic factor (BDNF) Val66Met polymorphism and personality trait and intelligence in healthy young females. Neuropsychobiology. 2004; 49:13–16. [PubMed: 14730195]

Tsankova NM, Berton O, Renthal W, Kumar A, Neve RL, Nestler EJ. Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. Nat Neurosci. 2006; 9:519–525. [PubMed: 16501568]

Weickert CS, Hyde TM, Lipska BK, Herman MM, Weinberger DR, Kleinman JE. Reduced brain-derived neurotrophic factor in prefrontal cortex of patients with schizophrenia. Mol Psychiatry. 2003; 8:592–610. [PubMed: 12851636]

West AE, Chen WG, Dalva MB, et al. Calcium regulation of neuronal gene expression. Proc Natl Acad Sci USA. 2001; 98:11024–11031. [PubMed: 11572963]

Woo NH, Teng HK, Siao CJ, et al. Activation of p75NTR by proBDNF facilitates hippocampal long-term depression. Nat Neurosci. 2005; 8:1069–1077. [PubMed: 16025106]

Yano H, Ninan I, Zhang H, Milner TA, Arancio O, Chao MV. BDNF-mediated neurotransmission relies upon a myosin VI motor complex. Nat Neurosci. 2006; 9:1009–1018. [PubMed: 16819522]

Zagrebelsky M, Holz A, Dechant G, Barde YA, Bonhoeffer T, Korte M. The p75 neurotrophin receptor negatively modulates dendrite complexity and spine density in hippocampal neurons. J Neurosci. 2005; 25:9989–9999. [PubMed: 16251447]