Chapter

The Role of Brain-Derived Neurotrophic Factor in Psychiatric Disorders

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Abstract

Brain derived neurotrophic factor (BDNF) is one of the most extensively studied and widespread growth factors in the brain. BDNF and its receptors are the critical factors having multipotent impact on the central nervous system (CNS). The biological function of BDNF primarily mediated by two receptors, tropomyosin receptor kinase B (TrkB) receptor and p75 neurotrophin receptor. BDNF contributes a pivotal role in neuronal and glial development, modulation and maintaining overall synaptic plasticity of the brain; therefore, widely involved in psychiatric diseases. Current hypotheses indicates that abnormal BDNF level, a vital condition for psychiatric and neurodegeneration diseases are mainly due to the disruption of the BDNF-associated signaling cascades. It is, therefore, crucial to understand how BDNF coordinate the psychiatric diseases in the brain. This review begins with the history of BDNF and its biology in brain homeostasis and focuses on several aspects of BDNF signaling. In addition, the review addresses the impact of BDNF level in diverse neuropsychiatric disorders including major depressive disorder, schizophrenia, bipolar disorder, post-traumatic stress disorder and, possible biological mechanisms of BDNF that may shed new insight for future therapeutic use and drug development.

Keywords: BDNF, inflammation, brain homeostasis, brain plasticity, psychiatric disorders

1. Introduction

Brain-derived neurotrophic factor (BDNF) is a neurotrophin classified as dimeric polypeptide regulating a wide array of neuronal activities including but not limited to neurogenesis, neuronal growth, differentiation, excitability, and plasticity. BDNF was originally identified by Barde et al. [1] as a factor from cultured embryonic chick which showed survival of sensory neurons. Soon after its discovery, BDNF was recognized and laid a foundation for neuronal plasticity in the adult brain and further observed its' pivotal role in neuronal activity [2–4]. Subsequently, BDNF was considered for antidepressant treatments therapy as it was shown that neurotrophins promoted the growth and helped in maturation of neurons [5–7]. Interestingly, injection of BDNF in the hippocampus elicited antidepressant-like effects in rodents led to advocate a critical role for BDNF in the setting formulating antidepressant

drugs [8–10]. The line of research identified BDNF and its cognate receptor tropomyosin receptor kinase (TrkB, neurotrophic tyrosine kinase receptor, NTRK2) in the hippocampus and cortex suggested antidepressant drug action into neuronal plasticity [11].

BDNF contributed a key role in the development of the nervous system by regulating neuronal development, growth, differentiation, neurogenesis, synaptogenesis, and synaptic plasticity [12–14]. Moreover, neurodegenerative, and neuropsychiatric diseases appear to be linked with insufficient BDNF level leading to the defects in synaptic plasticity [15, 16]. As a result, strategies to increase the BDNF level in circulation was advocated for therapy in neurological diseases.

This article reviews the current understanding and future directions in BDNF-related research in the central nervous system, with an emphasis on the possible therapeutic application of BDNF in modifying fundamental processes underlying neural disease.

2. BDNF, a neurotrophin family member: synthesis, secretion and function

Nearly three decades earlier discovery of nerve growth factor (NGF) by Rita Levy-Montalcini [17], prompted Yves-Alain Barde searched for a growth factor with similar properties and function like NGF in neurons. The study culminated into a purified protein from pig brain named BDNF [1]. Later, amino acid sequence revealed that BDNF shared a significant homology with NGF along with other members like neurotrophin 3 and neurotrophin 4, together constitute a conserved neurotrophin family [18].

Synthesis and maturation of BDNF is a multistage process, involving formation of several precursor isoforms. BDNF is initially synthesized in the Golgi after cleaving the signal sequence from pre region as a precursor form (pro-BDNF) containing 129 amino acids N-terminal prodomain and a 118 amino acids C-terminal mature domain [19]. The mature domain forms a cysteine knot structure, leading to non-covalent dimerization of the mature domains [20]. When the prodomain is cleaved from intact pro-BDNF, through the actions of proconvertase at a conserved RVRR sequence, the dimeric mature domains are released, and are called mature BDNF, or simply BDNF [21]. Secretion of m-BDNF and pro-BDNF into the extracellular space enables their physiological action (see the diagram, **Figure 1**).

