

# The Biological Actions and Mechanisms of Brain-Derived Neurotrophic Factor in Healthy and Disordered Brains

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## Abstract

Brain-derived neurotrophic factor (BDNF) is a neurotrophin that elicits neuronal survival and differentiation, synaptic transmission, and the modulation of synaptic plasticity. The biological actions of BDNF are mediated via two distinct receptors: the high-affinity tropomyosin-related kinase B (TrkB) receptor and the low-affinity p75 neurotrophin receptor (p75NTR). Recent findings regarding the actions and mechanisms of BDNF are reviewed here. Activity-dependent synaptic plasticity, as exemplified by long-term potentiation (LTP) and long-term depression (LTD), underlies the cellular mechanism of learning and memory. An accumulating body of evidence shows that BDNF modulates synaptic plasticity. This function requires extracellular neurotrophin release, synaptic activity-dependent local protein synthesis. In addition, a precursor of BDNF, proBDNF, is emerging as a new ligand with biological activities that are distinct from those of BDNF. The proteolytic cleavage of proBDNF is also proposed as a mechanism that determines the direction of BDNF actions. This review discusses the post-translational processing of proBDNF, the modulatory roles of the human BDNF polymorphism Val66Met, recent reports of the novel mechanisms of BDNF expression, and clinical reports showing the roles of BDNF in the blood. Taken together, these data provide new insights into the biological roles of BDNF and its related molecules in the central nervous system.

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## Keywords

**Component, Brain-Derived Neurotrophic Factor (BDNF), Tropomyosin-Related Kinase B (TrkB), Synaptic Plasticity, Polymorphism, Proteolytic Cleavage**

### 1. Introduction

Levi-Montalcini and Hamburger first discovered that a mouse sarcoma tumor implanted near the spinal cord of the developing chicken released a soluble protein that increased neurite outgrowth from sympathetic neurons [1]. This factor is named nerve growth factor (NGF) [2]-[4]. Over 20 years after the discovery of NGF, Barde and colleagues isolated a neuronal survival-eliciting factor from the pig brain, named brain-derived neurotrophic factor (BDNF) [5]; the successful molecular cloning of BDNF cDNA came not long after [6]. BDNF is highly homologous to NGF at the amino acid sequence level. This finding led to the identification of two additional neurotrophins: neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5) [7]-[9].

There are two forms of BDNF: proBDNF and mature BDNF (mBDNF), which are synthesized by intracellular and/or extracellular proteolytic enzymes (e.g., furin, pro-hormone convertase, and plasmin) [10]. The pro-domain of neurotrophin is implicated in the protein folding of BDNF [11]. In the *BDNF* gene, a single nucleotide polymorphism (SNP), which substitutes methionine (Met) to valine (Val) at amino acid position 66 in the pro-region of human BDNF protein, was identified, and it was demonstrated that the Val66Met mutation (Val66Met or Rs6265) influences the activity-dependent secretion of BDNF [12]. Since this report, accumulating evidence suggests that the Val66Met genetic variant increases the susceptibility of an individual to a variety of brain disorders [13].

### 2. Neurotrophin Receptors

The NTs interact with two distinct classes of receptors. The first receptor, the p75 neurotrophin receptor (p75NTR), is a member of the tumor necrosis factor (TNF) receptor family [8]. p75NTR was originally identified as a receptor for NGF, but was subsequently shown to bind to BDNF, NT-3, and NT-4/5 with a similar low affinity [8] [9]. The extracellular domain of p75NTR has cysteine-rich motifs. The cytoplasmic domain includes a “death” domain, the cytoplasmic domain found in other members of the TNF receptor family [14] [15]. Although p75NTR does not contain a catalytic kinase motif, it interacts with several proteins that play important roles in regulating neuronal survival and differentiation [16].

