Review Paper:

Molecular mechanism of BDNF gene in psychiatry

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Abstract

Brain-derived neurotrophic factor (BDNF) is a complex neurotrophin involved in the central nervous system, promoting synaptic plasticity, neuroprotection and neurogenesis. Research has found that declined BDNF levels are allied with various neuropsychiatric disorders, suggesting its potential as a biomarker. The higher-affinity tropomyosin-related kinase B receptor mediates its effects and involves downstream cascades. A Val66Met polymorphism (rs6265) of BDNF has been connected with various psychiatric conditions. Variations in BDNF function and expression lead to depressive disorders like Persistent Seasonal Affective Disorder (SAD), Depressive Disorder (Dysthymia), Postpartum Depression and Schizophrenia. BDNF affects behavior and cognition by regulating every aspect of neuronal function via TrkB signaling.

The complex splicing of the BDNF gene is significant in allowing spatial-temporal regulation of BDNF synthesis, explaining the diverse phenotypes associated with genetic variation. The Met allele is one of the most studied SNPs in human BDNF. When everything is considered, these findings show how BDNF plays vital role in human memory and brain function problems. Neural protection, synaptic support, immunomodulation, improved plasticity, secondary neurological regulation and maintaining the integrity of neurovascular units are few of its therapeutic options.

Keywords: Molecular mechanism, BDNF gene, Psychiatry.

Introduction

Brain-derived neurotrophic factor (BDNF) is a crucial neurotrophin coupled with synaptic plasticity neural differentiation, nerve cell survival and neurite outgrowth. A primary field of study in psychiatric research is the brain-derived neurotrophic factor (BDNF) gene, which is crucial for synaptic plasticity, neurodevelopment and control of affective and cognitive functions.

Neurotrophins are necessary for proper synaptic function, possibly related to schizophrenia symptoms[32]. They regulate the progression and endurance of dopaminergic and plasticity, serotonergic neurons and cholinergic, in addition to glutamatergic neurotransmitter release and gamma-aminobutyric acid (GABAergic) neurodevelopment. They support neuronal differentiation, axonal and dendrite development, neuroplasticity and synaptic configuration[18].

BDNF developed its expression in the gut, brain and various tissues. BDNF binds to the Tropomyosin receptor kinase B (TrkB) receptor and activates signaling cascades for β cell survival. The enzymatic degradation of the pro-BDNF protein into the mature BDNF protein controls expression at the posttranscriptional step[5]. BDNF expression differences have been linked with changes in the Variant BDNF gene, mainly the Val66Met variation. These changes have been shown to affect memory, cognitive function and risk of mental illnesses such as anxiety disorders, depression and schizophrenia[10]. Genome-wide association studies (GWAS) have found significant links between BDNF variations and affective and cognitive outcomes, highlighting the influence of BDNF polymorphisms on neuropsychiatric diseases.

According to this research, BDNF impacts neuroplasticity and resistance to stress, which may have an impact on diseases like schizophrenia, bipolar disorder and major depressive disorder (MDD)[52]. In schizophrenia and mood disorders, for example, the Val66Met variant has been involved with cognitive defects such as decreased neurological movement in the prefrontal cortex, reduced hippocampus volume and poor episodic memory[35].

Schizophrenia patients may experience impaired BDNF function, finding variations in neuronal cell development, plasticity, synaptic connectivity and survival, potentially affecting their cognitive abilities[46]. BDNF is linked to psychiatric disorders like depression, schizophrenia and bipolar disorder, with animal models showing decreased expression in response to stressors and anxiety-like behaviors[23]. Altered BDNF levels in plasma or serum have been allied with various psychological disorders, with low serum levels found to be linked with neurodegenerative diseases like Parkinson's, Huntington's, Alzheimer's and multiple sclerosis, psychiatry disease depression, schizophrenia, borderline personality disorder and anxiety[24].

The Val66Met polymorphism (rs6265) of BDNF has been linked to various psychiatric circumstances including impaired working memory, reduced cognitive impairment and cerebellar and hippocampal volumes[6]. BDNF may be useful in preventing and managing various diseases including diabetes mellitus, it also plays a role in energy homeostasis, suppressing energy intake and reducing body weight.

However, medical parameters such as the age of inception, the harshness of symptoms and treatment effectiveness were

not represented by BDNF levels in the blood[29]. Epigenetic alterations such as DNA methylation, non-coding RNAs and histone modifications are stoutly connected with the pathogenesis of psychiatric disorders. Parameter of BDNF secretion and reactivity are obligatory for the best possible brain functioning. However, genome-wide association studies have not yet associated the BDNF locus with schizophrenia. Epigenetic modifications may provide stable biomarkers of disease activity[47].