In neuronal cells, both pro-BDNF and m-BDNF are released following cellular membrane depolarization and maintained a dynamic balance [22–24]. Both isoforms are important in neuronal function in the brain, but mature-BDNF (m-BDNF) appeared to offer neurogenesis, neuroprotection, synaptic plasticity, and synaptic function in neurons [25, 26]. The m-BDNF is axonally delivered into axon vesical terminals followed by the secretion into axonal cleft [22]. Mechanistically, BDNF requires to bind its' partner/receptor, Tr, located both pre- and post-synaptic membrane, to complete its function. BDNF is highly conservative and is expressed as a single gene, *Bdnf* transcript and is dynamically regulated and showed cell-specific neural activity. The human *Bdnf* gene, a ~ 70 kb, is in the chromosome 11 consisting of 11 exons (I-IX along with Vh and VIIIh) in the 5′ end and 9 promoters in tissues and brain regions [27, 28]. Apart from the above-mentioned BDNF isoforms, the function of BDNF is potentially affected by single nucleotide polymorphism of methionine (Met) to valine (Val) substitution at 66th position of *Bdnf* gene.

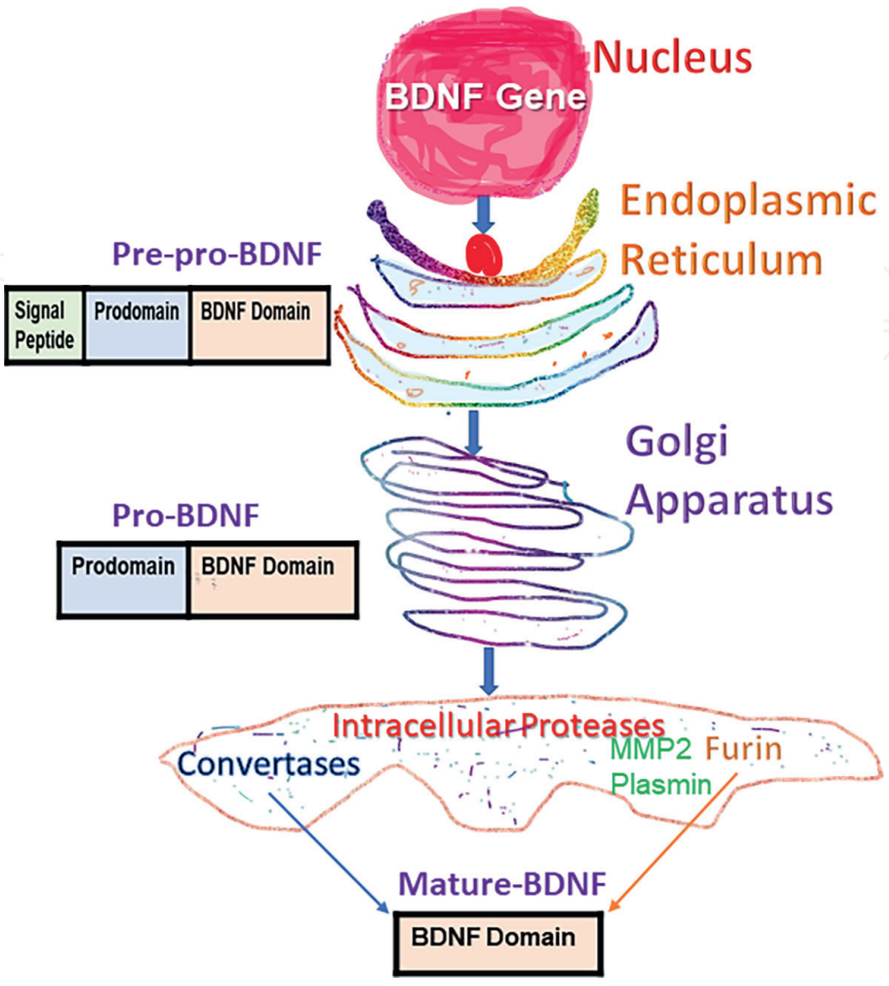

Figure 1.
Schematic presentation of synthesis and maturation of BDNF. In the intracellular pathway, the pre-pro-BDNF precursor molecule is produced in the endoplasmic reticulum and transported to the Golgi apparatus. During intracellular cleavage, the pre-region is removed, resulting in formation of immature isoform of BDNF called pro-BDNF. Finally, the pro-domain is removed and the mature isoform of BDNF, m-BDNF is produced. The cleavage process is mediated by intracellular proteases, convertases, and furin resulting the release of both pro-BDNF and m-BDNF isoforms into the extracellular space. Here, it is further processed by metalloproteinases 2 and 9 (MMP2 and MMP9), and plasmin.

