

The Effect of BDNF Gene on Bipolar Disorder

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Abstract. BDNF (brain-derived neurotrophic factor) is a kind of neurotrophic protein, widely distributed in the brain and spinal cord. BDNF is engaged in regulating the growth and migration of neurons, and can promote the repair of damaged neurons. While disorders of BDNF expression can lead to mental diseases such as bipolar disorder. The main way in which the BDNF gene affects bipolar disorder is through BDNF's interaction with TrkB receptors. In addition, BDNF also causes bipolar disorder by affecting the amygdala and hippocampus, promoting neuronal regeneration, and participating in synaptic plasticity. At present, there are still some questions in the field of bipolar disorder and BDNF gene research. The pathological mechanism of bipolar disorder is still unclear, and the clinical application of BDNF has many difficulties. This article reviews the BDNF gene influences the role and mechanism of bipolar disorder and the evidence that BDNF gene causes bipolar disorder, hoping to provide a new direction for the treatment of bipolar disorder.

Keywords: BDNF gene; bipolar disorder; Neuroregeneration.

1. Introduction

Bipolar disorder (BD) is a mental disease that can cause abrupt shifts in a patient's moods and cognition ability. Generally, patients with this disorder show alternation between depression and mania. The depression episode is usually characterized with tired, down, sad, and helpless feelings, while the manic period would give the patient high energy, confidence, and lack of need for sleep. Patients can be diagnosed for Bipolar I disorder, which depressive episodes intersect with manic periods, or Bipolar II disorder, which manic periods followed by depression are less frequent and severe. Patients in all types of bipolar disorder also show decline in cognitive functions like memory ability, language use, and attention. A meta-analysis based on more than 200 thousand participants shows that the lifetime prevalence for Bipolar I disease is 1.06%, and for Bipolar II disease, this number is 1.57%, using DSM-IV criteria [1].

BDNF (brain-derived neurotrophic factor) is a type of neurotrophic protein first found in the pig brain in 1982 by Barde et al. It is broadly dispersed throughout the central nervous system and generated in neurons and glial cells, and the cerebral cortex and hippocampal regions possessed the largest concentrations. On human chromosome 11, the BDNF gene contains nine promoters that control the expression of several BDNF transcripts, all of which encode the identical BDNF protein. The two types of BDNF found in the body are the precursor BDNF (pro-BDNF) and the mature BDNF (m-BDNF). To carry out biological functions, the BDNF gene is first transcribed and translated into pro-BDNF, which is subsequently cleaved into the m-BDNF protein by serine protease in the Golgi and endoplasmic reticulum. Pro-BDNF can act biologically in a variety of ways by being directly secreted into the cell via neural synapses in addition to being a precursor form of BDNF. There is a dynamic balance between the different forms of BDNF, and the ratio of pro-BDNF to m-BDNF fluctuates depending on the particular stage and location of brain development. Pro-BDNF and m-BDNF are both released in neuronal cells after cell membrane depolarization. Pro-BDNF has higher concentration in the early stages, but m-BDNF takes over when the cell is more mature. Therefore, it is thought that a key element in controlling brain function throughout early development is the ratio of pro-BDNF to m-BDNF. On the other hand, m-BDNF is critical for neuroprotection and synaptic plasticity following maturation. Among its many roles in the nervous system, BDNF is crucial in



controlling the survival and differentiation of neuronal populations while they are developing. It can promote the differentiation and development of nerve cells and protect nerve cells from injury or disease. Additionally, BDNF has a significant impact on brain architecture, function, development, and synaptic plasticity. The biological activity of neurons can be enhanced by BDNF, which can also encourage the development of axons and dendrites as neurons expand, control the release and uptake of neurotransmitters, take part in the maturation of synapses, and control synaptic plasticity.