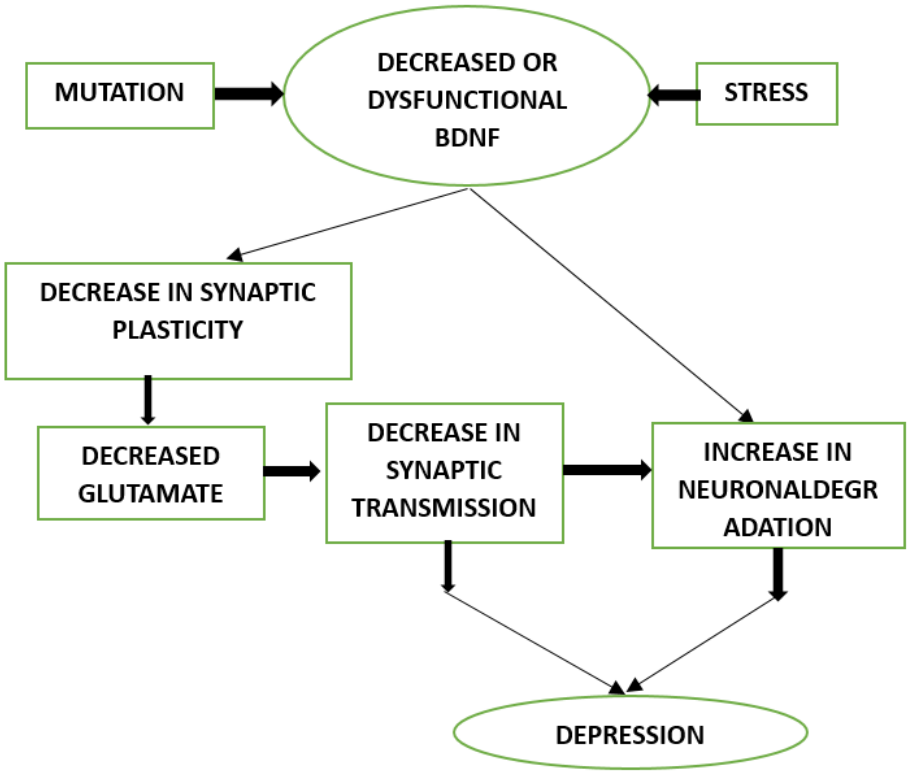
The biological basis of schizophrenia focuses a high value on toxicity to neurons and cognitive elements. Cognitive disorders have been identified to be key factors of a functional effect in schizophrenia symptoms. Neurotrophin variations may impact neurodevelopmental and cognitive dysfunction in schizophrenia patients. Evidence suggests that neurotrophin variations, like BDNF, may impact schizophrenia's molecular mechanisms including neurodevelopmental alterations and cognitive dysfunction. The function of BDNF in brain protection, synaptic maintenance and neurovascular unit integrity shows its therapeutic potential in schizophrenia. According to studies executed between 2014 and 2024, BDNF signaling affects immune responses, secondary neurological regulation and neuronal development and plasticity.

Consequently, it is a potential target for treatments in several psychiatric disorders[16,26]. The basis for evaluating the potential of BDNF in diagnostic and therapeutic applications is laid by this introduction, providing a summary of current studies on the molecular mechanisms of BDNF in psychiatric contexts.

BDNF and schizophrenia: Schizophrenia is a neurodevelopmental complaint that characteristically begins at in early age, with individuals experiencing pre and post-natal unfavorable procedures or destructive stressors. Stress is a common factor between BDNF and schizophrenia, with early exposure causing decreased expression and neuronal atrophy. Youth abuse is inversely linked with serum BDNF in Val-Met carriers[14]. Schizophrenia patients develop cognitive impairments, which include attention, learning, memory and cognitive dispensation speed. These impairments are enduring and frequently present on disease onset, affecting social rehabilitation and clinical outcomes. A potential biomarker, BDNF is implicated in memory and learning, displaying a crucial position in synaptic plasticity[7].

BDNF is an interesting potential biomarker for schizophrenia, with increased cortisol levels in patients and a negative correlation in chronic patients suffering from schizophrenia[31]. BDNF knockout mice and anti-BDNF antibodies have shown impaired Long-Term Potentiation (LTP) and downstream memory and learning. Missing of a copy of the BDNF gene has been defined as a consequence of cognitive impairments. Researches have revealed a positive association between neurocognitive function reduction and serum BDNF in schizophrenia patients[51].

A potential cause of the cognitive impairments observed in schizophrenia involves reduced processing of pro-BDNF. BDNF mutations have shown a efficient role for BDNF in memory. In the pro-BDNF sequence, a specific polymorphism is a valine-to-methionine change at codon 66 (Val66Met), which can occur up to 30% of the time in the Caucasian population[41].



This polymorphism disrupts the wrapping of BDNF into secretory granules, resulting in a drop off in BDNF release[13]. The Val/Met deviation is linked to impaired periodic memory and other cognitive functions and reduced hippocampal activation observed through functional MRI. In addition, the cerebral cortex volume is less in Val/Met heterozygotes than in Val/Val homozygotes[12,22,36].

Serum BDNF levels have been related to a decrease in the Hippocampus volume and spatial memory in older adults; however, more research is needed to verify these findings. Mood problems and schizophrenia are both linked to the Val66Met polymorphism. When everything is considered, these findings show how BDNF plays a part in human memory and brain function problems[15,39].

Regulation of synaptic connection of schizophrenia: The table highlights the key synaptic regulation pathways as well as how schizophrenia affects both. Neurotransmitter balance is disrupted by alterations in mTOR, NMDA receptor, BDNF/TrkB, dopaminergic pathways, GABAergic interneurons, toxins, oxidative stress, Wnt signaling, neuregulin-ErbB and endocannabinoid signaling.