Considering BDNF neuronal function, it is more appreciated as differentiation factor than survival neurotrophin [29, 30]. In addition to synaptic transmission, BDNF elicits long-term potentiation in hippocampus and modulate neuronal circuit function [31]. Moreover, changes in BDNF level in rodent models demonstrated aberrant function in hippocampal regions, including impaired memory, aggression, and hyperphagia [32].

3. BDNF receptors and intracellular signaling

BDNF signals are mediated by TrkB receptor and p75 neurotrophin receptor. BDNF binds with high affinity with TrkB, a tyrosine kinase receptor family, and the p75 neurotrophin receptor (p75 NTR), a member of the tumor necrosis factor (TNF) receptor family and low with p75 receptor. The TrkB is widely expressed in brain including cortex, hippocampus and in spinal cord nuclei [33]. It is noted that the

mature BDNF binds to TrkB whereas pro-BDNF binds to p75NTR. The pro-BDNF/p75NTR signaling primarily promoting synaptic elimination by activating c-Jun N-terminal Kinase (JNK) pathway and triggers apoptosis. Other family members of Trk are TrkA which is specific to NGF [34] and TrkC which binds other neurotrophins [35]. This review will focus TrkB and its' signaling.

Activation of BDNF begins by binding to TrkB, and dimerizing and activating intrinsic kinase cascade before going to autophosphorylation. The BDNF/TrkB complex gets internalized into the neuron and serves as a docking site for diverse signaling platforms, protein phosphorylation and secondary signaling events [36, 37]. Next, the binding of BDNF to TrkB receptor, BDNF/TrkB in complex, leads to phosphorylation and translocation of TrkB into cellular membrane lipid rafts, and activating diverse important intracellular signaling cascades for performing cellular functions that include mitogen-activated protein kinase/extracellular signal-related kinase (MAPK/ERK), guanosine triphosphate hydrolases (GTP-ases) of the Ras homolog (Rho) gene and phospholipase C-γ (PLC-γ), phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathways [38–41]. It is evidenced that PI3K/AKT pathway contributed to synaptic plasticity and cell survival or antiapoptotic activity response by modulating N-methyl-D-aspartate receptor (NMDAR) [40, 42]. Furthermore, BDNF-dependent neuroprotection is mediated via NMDAR/Ca^{2+} synaptic signaling resulting eliminating glutamatergic toxicity and preventing mitochondrial dysfunction and cellular apoptosis [43, 44]. The PLC g-dependent signaling triggers Ca^{2+}-calmodulin-dependent protein kinase (CAMK) and protein kinase C (PKC) to stimulate actin/microtubule synthesis and enhance synaptic plasticity and neuronal fiber growth [40, 45, 46]. The MAPK/Ras signaling regulates neural differentiation [45]. The ERK ½ and cAMP response element-binding protein (CREB) activation are necessary for cytoskeleton protein synthesis for dendritic growth and branching [40, 47]. In summary, the participation of BDNF in several physiological roles in the brain involves different signaling and is pivotal in maintaining a dynamic balance between the stimulus and its' function. A diagrammatic presentation of BDNF receptor and signaling is shown in **Figure 2**.