At present, although the research on bipolar disorder and BDNF gene has made some achievements, there are still many problems in this field. The pathological mechanism of bipolar disorder is not well understood. Most scholars believe that neuroendocrine disorders and neurocyte abnormalities cause nervous and mental system disorders, and then lead to bipolar disorder, so patients with bipolar disorder often show abnormal neurocytes. BDNF can aid in the repair of injured neurons and is involved in controlling the growth and migration of neurons. In addition, the clinical application of BDNF has been difficult. The most challenging issue for BDNF is how to effectively treat its extremely short half-life, which severely restricts the efficacy of recombinant protein and can result in protein degradation, immune reaction, and failure to cross the blood-brain barrier in large quantities. A range of medication administration techniques were investigated in the preclinical investigation, including intravascular perfusion or intracerebral injection, viral gene therapy delivery methods, liposome-encapsulated pharmaceuticals, intravenous administration of monoclonal antibody conjugated drugs, etc. Each technique, though, has drawbacks, and there isn't yet a safe and efficient way to distribute drugs in clinical practice.

Nowadays, neuropsychiatric diseases such as BD are paid more and more attention. People are aware that neurological diseases such as BD have a huge impact on people's quality of life, and they are actively seeking better treatments. The pathological process of BD is accompanied by the change of BDNF expression level. Therefore, determining the relationship between BDNF and BD is of great significance for finding new therapeutic directions. In summary, this paper mainly introduces the effect and mechanism of BDNF on BD and four factors of BDNF on BD, and discusses the treatment of BD by gene editing key genes combined with CRISPR technology.

2. BDNF Gene Influences the Role and Mechanism of Bipolar Disorder

The connection between BDNF and the tropomyosin-related kinase B (TrkB) receptor is crucial to BDNF's function in the central nervous system. The majority of BDNF's known actions are controlled by TrkB, which is located on the dendrites, axons, and cell bodies of excitatory and inhibitory neurons. The major phospholipase C-1 (PLC-1) and Ras-mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinases (PI3K)-AKT signaling pathways are activated when BDNF and TrkB combine. Phosphorylated cAMP-response element binding protein (CREB) in the nucleus is then signaled by the activated pathways. The transcription factor CREB can control the expression of BDNF and is intimately linked to BDNF expression. TrkB and BDNF work together to control at least three intracellular signaling pathways. The first one is the phospholipase C (PLC) route that activates protein kinase C (PKC). In the second, Ras can be activated by mitogen-activated protein (MAP) kinases, which can have subsequent effects. Phosphatidylinositol-3 'oh-kinase (PI3K), a third signaling route, promotes the AKT-mTOR pathway [2] (figure 1).