The second class is the tropomyosin-related kinase (Trk) family of receptor tyrosine kinases (TrkA, TrkB, and TrkC) [9]. NGF specifically binds TrkA; BDNF and NT4 activates TrkB; NT3 activates TrkC. In some cellular contexts, NT3 is able to activate TrkA and TrkB [9]. The extracellular domain of each Trk receptor consists of a cysteine-rich cluster followed by a series of leucine-rich repeats and two immunoglobulin-like domains. The Trk receptors have a transmembrane domain and a cytoplasmic domain that has tyrosine kinase activity. The activation of NTs, through Trk receptors, leads to the activation of Ras, phosphatidylinositol 3-kinase (PI3K), and phospholipase C- $\gamma$ 1. These signaling pathways control the activity of downstream molecules such as mitogen-activated protein (MAP) kinases [9]. The NT receptors and their signaling mechanisms have been extensively reviewed by others [9] [10] [16] and so will not be discussed in this review article.

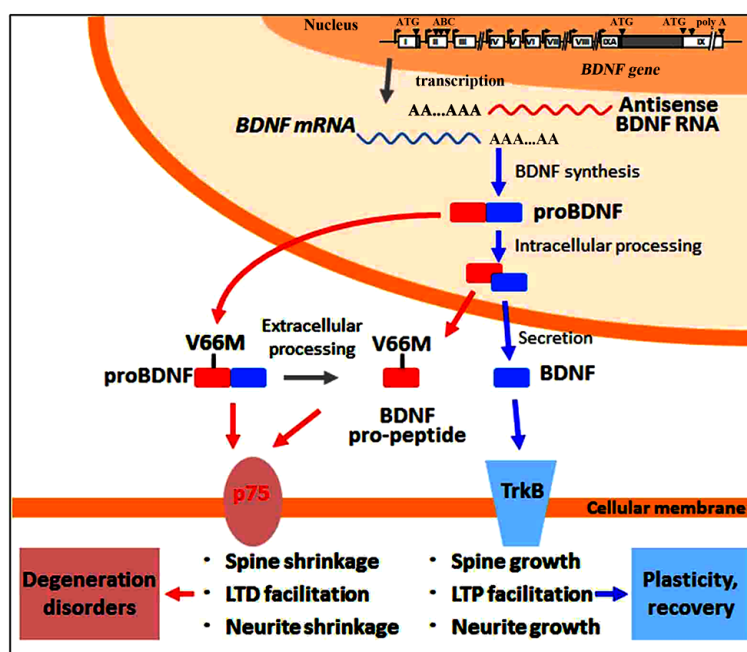
### 3. ProBDNF, Pro-Peptide of BDNF, and BDNF

Lee and colleagues reported that the proteolytic cleavage of NTs (from the precursor form to the mature form) is an important process in their post-transcriptional mechanism, and determines their specific action [17]. A precursor of NGF (proNGF) promotes neuronal death, while mature NGF elicits neuronal survival [17]. Also, proBDNF induces the death of sympathetic neurons, cerebellar neurons, and motor neurons *in vitro* [18]-[20]. Furthermore, proNGF and proBDNF bind to the p75NTR and the sortilin receptor complex with high affinity [18]-[21]. Thus, the cellular responses to pro- and mature neurotrophins can be engaged by different combinations of Trk receptors, p75NTR, or sortilin family members. The roles of the precursor and the mature forms of BDNF in neuronal morphology and synaptic transmission will now be discussed.

The intracellular cleavage of the pro-domain of BDNF is performed by the pro-protein convertases (PC1/3, PC2, PC4, PC5/6, PC7) and furin [22]. The activity of these serine proteinases is dependent on  $\text{Ca}^{2+}$  concentrations (10  $\mu\text{M}$ ) and pH is in the range of 5 - 7, typically present in the trans-Golgi network (TGN) and secretory granules [23]. Pro-protein convertases are dominantly expressed in neurons, while furin is expressed in all tissues [24]. These convertases cleave the pro-peptide behind a pair of or single basic residues (Arg-Arg or Lys-Arg) and at the C-terminus of the pro-domain [23] [24].

