REVIEW

New insight in expression, transport, and secretion of brain-derived neurotrophic factor: Implications in brain-related diseases

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Abstract

Brain-derived neurotrophic factor (BDNF) attracts increasing attention from both research and clinical fields because of its important functions in the central nervous system. An adequate amount of BDNF is critical to develop and maintain normal neuronal circuits in the brain. Given that loss of BDNF function has been reported in the brains of patients with neurodegenerative or psychiatric diseases, understanding basic properties of BDNF and associated intracellular processes is imperative. In this review, we revisit the gene structure, transcription, translation, transport and secretion mechanisms of BDNF. We also introduce implications of BDNF in several brain-related diseases including Alzheimer's disease, Huntington's disease, depression and schizophrenia.

Core tip: Brain-derived neurotrophic factor (BDNF) plays essential roles in the central nervous system (CNS) through a specific tropomyosin-related kinase receptor B (TrkB), contributing to neuronal survival, neurite outgrowth, and synaptic function. It is critically required for normal development and functions of the brain. A number of reports have shown an importance of BDNF in the pathophysiology of brain-associated diseases. This review describes molecular mechanisms underlying gene expression, transport, and secretion of BDNF and its function in the CNS. We further introduce recent findings on the possible involvement of BDNF in the pathophysiology of neurodegenerative and psychiatric diseases, and the potential effectiveness of enhancing BDNF/TrkB system for therapeutic applications.

INTRODUCTION

Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin (NT) family, was purified in 1982 from pig brain as a cell survival-promoting factor for sensory neurons[1] about 30 years after the discovery of nerve-growth factor (NGF)[2]. In the past three decades, two other neurotrophins, neurotrophin 3 (NT3) and neurotrophin 4 (NT4), have been identified in the mammalian brain and their function in neuronal survival, neurite outgrowth, and synaptic plasticity in the nervous system extensively investigated[3]. Each neurotrophin has a common receptor p75NTR and a specific tropomyosin-related kinase receptor (Trk); TrkA for NGF, TrkB for BDNF and NT4, TrkC for NT3. All neurotrophins are synthesized as 32 kD precursor proteins called pro-neurotrophins that are intra- and extracellularly cleaved to produce the mature neurotrophin form[4-6]. Mature neurotrophins bind to Trk receptors with high affinity while pro-neurotrophins preferentially bind to p75NTR[4-6]. Neurotrophins exert their biological function through several signaling pathways activated by Trk receptors or p75NTR after binding of neurotrophins. Binding of the BDNF dimer to TrkB induces dimerization and autophosphorylation of TrkB, resulting in sequential phosphorylation in three intracellular signaling pathways; Mitogen-activated protein kinase/extracellular signal-regulated protein kinase, phospholipase Cγ (PLCγ), and phosphatidylinositol 3-kinase (PI3K) pathways[7-10].

BDNF is the most studied and characterized neurotrophin in the central nervous system (CNS) and has received remarkable attention from clinicians because of its importance in the development and maintenance of normal brain functions. This is especially important, as growing evidence suggests a role of BDNF in the pathophysiology of brain-associated illnesses including both neurodegenerative and psychiatric diseases[11,12]. Appropriate intracellular processes including transcription from the *BDNF* gene, translation to protein, BDNF protein sorting to secretory vesicles, BDNF-containing vesicle transport, and BDNF secretion are essential to achieve normal BDNF functions as well as to activate the signaling pathways after TrkB phosphorylation. As decreased expression levels of BDNF in several brain regions are evident in postmortem studies of patients with the brain-related diseases[11,12], precise knowledge about *BDNF* gene expression is critical. Specifically, the responsible gene of Huntington's disease, huntingtin, has been shown to directly regulate intracellular transport of BDNF[13,14]. Furthermore, we recently reported impaired BDNF secretion and TrkB signaling in a cellular model of schizophrenia[15].

In this article, we review both converting (from gene to mature protein) and spatial regulation (transport and secretion) processes of BDNF. We will also highlight recent findings suggesting implications of BDNF in the pathophysiology of the brain-related diseases.

BDNF GENE STRUCTURE

BDNF mRNA and protein are abundantly expressed in the hippocampus, cerebral cortex, amygdala, and cerebellum in the mammalian brain[16-19]. Although BDNF is widely expressed in other tissues such as the heart, kidney, lung and testis, BDNF expression is higher in the brain than any other tissue during development[20]. It is also known that BDNF expression is dramatically increased in the rodent visual cortex with a peak at postnatal days 20-40 when visual plasticity is high[21,22].

The *BDNF* gene consists of at least eight 5' exons (exon I -VIII) with each respective promoter and one 3' exon (exon IX) encoding BDNF protein in both human and rodent[23-25] (Figure 1). Pruunsild *et al*[25] recently identified two human-specific exons named exons Vh and VIIIh. Exon Vh has a specific promoter while exon VIIIh is not linked to an independent promoter. Transcription of the *BDNF* gene is initiated at each of 5' noncoding exons that are spliced onto the pre-proBDNF protein-coding 3' exon IX[24,25]. Rodent exon I and human exons I , VII and VIII of the *BDNF* gene contain the ATG sequence from which translation could be started, which could produce the distinct pre-proBDNF proteins with longer amino acid sequences at the N-terminal end of the protein[24,25]. Other exons are untranslated exons, and translation of the transcripts (mRNAs) containing these exons only starts from the ATG sequence located at the exon IX[25]. Moreover, transcription of the BDNF gene terminates at two alternative polyadenylation sites in exon IX, giving rise to two distinct populations of mRNA with either short (approximately 0.35 kb) or long (approximately 2.85 kb) 3' untranslated regions (3' UTRs)[26,27]. To produce an identical pre-proBDNF protein, the evolutionary change in *BDNF* gene structure has remained a complex transcription mechanism that results in the expression of multiple BDNF mRNA variants. The diversity of BDNF mRNA leads to different neuronal distribution. The short 3' UTR BDNF mRNA variant is restricted to the cell body in hippocampal neurons while the long 3' UTR mRNAs are also observed in dendrites[27], indicating a specific dendritic transport system for the long 3' UTR BDNF mRNA and local dendritic translation.