4. BDNF and brain homeostasis

Homeostasis is a fundamental process and equates to a dynamic balance between interdependent element and the physiological function in the organ of a living system. BDNF plays a significant role in neuronal plasticity in the central and peripheral nervous system [48]. BDNF is expressed throughout the development and adulthood in neurons of the brain and contributing a critical role in many physiological functions. One of the functions is energy homeostasis in the hypothalamus. Energy homeostasis is a complex gets interaction between the brain and peripheral tissues. Neuronal circuitry in the hypothalamus and hindbrain contributes a critical role in orchestrating the peripheral signals associated with energy storage by regulating nutrient intake and energy expenditure. BDNF is synthesized in several regions of hypothalamus including ventromedial hypothalamic nucleus (VMH), the dorsomedial hypothalamic nucleus (DMH), the paraventricular nucleus (PVH) and the lateral hypothalamic area (LH) [49, 50]. In particular, the energy balance is reported to be in the PVH region as evidenced by loss of body weight by injecting BDNF in this region [51]. The report showed that decrease in food intake resulted in increased resting metabolic rate, partly due to upregulation of uncoupling protein 1 (UPC1)

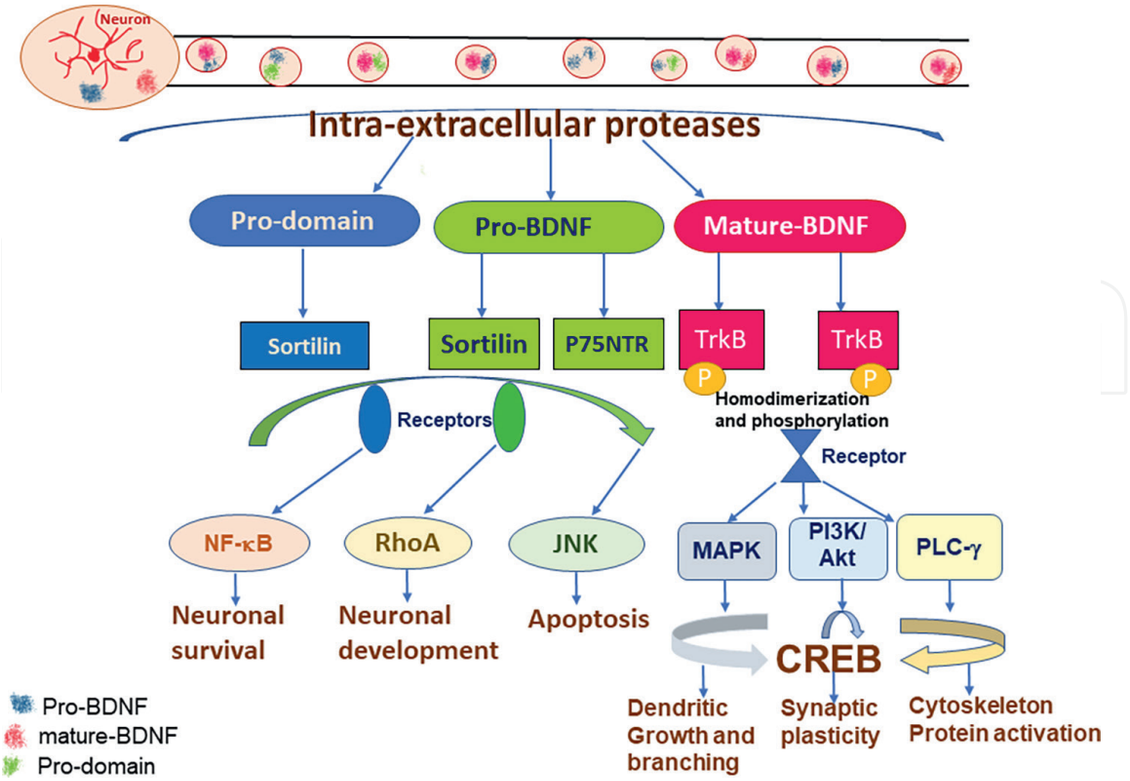

Figure 2.
BDNF signaling cascade. The BDNF is primarily transcribed as a precursor (pro-BDNF) which is later cleaved intra or extracellularly into mBDNF. The pro-BDNF exhibits affinity to sortilin and p75NTR receptors leading to the activation of nuclear factor κB (NF-κB), RhoA and JNK signaling pathways. The functional outcome of theses pathways includes neuronal survival, development, and apoptosis. The mBDNF showed highest affinity towards TrkB receptors. The mBDNF/TrkB complex triggers signaling pathways linked to phosphatidylinositol 3-kinase (PI3K), phospholipase C-γ (PLC-γ) and mitogen activated protein kinase (MAPK) via CREB. The pathways are involved in dendritic growth and branching, synaptic plasticity, and cytoskeleton protein activation.