In the case of BDNF, 120 amino acid N-terminal fragment, namely the BDNF pro-peptide, is produced from proBDNF by proteinase cleavage (Figure 1). Dieni and her colleagues demonstrated that the BDNF pro-peptide is detectable in hippocampal tissues [25]. They investigated the distribution of both BDNF and its pro-peptide in the adult hippocampus using light and electron microscopy and by using genetically engineered mouse strains and antibodies generated by Koshimizu *et al.* [19]. BDNF and its pro-peptide are present in hippocampal extracts at similar concentrations [25], suggesting that both peptides are stored after cleavage. Both BDNF and its pro-peptide are detected in the same sub-population of large secretory vesicles in presynaptic terminals, showing that neuronal stimulation leads to the exocytosis of secretory vesicles and may promote their delivery to the postsynaptic neurons. Another possibility raised from this report is that, as in the case of neuropeptides such as beta-endorphin [26], the BDNF pro-peptide may exert biological functions beyond assisting the folding of BDNF. This notion is indicated by several reports. Second, as described earlier, Val66Met polymorphism also affects the activity-dependent secretion of BDNF and memory function in human [12]. This report provided two interpretations. First, the BDNF pro-domain plays an important role in activity-dependent-secretion of BDNF. Second, this regulated-secretion mechanism might be crucial for human memory function.

Interestingly, Anastasia *et al.* (2012) showed that Val66Met polymorphism alters prodomain structure, resulting in a change in the biological activity of the BDNF pro-peptide to induce neuronal growth cone retraction [27]. This group also investigated whether the Val66 and Met66 BDNF pro-peptides adopted different structures to elicit distinct biological activities, and showed that the structural changes induced by the Val66Met substitution confer bioactivity to the BDNF pro-peptide (as only the Met66 BDNF pro-peptide acutely alters neuronal



**Figure 1.** Synthesis and processing of BDNF. The BDNF gene is transcribed to BDNF mRNA, which is then targeted by antisense RNA molecules [76] [86]. BDNF mRNA is translated to proBDNF, which is either released or cleaved to yield mature BDNF (mBDNF) and the pro-peptide. mBDNF activates the TrkB receptor to promote plasticity and recovery from neuronal trauma or disorders. proBDNF interacts with the p75 receptor to induce degeneration, which leads to neurological and neuropsychiatric disorders.

morphology) and exerts this effect through differential interaction with SorCS2, the sortilin-related Vps10p domain sorting receptor [27].

#### 4. Molecular Mechanisms Underlying BDNF and ProBDNF Actions on Neurite Growth

BDNF promotes alternatively the growth or pruning of the axons intracellular mechanisms, which depend on the extent of the activity of TrkB or p75NTR receptors. These mechanisms must feed into the cytoskeletal regulation required for axonal and dendritic growth. BDNF induces branch formation via a combination of local and long-range signals, and the formation and maintenance of axonal branches is tightly coupled with activity-dependent events [28]. BDNF-mediated TrkB activation at the distal axon induces a retrograde Erk1/2 signal, which in turn activates immediate early gene transcription in the nucleus [29]. In addition to the axon growth, BDNF mediates the degeneration of sympathetic axons that express TrkA and p75NTR. The sympathetic neurons do not express the BDNF receptor TrkB; however, BDNF is secreted from active axons to stimulate p75NTR activity. The two receptors in the sympathetic neurons, p75NTR and TrkA, form high affinity binding sites for NGF, a process that depends upon the ratio of the two receptors [30] [31]. Another mechanism underlying the negative control of axonal growth involves components of myelin, which are largely responsible for inhibitory signals during regeneration [32]. BDNF-p75NTR signaling plays a role in the myelin-induced axonal degeneration of sympathetic axons. The myelin/BDNF/p75NTR signaling pathway activates the RhoA ROCK-cofilin pathway [33], which mediates axonal retraction, suggesting that BDNF-p75NTR signaling can potentially lead to axonal degeneration. Indeed, BDNF is a potential regulator of dendritic growth in CNS neurons [34]. We previously reported that BDNF led to increases in the number of primary dendrites [35].