TRANSCRIPTIONAL REGULATION IN *BDNF* GENE

Using multiple promoters in BDNF transcription allows for appropriate responses to intracellular processes and varying extracellular environments. Membrane depolarization is a well-known neuronal gene expression regulator, and more than 300 gene transcriptions have been identified as activity-dependent in neurons[28]. The transcription of BDNF in neurons is positively regulated by membrane depolarization induced by seizures[29], sensory stimuli[30-32] and activation of glutamate receptors such as N-methyl-D-aspartate (NMDA) receptors[33-35], suggesting its important function in experience-dependent modifications of neural circuits and brain development. Neuronal activity stimulates transcription initiation of the BDNF gene, which is regulated by elevation of intracellular Ca^{2+} concentration *via* NMDA receptors (NMDAR)
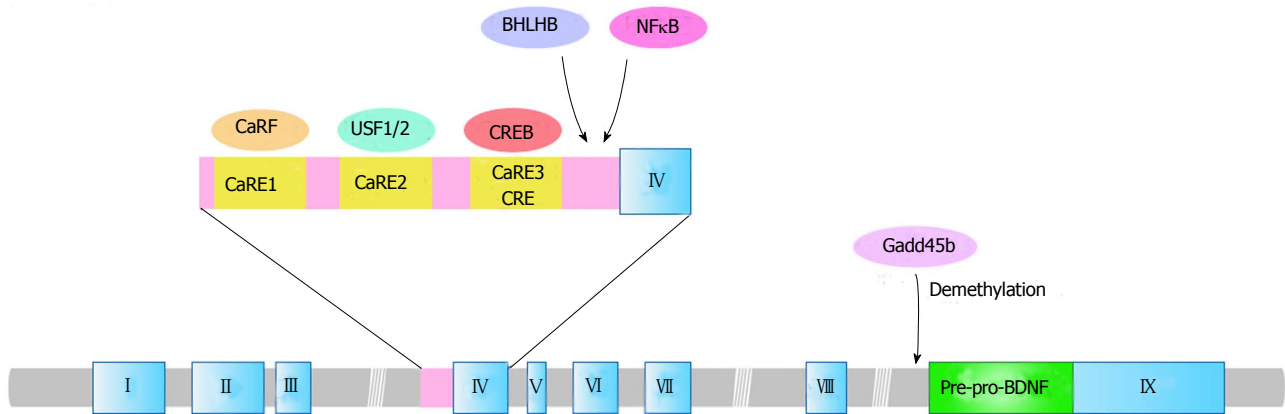
Figure 1 Schematic illustration of the activity-dependent regulators for Brain-derived neurotrophic factor gene transcription. A variety of transcriptional factors and regulators participate in the activity-induced transcription of *BDNF*. *BDNF* gene structure and Ca²⁺-dependent regulation in *BDNF* exon IV and epigenetic regulation at the exon IX promoter region are presented. We referred to the description by Zheng *et al*[38], also see[180]. BDNF: Brain-derived neurotrophic factor; CaRF: Calcium responsive factor; USF: Upstream stimulatory factors; BHLHB: Basic helix-loop-helix; CREB: Cyclic AMP-responsive element binding protein; NFκB: Nuclear factor-κB.

or L-type voltage-gated calcium channels (L-VGCC)[35]. The activity- and Ca²⁺-dependent transcription of the BDNF gene occurs predominantly through exons I and IV. The promoter region of BDNF exon IV contains three Ca²⁺-response elements CaRE1, CaRE2 (also known as USF-binding element, UBE) and CaRE3 (also known as calcium response element, CRE)[36-38] (Figure 1). CaRE1 is located at 64-73 bp upstream of the transcription initiation site in exon IV. CaRE2 and CaRE3 are 43-52 bp and 29-36 bp upstream, respectively[38]. Regulation of exon IV transcription *via* CaRE3 has been extensively investigated. Cyclic AMP-responsive element binding protein (CREB), which is phosphorylated at multiple sites by calcium/calmodulin (CaM)-dependent protein kinases, cAMP-dependent protein kinase A (PKA) and MAPK cascades binds to CaRE3/CRE to activate the promoter[37-39]. Knock-in mice with a subtle mutation at the CREB binding site in endogenous CaRE3/CRE showed a disrupted sensory experience-dependent increase of the BDNF exon IV transcript in the cortex[40]. Greenberg and colleagues identified novel transcription regulators for BDNF exon IV such as CaRF (calcium responsive factor) and USFs (upstream stimulatory factors) for CaRE1 and CaRE2, respectively[36,41] (Figure 1). CaRF knockout mice showed reduced exon IV mRNA levels in the cerebral cortex with normal levels in the hippocampus and striatum, suggesting brain region-specific regulation of CaRF-CaRE1 at the BDNF promoter IV[42]. Recently, Zheng *et al*[37] revealed intriguing Ca²⁺-dependent activation mechanisms of each CaRE, using cultured cortical neurons at DIV 11. Ca²⁺ entry through NMDAR or L-VGCC stimulated only CaRE1 and CaRE3 but not CaRE2, and CaRE1 and CaRE3 were activated *via* different sets of protein kinases depending on the route of calcium entry[37]. For example, CaRF is essential only for the L-VGCC-induced, not the NMDAR-induced, transcription of BDNF exon IV[37,38], indicating that other transcriptional regulators stimulate the NMDAR-dependent activation of CaRE1. Furthermore, the L-VGCC-dependent CaRE1 activation depends on protein kinase A (PKA), calcium/calmodulin-dependent protein kinase

I (CaMKI), and CaMKIV, while CaRF activation requires MEK, PI3K and CaMKII[37,38]. On the other hand, CaRE3 activity is regulated by Ca²⁺ influx through both L-VGCC and NMDAR. MEK, PI3K, and PKA activity are required in both the L-VGCC - and NMDA-induced CaRE3 activation[37,38]. CaM and CaMKIV are needed in the L-VGCC-induced CaRE3 activation while CaMKI and CaMKIV are required in the NMDAR-mediated CaRE3 activation[37,38]. Although CaREs play a central role in the regulation of BDNF promoter IV, there are also other possible regulators for the promoter including basic helix-loop-helix B2 (BHLHB2) and nuclear factor-κB (NF-κB)[43,44] (Figure 1). Furthermore, neuronal activity stimulates BDNF promoter I as well as promoter IV. Several transcription factor binding sites such as CREB, USFs, myocyte enhancer factor 2D, and NF-κB have been suggested to stimulate BDNF promoter I[45-47], though the regulatory mechanisms have not been elucidated. Futhermore, Timmusk and colleagues have identified a cis-element PasRE (bHLH-PAS transcription factor response element) in both promoter I and IV. They also demonstrated that transcription factors ARNT2 (aryl hydrocarbon receptor nuclear translocator 2, a basic helix-loop-helix (bHLH)-PAS transcription factor) and NPAS4 (neuronal PAS domain protein 4) bind to PasRE (bHLH-PAS transcription factor response element) in both promoters, which is required for full induction of neuronal activity-dependent transcription from each exon[48,49].