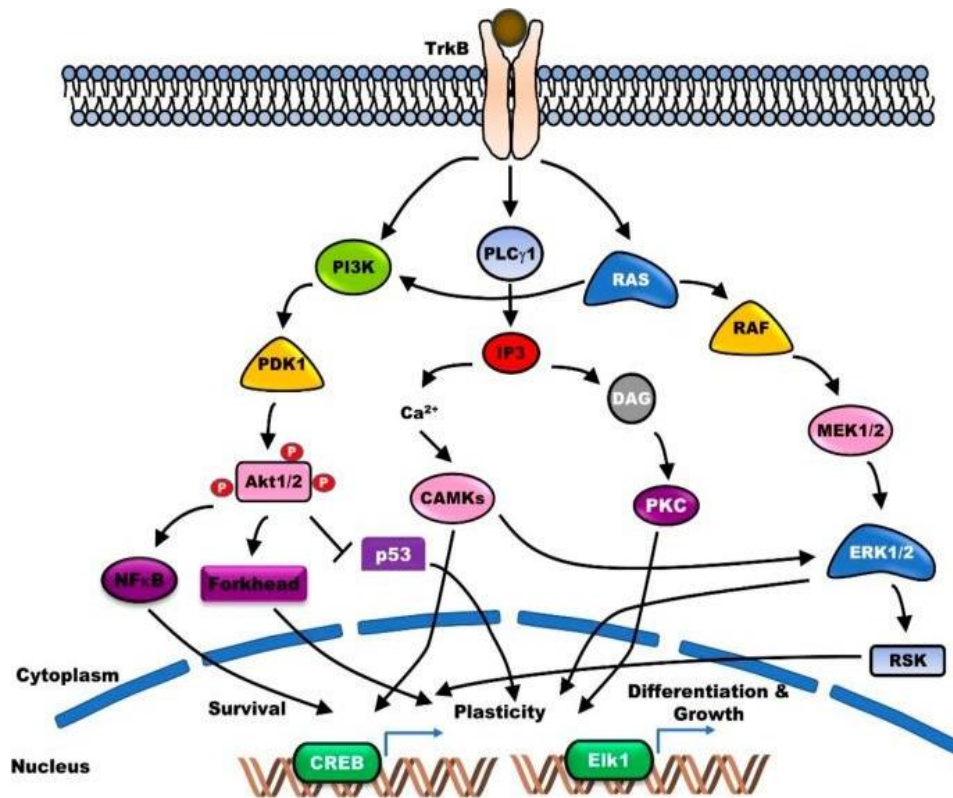


Figure 1. BDNF and TrkB signaling pathways [16].

The neuronal migration and growth are regulated by BDNF, and it can promote the repair of damaged neurons. While disorders of BDNF expression can lead to mental diseases such as bipolar disorder. The BDNF gene has been identified to have single nucleotide polymorphisms (SNPS), the most recognizable of which is in the pre-BDNF region and changes codon 66 from a valine (val) to a methionine (met, i.e. val66met) [3]. The impaired hippocampus function seen in people with the val66met SNP is considered to be caused by problems with intracellular transport and actively-dependent BDNF production. The val66met SNP is also thought to play a role in neurological disorders such as bipolar disorder. The study found human-like symptoms in mice genetically modified to carry the human BDNF val66met allele. These mice showed symptoms of bipolar disorder such as anxiety and depression during the experiment [4]. Additionally, the hippocampus and the medial prefrontal cortex (mPFC) of these mutant mice displayed decreased synaptic plasticity and synaptic transmission. Another SNP, BE5.2, has been discovered in the cis-regulatory area that regulates the activity of the BDNF promoter in the hippocampus, cortex, and amygdala [5]. This SNP has also been connected to mood disorders and decreases the induced release of BDNF in the cortex and hippocampus. However, higher BE5.2 caused BDNF release in the amygdala, which may offer explanation for this SNP's association with the onset of bipolar disorder.

3. Evidence that the BDNF gene causes bipolar disorder

3.1. Amygdala

The amygdala is an area of the brain that processes emotions, especially fear, anxiety, and other aversive emotions, while symptoms of bipolar disorder also include uncontrollable depressive episodes and mood changes. Structurally, some studies have supported that patients with Bipolar disorder have been discovered having an enlargement in the amygdala. However, it is suggested that BD is associated with an amygdala volume decline in adolescents. In addition, a study designed to explore the effects of lithium, a common drug used to treat BD, also showed that the left amygdala was significantly smaller in non-Li BD patients than in healthy controls [6]. Regarding the function of amygdala, current research has shown that amygdala and its related circuit in BP patients might be

hyperactive and dysfunctional. Amygdala related functions like facial recognition, emotional memory enhancement, and subjective perception of emotional impacts are also impaired in those patients. The impairments might differ in different emotional episodes. In the manic state, the parts that are responsible for motion and internal sensations of amygdala are more active, and especially in the right amygdala, the connection between amygdala and anterior cingulate cortex is weaker, which both the connection between two brain parts and the right amygdala are related to emotion controls. These findings could explain the increase in activity and energy and weaken of emotion control ability in manic states of BD. During depressive states, the left side of the amygdala showed an increase in connection with the Default Mode Network, which is responsible for internal thoughts. This suggests that there might be a stronger association between emotion processing in amygdala and negative thoughts in DMN during depression episodes.