Proneurotrophins inhibit the outgrowth of neurites in basal forebrain cholinergic neurons, dorsal root ganglia neurons, and cortical and hippocampal neurons [19] [36] [37]. The growth-inhibiting activities assigned to mBDNF signaling via p75NTR may also be a consequence of proBDNF rather than mBDNF. Recently, Sun and colleagues showed that proBDNF causes a collapse in neurite outgrowth of primary neurons. An alternative mechanism of proBDNF action on the actin cytoskeleton is the activation of the RhoA/ROCK/cofilin pathway downstream of p75NTR [37].

#### 5. Morphological Alterations within Synapses

Long-term potentiation (LTP) and long-term depression (LTD) are synaptic phenomena expressed at excitatory synapse in the mammalian brain. The synaptic activity-induced LTP/LTD may lead to the morphological changes within synaptic structures. The neuronal growth activity of BDNF [7] raises the possibility that the bidirectional structural changes within synapses could be mediated by BDNF. One hypothesis is opened with a body of observations [7]; “the neuronal growth activity of BDNF” and “the killing effect of precursor neurotrophins”. Indeed, exposure to BDNF causes the refinement of synapses in an activity-dependent manner [38]. Long-term treatment of hippocampal slices with BDNF increases the synapse number and the spine density of the apical dendrites of pyramidal neurons in the hippocampus [39]. BDNF acts on different types of spines depending on the presence of spontaneous synaptic transmission. Moreover, BDNF-mediated regulation of spine formation in the dendrites of hippocampal neurons is controlled by cyclic AMP (cAMP), a signaling molecule involved in late-LTP [40]. Taken together, the spontaneous neuronal activity and the consequent rise in the intracellular concentration of cAMP might be involved in BDNF-dependent spine formation.

The killing effect of precursor neurotrophins may correlate with pathological conditions of the nervous system, and may extend to other aspects of neurotrophin function. A recent study showed that proBDNF levels were decreased in the parietal cortex of subjects with Alzheimer’s disease [41]. Also, proNGF induces neuronal growth cone retraction through the inactivation of Rac and the interaction between p75NTR and SorCS2 [42]. Using cultured hippocampal neurons, we demonstrated that proBDNF reduces the density of dendritic spines, and that the amplitude of spontaneous activity was significantly reduced in proBDNF-treated cultures [19]. These findings show that BDNF could mediate bidirectional structural changes in the spines at the excitatory synapses.

#### 6. The Roles of BDNF and ProBDNF in Synaptic Plasticity

Synaptic plasticity is a crucial mechanism for the processing and encoding of information in the central nervous

system, and impairments in synaptic plasticity are associated with aging and brain diseases. LTP and LTD are forms of activity-dependent synaptic plasticity, which increase or decrease the strength of synaptic transmission, respectively. LTP and LTD are divided into at least two temporally distinct phases: early-LTP/LTD (E-LTP/LTD) and late-LTP/LTD (L-LTP/LTD). E-LTP and L-LTP are parallel to the two forms of memory, short-term memory (STM) and long-term memory (LTM), respectively. In acute slices, E-LTP occurs during the first hour or two of LTP. It is also induced by high frequent tetanus stimulation (100 pulses at 100 Hz), leading to an increase in the strength of synaptic transmission and the activation of signaling molecules. L-LTP persists for longer and involves *de novo* synthesis of synaptic plasticity-related proteins (PRPs).

Given that BDNF expression is predominantly observed in the hippocampal pyramidal cell layer, it raises questions regarding the roles that BDNF and proBDNF play in synaptic plasticity. A substantial body of evidence shows that mBDNF is necessary and sufficient for the regulation of E-LTP and the maintenance of L-LTP through the TrkB receptor, whereas proBDNF promotes LTD by activating p75NTR [43]. High-frequency stimulation favors BDNF release and TrkB-dependent LTP in the CA1 zone of the hippocampus, while low-frequency stimulation activates proBDNF release [44].

