The role of brain-derived neurotrophic factor (BDNF) in cognitive functions

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ABSTRACT

Nerve growth factor (NGF) was uncovered in near beginning the 1950s which had a growth effect on sympathetic and sensory neurons. In the dorsal root neuron ganglion, the second member of a group of neurotrophic factors widely known as the brain-derived neurotrophic factor (BDNF) appeared. Like other members of the neurotrophin group, such as neurotrophin 3 (NT-3) and NT-4/5, it is explained to have trophic effects on peripheral and central neurons. Since BDNF purification in 1982 evidence of its involvement in development, physiology, and brain pathology demonstrated. BNDF is significant within the molecular mechanism of synapse plasticity regarding neuronal growth and cell survival. The initial step associated with the central nervous system depends on its adaption of synapse transmission, especially in the hippocampus and neocortex. Pathological intensities of the BDNF relationship and synapse plasticity affect sort of situations such as epilepsy and chronic pain sensitization, where BDNF applications can affect therapy in neurodegenerative diseases and neuropsychiatric diseases. BDNF plays a pivotal role in cognitive processes, affecting the advancement and brain structures' motion. Predominantly in the hippocampus and prefrontal cortex, by modulating synaptic neurotransmission, it changes the plasticity and proliferation of neurons through regulation of neuronal migration processes such as differentiation, perseveration, neuronal modification and replacement of synaptic structures. BDNF also affects the development of dopaminergic, serotonergic, cholinergic and GABAergic. BDNF further causes rapid postsynaptic reactions in ion channels and N-Methyl D-Aspartate (NMDA) receptors. BDNF as a vital component in the normal functioning of the brain is one of the neurotrophins that contributes to the development, maintenance of function and healthy neuron cells and cynical plasticity.

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INTRODUCTION

BDNF is a promoter of synaptic plasticity and is articulated allowing to a developmental curve, indicating that dysfunction in the expression, secretion or binding of BDNF to its high-affinity tropomyosin-related kinase B (TrkB) receptor at critical points of expansion may have discrepancy effects on the structure, formation and working as discrete neural circuits.[1]

Nerve growth factor (NGF) was unearthed in the early 1950s due to its trophic (survival- and growth-promoting) effects on sensory and sympathetic neurons. Brain-derived neurotrophic factor (BDNF) that belongs to the second member of the "neurotrophin" family of neurotrophic factors was revealed to articulate survival of a subpopulation of dorsal root ganglion neurons in 1982 and filtered from pig brain afterward. After revealed, other members of the neurotrophin family, for instances neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5) have been portrayed with a different profile of trophic effects on subpopulations of neurons in the peripheral and central nervous systems.[2]

Variety of cells play a crucial role in producing BDNF such as sensory neurons, motor neurons, and immune cells (i.e., BDNF produced by leukocytes will be functioned as communication molecule microglia and astrocytes). At large, BDNF operates as the administer of synaptic plasticity in the peripheral and CNS, where it has a solid protective action stimulating neuronal survival and neurogenesis.[3]

GENE AND PROTEIN STRUCTURE

The BDNF gene (in humans mapped to chromosome 11p) has four 50 exons (exons I–IV) which are linked to discrete promoters, and one 30 exon (exon V) that translates the mature BDNF protein. Eight distinct mRNAs are copied, with transcripts containing exons I–III conveyed predominantly in brain and exon IV located in lung and heart.

BDNF has about 50% amino acid identity with NGF, NT-3, and NT-4/5. Each neurotrophin contains a noncovalently-linked homodimer and comprises of (1) a signal peptide following the initiation codon, and (2) a proregion encompassing an N-linked glycosylation site.[2]

It is synthesized as a 32-kDa precursor (proBDNF) that is able to be administered "intracellularly" to the 14-kDa mature form (mBDNF) by furin, or by extracellular plasmin or matrix metalloprotease-7 once veiled. ProBDNF and mBDNF are expected to generate contrasting physiological responses mediated by the instigation of 2 distinct classes of transmembrane receptors, the p75NTR, and the TrkB, respectively.[4]