BDNF level is highly related to amygdala related functions. The val66met single nucleotide functional polymorphism is likely to decrease the production of BDNF protein and impair amygdala functions. A study examined major depressive disorder adolescents who have val66met variant of BDNF gene shows a significant increase in amygdala activation when exposed to emotional stimuli, and in adult with borderline personality disorder patients, the val66met genotype would lead to constant activation of amygdala when repeatedly exposed to adverse pictures [7]. The hyper-activation of amygdala associated with BDNF gene mutation aligned with the discoveries related to amygdala function and Bipolar disorder. Patients with higher levels of BDNF methylation had a stronger amygdala response to negative emotions, blocking gene expression. Interestingly, in contrast with previous research, this study shows that although val66met variation influences the methylation process, it does not directly affect amygdala reactivity. In addition, BDNF also influenced the cognitive ability related to amygdala. Research shows that the Pavlovian fear conditioning, pairing a neutral stimuli with an aversive one, will lead to an increase in expression of BDNF gene and activate Trk receptors. The Val66Met mutation has also been found related to reduction in fear learning and emotional memory. Moreover, the BDNF gene is related to fear extinction. Humans and rodents with the Val66Met variants both show impaired extinction learning that might be actualized during their development. Another study shows that BDNF level and activation of TrkB largely contribute to the enhancement of long-term potentiation, a crucial learning mechanism in the brain, in the amygdala region. External input of BDNF will also lower the threshold for LTP. These cognitive deficits in amygdala related areas elicited by BDNF gene disorder might be able to explain the cognitive dysfunction in BP patients.

3.2. Hippocampus

The hippocampus, another brain region associated with bipolar disorder, is responsible for the formation and retrieval of long-term memories and is also responsible for emotional control and emotion regulation. Most researches have confirmed a reduction in hippocampus volume is related to BD. In a research examination on severe psychological disorders, specifically major depression, bipolar disorder, and schizophrenia, the left hippocampus volume of all diseases are lower than the healthy controls. The left hippocampal gray matter volume is highly related to executive functions and working memory. Yet, other studies comparing schizophrenia (SZ) and BD patients emphasize the smaller right side hippocampus in BD patients compared to control and SZ. Given that pre- and perinatal problems are risk factors for BD, many studies have shown that BD patients with perinatal asphyxia and severe obstetric complications are related to small size of hippocampus. The previously discussed article which investigated lithium effects to BD also discovered that non-Li BD patients have significantly reduced hippocampal volumes. Contrast with popular findings, there was one study that showed an increase in hippocampus gray matter volume compared to HCs in BD patients who have experienced childhood trauma [8]. In addition to the size of the hippocampus, BD patients have fewer parvalbumin-expressing cells and somatostatin-positive cells in the hippocampus. The two cells separately help memory formation and mood regulation, which are impaired in BD cases. The same study also found reduction of size in many other neurons in the hippocampus of BD patients than healthy people, which might be caused by genetic factors.

BDNF gene is also related to BD and hippocampus volume and functions. Generally, BDNF gene mutation, especially the val66met SNF, is connected to impaired episodic memory and smaller hippocampal volume. A fMRI imaging studies shows that BD patients with val66met BDNF variant have a reduction in hippocampus volume compared to healthy controls and patients with MDD. The subjects also show deficits in cognitive functions like language usage and comprehension as well as memory abilities in cognitive tests. Research shows that BDNF val66met carriers who have experienced severe childhood trauma display a great deficit in cognitive functions compared to val66val carriers. [9]. In the same study, researchers also found association between intense childhood sexual abuse in met carriers and reduction of right hippocampal volume [9]. The relationship between hippocampus, bipolar disorder, and BDNF gene also shown in study about lithium medications. Lithium has been used to treat bipolar disorder since the discovery of its effectiveness in repressing manic moods. In a study using rodents, medication of lithium would augment BDNF gene expression in the hippocampus and prefrontal cortex. Both areas are highly related to emotion control, suggesting that hippocampus may be essential to mood stabilizing in BP patients.

3.3. Promote neuron regeneration

In the central nervous system, BDNF is crucial for the regeneration, proliferation, and repair of neurons after nerve damage. It does this primarily by encouraging neural stem cells to differentiate into neurons, encouraging the growth of neuronal processes, and raising the differentiation and migration of neuronal precursor cells. The high-affinity TrkB receptor and the low-affinity p75 receptor are two of the receptors that BDNF affects. Lachyanka et al. experimentally proved that 80% of neural stem cells expressed p75 receptors and 60% to 70% expressed TrkB receptors, which to some extent suggested that BDNF had a non-negligible impact on the differentiation, maturity and survival of neural stem cells [10]. BDNF can improve the rate of differentiation of neural stem cells into neurons, such as encouraging unshaped neural stem cells to grow into neurons or encouraging the expression of neuronal antigen during the differentiation of neural stem cells, promoting the growth of neuronal precursor cells derived from neural stem cells, and promoting the survival of neuronal precursor cells and differentiated mature neurons. Therefore, BDNF not only plays an important effect on the conversion of neural stem cells into neurons, but also on the subsequent growth and maturation of developing neurons. Numerous studies have demonstrated that BDNF and its downstream pathways play a variety of roles in the central nervous system and are connected to the formation and progression of neurological disease like bipolar disorder. In the onset and progression of neurological disorders, BDNF has neurotoxicity, and it can also produce A synergistic toxic effect with amyloid β -protein ($A\beta$), increasing the neuronal damage of patients, thus leading to further deterioration of the disease.