Epigenetic regulations in transcription of the *BDNF* gene have also been reported. Decreased methylation of cytosine residues in CpG dinucleotides (CpG) of BDNF promoter IV, at least in part, mediates neuronal activity-dependent induction of BDNF transcription. Methyl-CpG-binding protein 2 (MeCP2), a member of the methyl-CpG-binding protein family, binds to methylated DNA in the BDNF promoter IV region and functions as a transcriptional regulator[50]. It is still controversial whether MeCP2 functions as an activator or a repressor for BDNF transcription. Because MeCP2 protein is released from the BDNF promoter IV region in response to neuronal activity-induced reduction of CpG methyla-
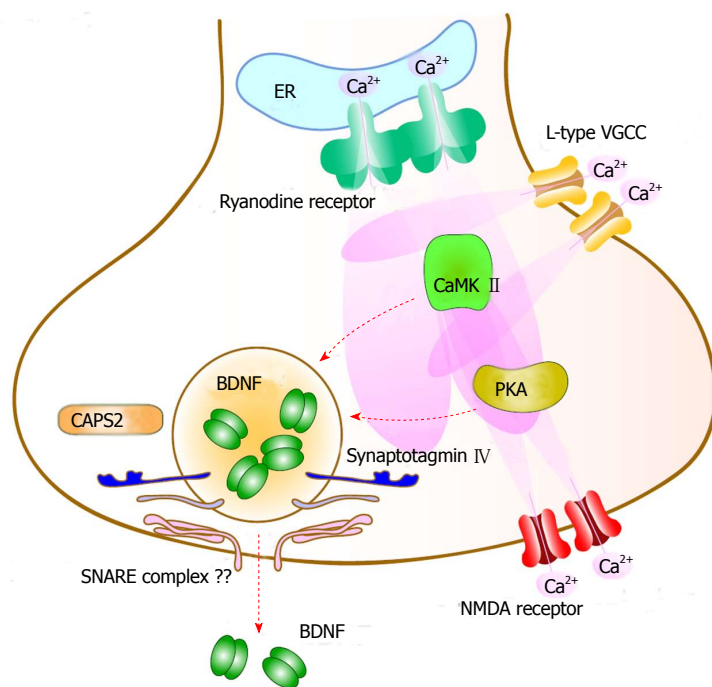
Figure 2 Schematic illustration of activity-dependent brain-derived neurotrophic factor secretion. A possible mechanism of intracellular Ca^{2+}-dependent secretion of BDNF suggested in literature. Ca^{2+} influx through NMDA receptor/L-type VGCC and subsequent Ca^{2+} release of internal stores via ryanodine receptors are required for secretion. CaMK II, PKA, synaptotagmin IV, and CAPS2 also critically contribute to the membrane fusion process of BDNF-containing vesicles. VGCC: L-type voltage-gated calcium channels; CaMK II: calcium/calmodulin-dependent protein kinase II; PKA: protein kinase A; CAPS2: Ca^{2+}-dependent activator protein for secretion 2; BDNF: Brain-derived neurotrophic factor.

tion, it had been recognized as a transcriptional repressor for the *BDNF* gene[50]. However, both BDNF mRNA and protein levels were decreased in MeCP2-null mice[51], suggesting a possible repressive function of MeCP2 on BDNF expression. Furthermore, a combination mechanism of MeCP2 and CREB in BDNF transcription[52], and an additional function of MeCP2 other than transcriptional regulation, has also been indicated[3]. Recent findings demonstrated a novel epigenetic regulation in BDNF exon IX. Gadd45b, a neural immediate early gene, promotes activity-dependent demethylation in the BDNF exon IX promoter region[53] (Figure 1). Considering that electric stimulation-induced BDNF transcription was dramatically reduced in Gadd45b knock-out mice and that Gadd45b interacts and demethylates the promoter region of BDNF exon IX encoding pre-pro-BDNF[53], a gating function of Gadd45b in neuronal activity-dependent BDNF gene transcription was indicated.

BDNF TRANSPORT AND SECRETION

The secretion process of neurotrophins involves either the constitutive or regulated pathway, depending on whether secretion occurs spontaneously or in response to neuronal activity, respectively. Unlike other neurotrophins including NGF and NT-3 that are mainly secreted by the constitutive pathway, BDNF seems to be preferentially sorted into the regulated pathway[54-56]. As described above, the 32 kDa precursor form of BDNF (pre-pro-BDNF) is translated at the rough endoplasmic reticulum (ER) and then proteolytically cleaved to generate the 13 kDa mature form of BDNF. The pre-pro-BDNF is conveyed to the Golgi apparatus and sorted into the membrane stacks of the trans-Golgi network (TGN) where BDNF-containing dense core vesicles (DCVs) bud off. The pro-region of BDNF is implicated in the sort-

ing step of BDNF into secretory vesicles[57,58]. A single nucleotide polymorphism (SNP) at nucleotide 196 in the pro-region of the human BDNF gene that produces an amino acid substitution from valine to methionine (val-66met) has a negative effect on the sorting of BDNF into vesicles[57]. The BDNF pro-region also binds to the lipid-raft-associated sorting receptor carboxypeptidase E (CPE) in the TGN, which is an important step for sorting into secretory vesicles[58]. Furthermore, a transmembrane protein sortilin which mainly resides in the membrane of the Golgi apparatus interacts with the pro-region of BDNF and regulates its sorting. BDNF vesicular sorting was impaired in pheochromocytoma PC12 cells that express the luminal domain sortilin lacking the transmembrane and cytoplasmic domains[59].

BDNF-containing vesicles are transported to secretion sites by motor protein complexes in polarized neurons, although the subcellular localization of BDNF secretion sites in neurons of the adult CNS is still controversial. Transport and secretion of BDNF-containing vesicles into axons and dendrites have been observed in cultured cortical and hippocampal neurons by visualization using exogenously transfected fluorescent protein-tagged BDNF[56,60,61], while knock-in mice expressing Myc-tagged BDNF showed specific localization of BDNF-containing vesicles at presynaptic terminals in the adult (8-wk-old) hippocampus[62]. Intriguingly, the Golgi apparatus present in dendrites was revealed in cultured hippocampal neurons and adult rat hippocampus, with fluorescent protein-tagged BDNF localized to the dendritic Golgi, indicating a local BDNF secretory pathway as well as local translation in dendrites[63,64]. Although BDNF transport properties are still not fully elucidated, bidirectional (anterograde and retrograde) trafficking of BDNF-containing vesicles in axons and dendrites have been reported in cultured neurons[56,65,66]. Furthermore,

the anterograde BDNF vesicle transport is microtubule-based with a motor protein kinesin and a coordinator dynactin[13,66]. Several important studies revealed that huntingtin, a polyglutamine-containing protein associated with Huntington disease (HD), and CPE are also involved in the motor protein complex for BDNF-containing vesicle transport and affect properties such as velocity and direction[13,14,65,66].

Evidence suggests that BDNF can be secreted from the cell soma, axon and dendrites of cultured cortical and hippocampal neurons in a neuronal activity (depolarization)-dependent manner[67,68] (Figure 2). Lessmann *et al*[68] clearly showed that activity-dependent BDNF secretion requires Ca^{2+} influx *via* ionotropic glutamate receptors or L-type VGCC and subsequent amplification of the initial Ca^{2+} elevation through Ca^{2+}-induced Ca^{2+} release from internal stores (the endoplasmic reticulum) *via* ryanodine receptors. Activation of Trk receptors or Na^+ channels, on the other hand, is not directly associated with BDNF secretion[68-70]. They further revealed that activation of both CaMK II and PKA were also required for secretion[67,70] (Figure 2). Considering the shared signaling pathways between the activity-dependent secretion and transcription of BDNF, decreased BDNF levels after secretion may be restored immediately with simultaneous induction of BDNF transcription. Although molecular mechanisms underlying the vesicle fusion step in BDNF secretion remain unclear, two proteins are suggested to regulate this step: Synaptotagmin IV and Ca^{2+}-dependent activator protein for secretion 2 (CAPS2). Synaptotagmin IV, a soluble NSF attachment protein receptor (SNARE) complex binding protein localized to BDNF containing vesicles, negatively regulates BDNF secretion at both axons and dendrites in hippocampal neurons[71]. It was also reported that CAPS2, a DCV-associated protein, enhanced activity-dependent BDNF secretion efficiency[72,73]. However, it is still unclear whether BDNF-containing vesicles use SNARE-dependent membrane fusion similar to synaptic vesicle exocytosis.