Working Mechanism

Neuronal cell growth is moderated by factors such as brain-derived neurotrophic factor (BDNF). BDNF is highly concentrated in the hippocampus, vital in synaptic plasticity, and adds to neurogenesis in the dentate gyrus.[5]

It is also discovered on chromosome 11p13–14 and comprises of one central coding exon that is controlled by numerous promoters to direct site-specific transcription of the mature BDNF protein. However, it is not produced in its mature form; it is eventually first synthesized as a 32 kDa pre-cursor molecule known as proBDNF.[4]

The proBDNF molecule is biologically vigorous and binds with high affinity to the p75 neurotrophin receptor and sortilin as a proapoptotic ligand, though proBDNF may also bind with lower affinity to TrkB receptors. The proBDNF molecule is

proteolytically smitten intracellularly and extracellularly by plasmin, furin, and proprotein convertases to form a 28 kDa sized truncated proBDNF molecule or a 14 kDa mature BDNF (mBDNF) molecule. It shows, however, that this 28 kDa truncated molecule is not an intermediate molecule in the production of mBDNF and characterizes a final peptide product. While the functions of truncated proBDNF remain vague, mBDNF demonstrates a range of neurotrophic functions by initiating the mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (Pl3K), and phospholipase C- (PLC) signaling cascades through binding to the TrkB receptor.[6]

It also travels in the blood, where it materializes to be kept in platelets and is discharged through physical or chemical platelet activation. While BDNF can cross the blood-brain barrier, the extent to which blood-derived BDNF levels are a sensible proxy for BDNF in the central nervous system is imprecise.[5]

BDNF Signal Transduction

Each neurotrophin binds one or more of the tropomyosin-related kinase (Trk) receptors that belong to members of the family of receptor tyrosine kinases. Ligand-induced receptor dimerization marks in kinase activation; subsequent receptor autophosphorylation on multiple tyrosine residues makes specific binding sites for intracellular target proteins. This process then binds to the activated receptor via SH2 domains. These encompass PLCg1 (phospholipase C), p85 (the noncatalytic subunit of PI-3 kinase) and Shc (SH2-containing sequence); stimulation of these target proteins will be able to lead to a variety of intracellular signaling cascades such as the Ras-MAP (mitogen-activated protein) kinase cascade and phosphorylation of cyclic AMP-response element binding protein (CREB).

TrkA binds NGF (with low-affinity binding by NT-3 in some systems); trkB binds BDNF and NT-4/5 with lower affinity binding by NT-3, and trkC binds NT-3. Trk receptors present in both a full-length (trkB.FL) form as well as truncated (trkB.T1, trkB.T2) forms lacking the kinase domain. Although most functions attributed to BDNF are associated with full-length trkB, several roles have been proposed for truncated receptors, including growth and development.[2]

BDNF Gene Regulation

Stimuli, such as neural activity, regulates distinct BDNF 50 exons. For instances, exons I–III, instead of exon IV, rise after kainic acid-induced seizures or other stimuli that escalate activity. Protein synthesis is compulsory for the effects of activity on exons I and II, but not III and IV, triggering the possibility
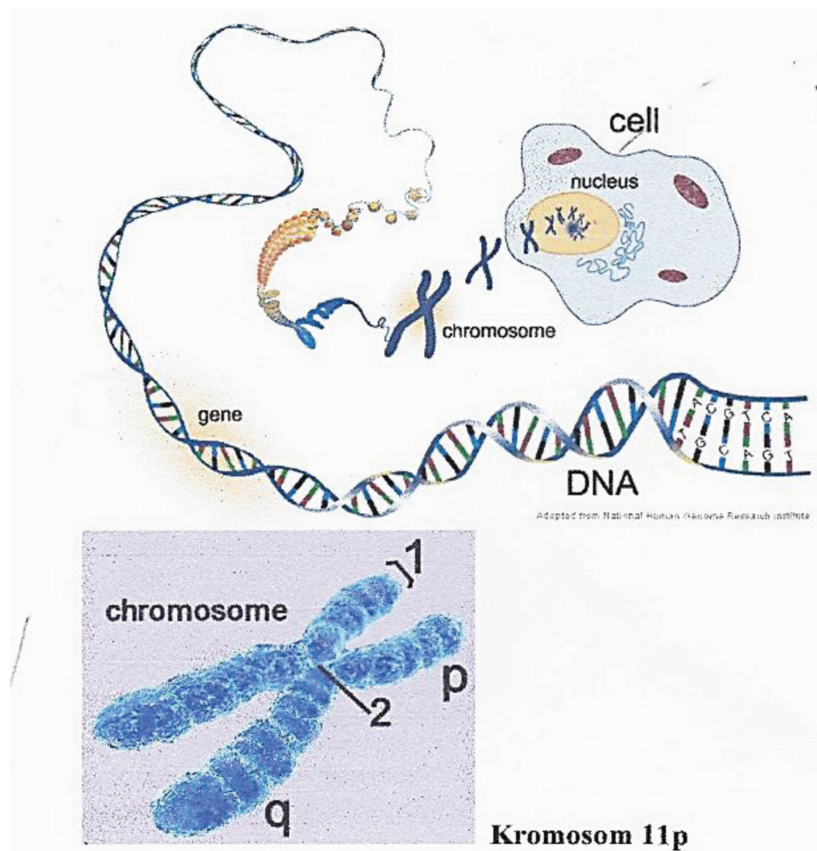