in the brown adipose tissue [51]. Hypothalamic injection of BDNF promotes switching white adipose tissue to brown adipose tissue via sympathetic neuron activation and accelerates UCP-1 expression [52, 53]. This is an example of the role of BDNF in increasing energy expenditure by modulating metabolic rate and temperature. The data indicated that BDNF enhanced energy expenditure suggesting an anorexigenic function [52]. Another finding attested the role of BDNF in thermogenic regulation in lateral hypothalamus [54]. On the contrary, deletion of *Bdnf* gene caused hyperphagia, decreased locomotor activity and impaired thermoregulation [54]. Moreover, it is evident that mutation in the *Bdnf* gene or its receptor (TrkB) leads to obesity in mice [55, 56]. The *Bdnf* gene mutation data is corroborated with hyperphagia and impaired cognitive functions in humans [57–62]. Together, it is suggested that PVH region is critical in energy balance in the brain.

In addition, BDNF plays a key role in energy management in non-neuronal cells. Selective ablation of BDNF in liver cells in mice showed reduction in hyperglycemia and hyperinsulinemia caused by a high fat diet [63]. Compromised BDNF signaling is also linked with obesity and the metabolic syndrome in humans [64]. Furthermore, BDNF administration reduced serum glucose and insulin in obese *db/db* mice or improvement of glucose tolerance compared to their vehicle treated counterparts [65, 66]. The underlying molecular mechanism may be the interaction of BDNF with glucagon like peptide 1 (GLP1). Gotoh et al. showed that administration of BDNF

decreased the portal glucagon level and did not show any effect on insulin [67]. It is also observed that the intraportal administration of GLP-1 increases BDNF levels in the pancreas and reduces glucagon secretion [67]. Recent study also suggested a role on pancreatic-islet-expressed TrkB to promote peripheral insulin secretion [68]. In addition to BDNF and TrkB, the pro-BDNF receptor, p75NTR is suggested to play a role in glucose homeostasis and insulin sensitivity. Conditional knockout of p75NTR showed improvements of glucose and insulin tolerance in adipose and skeletal muscle [68, 69]. Regarding signaling context of BDNF and metabolic homeostasis, it is yet to be defined which receptor mediated action is more appropriate. The rational lies that pro-BDNF exclusively binds to p75NTR and appeared to show an opposite effect to BDNF-TrkB activity [70]. It established that a single nucleotide polymorphism (SNP) in pro domain of BDNF (Val66Met) is linked with neuropsychiatric disorders in humans and seemed to function through p75NTR [71]. The SNP (Val66Met) variant indicated increased appetite in mice via p76NTR [72], along with alteration of anxiety and anorexic-related behavior [73, 74]. The data may suggest a unique control of energy balance in food intake and anxiety. Finally, the downstream signaling between pro-BDNF and mature BDNF are quite distinct and may appeared to reflect different outcome in neuronal cells. TrkB promotes MAPK/ERK, PI3K, and PLCg1, pathways, while p75NTR promotes JNK and Rho pathways [36, 41, 75–77].

5. BDNF and psychiatric diseases and disorders

We often use the term disorder and diseases in psychiatric illness. There is a subtle difference exists between them however, they are considered as mental illness. The term disease defines an involuntary response of biological, physiological, or pathological consequences of illness and, the underlying cause can be measured. The disorder defines disturbance of normal physical or mental health status and is a collection of signs and symptoms closely associated with specific disease. In general speaking, we can say that all diseases are disorders but not all disorders are diseases.

BDNF is one of the most widely studied neurotrophin signaling molecules in the brain responsible for neurite growth, maturation of synapses during development, and synaptic plasticity. We have discussed BDNF's biology, receptor alignment for signaling events in the brain. Essentially, BDNF-TrkB signaling, and its intermediate proteins contributed a critical role in different phases of synaptic development and neuroplasticity in the brain [78]. Moreover, BDNF regulates learning and memory process in young and adult humans [79]. Therefore, aberrant expression or imbalance in BDNF level and its cognate TrkB receptor are associated with many psychiatric disorders (diseases) and neurodegenerative diseases. In addition, anomaly of BDNF level and signaling are linked to diverse cardiovascular, metabolic, and inflammatory diseases [80–85]. This section will discuss the contribution of BDNF in brain illness or psychological diseases (disorders) including major depressive disorder (MDD), schizophrenia (SZ), bipolar disorder (BD) and post-traumatic stress disorder (PTSD).