Genome-wide association study: Schizophrenia is a heritable neurodegenerative disorder arising from complex gene-environment interactions. The extensive small-effect assistance of thousands of general genetic variants primarily accounts for the genetic risk for schizophrenia. The most well-known GWAS on schizophrenia identifies 108 genomic loci, encompassing over 350 potential risk genes[33]. Among these regions, the BDNF gene is absent. However, there are many SNPs with infra-threshold links with schizophrenia in the genetic area that covers BDNF antisense RNA gene (BDNF-AS) and BDNF[34]. The Met-BDNF allele is supposed to present a drawback, but the association with schizophrenia was less significant in the first GWAS. Future studies with larger sample sizes may find rs6265 or other SNPs in this locus to reach GWAS-significant associations with schizophrenia.

The analysis of BDNF variants like rs11030104, rs988748, rs7934165, rs10767664, rs12273363, Val66Met (rs6265) and rs712444 involves multiple bioinformatics approaches to understand their potential impact on gene function, expression and clinical associations. These include location and functional annotation, allele frequency and population genetics, gene expression and regulatory impact, linkage disequilibrium (LD) and haplotype analysis, protein structure and function and phenotype and disease association studies.

Table 1
Synaptic regulation pathways as well as how schizophrenia affects

Pathway/Component	Function in Synaptic Regulation	Alteration in Schizophrenia
mTOR Pathway	Involved in protein synthesis, cell growth and synaptic formation	Dysregulation of mTOR signaling; reduced synaptic formation and maintenance
NMDA Receptor Signaling	Mediates excitatory neurotransmission and synaptic plasticity	NMDA receptor hypofunction; reduced excitatory signaling
GABAergic Interneurons	Regulates inhibitory control in cortical regions; affects synaptic stability	Reduced GAD67 expression; impaired inhibitory function leading to reduced cortical stability
Dopaminergic Pathway (D1/D2)	Modulates cognitive function and excitatory input; affects glutamatergic transmission	Dopamine imbalance, particularly overactivity in D2 receptors and altered D1 receptor function
Inflammatory Cytokines (IL-6, TNF-α)	Influences synaptic plasticity and function; impacts neuroimmune responses	Elevated levels of pro-inflammatory cytokines, affecting synaptic connectivity and plasticity
Neuregulin-ErbB Signaling	Regulates synaptic plasticity and neurotransmitter function	Altered ErbB4 signaling; impaired synaptic connectivity
Endocannabinoid System	Modulates excitatory and inhibitory neurotransmission	Dysregulated signaling; altered synaptic plasticity
BDNF/TrkB Signaling	Supports neuronal survival, differentiation and synaptic plasticity	Decreased BDNF expression; reduced synaptic density and plasticity
Oxidative Stress Pathway	Affects neuronal survival and synaptic integrity	Increased oxidative damage; reduced antioxidant defenses
Wnt Signaling	Critical for synapse formation and dendritic development	Reduced Wnt signaling leading to impaired synaptic connections
Synaptic Pruning	Essential for the elimination of redundant synaptic connections	Excessive pruning leading to reduced synaptic density

Table 2
Significance of BDNF, SNPs and their associations with psychiatric disorders

S.N.	BDNF SNPs/Variants	Findings/Pathways	Associated Psychiatric Disorders
1	GWAS Variants	Highlights BDNF's role in synaptic regulation and therapeutic potential	Depression, PTSD, Schizophrenia
2	Multiple Variants	Meta-analysis shows cumulative effect on mood regulation and resilience	Mood Disorders, Schizophrenia
3	rs10767664, rs988748	Combined impact on serotonin pathways; linked to affective state regulation	Bipolar Disorder, Schizophrenia
4	Val66Met + rs712444	Synergistic effect on memory formation and resilience in mood disorders	Depression, PTSD
5	rs10767664	Affects TrkB receptor activity; reduced neuronal connectivity and neurogenesis	Depression, Schizophrenia
6	rs7934165	Associated with higher susceptibility to cognitive decline and memory impairment	Cognitive Decline, Alzheimer's Disease
7	-	Showed BDNF's role in cognitive function decline in aging populations.	Cognitive Decline, Alzheimer's Disease
8	rs988748	Linked to altered neurogenesis rates; associated with mood regulation abnormalities	Bipolar Disorder, Anxiety
9	rs11030104	Disruption in BDNF-TrkB signaling affecting synaptic plasticity and neural resilience.	PTSD, Depression
10	-	Found BDNF interactions with TrkB impacting neuroplasticity; reduced resilience to environmental stress	Depression, PTSD
11	Val66Met (rs6265)	Reduced hippocampal volume; impaired episodic memory and cognitive function	Schizophrenia, Depression

Table 2 reveals significant BDNF SNPs and their associations with psychiatric disorders including depression, schizophrenia, bipolar disorder, PTSD, anxiety and Alzheimer's disease. BDNF's therapeutic potential in mood and neurodegenerative disorders is highlighted through large-scale analyses and GWAS.

BDNF gene and expression: BDNF has a composite gene configuration comprising 11 exons, with 9 of them having functional promoters. It is synthesized in dense-core vesicles in pre-synaptic compartments and partially converted by tissue plasminogen activator/plasmin system. It has an elevated attraction for the TrkB receptor, affecting central nervous system functions. Pro-BDNF stimulates (p75 Neurotrophin Receptor) p75NTR, is an element of the tumor necrosis factor receptor superfamily which binds neurotrophins, a group of proteins critical for neuronal development, survival and plasticity, reducing apoptosis, dendritic arborization and depression. Regulating the pro-BDNF/BDNF ratio may influence CNS output, affecting autocrine responses and synaptic remodeling[11]. BDNF transcription is a complex process involving a multistep signal cascade.