**Figure 1** BDNF Gene and Protein Structure[2]

that the latter act as direct early genes. The transcription factor CaRF stimulates transcription of exon III under the control of a calcium response component, CaRE1. CREB, which can be triggered by various stimuli ranging from activity to chronic antidepressant healing, also moderates exon III transcription. Recent evidence also shows that neural activity prompts calcium-dependent phosphorylation and discharge of methyl-CpG binding protein 2 (MeCP2) from BDNF promoter III to derepress transcription.[2]

The activity of neuronal stimulates transcription instigation of the BDNF gene, which is administered by elevation of intracellular Ca2+ level via NMDA receptors (NMDAR) or L-type voltage-gated calcium channels (L-VGCC). The activity- and Ca2+-dependent transcription of the BDNF gene occurs mainly through exons and. The promoter region of BDNF exon comprises of three Ca2+-response elements CaRE1, CaRE2 (also known as USF-binding element, UBE) and CaRE3 (also known as calcium response element, CRE). CaRE1 is located at 64-73 bp upstream of the transcription initiation site in exon. CaRE2 and CaRE3 are 43-52 bp and 29-36 bp upstream, respectively. The extensive investigation on the regulation of exon IV transcription via CaRE3 has been carried out. 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 bind to CaRE3/CRE to activate the promoter. Also, neuronal activity triggers BDNF promoter I as well as promoter IV. Several transcription factors on the binding sites such as CREB, USFs, myocyte enhancer factor 2D, and NF-κB have been suggested to stimulate BDNF promoter, though the regulatory tools have not been explained.[7]
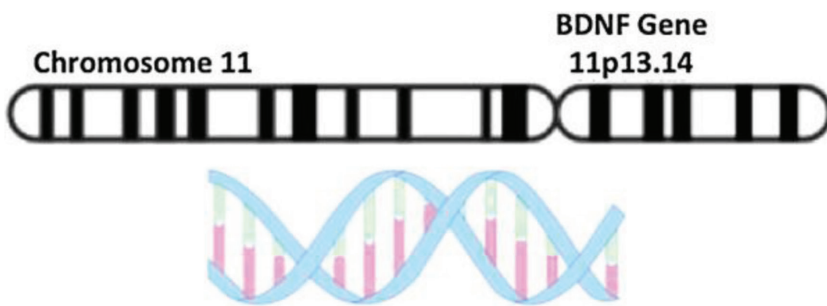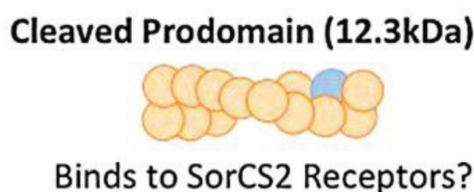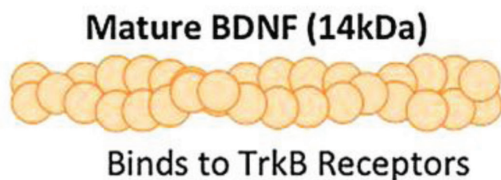
Localization, Transport, and Release