3.4. Involved in synaptic plasticity

Synaptic plasticity refers to the ability to change the connection and transmission efficiency between synapses under the condition of external environment change. This change is persistent, which is reflected in the synaptic morphological structure and synaptic function. In the rat hippocampus, Tyler et al. studied the physiology and morphology of CA1 pyramidal neurons and discovered that BDNF increased dendritic spine density regardless of synaptic transmission level, and that the morphology of individual BDNF-induced dendritic spines demonstrated significant differences in different levels of spontaneous synaptic activity [11]. It is suggested that BDNF regulates synaptic shape and function to maintain healthy neuronal connection between excitatory synapses in the hippocampal nucleus. Chronic mild unforeseeable stress (CUMS) can induce depression-like behavior in rats, accompanied by decreased dendritic spine density and BDNF expression levels in the CA1 vertebrae of the hippocampus. Studies have shown that exogenous BDNF injection into the stressed rat hippocampal CA1 region has been found to reverse depressive-like behavior brought on by CUMS and stop the loss of dendritic spines in spinal neurons. In contrast, exogenous proBDNF injection in the CA1 area of neonatal rats led to depression-like behavior and a decline in dendritic spine density. These findings suggest that the degree to which BDNF and proBDNF are expressed influences the change in

dendritic spine density [12]. BDNF exerts its antidepressant effect by increasing total dendrite length and dendrite spine density to improve neuroplasticity. Synaptic plasticity has recently been discovered to be intimately associated with bipolar disorder. Synaptic plasticity was affected by BDNF expression level. Studies have revealed that lower levels of BDNF in brain tissue may be connected to people with bipolar disorder's diminished synaptic plasticity in the central nervous system. Through controlling neuronal plasticity in the dentate gyrus of the hippocampus, BDNF may contribute to the onset of bipolar disorder.

4. Limitations and future development

Although it was agreed that bipolar disorder is strongly related to BDNF related abnormality, few limitations still existed among those researches. Most studies were done with a small sample size and concluded with low correlation between variables, which should be considered when one wants to generalize any discoveries. It is also suggested that more longitudinal studies need to be performed instead of case-control ones. However, research has still suggested that the BDNF level might be a potential biomarker and potential research direction for treatments of bipolar disorder.

4.1. Lithium

Lithium has always been one of the most prominent treatments for bipolar disorder. The main function of Li is to reduce the frequency and severity of manic episodes. The way that Lithium affects our body is still unclear, but it is known that it can alter the central nervous system and helps with emotion control. A possible explanation for this is that it has been discovered that lithium treatment could increase the connection between amygdala and prefrontal cortex, which functioned in emotion control. A longitudinal study over more than 180 months shows that long term lithium treated BP I patients seemed to have larger limbic structures, including amygdala and hippocampus, than healthy controls. Lithium seems to reverse the reduction of volume in these areas in most BP patients [13]. Long term medication of Li can change the dendritic structure in the brain. These structural changes would enhance neuroplasticity, such as an increase in LTP in the hippocampus region. In addition, high doses of lithium help immature brain cells mature into specialized cells. This is in line with animal studies, suggesting that lithium helps new brain cells take on specific roles.