6. BDNF and MDD

BDNF is well studied molecule in MDD. Eisch et al reported that an increase level of BDNF in the ventral tegmental area (VTA)-nucleus accumbens (NAc) region

contributed the onset of depression in rats [86]. A following mechanistic study by the same group using viral-mediated mesolimbic dopamine-specific BDNF knockdown determined the pivotal role of BDNF in depression like behavior [87]. Interestingly, reduced BDNF in cornu ammonis (CA3) and dentate gyrus (DG) of the hippocampus and prefrontal cortex (PFC), resulting in depression-like behavior in mice [88]. Furthermore, targeted deletion of BDNF using NSE-tTA x TetOp-Cre line in the VTA area determined that BDNF in the DG was essential for therapeutic intervention as an antidepressant [89]. Similarly, reduced BDNF protein levels were observed in patients with MDD compared with the healthy control [90, 91]. Taken together, these findings suggest that BDNF acts within the VTA-NAc pathway to induce a depression-like phenotype, whereas in the hippocampus and PFC it produces antidepressant-like effects [92]. It is further observed that TrkB, the receptor for BDNF played a role in MDD. Patient with MDD showed elevated level of TrkB compared to the healthy control [93, 94]. However, it is unclear regarding the role of the partners in MDD and may be the focus of future investigation.

Epigenetic modification like DNA methylation is frequently studied in *Bdnf* gene and BDNF exon I and IV promoters. A methylation profile in CpG island of exon I of BDNF promoter showed differential pattern of methylation that can distinguish between major depression vs. and healthy controls and suggested to be a good biomarker for MDD [95]. But exon IV did not show any changes. A similar study reported higher methylation of BDNF exon I promoter in patients with MDD [96]. This study further showed reduced methylation pattern with antidepressants treatment [96]. Interestingly, patient with MDD showed poor treatment response when methylation of CpG site −87 of BDNF exon IV promoter was lacking [97].

An association between BDNF Val66Met polymorphism and MDD is extensively studied. Meta analyses revealed that there is no association between Val66Met polymorphism and MDD (depression) [98–100]. However, few studies have indicated that BDNF Val66Met polymorphism moderated the relationship between stress and depression [100–103].

7. BDNF and Schizophrenia (SZ)

Schizophrenia is a complex heterogenous disease characterized by multiple symptoms such as hallucinations, social avoidance, withdrawal, paranoia, cognitive deficit, and disorganized thought [104]. The role of BDNF in SZ is well studied because BDNF is involved in neurotransmission. In general, BDNF level is reduced in SZ patients [105, 106] and study has shown further that serum BDNF is positively correlated with antipsychotic drug (clozapine) [107]. This is an interesting finding for a therapeutic purpose. However, recent evidence implicated that BDNF mRNA expression remained unchanged in SZ patients compared to healthy control in postmortem brain samples [108].

Reports are emerging regarding epigenetic mechanism in *Bdnf* gene and development of SZ [109]. Epigenetic mechanism encompasses DNA methylation, histone modification, chromatin remodeling and DNA methylation is widely studied in SZ [109, 110]. A significant positive correlation was observed in BDNF gene methylation in patients with SZ compared to healthy controls [111]. Another study showed higher methylation level at BDNF promoter compared to controls [112]. Moreover, a differentially methylated CpGs has been identified in SZ patients of postmortem human brains [113]. Moreover the Val66Met SNP on the *Bdnf* gene has implicated

schizophrenia incidence and a recent meta-analysis provided evidence that there was an association between brain volume alterations and variations on the Val66Met SNP in patients of SZ [114–116]. While studies have shown a positive correlation between reduced level of BDNF and SZ episode, but have not evaluated the role of demographic characteristics such as age, gender, race, and education. Therefore, adequate meta-analysis including demographic factors should be added and warranted further investigation.