Compared to the factor model of the classical target-derived trophic factor that neurotrophins as NGF are reverted transported, there is now major evidence that BDNF could also be transported anterogradely in the brain. First, its protein is located to nerve terminals, and pathway transection or axonal transport inhibition revokes this terminal expression. Second, more sophisticated studies have revealed that BDNF is linked to dense-core vesicles, which are the main site for neuropeptide storage and discharge from nerve terminals. Third, further functional studies have backed the anterograde transport hypothesis. Fourth, pro-BDNF is traveled from the trans-Golgi network into secretory granules, where it is sliced by prohormone convertase 1 (PC1).[2]

Transport and secretion of BDNF-encompassing vesicles into axons and dendrites have been observed in cultured cortical and hippocampal neurons by visualization utilizing exogenously transfected fluorescent protein-tagged BDNF, while knock-in mice articulating Myc-tagged BDNF presented specific localization of BDNF-containing vesicles at presynaptic terminals in the adult hippocampus. The data suggest that BDNF can be veiled from the cell soma, axon and dendrites of cultured cortical and hippocampal neurons in neuronal activity (depolarization)-dependent manner.[7]

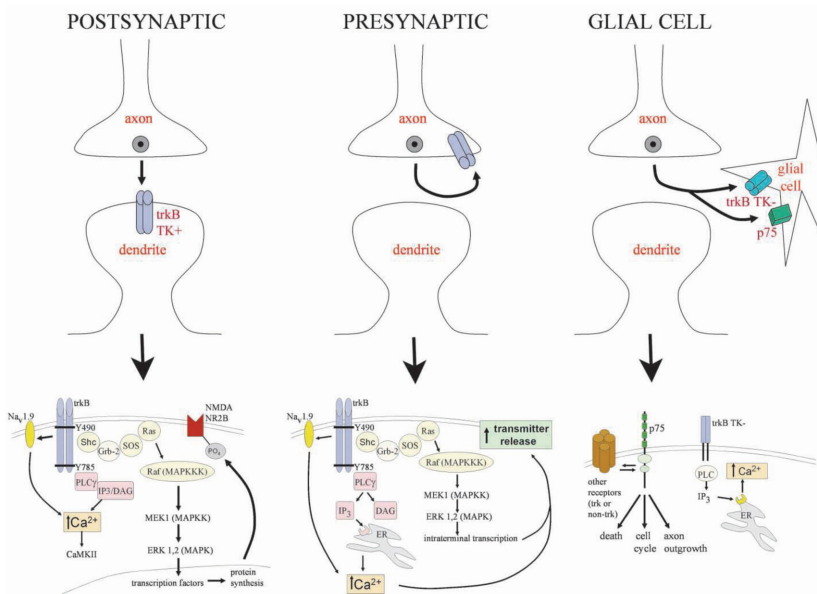**Figure 2**   BDNF Signal through TrkB Receptor[1]

Figure 3 Effect on Synaptic Transmission

BDNF and Its Development

On a variety of neurons, such as dorsal root ganglion cells and hippocampal and cortical neurons, BNDF has survival and growth actions. Several peripheral sensory neurons, especially those in vestibular and nodose-petrosal ganglia, differ on the presence of BDNF due to the BDNF homozygous (-/-) knockout mice is lack of these neurons. Sympathetic neurons and motor neurons, unlike NGF, are not affected. BDNF homozygous (-/-) knockout mice fail to endure in 3 weeks, but heterozygous BDNF knockout (+/-) mice are feasible and display a variety of phenotypes, including obesity, reduced seizure susceptibility, and diminished spatial learning. Interestingly, conditional postnatal BDNF gene deletion and reduction in trkB expression also instigate obesity.[2]