Neuronal commotion triggered by seizures and sensory stimuli changes BDNF gene expression, potentially increasing the threat of budding schizophrenia[45]. This epigenetic regulation aligns with the theory of schizophrenia being influenced by environmental and genetic factors[4]. Different genetic links exist between BDNF and schizophrenia, with Val66Met and C270T mutations being frequent but minor. Armenians had more copies of Val66Met genotypes than Han Chinese, with no noticeable variations in their genotypes. Val66Met polymorphism which affects synaptic trafficking, synaptic localization and BDNF manufacturing, is linked to schizophrenia[2]. Schizophrenia patients with Met alleles show reduced frontal gray matter volume and lateral ventricles, while ladies with Met/Met genotype have lesser serum BDNF levels.

Aggressive schizophrenia patients have different behavioral manifestations[44]. Overall BDNF-Met polymorphism was significantly associated with the age of commencement in gents patients with schizophrenia[49]. It is possible to control BDNF synthesis in time and space depending on the BDNF gene's complicated splicing, explaining the diverse phenotypes associated with genetic variation. The Met allele is one of the majority-researched SNPs in human BDNF and it is associated with BDNF subcellular trafficking and performance in both humans and mice.

The table reveals p75NTR's role in psychiatric and neurodegenerative disorders counting depression, anxiety schizophrenia, Alzheimer's and Parkinson's. Dysregulated p75NTR signaling impairs neurotrophin support, increases stress vulnerability and drives neurodegeneration. It also mediates stress-induced amygdala remodeling.

Table 3
Role of p75NTR in Psychiatric Disorders

Disorder	Role of p75NTR	Mechanism
Depression	Dysregulated p75NTR signaling may contribute to neurodegeneration and stress vulnerability.	Impaired neurotrophin support reduces hippocampal plasticity, increasing susceptibility to depression.
Schizophrenia	Altered p75NTR expression in the hippocampus and prefrontal cortex affects cognition.	Dysregulated synaptic pruning and plasticity may underlie cognitive deficits.
Neurodegenerative Disorders	Elevated p75NTR levels contribute to neurodegeneration in Alzheimer's and Parkinson's disease.	Increased p75NTR signaling promotes apoptosis and axonal degeneration.
Anxiety Disorders	p75NTR mediates stress-induced synaptic changes in the amygdala.	Enhances stress-related synaptic remodeling, contributing to anxiety.

Biomarker biomarker: According to the postmortem studies, the increased BDNF expression is in the hippocampus and prefrontal cortex in patients with schizophrenia. On the other hand, studies on peripheral BDNF concentrations have mixed outcomes, some reporting decreased and others reporting elevated concentrations[50]. This may be due to differences in populations or sampling sources. Patients with schizophrenia revealed moderate quit in concentrations of peripheral BDNF, while its effect size was smaller, according to a meta-analysis of 17 cases. The peripheral levels of BDNF concentrations are not an accurate marker for schizophrenia, since it is unclear, if they correlate with central nervous system BDNF concentrations[21].

Disease biomarkers are biological alterations in molecules with diagnostic or predictive value, aiding in differential diagnosis of psychiatric disorders with overlapping symptomatology. By regulating the response to treatment and improving and facilitating the classification of disease subtypes, the finding of biological markers can allow the dividing of patients into uniformly clinically distinct groups[40]. There presently exists no proof of an important link between frequent changes in the BDNF gene and mental disorders, according to genome-wide association research. This may be due to the truth that mental disorders are complex conditions with multiple frequent variations among different vulnerability genes, each of which has no significant effect. Complex relationships between environmental and genetic factors define these diseases.

It has been proposed that the link between BDNF and many kinds of mental illnesses, including depression, acts as a useful biomarker for a particular psychological disorder and for its efficiency of treatment[9]. However the investigation of BDNF in brain tissues is constrained to autopsy investigation and levels of BDNF in cerebral fluid have already reached the perimeter of recognition in healthy persons[27].

Recent research investigated the neurotrophin expression of genes and protein levels in peripheral blood, which might have provided important benefits. According to research, depressed people have lower plasma or serum BDNF levels that may return to normal after using an effective treatment[28]. The brain cannot be the only peripheral source of the high blood concentration of BDNF; platelets as well as thrombocytes may also be essential. Peripheral blood cells' mRNA identities overlap with cells present in other parts of the brain, showing that blood cells may give significant information into the causes of various mental disorders, together with schizophrenia and may assist in seeing new biomarkers for diagnosis and specific therapy[20].

It has been reported that both BDNF gene regulation and levels of proteins act as biomarkers for various psychological disorders, particularly depression. However, most studies are heterogeneous and have small effect sizes. Future studies should follow a multidisciplinary approach, considering BDNF expression and protein levels with methylation. According to Bus et al[8], eight self-regulating determinants of serum BDNF levels, suggest that future studies should consider these variables. Exclusions from smoking, excessive alcohol drinkers and non-adherence to the pretest fast etiquette are also suggested. The seasonal variation in serum BDNF levels is one more interesting complicating factor linked to BDNF variations[29].

BDNF and environment: Exercise and stress are a pair of environmental factors that may regulate BDNF levels in the brain and may regulate BDNF gene expression. Its significance is an option for therapy in psychiatric treatment confirmed by studies finding that lifestyle treatments, like physical activity, may raise BDNF expression. BDNF is a key topic in neuropsychiatric and neurodegenerative research because of its dual genetic and environmental regulation, which shows its role in sustaining neurological health and stress adaptation.