It is a matter of continuous debate where and how pre-pro-BDNF is converted to the mature form of BDNF in the CNS. It was previously concluded that pro-neurotrophins are cleaved by proteases such as furin and pro-protein convertases (PCs) in TGN or in DCVs prior to secretion[74]. Several recent studies, however, showed that hippocampal neurons secreted a considerable amount of pro-BDNF that was subsequently processed extracellularly to mature-BDNF by plasmin or matrix metalloproteinases[6,75]. More recently, immediate intracellular conversion of pro-BDNF to mature-BDNF along with co-localization of the cleaved pro-peptide region and mature-BDNF in secretory vesicles in hippocampal neurons were confirmed[62,76]. Resolving the discrepancy of whether neurons secrete pro-BDNF is a very important issue because pro-BDNF preferentially binds to p75NTR rather than TrkB, which in turn causes cell death or synaptic depression in neurons[77,78]. Where pro-neurotrophin cleavage takes place and which proteinases participate in the process might be dependent upon the developmental

stage of neurons or the location of BDNF translation (the cell soma or dendrites)[79].

PHYSIOLOGICAL ROLES OF BDNF IN THE CNS

Neurons exhibit several distinct features such as a polarized structure, inter-connected circuits, and electrical activity. Many studies have revealed a variety of BDNF functions associated with these features in the developing and mature brain. BDNF acts as a neurite outgrowth and elongation factor, pro-survival factor, and synaptic regulator in the CNS. BDNF promotes axon initiation through two distinct signaling pathways. BDNF induces TrkB-dependent local elevation and stabilization of cAMP/PKA activity that are essential for axon initiation in undifferentiated neurites of hippocampal neurons[80,81]. Furthermore, BDNF/TrkB-induced Akt phosphorylation reduces GSK-3 activation which in turn decreases production of the active form of collapsin response mediator protein-2 that plays a critical role in microtubule assembly during axon elongation and branching in rat hippocampal neurons[82,83]. BDNF also promotes axon elongation and branching of sensory neurons both *in vitro* and *in vivo*[83,84]. A BDNF concentration gradient produced by a BDNF-containing micropipette demonstrated an attractive turning effect on the axonal growth cone in cultured *Xenopus* spinal neurons[83,84]. Interestingly, application of specific inhibitors for cAMP or PKA resulted in repulsive turning in the same BDNF gradient, indicating the critical role of cAMP levels to determine the growth cone's response between attraction and repulsion to the same BDNF gradient[83]. A comprehensive study on BDNF function in dendritic growth done by Wirth *et al*[85] revealed that overexpressed BDNF affected pyramidal cells by increasing length and number of apical dendritic segments in layer VI, and basal dendrites in layer V in rat cortical slice cultures. It is important that such BDNF-promoted dendritogenesis and dendrite growth were observed only in BDNF-overexpressed neurons themselves, suggesting the autocrine action of BDNF[85]. Studies using primary cultured neurons have revealed the importance of MAP kinase and PI3 kinase activation *via* TrkB phosphorylation to promote BDNF-dependent dendritic growth[86,87]. It is also important to note that acute elevation in BDNF concentration promotes total growth of dendrites and the number of primary dendrites while gradual BDNF elevation increases branching number[88].

BDNF also plays a role in synapse formation and stabilization[89]. TrkB knockout mice showed a significant decline in the number of hippocampal synaptic structures[90]. TrkB conditional-mutant mice in which TrkB is deleted in the cerebellum resulted in a reduction of inhibitory synapses[90]. BDNF as a regulator of synaptogenesis *in vivo* was also confirmed in *Xenopus* optic axons[91]. Using the time-lapse imaging technique with GFP-tagged synaptobrevin II as a marker for functional synapses, BDNF-induced retinal ganglion cell axon arborization and synaptogenesis were shown[91]. Furthermore, neu-

tralization of endogenous BDNF by function-blocking antibodies for BDNF rapidly (within 2 h) dismantled pre-existing GFP-synaptobrevin clusters, suggesting its importance in synaptic stabilization[92]. Exogenously applied BDNF induced functional excitatory and inhibitory synapse formation in cultured rat hippocampal neurons[93] and increased excitatory synapse numbers in rat hippocampal slices[94]. On the other hand, there are lines of evidence showing synaptogenic function of BDNF and TrkB in inhibitory GABAergic connections in the visual cortex[95-97], cerebellum[98], organotypic slice cultures of the rat hippocampus[99] and organotypic cerebellar cultures of mice[100]. BDNF serves as an important modulator for synaptic connections in mature neuronal circuits as well as in developing neuronal circuits. BDNF modulates synaptic efficacy and synaptic plasticity such as long-term potentiation (LTP) and long-term depression (LTD) in the developed CNS (for reviews, see[3,101,102]). For example, acute and chronic application of exogenous BDNF potentiates synaptic efficacy by increasing glutamate transmission in rat brain slices of the hippocampus[103], visual cortex[104], and hippocampal dissociated cultures[105,106]. Modulation of NMDA receptor function[107,108] and ion channels including Na_v[109], $K_v1.3$[110], and TRPC3 channels[111] by BDNF contributes to enhancement of excitatory synaptic efficacy. BDNF also promotes spine growth[112,113] and membrane insertion of NMDA[114] and AMPA[115] receptors at the postsynaptic cites of excitatory synapses. Contrary to its enhancing action on excitatory synapses, BDNF has been reported to modulate the efficacy of GABAergic synapse transmission both presynaptically and postsynaptically in a bidirectional manner. Presynaptic GABA transmission was suppressed by acute BDNF application in hippocampal slices[116] as well as chronic application in hippocampal cultures[117], while chronic BDNF in cultured hippocampal neurons potentiates presynaptic GABA transmission[118]. BDNF shows a bi-directional modulation also on postsynaptic GABA$_A$ receptor function. BDNF potentiated[119] and depressed[120,121] GABAergic postsynaptic currents through modulating GABA$_A$ receptor functions and regulating membrane insertion of GABA$_A$ receptors. Interestingly, BDNF decreased and increased inhibitory postsynaptic currents (IPSCs) when recorded from excitatory and inhibitory neurons, respectively[122]. Furthermore, IPSCs amplitude was increased by acute BDNF treatment in hippocampal slices obtained from postnatal day 6 rats whereas the opposite effect was observed in slices from postnatal day 14 rats[123]. These data indicate the complicated function of BDNF, especially in the modulation of basic properties of developed GABAergic synapses, depending on the region in the brain, stage of maturity, and duration of exposure to BDNF.