Effect on Synaptic Transmission

The increase of BNDF frequency of miniature excitatory postsynaptic currents (EPSCs) in Xenopus cultures was the result of first studies observing BNDF effects on synaptic transmission. Several studies have scrutinized the actions of BDNF. Overall, BDNF seems to reinforce excitatory (glutamatergic) synapses and deteriorate inhibitory (GABAergic) synapses. Schuman and colleagues showed that contact of adult rat hippocampal slices to BDNF led to an enduring potentiation of afferent input to hippocampal. Follow-up studies have contributed to enriching the explanation on the role of BDNF in LTP. For instances, incubation of hippocampal or visual cortical slices with trkB inhibitors inhibits LTP, and hippocampal cuts from BDNF knockout animals display impaired LTP induction which is restored by restoration of BDNF.[2]

It is also added to the regulation of activity-dependent synaptic plasticity by pre- and post-synaptic tools. BDNF is significant for pre-synaptic vesicle cycling, which is reliant on NMDA (N-methyl D-aspartate) receptor initiation in cultured neocortical neurons of BDNF-knockout mice. This paracrine (retrograde messenger) function of BDNF was later verified, and it appeared that application of BDNF to hippocampal sections restored spine actin polymerization and LTP (long-term potentiation) steadiness in rats. Furthermore, its concentrations not only increased NMDA levels and intracellular calcium levels but also relieved Mg2+ block of NMDA receptors, stimulating long-term changes to the synaptic activity. The declining of TrkB and BDNF secretion also reduced LTP induction. Thus, BDNF is included in NMDA receptor trafficking by uplifting calcium influx, which causes the post-synaptic BDNF release that, in turn, upsurges pre-synaptic vesicle cycling, which enhances LTP and synaptic plasticity.[8]

Align with the reduction in regulated secretion of BDNF, synaptic plasticity in Met66BDNF mice was drastically altered. While the basal glutamatergic transmission remained unchanged in the Met66BDNF animals (no alteration in input/output curve paired-pulse facilitation), both NMDAR-dependent LTP and LTD were significantly reduced.[9]

Neurogenesis

BDNF also plays a role in enhancing neurogenesis. Take an intraventricular infusion of BDNF or adenoviral- induced BDNF activity as an example which the increase of the number of neurons in the adult olfactory bulb, striatum, septum, and thalamus, that can be potentiated by simultaneous inhibition of glial variation of subependymal progenitor cells. Studies of cultured progenitor cells have clarified several of the signaling mechanisms, which seem to involve trkB activation, followed by the instigation of the MAP kinase and PI3-kinase pathways and downstream alteration of basic helix-loop-helix transcription features. Although some studies have established that the main effect of BDNF is on proliferation, other experiments advise a pivotal effect on endurance. The effects of BDNF relies on a previous history of ischemic damage.[10]

Animal studies reveal that the process of positive neuroplasticity may be mediated by brain-based new cell growth (neurogenesis). This reflects in peripheral blood concentration levels of the biomarker brain-derived neurotrophic factor (BDNF).[11]

The adult neurogenesis, stages which neurons are created from neural stem cells and progenitor cells, is also affected by the BDNF. Moreover, despite the process is lively during the prenatal stage and early development, adult neurogenesis has been revealed to take place in multiple brain structures, including the hippocampus and the olfactory bulb. In terms of regulating adult neurogenesis, hence, BNDF has been founded as a firm molecule. For instances, the upsurging levels of BDNF via either intraventricular infusion or adenoviral infection increases neurogenesis.[12]

BDNF and Cognitive Function

BDNF has a significant role in age-related memory impairments and is associated with age-related atrophy of the hippocampus.[13] The former studies have stated that serum BDNF levels are decreased in AD, major depression disorder, and depressive symptoms. A study of neuronal cell cultures discovered that amyloid peptide at sublethal concentrations interfered with neuronal plasticity mediated by BDNF signaling cascade. Neuronally differentiated P19 mouse embryonic carcinoma cells instigated by BDNF presented a steady decrease in tau phosphorylation. However, clinical examinations which report minor serum BDNF levels are challenging to interpret due to the limited data of potential confounders and mixed findings based on patient's age and sex. Hence, there is no normal distribution in serum BDNF level, and this may lead to misinterpretation of BDNF concentration in studies that utilized parametric observation with small sample sizes.[14,15]