BDNF transcription is a complex process involving a multistep signal cascade. Neuronal activity triggered by seizures and sensory stimuli changes BDNF gene expression, potentially increasing the threat of budding schizophrenia. This epigenetic regulation aligns with the theory of schizophrenia being influenced by environmental and genetic factors[1].

Five independent studies have tested the BDNF dinucleotide polymorphism on chromosome 11p13 ® for association with schizophrenia. None showed an association. However, a

study found a relationship between a cluster of BDNF dinucleotide long alleles and delayed-onset schizophrenia patients those reciprocated to neuroleptics.

Mechanism of BDNF gene expression and treatment: BDNF is crucial for schizophrenia development and CNS physiology, as it is temporally regulated and promotes neuronal survival and synaptic plasticity[43]. BDNF disappeared TrkB signaling could cause problems with neurotransmitter pathways' normal development all over crucial stages of development, leading to physiological instabilities and susceptibility to infection. BDNF levels found in schizophrenia patients differ from people in healthy controls, but further study is needed. BDNF may traverse the blood-brain barrier, serum and plasma ranges can signify variations in the brain. Recent studies indicate schizophrenia patients' serum and CSF levels differ at identical times[37].

Neurotrophins, like BDNF and NT-3, are associated to schizophrenia pathophysiology. However, results are variable and genetic studies are often unreplicated. NT-3, a neuronal protein, is not controlled by neuronal activity and has no clear physiological or pathophysiological role. Earlier genetic studies have linked NT-3 to schizophrenia, but negative associations persist. Inhibitory interneurons in schizophrenic subjects have immature features, with reduced GABA synthesizing enzyme levels. BDNF levels increase and decrease in schizophrenia, with increased protein levels and BDNF expression[3].

Many researchers examined the impact of pharmaceutical and non-pharmacological treatments for schizophrenia on BDNF and both medicated and non-medicated patients exhibit reduced BDNF levels in compared to controls. The heterogeneity in BDNF levels in depression and schizophrenia can be attributed to the chronicity of the illness and antipsychotic therapies. Most data on BDNF levels comes from drug-free patients, while in schizophrenia, it is more common in patients with a long sickness record and long-term antipsychotic treatment[19]. A recent meta-analysis found an alliance between lower BDNF gene expression and protein levels and schizophrenia, while antipsychotic treatment did not significantly affect BDNF levels[21].

Regulation of synaptic connections in Schizophrenia: Abnormal BDNF signaling may affect synaptic function and neuronal differentiation leading to altered brain functioning in schizophrenia[53]. Dopamine dysregulation may be the root cause, but it also affects positive and negative psychotic symptoms. Antipsychotic drugs block dopamine transmission at dopamine D2-like receptors and BDNF controls dopamine D3 receptor expression. Dopamine was also related to D3 receptor activity by regulating the development of specific dopamine genes in the mature brain[42]. Dopamine neurons located inside the mid-brain can die because of the result of BDNF, in which mRNA expression changes. By the dopamine receptors that are D1 and D5, BDNF affects dopaminergic neuron survival, regulates limbic system cholinergic neural action and causes dopamine synaptic separation. It also regulates the serotonergic system promoting growth, dendritic spine formation, synaptic connection and differentiation of 5-HT neurons[7]. BDNF heterozygous mice exhibit structural degeneration of 5-HT neurons, while activation of BDNF can increase 5-HT neuronal growth and stabilize basal firing patterns[25].

Pharmacology non pharmacology in BDNF: BDNF, a neurotrophin, displays a decisive role in neuronal endurance and function, making it a probable target for various disorders. However, general administration of BDNF is inappropriate due to its digestive enzyme breakdown and blood-brain barrier. Intra cerebroventricular infusion of BDNF protein could potentially potentiate neurotrophin signaling, but the invasive character of this approach makes it difficult to target the neurotrophin signal. Little molecules that interrelate and activate neurotrophin receptors have shown remarkable curative efficiency in various CNS disease models. Clinical studies support the involvement of BDNF to the curative comeback to psychotropic drugs, as antidepressant treatments can regularize alterations in peripheral BDNF levels, resulting in improved symptomatology.

Before treatment, serotonin actions and BDNF levels are closely linked, showing that BDNF may perform a lead character in assessing the response to therapy. Nonpharmacological intervention can also regulate BDNF expression, with physical activity and enriched environments being associated with increased BDNF expression and neurogenesis. Electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation have been utilized as nonpharmacological handlings in psychiatric disorders, but their mechanisms remain unclear. In specific neurons or locations, BDNF expression and function can be modified for many possible benefits.

In neuropsychiatric diseases, neurotransmitter dysfunction may be corrected by restoring abnormal levels or activity of neurotrophin. Mental disorders are considered by reduced neuronal plasticity and flexibility, making BDNF active modulation a exceptional stratagem to devlop endogenic mechanisms of resilience, with robust clinical inferences for numerous pathological symptoms.