It has been frequently reported that synaptic BDNF is involved in LTP and LTD. LTP was first identified in the rat hippocampus as a long-lasting activity-dependent synaptic modification[124,125], and it is the leading hypothesis of the mechanism underlying experience-dependent learning and memory. Important roles of BDNF/TrkB

signaling in specific high-frequency electrical stimuli (tetanus or Theta burst stimulation)-induced LTP in brain slices prepared from the hippocampus and cortex have been shown (for reviews, see[102,126]). A severe impairment in hippocampal LTP was confirmed in independent lines of BDNF knockout and heterozygous mice[127]. Interestingly, in heterozygous mice in which BDNF expression in the hippocampus is suppressed to approximately 60% of wild type levels, the same degree of impairment was found in LTP as that of knockout mice. Furthermore, supplementation of exogenous BDNF rescued this impairment, suggesting that BDNF plays a critical role in hippocampal LTP and a threshold level of BDNF is essential to assure LTP induction[128]. Of note, acute hippocampus-specific deletion of the *BDNF* gene in adult mice showed impaired novel object recognition and spatial learning in the Morris water maze[129]. These mice also demonstrated reduced extinction of conditioned fear in spite of normal acquisition and expression fear, suggesting a critical role for BDNF in hippocampal-dependent cognitive function and memory extinction[129]. TrkB knockout mice also exhibited impaired hippocampal LTP, illustrating the importance of TrkB in hippocampal-dependent learning involved in spatial memory tasks[130]. Mutant TrkB knock-in mice carrying a point mutation in the kinase domain of TrkB demonstrated that PLCγ-dependent activation of CREB and CaMKIV phosphorylation are critical factors for BDNF/TrkB-dependent hippocampal LTP[131]. Recently, mammalian target of rapamycin (mTOR) was also identified as a contributor to BDNF/TrkB-dependent hippocampal LTP[132]. Considering that PI3K and Akt are the upstream regulators of mTOR, the PI3K-AKT-mTOR pathway is thought to play a significant role in BDNF-dependent LTP. The PI3K-AKT pathway was also shown to enhance dendritic transport of PSD-95 to postsynaptic sites depending on BDNF/TrkB signaling[113], suggesting its involvement in persistent structural changes of spines after LTP induction. In contrast to mature BDNF, pro-BDNF mainly plays a role in LTD which is induced by low frequency stimulation (LFS). It has been reported that pro-BDNF enhanced NMDA receptor (NR2B)-dependent LTD in the hippocampus through p75NTR activation[78]. Application of pro-BDNF facilitated NR2B-mediated hippocampal LTD only in the wild type, but not in p75NTR knockout mice[78]. Interestingly, other forms of synaptic plasticity such as NMDA receptor-dependent LTP and NMDA receptor-independent LTD were intact in p75NTR knockout mice[78], suggesting a specific role of pro-BDNF in hippocampal LTD. Considering that p75NTR activation negatively affects dendrite complexity and spine density in hippocampal neurons[133], secreted pro-BDNF, which escapes processing by proteinases, modulates neurite morphology and synaptic plasticity in the opposite way as mature BDNF. Taken together, BDNF is deeply associated with neuronal connectivity through modulating the development of neural circuitry and regulating synaptic efficacy throughout the CNS. Therefore, impairment of BDNF function in the devel-

oping and mature brain is implicated in many psychiatric and neurodegenerative diseases.

CRITICAL BDNF GENE POLYMORPHISM

A critical non-synonymous SNP in the human BDNF gene was first reported in 2003[57], involving an amino acid substitution at valine 66 to methionine (Val66Met)[57]. The BDNF Val66Met polymorphism predominantly affects the sorting process of synthesized BDNF into secretory vesicles[57], resulting in reduction in activity-dependent BDNF secretion[12,57]. Inconsistent with critical BDNF roles in hippocampal LTP, met allele carriers (BDNF[met] carriers) showed impaired performance in episodic memory[57,134], verbal memory[135], and cognitive performance[136]. However, it is still controversial whether carrying the met allele causes significant reduction in human hippocampal volume despite the essential roles of BDNF in neurite development[12,137]. A mouse model of the polymorphism BDNF[met/met] knock-in mice showed an approximately 15% reduction in hippocampal volume and dendritic arbor complexity[138]. Cultured neurons from BDNF[met/met] knock-in mice exhibited normal levels of total BDNF protein but significantly reduced amounts of activity-dependent secretion of BDNF[138]. Interestingly, the BDNF[met/met] knock-in mice showed anxiety-related behaviors that did not improve with chronic antidepressant fluoxetine treatment[138]. Detailed electrophysiological analysis of hippocampal slices of BDNF[met/met] knock-in mice revealed normal basal glutamatergic transmission but reduced NMDA receptor-mediated current and NMDA receptor-dependent LTP[139]. It is clear that further investigation of BDNF transport and secretion processes are important for more detailed understanding of the neurotrophin and for the development of BDNF-based therapy for patients with brain-related diseases.

IMPLICATION OF BDNF IN BRAIN DISEASES

BDNF has been implicated in multiple brain-related diseases, as it plays a critical role in neuronal development, survival, and synaptic function. Although studies show involvement of BDNF in the pathophysiology of multiple brain-related illnesses such as bipolar disorder[140], Parkinson's disease[140], stroke, epilepsy[141], eating disorders[142], and substance use[142], we review four neuropsychiatric illnesses associated with BDNF dysfunction.

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is the most common age-related neurodegenerative disorder with noticeable impairment of cognitive function. Patients with AD show progressive loss of synapses and neurons especially in the entorhinal cortex and hippocampus, which causes a loss of their ability to acquire new memories[11,143-145]. A wide range of evidence exists due to brain cohort differences[146],

though decreased expression levels of BDNF protein and mRNA have been consistently reported in the hippocampus and cortex of individuals with AD[147-151] as well as in serum[152] (Table 1). Furthermore, firm conclusions regarding involvement of the Val66Met polymorphism on disease onset or progression of AD have not been made (for review, see[140]). On the other hand, Nagahara *et al*[153] recently reported that BDNF gene delivery to the entorhinal cortex ameliorated entorhinal cortical and hippocampal neuronal degeneration in a mouse model of AD. Mice in this model expressed the human amyloid precursor protein (APP) with mutations and exhibited AD-like pathology such as cortical plaques, progressive cell loss in the entorhinal cortex and cognitive decline by 6-7 mo after birth[153,154]. Direct injection of lentiviral vector constitutively expressing BDNF into the entorhinal cortex of the mice after disease onset reversed synapse loss in both the entorhinal cortex and hippocampus, and restored learning and memory deficits[153]. Such *BDNF* gene delivery was similarly effective to the reduced memory function in normally aged (24-mo-old) rats and primates[153]. Because the entorhinal cortex is a primary input to the hippocampus, the rescued synaptic loss in the hippocampus of these model animals could be attributed to BDNF transport from the cortical region. Other AD mouse models with amyloid-β overproduction caused by APP mutations exhibited significant reduction in cortical BDNF mRNA[155]. Hippocampal BDNF protein is reduced in the 5XFAD transgenic mice expressing five familial AD mutant forms of human APP, with memory deficits rescued by a specific TrkB agonist, 7,8-dihydroxyflavone (7,8-DHF), without affecting endogenous BDNF levels[156]. Furthermore, neural stem cell (NSC) transplantation also improved cognitive function in AD model mice *via* BDNF secreted by NSC[157]. BDNF-based therapy is increasingly expected to ameliorate the symptoms of AD.