The relationship between BDNF action and the balance between excitatory and inhibitory synaptic activity is an interesting issue in the field of synaptic plasticity [45]. Glutamate receptors, including NMDA (N-methyl-D-aspartate) and non-NMDA receptors, play distinct roles in synaptic plasticity. BDNF phosphorylates the NR1 and NR2B subunits of the NMDA receptor and up-regulates the GluR1 subunit of the  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor (in addition to the GluR2/3 subunits). Moreover, mature form of BDNF reduces the excitability of GABAergic inter-neurons by activating TrkB, whereas proBDNF does not affect GABAergic activity [46]. GABAergic function, at least under certain conditions, plays a crucial role in regulating the induction of LTP and LTD [47].

The regulation of hippocampal E-LTP by BDNF was demonstrated using BDNF gene knockout mice and BDNF-scavenging proteins. For example, expression of E-LTP is markedly impaired in BDNF knockout mice [48] [49]. Furthermore, the *in vitro* scavenging of endogenous BDNF by a TrkB-IgG fusion protein [50] reduces the magnitude of E-LTP. Numerous studies indicate that BDNF acutely enhances E-LTP expression by increasing synaptic responses to tetanic stimulation and by enhancing the docking of synaptic vesicles, possibly through changes in the extent of phosphorylation of several synaptic proteins [51]–[53]. To this end, the application of BDNF-scavenging proteins and BDNF blocking antibodies abolish E-LTP after LTP-inducing tetanic stimulation [54] [55]. Moreover, BDNF elicits E-LTP in the dentate gyrus of the hippocampus, thereby increasing the function of NMDA receptors [56] [57].

L-LTP is modulated by BDNF/TrkB signaling. L-LTP expression was inhibited in both BDNF knockout mice and in the presence of a TrkB blocking antibody [58]. The conversion of proBDNF to BDNF by tissue plasminogen activator (tPA)/plasmin is essential for L-LTP [59], and L-LTP is impaired in mice harboring a targeted mutation in the phospholipase C- $\gamma$  (PLC- $\gamma$ ) docking site (not Shc docking site) on TrkB [60]. Initial reports suggested that BDNF and proBDNF have opposite effects on synaptic plasticity [10]. Woo and colleagues showed that proBDNF facilitates hippocampal LTD by activating p75NTR, and that this facilitation requires NR2B activation [43]. Thus, BDNF and proBDNF might modulate synaptic plasticity bidirectionally through TrkB and p75NTR, respectively. The BDNF pro-peptide is cleaved out of proBDNF to produce mBDNF. The pro-peptide was detectable endogenously. However, the biological role of the BDNF pro-peptide is not fully understood. We found that the BDNF pro-peptide itself facilitates hippocampal LTD and elicits endocytosis of the AMPA-type receptor (Mizui *et al.*, in submission), suggesting a novel role for the BDNF pro-peptide in synaptic plasticity.

## 7. Transcriptional Regulation of BDNF Expression by Neuronal Activity and a Newly Emerging Role in the Regulation of BDNF by Non-Coding BDNF Transcripts

Learning, training, and memory formation can alter the amount of *bdnf* mRNA and protein in the hippocampus. For example, the induction of LTP in the hippocampus rapidly and selectively increases the level of *bdnf* mRNA [61] [62], and learning increases hippocampal BDNF, proBDNF, and TrkB protein content [63]. Tongiorgi and colleagues reported that *bdnf* mRNA is transported into the dendrites of hippocampal neurons by neuronal depolarization *in vitro* [64], and by epileptogenic stimulation *in vivo* [65] [66]. These findings suggest that the dendritic movement of *bdnf* mRNA and the local translation of BDNF may promote activity-dependent synaptic

plasticity.