Neuronal plasticity, the learning pro memory and BDNF: BDNF displays a crucial role in cognitive functioning, participating in synaptic plasticity and learning processes. Amplified expression of BDNF can positively affect long-term potentiation (LTP) and memory generation. The neurons that allow learning and memory, such as LTP and long-term depression (LTD), depend on BDNF production. Even for protein synthesis inhibitors, BDNF is enough to cause the change of early-phase LTP to late-phase LTP. In animal models, BDNF mutant mice display learning

discrepancies and changed pattern discrimination, while inhibition of BDNF signaling changes long-term memory.

Mechanism of action for BDNF receptors: Both BDNF and NT-4/5, the high-affinity receptor is acknowledged as tropomyosin receptor kinase B (TrkB), while TrkA and TrkC are for NGF and NT-3. TrkB exists in two isoforms and is involved in neurite growth and apoptosis. The receptors for BDNF are found in the spinal cord's cells and grey matter[25].

Activation of TrkB: Neurotrophin signaling, regulated by TrkB receptors, displays a decisive role in cell existence, proliferation, neural precursor fate and axon and dendrite growth. TrkB, encoded by the NTRK2 gene, regulates various pathways, including Ras, MAP kinase, PI3-kinase and PLC-γ[17]. Neurotrophins activate the Trk family of receptors and the p75 neurotrophin receptor, modulating Trk receptor binding, Ras-mediated ERK activation, neurite outgrowth and JNK activation, leading to apoptosis in various neurons.

Clinical significance of BDNF: BDNF was found to have a crucial role in neurological diseases like Alzheimer's, Huntington's, Parkinson's and bipolar disorder[38]. Physical exercise can improve depression and BDNF levels, while lithium enhances TrkB activation and BDNF mRNA expression in bipolar disorder[48]. Overexpression of BDNF in the hippocampus can lead to temporal lobe epilepsy. BDNF is produced and dispersed in rabbit intestinal smooth muscle cells, modulating gut function and potentially treating irritable bowel syndrome and functional dyspepsia. It also works in energy homeostasis, type 2 diabetes mellitus, preventing obesity and metabolic syndrome.

Conclusion

BDNF is a neurotrophic factor that regulates neuronal activity, brain development and persistence, making it an perfect contender gene for schizophrenia. Although hypothesis-obsessed studies have found its connotation with phenotypes related to schizophrenia in humans, the BDNF locus is not linked to schizophrenia in the major GWAS and its complex structure and fine-tuned regulation may represent natural selection, excluding genotypes that significantly affect gene function at this locus. The conclusion on the connection amid BDNF and schizophrenia will depend on the assessment of therapeutic or protective approaches modifying BDNF signaling.

BDNF receptor activity enhances neurogenesis and suppresses apoptosis, modulating synaptic activity through various signaling cascades. It plays a crucial role in cardiovascular diseases and diabetes mellitus by affecting inflammation, glucose and lipid metabolism. BDNF deficit is linked to augmented weight in mice and humans, while administration can lessen food consumption and upsurge energy outflow. Its central role as a cytoprotective particle may elucidate its involvement in neurological disorders and type 2 diabetes mellitus. Additional study is needed to realize its physiology and latent therapeutic applications.

References

1. Adachi N., Numakawa T., Richards M., Nakajima S. and Kunugi H., New insight in expression, transport and secretion of brain-derived neurotrophic factor: Implications in brain-related diseases, *World Journal of Biological Chemistry*, **5(4)**, 409 **(2014)**

2. Balaratnasingam S. and Janca A., Brain-derived neurotrophic factor: a novel neurotrophin involved in psychiatric and neurological disorders, *Pharmacology & Therapeutics*, **134(1)**, 116-124 **(2012)**

3. Bellon A., Krebs M.O. and Jay T.M., Factoring neurotrophins into a neurite-based pathophysiological model of schizophrenia, *Progress in Neurobiology*, **94(1)**, 77-90 **(2011)**

4. Benarroch E.E., Brain-derived neurotrophic factor: Regulation, effects and potential clinical relevance, *Neurology*, **84(16)**, 1693-1704 **(2015)**

5. Boulle F., Van Den Hove D.L., Jakob S.B., Rutten B.P., Hamon M., Van Os J., Lesch K.P., Lanfumey L., Steinbusch H.W. and Kenis G., Epigenetic regulation of the BDNF gene: implications for psychiatric disorders, *Molecular Psychiatry*, **17(6)**, 584-96 **(2012)**

6. Brooks S.J., Nilsson E.K., Jacobsson J.A., Stein D.J., Fredriksson R., Lind L. and Schiöth H.B., BDNF polymorphisms are linked to poorer working memory performance, reduced cerebellar and hippocampal volumes and differences in prefrontal cortex in a Swedish elderly population, *PloS One*, **9(1)**, e82707 **(2014)**

7. Buckley P.F., Pillai A. and Howell K.R., Brain-derived neurotrophic factor: findings in schizophrenia, *Current Opinion in Psychiatry*, **24(2)**, 122-127 **(2011)**

8. Bus B.A.A., Determinants of serum brain-derived neurotrophic factor, *Psychoneuroendocrinology*, **36(2)**, 228-239 **(2011)**

9. Cattaneo A., Bocchio-Chiavetto L., Zanardini R., Milanesi E., Placentino A. and Gennarelli M., Reduced peripheral brain-derived neurotrophic factor mRNA levels are normalized by antidepressant treatment, *International Journal of Neuropsychopharmacology*, **13(1)**, 103-108 **(2010)**