HUNTINGTON DISEASE

Huntington's disease (HD) is a neurodegenerative and autosomal dominant disease caused by repeats of the CAG trinucleotide in the huntingtin (htt) gene, which produces abnormal htt proteins with polyglutamine expansion (polyQ). Degeneration of striatal neurons is thought to induce progressive psychiatric, cognitive and motor dysfunction[158]. Possible link between HD and BDNF function has been reported. Given that substantial levels of BDNF protein are detectable in adult rodent striatum while TrkB mRNA, but not BDNF mRNA, is present along with the fact that cortical neurons projecting to the striatum contain high levels of BDNF mRNA, most striatal BDNF is anterogradely transported from the cortex[159]. It was revealed that wild-type htt but not mutant (polyQ) htt stimulated transcription from BDNF exon II in the cerebral cortex[160,161]. Postmortem studies have revealed reduced BDNF mRNA and protein levels in the cortex[162,163], caudate-putamen[163,164], striatum[163], cerebellum[163], and substantia nigra[163] in patients with

HD. Decreased serum BDNF levels in patients was also reported[165]. The mouse models of HD expressing exon 1 of the human HD gene with expanded polyQ region recapitulate many of the features of human HD such as progressive behavioral deficit, impaired motor functions, cognitive decline, and premature death[166-169]. Reduced expression of BDNF was confirmed in the cortex[166,167] and striatum[168,169] of three HD mouse models (R6/1, R6/2, and YAC128). The antidepressant sertraline increased BDNF protein levels in the hippocampus and striatum, improving lifespan and motor performance, and ameliorated brain atrophy in R6/2 HD mice[170]. Genetically overexpressed BDNF in the cerebral cortex and striatum of YAC128 HD mice alleviated loss of striatal neurons and motor dysfunction, and improved procedural learning[168]. BDNF overexpression in the striatum improved cortico-striatal connectivity and motor function in R6/2 HD mice[167]. Furthermore, 7,8-DHF and its derivative 4'-dimethylamino-7,8- dihydroxyflavone (4'-DMA-7,8-DHF) extended survival, ameliorated brain atrophy, and improved motor deficits in N171-82Q HD mice[171]. Importantly, forebrain-specific BDNF-knock-out mice (Emx-BDNF KO mice) show a similar phenotype to that observed in the mouse models of HD[172,173]. In contrast to evidence suggesting involvement of BDNF in the pathophysiology of HD, no association between the Val-66Met polymorphism of the *BDNF* gene and onset/progression of HD has been reported[174-178].

Gauthier *et al*[13] have unveiled an important htt function in BDNF transport. Mutant htt reduced post-Golgi microtubule-based axonal transport velocity of BDNF-containing vesicles while wild-type htt accelerated transport velocity in cultured cortical neurons[13]. These findings suggest that mutations in htt lead to decreased amounts of BDNF in the striatum by inhibiting both BDNF transcription and axonal transport of BDNF-containing vesicles in cortical neurons. Furthermore, the direction of transport was regulated by phosphorylation of htt at serine 421[14]. Phosphorylated htt recruited motor protein kinesin-1 to BDNF-containing vesicles to facilitate anterograde transport, though wild-type htt enhances both anterograde and retrograde transport efficiency in cortical neurons. In contrast, retrograde transport was increased in the absence of htt phosphorylation at the serine 421 site[14]. Interestingly, mutant htt impairs the post-Golgi transport only in val-BDNF-containing vesicles but not in met-BDNF, which in turn produces a reduction in the amount of activity-dependent secretion of val-BDNF in cell lines[179]. Severely reduced BDNF levels in R6/1 HD mice hippocampus and striatum were rescued by environmental enrichment[169]. The enrichment, consisting of small cardboard boxes, small open wooden boxes, cylindrical cardboard tunnels, and folded sheets of paper prevented body weight loss and ameliorated motor symptoms of the mice[169]. Considering that the striatum itself does not produce BDNF and receives BDNF supply from the cortex, such enrichment may compensate by attenuating the mutant htt-induced

impairment of anterograde transport of BDNF to the striatum[169,170]. Given the functional interaction between BDNF and htt, exogenous supplementation of BDNF or TrkB agonists to the striatum would be the primary choice for the treatment of HD patients.

DEPRESSION

Several lines of evidence implicate BDNF in the pathophysiology of psychiatric disorders[10-12,180]. Specifically, reduced BDNF expression levels and impaired BDNF function have been reported in patients with depression and schizophrenia[181-184]. Reduced BDNF[185-187] or TrkB[188] levels in the prefrontal cortex[185,186,188], hippocampus[185,186], amygdala[187], and serum[189-191] have been demonstrated in patients with depression, especially in suicide victims[185,186,189]. Considering that BDNF protein levels were unchanged in hippocampal and cortical tissue of suicide subjects who had been treated with antidepressants[186], increased levels of BDNF in these brain regions may be facilitated by treatment with antidepressants. Decreased serum BDNF levels have been also reported in patients with depression[189-191], which was recovered by antidepressant drug treatment[191-193]. Increased expression of BDNF or TrkB mRNA in the cerebellum[194] was also shown after chronic antidepressant treatment in subjects with depression. Decreased BDNF and TrkB expression levels are also evident in rodent models of depression. A variety of stressors on rodents such as social defeat[195], restraint (immobilization)[196,197], maternal deprivation[198], and glucocorticoid administration[196,199-201] can reduce BDNF and TrkB expression levels in the hippocampus, cortex, and amygdala. In the normal rat brain, hippocampal and cortical BDNF/TrkB levels were increased after administration of tricyclic antidepressants (TCA; including imipramine, desipramine)[202-204], selective serotonin reuptake inhibitors (SSRI; fluoxetine, paroxetine, sertraline)[202,204-206], noradrenergic and specific serotonergic antidepressants (NaSSA; mirtazapine, mianserin)[202,207], and monoamine oxidase inhibitors (MAOIs; tranylcypromine)[202-204]. Electroconvulsive seizures also significantly induced BDNF expression in the cortex[202,208] and hippocampus[202,209-211]. 7,8-DHF, a specific TrkB agonist, and its O-methylated metabolites showed an antidepressant-like effect in the forced swimming and tail suspension tests[212]. Of note, direct BDNF infusion into the rat midbrain induced antidepressant-like effects[213]. Interestingly, TrkB phosphorylation was also increased by antidepressants in the rat brain[214]. An antidepressant imipramine, however, induced TrkB phosphorylation even in the conditional BDNF knock-out mice, suggesting the antidepressant-induced TrkB activation might be BDNF-independent[215]. Despite compelling evidence of BDNF contribution to depression onset and symptoms, meta-analysis with inconsistent results from genetic association studies of the BDNF val66met polymorphism revealed no significant association between the val66met polymorphism and depression[216]. It must be noted, however,
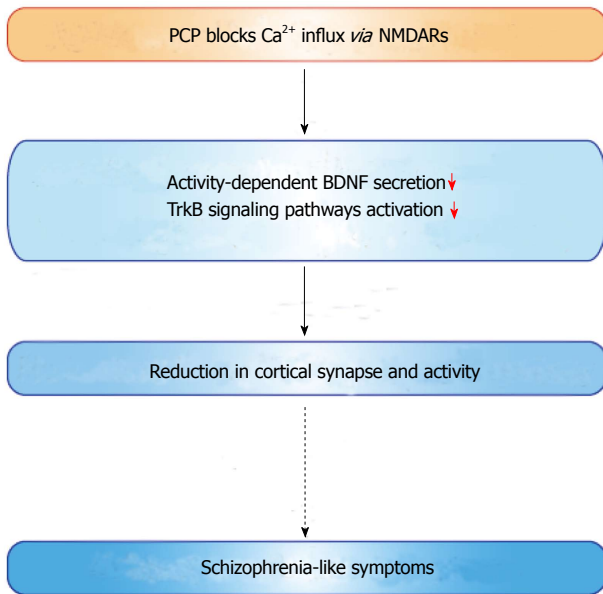
Figure 3 Molecular mechanisms of phencyclidine-induced synaptic loss as a cellular model of schizophrenia. Phencyclidine decreased the number of synaptic sites in cultured cortical neurons through blockade of Ca²⁺ influx via NMDARs and resultant suppression of BDNF secretion. The impairment in BDNF secretion reduced TrkB activation and resulted in decreased synaptic connectivity[15]. BDNF: Brain-derived neurotrophic factor; NMDAR: N-methyl-D-aspartate receptors; PCP: Phencyclidine.