BDNF-induced L-LTP depends on local protein synthesis in hippocampal dendrites [67] [68]. A body of biochemical data showed that BDNF stimulated the dendritic synthesis of different proteins by trafficking mRNA into the dendrites and by increasing the local translation of existing dendritic mRNA. In cultured neurons, BDNF induces the dendritic synthesis of synaptic proteins, which include activity-controlled cytoskeleton-associated proteins (Arc/Arg3.1), Ca<sup>2+</sup>/calmodulin-dependent protein kinase II $\alpha$  (CaMKII $\alpha$ ), Homer2, and Lim kinase 1 (Limk1) [69]-[73].

There are important questions regarding how and where this factor is produced by transcriptional and translational mechanisms in neuronal cells. The first report identified four promoters upstream of the 5' untranslated region (UTR) on rat BDNF gene (termed promoter I, II, III, and IV) [74] and, until recently, additional six (human) and five (rodent) promoters in human and rodent *BDNF* have been identified, respectively (leading to the new nomenclature of *BDNF* 5' UTR promoters termed I-V, Vh, VI-IXa in human and I-IXa in rodent) [75] [76]. Notably, in both rodent and human, *BDNF* gene expression is controlled by multiple activity-dependent (see below) and tissue-specific promoters [72] [73]. In rodent, promoter IV (previously known as promoter III) is activated by the stimulation with neuronal activity. Promoter IV also contains multiple Ca<sup>2+</sup>-responsive sequences and elements to which CaRF and CREB bind, respectively; therefore, the activation of this promoter is positively controlled by various stimuli encoded by Ca<sup>2+</sup> and/or cAMP signals [77]-[80]. Human promoter I is induced by neuronal activity and the activation was controlled by bHLH-PAS-type transcription factor ARNT2-NPAS4 heterodimer. In promoter IV, however, CREB, ARNT2-NPAS4, and USFs are the key factors required for activation of the promoter by neuronal activity, and PasRE- and CRE-like elements regulate human BDNF promoter IX [81]. Furthermore, *bdnf* transcripts differ in their subcellular localization. An *et al.* (2008) recently reported that mouse *bdnf* mRNA with a short 3' UTR accumulates in the neuronal soma whereas *bdnf* mRNA with a long 3' UTR is trafficked to dendrites [82]. It was also reported that spatial segregation of *bdnf* transcripts allowed BDNF to differentially shape distinct dendritic compartments [83].

Several reports suggest that non-coding natural antisense RNA controls the expression of protein-coding transcription in human and mouse (e.g. *Wrap53* and *BACE1-AS*) [84] [85]. The human *BDNF* gene comprises 11 exons and nine functional promoters that are used in specific tissue and brain regions, and the non-coding natural antisense RNAs are transcribed from the *BDNF-AS* (anti-sense) gene within the *BDNF* gene locus. At least four *BDNF-AS* transcripts are co-expressed in the brain, and form RNA: anti-sense RNA duplexes [76]. Furthermore, a recent study found that inhibition of mouse *bdnf-AS* results in the up-regulation of *bdnf* mRNA expression [86]. *Bdnf-AS* represses the transcription of *Bdnf-SENSE* (sense) by altering the chromatin landscape at the gene locus, causing a decrease in the levels of BDNF protein. Oligonucleotides targeting *bdnf-AS* were intra-cerebroventricularly delivered to mice; consequently, *bdnf* mRNA levels in the forebrain regions of these were higher than those in control oligonucleotide-treated mice. Several neurodegenerative and psychiatric disorders are associated with impaired levels of neurotrophins, suggesting that the up-regulation of BDNF has beneficial effects on several disorders. Therefore, pharmacological approaches that target growth factor-related antisense transcripts warrant further study in preclinical model systems of neurological and psychiatric disease, and could complement new drug treatments aimed at shifting the balance between active and repressive chromatin markers in the brain [87].