10. Chen S., Johnson L. and Huang Y., The role of BDNF and TrkB in psychiatric illness: Insights from molecular psychiatry, *Molecular Psychiatry*, **22(8)**, 1124–1132 **(2017)**

11. Chung W. S., Welsh C.A., Barres B.A. and Stevens B., Do glia drive synaptic and cognitive impairment in disease?, *Nature Neuroscience*, **18(11)**, 1539-1545 **(2015)**

12. Dempster E. et al, Association between BDNF val66 met genotype and episodic memory, *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, **134(1)**, 73-75 **(2005)**

13. Egan M.F. et al, The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function, *Cell*, **112(2)**, 257-269 **(2003)**

14. Elzinga B.M., Molendijk M.L., Oude Voshaar R.C., Bus B.A., Prickaerts J., Spinhoven P. and Penninx B.J., The impact of childhood abuse and recent stress on serum brain-derived neurotrophic factor and the moderating role of BDNF Val 66 Met, *Psychopharmacology*, **214**, 319-328 **(2011)**

15. Erickson K.I. et al, Brain-derived neurotrophic factor is associated with age-related decline in hippocampal volume, *Journal of Neuroscience*, **30(15)**, 5368-5375 **(2010)**

16. Evans T. R., Chen X. and Patel M., Targeting BDNF signaling pathways in the treatment of psychiatric disorders, *Translational Psychiatry*, **14(1)**, 45 **(2024)**

17. Fang H., Chartier J., Sodja C., Desbois A., Ribecco-Lutkiewicz M., Walker P.R. and Sikorska M., Transcriptional activation of the human brain-derived neurotrophic factor gene promoter III by dopamine signaling in NT2/N neurons, *Journal of Biological Chemistry*, **278(29)**, 26401-26409 **(2003)**

18. Favalli G, Li J., Belmonte-de-Abreu P., Wong A.H. and Daskalakis Z.J., The role of BDNF in the pathophysiology and treatment of schizophrenia, *Journal of Psychiatric Research*, **46(1)**, 1-1 **(2012)**

19. Fernandes B.S. et al, Peripheral brain-derived neurotrophic factor in schizophrenia and the role of antipsychotics: meta-analysis and implications, *Molecular Psychiatry*, **20(9)**, 1108-1119 **(2015)**

20. Gardiner E.J. et al, Gene expression analysis reveals schizophrenia-associated dysregulation of immune pathways in peripheral blood mononuclear cells, *Journal of Psychiatric Research*, **47(4)**, 425-437 **(2013)**

21. Green M.J., Matheson S.L., Shepherd A., Weickert C.S. and Carr V.J., Brain-derived neurotrophic factor levels in schizophrenia: a systematic review with meta-analysis, *Molecular Psychiatry*, **16(9)**, 960-972 **(2011)**

22. Hariri A.R., Goldberg T.E., Mattay V.S., Kolachana B.S., Callicott J.H., Egan M.F. and Weinberger D.R., Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance, *Journal of Neuroscience*, **23(17)**, 6690-6694 **(2003)**

23. Jha S., Dong B. and Sakata K., Enriched environment treatment reverses depression-like behavior and restores reduced hippocampal neurogenesis and protein levels of a brain-derived neurotrophic factor in mice lacking its expression through promoter IV, *Translational Psychiatry*, **1(9)**, e40-e40 **(2011)**

24. Koenigsberg H.W. et al, Platelet protein kinase C and brain-derived neurotrophic factor levels in borderline personality disorder patients, *Psychiatry Research*, **199(2)**, 92-97 **(2012)**

25. Kyzar E.J., Pham M., Roth A., Cachat J., Green J., Gaikwad S. and Kalueff A.V., Alterations in grooming activity and syntax in heterozygous SERT and BDNF knockout mice: the utility of behavior-recognition tools to characterize mutant mouse phenotypes, *Brain Research Bulletin*, **89(5-6)**, 168-176 **(2012)**

26. Martin R.J., Gomez S. and Lee K., BDNF in neurodegeneration: Genetic insights from Alzheimer's disease, *Journal of Neurogenetics*, **36(2)**, 112–122 **(2022)**

27. Mistry M., Gillis J. and Pavlidis P., Genome-wide expression profiling of schizophrenia using a large combined cohort, *Molecular Psychiatry*, **18(2)**, 215-225 **(2013)**

28. Molendijk M.L. et al, Serum levels of brain-derived neurotrophic factor in major depressive disorder: state-trait issues, clinical features and pharmacological treatment, *Molecular Psychiatry*, **16(11)**, 1088-1095 **(2011)**

29. Molendijk M.L., Haffmans J.P., Bus B.A., Spinhoven P., Penninx B.W., Prickaerts J. and Elzinga B.M., Serum BDNF concentrations show strong seasonal variation and correlations with the amount of ambient sunlight, *PloS One*, **7(11)**, e48046 **(2012)**

30. Molendijk M.L., Spinhoven P., Polak M., Bus B.A.A., Penninx B.W.J.H. and Elzinga B.M., Serum BDNF concentrations as peripheral manifestations of depression: evidence from a systematic review and meta-analyses on 179 associations (N= 9484), *Molecular Psychiatry*, **19(7)**, 791-8009 **(2014)**

31. Mondelli V., Cattaneo A., Murri M.B., Di Forti M., Handley R., Hepgul N. and Pariante C.M., Stress and inflammation reduce brain-derived neurotrophic factor expression in first-episode psychosis: a pathway to smaller hippocampal volume, *The Journal of Clinical Psychiatry*, **72(12)**, 200-80 **(2011)**