Correlational evidence with older adults has revealed that peripheral measures of BDNF (pBDNF) are linked to the hippocampal volume and spatial memory. Erickson et al. performed a cross-sectional analysis, using MRI, enzyme-linked immunosorbent assays (ELISA's), and measures of spatial memory to assess the link between age-related reductions in brain capacity, pBDNF, and memory in older adults. Results showed that older participants had significantly lower concentrations of pBDNF, smaller hippocampal volumes, and poorer performance on spatial memory tasks as compared to younger participants.[16]

Learning Process and Memory

Great interest was developed in BDNF's role in learning and memory as it emerges to contribute in activity relying upon synaptic plasticity. Its action depends on the hippocampus which is necessary for numerous forms of human and animal memory in the long-run. Rapid and selective induction of BDNF manifestation in the hippocampus during contextual learning has been confirmed, and

function-blocking antibodies to BDNF, BDNF knockout, knockout of forebrain trkB signaling or overexpression of truncated trkB in mice damages spatial learning. Another study showed that upregulation of BDNF in monkey parietal cortex related to tool-use learning. A valine to methionine polymorphism at the 50 pro-region of the human BDNF protein was found in humans, to be associated with poorer episodic memory; in vitro, neurons transfected with met-BDNF-GFP demonstrated reduced depolarization-induced BDNF secretion.[17]

Substantial evidence backings a crucial role of BDNF in LTM. The rise in BDNF mRNA level in the hippocampus has been spotted following the acquisition of spatial functions such as Morris water maze and radial arm maze; inhibitory avoidance; contextual fear conditioning; olfactory recognition; and habituated taste aversion memory. Furthermore, the level upsurge of BDNF mRNA in the hippocampus was caused by the spatial retrieval memories, following the conditioning of contextual fear and Morris water maze training. Also, a remarkable rise of BDNF countenance is observed to follow the new form of learning, the extinction of previously developed memories (e.g., accustomed fear) in the prefrontal cortex and amygdala. In addition, over-expression of truncated TrkB damaged the long-run spatial memory, meanwhile over-expression of TrkB caused in improved learning and memory in the water maze, the conditioning of contextual fear, and conditioned taste aversion tests. Unexpectedly, over-expression of BDNF also resulted in modest learning deficits in spatial memory tasks, potentially due to advanced effects of BDNF on the development of multiple circuits, leading to abnormal wiring in the CNS.[9,18]

DISORDERS RELATED TO BDNF

BDNF with Alzheimer's Disease

Some studies show BDNF serum is greater in controls than persons with mild cognitive impairment (MCI), AD or dementia, others indicate the opposite course of association, and some studies even portray no association. Two findings were revealed on BDNF levels. First, AD patients tend to have lower levels compared to the controls in the hippocampus and cortical regions linked to AD in humans. Contrarily, the healthy adult mouse has higher levels of BDNF in brain regions associated with AD[5]

In 1991, BDNF mRNA was found decreasing in the hippocampus of individuals with AD, suggesting that BDNF may contribute to the escalation of cell loss in AD. Different stages of AD involve the damage of BDNF synthesis, and those are able to prompt abnormal accumulation of Aβ and synaptic

dysfunction and then cause cognitive deterioration. Also, BDNF gene polymorphism (Val66Met, 270C/T, 11757G/C) have a significant role in AD pathogenesis, and Met carrier is connected to lower BDNF concentration, certain brain structure atrophy, and damaged cognitive ability.[16]

Preclinical reports have investigated probable pharmacological treatments to raise the BDNF levels in transgenic mice or animals subjected to administration of amyloid β peptide. Treatments with caffeine in AD transgenic animals reveals the increased levels of BDNF, and chronic treatments with caffeine enhanced both BDNF levels and cognitive impairment.[17]

BDNF and Trauma Brain Injury

BDNF, a ubiquitously expressed neurotrophin in the brain, is an intriguing target for TBI intervention research due to its role in neuronal survival, neurogenesis, and plasticity. Meanwhile, in experimental TBI, acute infusions of BDNF did not improve motor, cognitive recovery or neuronal survival postinjury. BDNF is also intriguing marker during TBI rehabilitation due to its important effects on the autonomic nervous system through hypothalamic metabolic regulation and brainstem control of the cardiovascular system. TBI causes a sustained stress response and variation individual stress hormone production which may lead to different outcomes post-injury. Reduced serum BDNF levels have also been connected to mortality in uninjured populations.[18]