Lithium could actually increase BDNF level, especially in the hippocampus and extracellular region of cortical neurons. After Lithium enters the body, it first interacts with adenylyl cyclase enzymes, which have a major role in producing cyclic adenosine monophosphate. Once cAMP production is increased, more cAMP response element binding protein would be activated. The activation of CREB through phosphorylation would then boost the transcription of BDNF. Lithium can also affect the promoter exons of the BDNF gene. A study done on rats has shown that lithium would increase the activity of exon IV, which would thus promote the expression of BDNF protein [14]. This increment of BDNF level would thus enhance neurogenesis, development of nerve cells, and neural plasticity, which could potentially alter mood control ability and cognitive functions of BD patients.

4.2. Antidepressants

Antidepressants are another factor that could lead to an increase in BDNF level. Antidepressants including SSRIs and SNRIs can increase BDNF level after a period of treatments, while sertraline could have the same effect in an even shorter period of time. Also, both serotonin and BDNF pathways can control the maturation and plasticity of mood-controlling neuron circuits. However, Antidepressants are not a common medication for bipolar disorder. The reason is that while some people use antidepressants to help control depression episodes of bipolar disorder, these medications might actually lead to more frequent manic states.

4.3. CRISPR

Lastly, regarding directly changing the function of a gene, CRISPR technology became an important tool in research and potential treatment. Clustered regularly interspaced short palindromic repeats-Cas (CRISPR associated) systems are cell defense mechanisms in bacteria that detect and cut invaded DNA. The most commonly used type II CRISPR involved the cas 9 protein to cut the DNA and single guide RNA to guide Cas 9 to the target. The Cas9-SgRNA system will first scan the DNA for a specific sequence called PAM (protospacer-adjacent motif). As the complex recognizes the NGG PAM, (N=A, C, G or T), the complex will form an "R-loop" structure and cut a few bases before the PAM. CRISPR is a very efficient and economic tool today, and it has many potential uses in different fields of study. Many studies have supported the usage of this technology on the BDNF gene. An animal study used CRISPR to result in a specific BDNF variation (met/met) in mice. It has been shown that the mice express more anxious behavior than control and have less response to antidepressants. This study has also shown that there might be a similar effect of this genetic mutation on humans. A new CRISPR technology CRISPRi was developed to repress any target gene. It has also successfully been used on BDNF genes, and they nearly shut down the entire gene without affecting other parts of the DNA. The application of this new method was shown in an animal study. Investigating gene's impact on Huntington diseases, researchers limit the expression of BDNF in mice by altering the 5 Htt gene using CRIPRi. Although the disease was not treated, the gene editing successfully ceased the progression of the disease. Another innovation of CRISPR, CRISPRa, in contrast, could help turn on a target gene. In the study, CRISPRa could create multiple gene variants without affecting other genes, and they found that specific gene variation is enough to upregulate BDNF, resulting in a spike in matured hippocampal neurons [15]. This could possibly counteract the decrease of BDNF level in BP patients. However, to truly apply the CRISPR/Cas9 system to treat bipolar disorder, there are still many inevitable limitations, such as off-target effects, difficulties in implementing on human cells, and ethical issues [16].

5. Conclusion

This review mainly aims to examine how BDNF genes could potentially cause Bipolar Disorder. BDNF gene is crucial in regeneration, proliferation, and repair of neurons in the central nervous system. Impairments in the BDNF gene, for example, the val66met single nucleotide polymorphisms (SNP), which decrease the expression of BDNF, could damage the connection between neurons, affect synaptic functions, and decrease the density of dendritic spine. This will result in deterioration in mental diseases like BD and depression. Bipolar disorder symptoms also correlate to abnormalities in amygdala and hippocampus. BD patients express larger or smaller volumes of hippocampus and amygdala as well as reduction in mood control ability cognitive functions like emotion memory and comprehension capability, which are regulated by these two brain regions. Interestingly, most of these abnormalities showed in studies which BDNF expression is less than control, suggesting that BDNF gene impairments might lead to BD through damaging hippocampus and amygdala. Although current studies bring insights to curing BD, the limitations of current studies are the lack of longitudinal studies, low correlation quotients, and small sample sizes. Promising studies about treatment for BD, regarding its relationship with BDNF gene, could be focused on utilizing lithium and antidepressant as well as the gene editing technology CRISPR. However, all three methods have certain drawbacks that require further studies.

Author contribution

All the authors contributed equally and their names were listed in alphabetical order.

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