that the polymorphism may affect the development of depression more in men than in women[216].

Chronic stress-induced hypothalamic pituitary-adrenal (HPA) axis abnormalities result in increased serum levels of glucocorticoids that are implicated in the pathogenesis of depression[10,217,218]. The HPA axis is an important endocrinological coping mechanism against stressful stimuli that includes release of hormones such as corticotropin-releasing hormone (CRH) from the paraventricular nucleus (PVN), CRH-trigged adrenocorticotropic hormone (ACTH) from the anterior pituitary, and ACTH-induced glucocorticoids from the adrenal glands. We recently reported that the glucocorticoid receptor (GR), which has both genomic and non-genomic properties in cortical neurons, requires TrkB interaction for full activation of the BDNF-induced PLCγ pathway[219]. Chronic treatment with glucocorticoids decreased GR protein levels, and inhibited TrkB-GR interaction and resultant BDNF-induced glutamate release via the PLCγ pathway[219]. On the other hand, Jeanneteau et al[220] showed TrkB activation by acute administration of glucocorticoids in cortical neurons. The activation of TrkB by glucocorticoids promoted neuronal survival through the transcriptional function of GR and Akt signaling pathway activation[220]. They also revealed that BDNF/TrkB signaling regulates GR transcriptional activity by stimulating GR phosphorylation at S155 and S287[221,222]. These results suggest a possible involvement of the impaired reciprocal interaction between BDNF and the HPA axis in the pathogenesis of depressive disorders. Taken together, BDNF-based therapy for depressed patients could target GR function or the direct activation of TrkB[12].

SCHIZOPHRENIA

Approximately 1% of the world population is affected by schizophrenia. This psychiatric condition manifests in three major ways: Positive symptoms (hallucinations, delusions, thought and movement disorders), negative symptoms (flat affect, lack of pleasure and ability to begin and sustain planned activities), and cognitive symptoms (impaired ability to understand and use information, and problems with "working memory")[223]. Several brain regions have been implicated in the pathophysiology of this illness. Studies on postmortem brain tissue of schizophrenia patients demonstrates that the overall number of neurons in the prefrontal cortex is not decreased[224]. However, reduced synaptophysin (presynaptic protein) immunoreactivity and dendritic spine density of pyramidal cells were observed in the cortex[225,226], suggesting synaptic dysfunction in the pathogenesis of the disease. Because symptoms usually start between ages 16 and 30 with only rare cases reported after age 45[227], deficits in synaptic maturation and overall brain development may be heavily involved in disease onset. Expression levels of BDNF or TrkB have been investigated in brains of patients with schizophrenia. Whether or not BDNF levels are altered in brain tissue or serum of patients with schizophrenia is a controversial topic[184,228,229]. Some postmortem studies demonstrated elevated BDNF protein levels in the hippocampal and cortical tissue in schizophrenic patients[230,231], while decreased BDNF levels have also been shown in these brain regions[231-234] (Table 1). Reduced BDNF mRNA and protein levels in serum of patients with schizophrenia have been consistently reported (Table 1). There are some reports showing that clozapine treatment increased serum BDNF mRNA levels in patients[235,236]. A meta-analysis examining blood BDNF levels in schizophrenia found a moderate effect of reduced BDNF in patents with schizophrenia compared with controls[237]. Furthermore, val/met and met/met BDNF genotypes were reported in a meta-analysis to increase the risk of schizophrenia[142]. Decreased BDNF mRNA and protein levels have also been confirmed in animal models of schizophrenia induced by phencyclidine (PCP)[238], MK-801[239] or ibotenic acid[240]. In contrast to human patients, antipsychotic administration in rodents significantly reduces BDNF expression levels (Table 1). Second-generation antipsychotics such as risperidone and olanzapine, in addition to first-generation antipsychotics such as haloperidol and chlorpromazine, all tend to reduce BDNF protein levels in the rat cortex, hippocampus, and striatum[241-243] (Table 1). Although it is challenging to approach the molecular mechanisms underlying the pathophysiology of schizophrenia, PCP, a psychomimetic drug, is known to produce beneficial animal and cellular models for schizophrenia. PCP acts as a non-competitive NMDA receptor blocker and generates schizophrenia-like behavioral changes in humans and rodents[244,245]. Interestingly, sub-chronic PCP (2 mg/kg, i.p. twice daily for 7 d followed by 6 wk drug-free) administration decreased BDNF mRNA levels in many brain