8. BDNF and bipolar disorder (BD)

Bipolar disorder is a multifactorial psychiatric disorder characterized by mood fluctuation or instability, depressive, manic episode, and euthymic states [117, 118]. BD makes a distinct category in Diagnostic and Statistical Manual of Mental Disorders, 5th edition into BD I, BD II based on severity of manic episodes [119]. The thirst for potential biomarker in BP is emerging and BDNF is extensively studied in this area. In 2005, Laske et al. first reported reduced BDNF level in the serum of manic and major depressed patients compared to healthy control [120]. Since, then several studies have been conducted in BD and majority of the studies suggested a decline level of peripheral BDNF and considered it as a marker [121–125], however, BDNF levels were not different in euthymia when compared to controls [126]. Furthermore, at transcription level, BDNF mRNA showed downregulation in postmortem brains of both manic and depressive subjects [127, 128]. Antipsychotic drugs like mood stabilizers are frequently prescribed for manic or depressive disorder but the study did not show any improvement of BDNF level in four weeks treatment [122]. However, another study of sixteen-week follow-up, using extended-release quetiapine showed increase in BDNF levels, but decreases with time in a manic/mixed episode [129].

A common genetic variation in *Bdnf* gene, the Val66Met, is established as a common platform linked with reduced secretion of BDNF and is associated with many neuropsychiatric disorders and BD is not an exception. Earlier finding suggested an association between BDNF Val66Met polymorphism and BP [130, 131] but recent meta-analyses showed opposite results [132, 133]. Therefore, more data are warranted to determine the role of Val66Met polymorphism in BD.

Epigenetic modulation is well documented in psychiatric disorders and a positive correlation is shown in CpG methylation in BDNF promoter and BD subjects [134–136]. Alterations in DNA methylation patterns in patients with BD have been extensively investigated for the past years, and possibly recognize a potential biomarker [137–139]. It may be the case that DNA methylation alters the differences in BDNF level and contributed in part in BD, so, targeting BDNF methylation could be strategy to treat BD.

9. BDNF and post-traumatic stress disorder

Post-traumatic stress disorder (PTSD) is a debilitating psychiatric disorder characterized by hyperarousal, re-experiencing, negative emotions, increased anxiety, and fearful memories following exposure to severe trauma [119]. The role of BDNF in PTSD is emerging. In 2009, a small human study was conducted in University of Pisa, Italy where they recruited 18 drug naïve PTSD patients (12 women and 6 men)

with no psychiatric comorbidity and 18 healthy controls in outpatients' facility. The finding showed reduced level of BDNF in the plasm compared with healthy control [140]. War Veterans have continuously suffered from PTSD and cognitive deficit caused by traumatic brain injury. The possible first combat Veteran study aiming BDNF as a marker in PTSD was investigated in Croatia, 2022. The results revealed a marked reduction in plasma BDNF in Veterans with PTSD and mild cognitive impairment compared with healthy controls [141]. The epigenetic influence in BDNF played a critical role in psychiatric disorders including PTSD, as few studies were conducted to investigate DNA methylation in CpG island and Val66Met polymorphisms. A study was conducted using US military service members deployed in the Middle east for Operation Iraqi Freedom (OIF)/Operation Enduring Freedom (OEF) with PTSD showing a significant association between BDNF Val66 Met genotype and traumatic stress in post deployment [142]. Another study of Vietnam war active service members from South Korea showed an association between higher DNA methylation in BDNF promoter in PTSD subjects suggesting a biomarker of PTSD [143]. Interestingly, another study of Vietnam war Veterans by the Australian or New Zealand Defense Force showed that PTSD was associated with decreased methylation at three BDNF CpG sites [144]. Furthermore, it was observed that BDNF Val66Met was linked with differential *Bdnf* expression in the peripheral tissues [144]. Another study supported the finding that methylation of CpG island (CpG1, CpG 7 and CpG 18) in BDNF promoter was closely related to PTSD and suggested as a biomarker to PTSD [145].