## 8. The Production and Secretion of ProBDNF

As previously mentioned, BDNF is initially synthesized as proBDNF, which is post-translationally cleaved by intracellular proteases to yield the mBDNF protein [88]. Recently, however, it was mentioned that this processing mechanism plays a key role in determining the cellular functions of the neurotrophin [88] [89].

Two leading groups of Professors Barde and Hempstead recently carried out extensive studies into the effect of the presence and absence of endogenous proBDNF [90] [91]. However, their findings appeared to be inconsistent. Matsumoto and colleagues demonstrated that proBDNF produced by neurons is converted into mBDNF very rapidly, and proposed that proBDNF is the intermediate product. However, Yang and colleagues showed that neurons could produce and secrete proBDNF, and that high levels of proBDNF were present in the postnatal central nervous system. To demonstrate this, they treated primary cultures that were almost free of glial cells with a plasmin inhibitor to block proBDNF proteolysis. They were not able to detect mBDNF, probably because the TrkB-Fc protein added to the culture medium sequestered the mBDNF produced by the neurons. Several

proteolytic enzymes must be present within distinct subcellular and extracellular locations to cleave proBDNF. Thus, when and where proBDNF is processed remains a key question that must be answered to understand the biological actions of mBDNF and proBDNF.

Although BDNF, its pro-peptide and proBDNF is now detectable [25], the intracellular trafficking and processing of BDNF is not fully understood [10]. After synthesis in the endoplasmic reticulum (ER), BDNF needs to be folded correctly and conveyed into the constitutive or regulated secretory pathway for secretions. It has been shown that BDNF-containing large dense core vesicles (LDCVs) are present and undergoes anterograde transport to axonal terminals [25] [92]. On the other hand, in the dendritic side, the activity-dependent translocation of BDNF mRNA into dendrites was significantly found [64].

The pro-domain of BDNF is conserved among vertebrate species, indicating that they have an important role in intracellular processing [93] [94]. Previously, it was demonstrated that Val66Met mutation in the BDNF pro-domain (**Figure 1**) affected the trafficking and secretion of BDNF [12] [95]. However, this result does not reveal the mechanisms by which the pro-domain controls the intracellular sorting of neurotrophins. Interestingly, a putative sorting motif in the mature domain of BDNF was found through homology modeling of BDNF to pro-opiomelanocortin (POMC). Indeed, replacing the two acidic residues with alanine resulted in decrease in the regulated secretion of BDNF as well as an increase in constitutive secretion of BDNF [96]. Additionally, a crucial interaction between the acidic residues in BDNF and basic residues in a sorting receptor carboxypeptidase E (CPE) was evaluated [96], and the activity-dependent secretion of BDNF was significantly decreased in cultured hippocampal neurons prepared from CPE-knockout mice. These reports suggest that the mature domain of BDNF contains a motif essential for sorting from the endoplasmic reticulum and/or Golgi network to the regulated secretory pathway.

What is the role of the BDNF pro-domain in secretion mechanism? There is a report suggesting that the interaction of the BDNF pro-domain with sortilin, a receptor that is localized mainly intracellularly, control the mode of BDNF secretion [97]. Sortilin is co-localized with BDNF in secretory granules in neurons, and interacts with two sub-regions in the BDNF pro-domain. Deletion of these sub-regions significantly reduced regulated secretion of BDNF. Therefore, these results indicate that the BDNF prodomain, in particular, the two sub-regions in pro-domain, is crucial for the regulated secretion of BDNF.