BDNF has a higher prognostic value amongst mild TBI subjects compared to the moderate/severe TBI subjects. The dysregulation of BDNF in TBI has been closely observed with equivocal conclusions by some studies utilizing animal models of TBI. Most studies show that the BDNF mRNA expression was measured in brain tissue with reports of upregulation of BDNF mRNA in the hippocampus and cerebral cortex. However, other studies offer alternatives like reduced secretion of brain BDNF protein after TBI, with subsequently increased secretion following experimental TBI treatment. Few studies also measured circulating BDNF in human TBI subjects.[19]

BDNF and Epilepsy

The seizure-induced expression of neurotrophic factors may play a role in the lasting structural and functional changes underlying epileptogenesis. This idea was derived from the discovery that limbic seizures increase the NGF mRNA levels. Recent in vitro and in vivo findings implicate BDNF in the cascade of electrophysiologic and behavioral alteration underlying the epileptic state.

BDNF mRNA and protein are markedly upregulated in the hippocampus by seizure activity in animal models, and infusion of anti-BDNF agents or use of BDNF knockout or truncated trkB-overexpressing mice inhibits epileptogenesis in animal models. Contrariwise, straight application of BDNF induces hyperexcitability in vitro, overexpression of BDNF in transgenic mice may trigger spontaneous seizures and intrahippocampal infusion of BDNF is adequate to induce seizure activity in vivo. The hippocampus and closely associated limbic structures are vital in the pro-epileptogenic effects of BDNF and indeed elevated BDNF expression in the hippocampus is found in specimens from patients with temporal lobe epilepsy. The findings of hyperexcitability associated with BDNF in epilepsy animal models are hoped to lead to novel anticonvulsant or anti-epileptogenic therapies.[10]

The most common medically intractable focal epilepsy is the medial temporal lobe epilepsy (mTLE). About 40% of patients portray that memory impairment and 30%-60% of those undergoing left anterior temporal lobe resection (ATLR) to control their seizures occurrence a substantial postoperative memory decline. BDNF has been investigated as a gene candidate for mechanisms of epileptogenesis regarding its role in modulating excitatory and inhibitory synaptic transmission,.[20]

BDNF and Pain

BDNF also has an essential neuromodulatory role in transducing the pain. Dorsal horn neurons synthesized and markedly upregulated the BDNF in inflammatory injury to peripheral nerves (along with NGF). BDNF acutely alerts nociceptive afferents and elicits hyperalgesia which is revoked by BDNF inhibitors. Central pain sensitization is an activity-dependent increase in excitability of dorsal horn neurons prompting a clinically intractable condition termed "neuropathic pain" in which typically nonpainful somatosensory stimuli (touch and pressure) become exquisitely painful (allodynia). Electrophysiological and behavioral data demonstrated the inhibition of BDNF signal transduction which inhibits central pain sensitization.[2]

BDNF has the capacity to change pain pathways at every level, from the peripheral nociceptors to spinal cord neurons and brain. The unstable pain pattern typically seen in CS pain patients is also assumed to be linked to the dysfunctional stress response system in many of these subjects. Stress typically caused by the increasing of adrenal cortisol production as an end product of the hypothalamus-pituitary-adrenal axis. Cortisol and BNDF levels are, to some extent, related to one another, in a way that upsurges the availability of cortisol

responding to stress is accompanied by reduced BDNF levels.[21]