Although studies have shown a positive correlation between BDNF level and Val66Met polymorphism in PTSD, there were reports that showed the opposite effect. There was a report showing no relationship between BDNF Val66Met and PTSD in victims of urban violence [146]. In addition, two case studies (small sample size) failed to establish the association between Val66Met and PTSD [147, 148]. Moreover, an elevated level of BDNF was observed in patients with PTSD suffering from trauma [149]. A meta-analysis showed that BDNF level is increased in PTSD patients compared to healthy subjects [150]. A discrepancy was noted in OEF/OIF Veteran study. Recently, Wu et al. reported for the first time that a higher serum level of BDNF in chronic combat PTSD Veterans independent of symptom severity [151]. These reports contradict previous findings.

Together it appeared that genetic variants of *Bdnf* gene and PTSD did not provide any conclusive relationship. The higher and lower value of BDNF were possibly observed due to heterogenous population or low percentage of homozygous Met alleles. More longitudinal and follow-up studies are necessary to make a definitive conclusion.

10. BDNF-miRNAs-psychiatric disorders

The miRNAs are non-coding RNAs, a new class of epigenetic modulators emerging as an attractive molecule for therapeutic intervention. The miRNAs are small 21–23 nucleotides that have the capability to inhibit mRNA and protein resulting in gene regulation [152]. Literature search showed 2844 articles have been published where miRNAs were associated with psychiatric diseases. Interestingly, BDNF-miRNA axis in psychiatric diseases showed 131 reports indicating therapeutic potential of BDNF. Recent studies indicated that several miRNAs target 3′ UTR of *Bdnf* gene modulated the function associated with psychiatric disorders [153–158].

In rodent model of anxiety disorder and schizophrenia, miR-124a regulated anxiety like behavior by targeting *Bdnf* gene [159] and miR-148b is implicated in regulating *Bdnf* gene in methylazoxymethanol acetate model [160]. In mouse model of PTSD, a set of miRNAs, miR-15a-5p, miR-497a-5p, miR-511-5p and let-7d-5p were shown to be associated with *Bdnf* and *FKBP5*, the two key PTSD-linked genes [157]. Moreover, a prolong stress induced rat PTSD model, miR-142-5p is shown to be upregulated in amygdala with a target gene, Npas4 which was reduced [161]. The inhibition of miR-142-5p appeared to reduce the PTSD symptoms by restoring Npas4 and BDNF level suggesting a crucial link between them. In BD condition, a human cohort study was conducted and revealed an association between miR-206 and BDNF polymorphism [162]. Another study showed a panel of miRNAs, miR-7-5p, miR-221-5p and miR-370-5p that are involved in BD II patients by modulating BDNF level [163].

In summary, the data showed promising direction in miRNA-BDNF-axis modulation in psychiatric disorders. However, a strong clinical correlation regarding miRNA-BDNF needs to be established for the development of new diagnostic and therapeutic application to mitigate the cognitive deficit.

11. Conclusion

BDNF is well studied in major psychiatric disorders or diseases. Modern techniques provided us new insights regarding BDNF's role in psychiatric disease progression and treatment responses. The dysregulation of BDNF/pro-BDNF and its receptors TrkBs resulting in a cascade of neuropathophysiological events leading to the impairment of synaptic plasticity and cognitive deficit. Several lines of evidence support the notion that BDNF is nodal mediator across an array of neuropsychiatric disorders. It is further to make a note that many second-generation antipsychotic drugs showed some promise in providing neuroprotection by enhancing BDNF level, however, a definitive conclusion cannot be made based on few medications. Future investigation including using small molecule compound (mimetics or agonists) for enhancing BDNF synthesis and gene therapy using nanoparticle mediated encapsulation of BDNF, is necessary to extend this efficacy at therapeutic standpoint. Peripheral BDNF level is used as a biomarker in many psychiatric disorders, however, in some cases like MDD, it showed disagreement. This may be due to heterogenous nature and epigenetic modifications that contributed significantly for making a universal conclusion. Nonetheless, it helped to pave the way for better understanding the role of BDNF deep inside human brains. Future studies are warranted to uncover the mechanism of methylation and SNPs of *Bdnf* gene for better therapeutic treatment.

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Conflict of interest

The authors state that they do not have any conflict of interest.

Notes/thanks/declaration

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