Thus, there are several intracellular mechanisms for controlling the intracellular maturation, trafficking and secretion of BDNF: 1) the interaction of CPE with the mature domain of BDNF for controlling the activity-dependent secretion of BDNF, 2) for facilitating proper folding of the mature domain, the interaction of intracellular sortilin with proBDNF in Golgi and 3) for sorting BDNF to the regulated secretory pathway, the interaction of sortilin with sub-regions in the BDNF pro-domain. Incorrect folding stimulates an accumulation of the protein in the endoplasmic reticulum and/or Golgi network, leading to an inability to target BDNF-containing vesicles to neuronal processes and/or synapses. To prevent this intracellular failure, three intracellular mechanisms might be crucial and promote an appropriate configuration, intracellular trafficking and secretion of BDNF. However, the Val66Met mutation selectively impaired the regulated secretion of BDNF without significant change in constitutive secretion of BDNF [12] [95], showing that at least the prodomain surrounding Val66 does not be important for the binary control of sorting neurotrophins to the constitutive or regulated pathway. Finally, there are reports showing the pro-domain facilitates the proper folding of NGF [94] [98]. In the case of NGF, while interactions of the pro-domain with sortilin might allow correct folding, the absence of a sorting motif on the mature domain of NGF prevents it from entering the regulated secretory pathway.

## 9. Serum BDNF and Its Role in Brain Disorders

BDNF is thought to be a biomarker and potential drug target in patients with mental disorders. Many reports show a relationship between serum levels of BDNF and the onset of mental disorders, in particular depression. Patients with major depressed disorder (MDD) and schizophrenia have low levels of serum BDNF [99] [100]. Eight weeks of antidepressant treatment raises serum BDNF levels in MDD patients [101]. Sen and colleagues independently tested these possibilities and replicated those findings [102]. Patients with post-traumatic stress disorder (PTSD) have significantly higher serum BDNF levels than controls [103]. By contrast, PTSD patients have low plasma BDNF levels [104].

Furthermore, Karege and colleagues measured the concentration of BDNF in the serum, plasma, and whole blood of MDD patients and controls and showed that although the BDNF levels in the serum and plasma of

MDD patients were significantly lower than those of the control group, there was no difference in the whole blood BDNF levels. However, the plasma concentrations of platelet factor 4 (PF4), an important indicator of platelet activity, were higher in MDD patients. There were no significant differences in the PF4 serum levels between MDD patients and the control group. Thus, this report suggests that platelet activity, as indicated by PF4 activity, does not regulate the BDNF concentration in serum [100].

BDNF is abundant in platelets [105], and MDD patients have significantly lower levels of platelet BDNF than controls [106]. However, there are issues that remain unaddressed with regard to BDNF levels in the blood. These include differences in the concentrations of blood BDNF, the correlation between BDNF levels in the brain and blood, the source of blood BDNF, and the mechanisms controlling blood BDNF concentrations. Molendijk and colleagues report that human serum BDNF levels vary according to the season [107]. Epidemiological studies of blood BDNF levels would provide biological insights into clinical psychiatry, and facilitate the development of a more convenient method of diagnosis.

## 10. Conclusion

Here, we reviewed the biological actions and functional mechanisms of BDNF, and, through those descriptions, sought to extend the discussion for the understanding of the pathological mechanisms underlying brain disorders and physiological dynamics within the brain. In spite of the extension of BDNF biology, this knowledge would be expected to help to develop new therapies and aid the diagnosis of brain diseases in the future. We previously demonstrated that a human BDNF polymorphism Val66Met causing amino acid substitution in the BDNF pro-domain impaired activity-dependent secretion of BDNF and human episodic memory. Since then, the intracellular mechanisms for controlling the intracellular maturation, trafficking and secretion of BDNF were extensively elucidated: 1) the interaction of CPE with the mature domain of BDNF for controlling the activity-dependent secretion of BDNF, 2) the interaction of intracellular sortilin with proBDNF in Golgi for facilitating proper folding of the mature domain and 3) the interaction of sortilin with sub-regions in the BDNF pro-domain for sorting BDNF to the regulated secretory pathway. Furthermore, by the development of the specific antibodies, the endogenous presence of BDNF, its pro-peptide and proBDNF has been ensured and their biological activities have been clarified. We expect that these new findings would develop the biology and provide new insights into the mechanical understanding of disordered brains.

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