BDNF and Neurodegenerative Disease

The inadequate supply of neurotrophic factors might cause the degenerative diseases of the nervous system. This condition has generated great interest in BDNF as a potential therapeutic agent. Many reports have documented evidence of decreased expression of BDNF in neurological disease. Selective reduction of BDNF mRNA in the hippocampus has been identified in Alzheimer's disease specimens, although in an animal model upregulation appears to take place in plaque-related glial cells. Decreased BDNF protein has been revealed in the substantia nigra in Parkinson's disease. Profoundly, the latest work has implicated BDNF in Huntington's disease as well. Huntington, the protein mutated in Huntington's disease, upregulates BDNF transcription, and loss of huntingtin-mediated BDNF transcription causes the loss of trophic support to striatal neurons which afterward degenerate in the hallmark pathology of the disease. A recent study has demonstrated that huntingtin typically hinders the neuron-restrictive silencer element (NRSE) involved in tonic repression of transcription from BDNF promoter II. The provision of BDNF or increasing endogenous BDNF production may conceivably be therapeutic if applied in the appropriate spatiotemporal context in all of these disorders.[2]

BDNF is a prime candidate for the treatment of HD, as it has been emerged to prevent cell death and to trigger the growth and migration of new neurons in the brain in transgenic mouse models. In the HD post-mortem human brain, BDNF levels are reduced. Preceding studies have shown BDNF to be a putative candidate for the treatment of HD. BDNF is known to mediate both the survival and function of striatal neurons. In post-mortem HD brain, cortical and striatal BDNF levels are reduced due to the inhibition of BDNF expression levels at the transcriptional level by the mutant huntingtin protein. This reduction in BDNF in the striatum is associated with onset symptom and heightened severity of the disease. Therefore, BDNF is considered a prime candidate to treat the underlying neuronal loss seen in HD.[12]

BDNF and Neuropsychiatric Disease

BDNF signaling may also contribute to affective behaviors. Environmental stresses such as immobilization that induce depression also reduce BDNF mRNA. Contrariwise, physical exercise is associated with decreased depression and increased BDNF mRNA. Prevailing treatments for depression are assumed to target primarily by rising the endogenous monoaminergic (i.e., serotonergic and noradrenergic) synaptic transmission, and contemporary studies have shown that effective antidepressants increase BDNF mRNA and protein. Exogenous delivery of BDNF helps the function and sprouting of serotonergic neurons in adult rat brains, and BDNF-deficient mice are also deficient in serotonergic innervation. Thus, new pharmacologic strategies concentrated on the potential anti-depressant role of BDNF.[2]

BDNF is expected to play a role in BD pathophysiology. Post-mortem studies of BD patients reveal decreased hippocampal BDNF, proBDNF and p75 receptor protein expression. During manic and depressive episodes, the concentration serum of BDNF is decreased which correlate inversely with symptom severity and upsurge with episode recovery. The levels of BDNF serum also decline during later stages of BD illness and are lower in BD patients with a trauma history, independent of symptom severity or PTSD diagnosis.[19]

Data which show an impact of mood stabilizers, have upon BDNF levels, have also been published in various preclinical models. Lithium and valproic acid, commonly prescribed therapies for bipolar disorder, have both displayed induction of BDNF IV in rat primary cortical neurons, and lithium increased BDNF expression in rat hippocampus with chronic treatment. Many studies have also shown central BDNF elevations in rodents that have chronically dosed with prescribed anti-depressants such as fluoxetine and other SSRIs. This has shown that BDNF has been suggested to have a significant role in antidepressant efficacy.[18]

CONCLUSION

Numerous studies have been showcased regarding its role in development, physiology, and pathological conditions in the brain started to be acknowledged since the discovery of the theory of BDNF in 1982. In order to add its role in the development of neurons and the capacity to support cells to survive, BDNF also has a critical role in the molecular mechanism in synaptic plasticity, cognitive function and the learning and memory processes. The changes in principal activity in the central nervous system are presumed to be reliant on BDNF modification in synapse transmission, particularly in the hippocampus and neocortex areas. Pathologic levels derived from synaptic plasticity that depend on BDNF are likely to contribute to few conditions such as epilepsy and pain sensitization, where the function of the tropical nature of BDNF can be the latest therapeutic options for neurodegenerative diseases and even neuropsychiatric disorders.

CONFLICT OF INTEREST

FUNDINGS

AUTHOR'S CONTRIBUTIONS

Dedi Silakarma and Anak Agung Raka Sudewi developed the comceptual framework of the study and preparing the manuscript.

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