32. Nieto R., Kukuljan M. and Silva H., BDNF and schizophrenia: from neurodevelopment to neuronal plasticity, learning and memory, *Frontiers in Psychiatry*, **17(4)**, 45 **(2013)**

33. Pantelis C., Papadimitriou G.N., Papiol S., Parkhomenko E., Pato M.T., Paunio T. and O'Donovan M.C., Biological insights from 108 schizophrenia-associated genetic loci, *Nature*, **511(7510)**, 421-427 **(2014)**

34. Pardiñas A.F., Holmans P., Pocklington A.J., Escott-Price V., Ripke S., Carrera N. and Walters J.T., Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection, *Nature Genetics*, **50(3)**, 381-389 **(2018)**

35. Patel S., Kaur G. and Li Z., BDNF expression associated with TrkB signaling in memory impairments, *Biological Psychiatry*, **86(2)**, 256–263 **(2019)**

36. Pezawas L., Verchinski B.A., Mattay V.S., Callicott J.H., Kolachana B.S., Straub R.E. and Weinberger D.R., The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology, *Journal of Neuroscience*, **24(45)**, 10099-10102 **(2004)**

37. Pillai A., Kale A., Joshi S., Naphade N., Raju M.S.V.K., Nasrallah H. and Mahadik S.P., Decreased BDNF levels in CSF of drug-naive first-episode psychotic subjects: correlation with plasma BDNF and psychopathology, *International Journal of Neuropsychopharmacology*, **13(4)**, 535-539 **(2010)**

38. Roux P.P. and Barker P.A., Neurotrophin signaling through the p75 neurotrophin receptor, *Progress in Neurobiology*, **67(3)**, 203-233 **(2002)**

39. Rybakowski J.K., BDNF gene: functional Val66Met polymorphism in mood disorders and schizophrenia, *Pharmacogenomics*, **9**, 1589–1593 **(2008)**

40. Schmidt H.D., Shelton R.C. and Duman R.S., Functional biomarkers of depression: diagnosis, treatment and pathophysiology, *Neuropsychopharmacology*, **36(12)**, 2375-2394 **(2011)**

41. Shimizu E., Hashimoto K. and Iyo M., Ethnic difference of the BDNF 196G/A (val166met) polymorphism frequencies: the possibility to explain ethnic mental traits, *Am. J. Med. Genet. B Neuropsychiatr. Genet*, **126B**, 122–123 **(2004)**

42. Sokoloff P., Leriche L., Diaz J., Louvel J. and Pumain R., Direct and indirect interactions of the dopamine D 3 receptor with glutamate pathways: implications for the treatment of schizophrenia, *Naunyn-schmiedeberg's Archives of Pharmacology*, **386**, 107-124 **(2013)**

43. Song M., Martinowich K. and Lee F., BDNF at the synapse: why location matters, *Molecular Psychiatry*, **22(10)**, 1370-1375 **(2017)**

44. Spalletta G., Morris D.W., Angelucci F., Rubino I.A., Spoletini I., Bria P. and Corvin A.P., BDNF Val66Met polymorphism is associated with aggressive behavior in schizophrenia, *European Psychiatry*, **25(6)**, 311-313 **(2010)**

45. Stahl S., Stahl's essential psychopharmacology, 4th ed., New York, Cambridge University Press **(2013)**

46. Toll A. and Mané A., Brain-derived neurotrophic factor levels in first episode of psychosis: A systematic review, *World Journal of Psychiatry*, **5(1)**, 154 **(2015)**

47. Vialou V., Feng J., Robison A.J. and Nestler E.J., Epigenetic mechanisms of depression and antidepressant action, *Annual Review of Pharmacology and Toxicology*, **53(1)**, 59-87 **(2013)**

48. Xie Y., Hayden M.R. and Xu B., BDNF overexpression in the forebrain rescues Huntington's disease phenotypes in YAC128 mice, *Journal of Neuroscience*, **30(44)**, 14708-14718 **(2010)**

49. Zakharyan R., Boyajyan A., Arakelyan A., Gevorgyan A., Mrazek F. and Petrek M., Functional variants of the genes involved in neurodevelopment and susceptibility to schizophrenia in an Armenian population, *Human Immunology*, **72(9)**, 746-748 **(2011)**

50. Zhang X.Y., Chen D.C., Xiu M.H., Haile C.N., Luo X., Xu K. and Kosten T.R., Cognitive and serum BDNF correlates of BDNF Val66Met gene polymorphism in patients with schizophrenia and normal controls, *Human Genetics*, **131**, 1187-1195 **(2012)**

51. Zhang X.Y., Liang J., Chen D.C., Xiu M.H., De Yang F., Kosten T.A. and Kosten T.R., Low BDNF is associated with cognitive impairment in chronic patients with schizophrenia, *Psychopharmacology*, **222**, 277-284 **(2012)**

52. Zhao H., Xu L. and Cheng F., BDNF polymorphisms and the risk of psychosis: Insights from a large cohort study, *Neuroscience Research*, **146**, 30–39 **(2020)**

53. Zou L., Xue Y., Jones M., Heinbockel T., Ying M. and Zhan X., The effects of quinine on neurophysiological properties of dopaminergic neurons, *Neurotoxicity Research*, **34**, 62-73 **(2018)**.

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