Table 1 Implications of BDNF in brain-related diseases

BDNF expression levels in brain diseases and animal models	Possible involvement of BDNF in therapies
Alzheimer's disease (patients)	
Decreased expression levels of BDNF mRNA	
Hippocampus: ref.[147,148]	
Cortex: ref.[148,149]	
Decreased expression levels of BDNF protein	
Serum: ref.[152]	
Hippocampus: ref.[150]	
Cortex: ref.[150,151]; no change ref.[247]	
Alzheimer's disease (animal models)	Alzheimer's disease (animal models)
Decreased expression levels of BDNF mRNA	*BDNF* gene delivery ameliorated age-related cognitive impairment in aged primates and rats. ref.[153]
Cortex: Aβ transgenic strains	7, 8-DHF improved memory deficits in 5XFAD transgenic mouse. ref.[156]
(APPNLh and TgCRND8) ref.[155]	
Decreased expression levels of BDNF protein	
Hippocumpus: 5XFAD transgenic mouse ref.[156]	
Huntington disease (patients)	
Decreased expression levels of BDNF mRNA	
Serum: ref.[165]	
Cortex: ref.[162]	
Caudate: decreased TrkB mRNA ref.[162]	
Decreased expression levels of BDNF protein	
Cortex: ref.[163,165]	
Striatum: ref.[163]	
Cerebellum: ref.[163]	
Substantia nigra: ref.[163]	
Caudate and Putamen: ref.[164]	
Huntington disease (animal models)	Huntington disease (animal models)
Decreased expression levels of BDNF mRNA	BDNF overexpression improved motor function in R6/2 mice. ref.[167]
Cortex: R6/2 mice, ref.[166,167]	BDNF overexpression ameliorated YAC128 mice phenotype. ref.[168]
Decreased expression levels of BDNF protein	Environmental enrichment-increased BDNF improved the phenotype in R6/1 mice. ref.[169]
Striatum: YAC128 mice, ref.[168];	Sertraline-increased BDNF improved the phenotype in R6/2 mice. ref.[170]
R6/1 mice ref.[169]	7, 8-DHF or 4'-DMA-7,8-DHF improved motor deficits in N171-82Q mice. ref.[171]
Depression (patients)	Depression (patients)
Decreased expression levels of BDNF mRNA	Antidepressants increased BDNF in serum. ref.[191-193,248]
Hippocampus: ref.[185] (suicidal)	Antidepressants increased BDNF and TrkB in the cerebellum. ref.[194]
Cortex: ref.[185] (suicidal),	
decreased TrkB mRNA ref.[188]	
Amygdala: ref.[187]	
Decreased expression levels of BDNF protein	
Serum: ref.[189-191]	
Hippocampus ref.[185] (suicidal)[186] (suicidal)	
Cortex: ref.[185] (suicidal)[186] (suicidal)	
Depression (animal models)	Depression (animal models)
Decreased expression levels of BDNF mRNA	Antidepressants increased BDNF in the rat brain
Hippocampus: social defeat stress, ref.[195];	Tricyclic antidepressants (TCA; including imipramine, desipramine), ref.[202-204]
restrain stress, ref.[196,197] (also TrkB);	Selective serotonin reuptake inhibitors (SSRI; fluoxetine, paroxetine, sertraline), ref.[202,204-206,251]
maternal deprivation, ref.[198];	Noradrenergic and specific serotonergic antidepressants (NaSSA; mirtazapine, mianserin), ref.[202,207]
dexamethasone, ref.[199];	Monoamine oxidase inhibitors (MAOIs; tranylcypromine), ref.[202-204]
corticosterone, ref.[196,200,201];	
foot shock stress, ref.[249]	
Cortex: social defeat stress, ref.[195];	Electroconvulsive seizures induced BDNF expression. ref.[202,208-211]
maternal deprivation, ref.[198];	7,8-DHF showed an antidepressant-like effect. ref.[212]
dexamethasone, ref.[199];	Direct BDNF infusion into the rat midbrain induced antidepressant-like effects. ref.[213]
cold swim stress, ref.[250]	
Amygdala: social defeat stress, ref.[193]	

Decreased expression levels of BDNF protein

Hippocampus: maternal deprivation, ref.[198];

        corticosterone, ref.[200,201];

        cold swim stress, ref.[250]

Schizophrenia (patients)	Schizophrenia (patients)
Decreased expression levels of BDNF mRNA	Clozapine treatment increased serum BDNF mRNA levels. ref.[235,236]
Serum: ref.[236,252];	
decreased TrkB mRNA ref.[253]	
Cortex: ref.[122,233,254,255];	
decreased TrkB mRNA ref.[255];	
incrased trunkated TrkB mRNA ref.[256]	
Serum: ref.[235,257-260]	
Hippocampus: ref.[231];	
abnormal expression of TrkB ref.[261];	
increased BDNF mRNA ref.[230]	
Cortex: ref.[232-234];	
increase BDNF mRNA ref.[230,231]	
Cerebrospinal fluid ref.[234]	

Schizophrenia (animal models)	Schizophrenia (animal models)
Decreased expression levels of BDNF mRNA	Mk-801-induced decline in hippocampal BDNF mRNA was normalized by olanzapine, but exacerbated by haloperidol. ref.[238]
Hippoaumpus: phencyclidine, ref.[238];	Haloperidol or risperidone decreased BDNF protein in the rat frontal cortex and hippocampus. ref.[241]
MK-801 ref.[239];	Haloperidol decreased BDNF and TrkB protein in the rat hippocampus. ref.[242]
ibotenic acid lesions, ref.[240]	Risperidon, olanzapine, haloperidol, and chlorpromazine decreased BDNF levels in the rat striatum and hippocampus. ref.[243]
Cortex: phencyclidine, ref.[238]	Haloperidol down-regulated BDNF mRNA expression in the rat hippocampus. ref.[262]
Amygdala: phencyclidine, ref.[238]	

BDNF: Brain-derived neurotrophic factor.

regions including the cortical, hippocampal, and amygdaloid regions in adult rats[238], while higher doses of PCP (10 mg/kg, *i.p.* for 14 d) increased BDNF levels in the hippocampus and entorhinal cortex of rat pups[246]. We recently demonstrated that PCP suppressed the activity-dependent secretion of BDNF in cultured cortical neurons through blockade of Ca^{2+} influx *via* NMDA receptors[15] (Figure 3). Decreased BDNF secretion subsequently caused a reduction in the activation of TrkB-dependent signaling pathways and resultant synaptic loss in cortical neurons[15], which is consistent with the observation that patients demonstrate reduced cortical synaptic structure[225-227]. Because of the multifactorial etiology of schizophrenia, whether the BDNF-based approach would be effective or not is unclear in this disease. Ultimately, the multiple, essential roles of BDNF in synaptic function, however, could influence future therapy for these patients.

CONCLUSION

Many efforts are being dedicated to understanding the intracellular processes of BDNF to develop BDNF-based effective treatments for the brain-related diseases. Although brain diseases are associated with an overall decrease in BDNF function, varying BDNF levels in specific brain regions may affect symptom attenuation. As BDNF does not cross the blood-brain barrier, researchers are challenged to develop *BDNF* gene or protein

delivery methods to the CNS[11]. Molecules that increase BDNF or TrkB expression levels, TrkB phosphorylation or membrane insertion, or conversion from pro-BDNF to mature BDNF are important and novel treatment options[12]. Even if BDNF itself is not the main gene responsible for the particular brain disease, BDNF-based treatments may provide valuable symptom relief. It is also critical to elucidate the basic molecular mechanisms of BDNF expression, transport, and secretion so that new therapeutic approaches may be developed to treat these debilitating neuropsychiatric conditions.

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