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Advances in Depression and Brain-Derived Neurotrophic Factor

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Abstract

In 2006, Duman *et al.* proposed "Neurotrophic Theory of Depression" [1]. According to the hypothesis, stress leads to a decrease in the expression of neurotrophic factors such as Brain-derived neurotrophic factor (BDNF) in the limbic structure, and antidepressant therapy can partially reverse the effect caused by stress. The reduction of BDNF and other neurotrophic factors promotes the atrophy of certain brain structures, especially the hippocampus and prefrontal cortex, while antidepressant treatment increases the level of BDNF in the brain, and improves synaptic plasticity and neuronal survival in related brain regions. Neurotrophic factors are a class of molecules that act on the nervous system and play an important role in maintaining cell function. They can regulate the growth, survival, differentiation and cell cycle of nerve cells. There is a hypothesis of neuroendocrine dysfunction in the neurobiochemical mechanism of depression, which is mainly the abnormal activity of the hypothalamic-pituitary-adrenal axis (HPA) and hypothalamic-pituitary-thyroid axis (HPT). This article reviews the related research on depression and brain-derived neurotrophic factors in order to guide clinical research and treatment.

Keywords

Depression, Brain-Derived Neurotrophic Factor, The Correlation

1. Background

Depression is a chronic, recurrent brain disease. According to the global Health Assessment report released by the World Health Organization (WHO) in 2017, about 322 million people worldwide suffer from depression, an increase of 18.4% in the 10 years from 2005 to 2015. About 4.2% of the population in China suffers from depression [2] Depression in clinical manifestations of the depression,

sleep disorders, often pessimistic and so on, patients often are in the mood of sadness, pain, depression, and loss of appetite, lack of sex and, sleep disturbance, dizziness headache, whole body unwell, the bosom is frowsty asthma, frequent urination urgency, gastrointestinal disorders, such as somatization symptoms, severe cases often appear suicidal impulses, is one of the most disabling diseases in the world [3]. Depression disorders account for 10% of the disability caused by non-infectious diseases and are the second-largest source of disease burden after cardiovascular diseases [4]. For many years, the research on neurotrophic factors, especially brain-derived neurotrophic factor (BDNF) and its tyrosine kinase receptor B (TtkB), has become the focus of depression and antidepressant medicine. Brain-derived neurotrophic factor (BDNF) is an important member of the neurotrophic factor family. BDNF was first discovered and purified by German biologist Brade and his colleagues in 1982, which has the function of preventing the death of neurons. Studies have shown that BDNF plays a role in differentiation, proliferation and nutrition of various types of neurons, and has a great influence on the plasticity of neurons and the synthesis of neurotransmitters and neurotrophic factors, and is related to the long-term enhancement effect and learning and memory function [5] So far, some scholars have proposed the BDNF hypothesis of depression, believing that the decrease of brain BDNF level is easy to lead to depression, and the increase of brain BDNF level may produce antidepressant effect. BDNF is an experience-dependent modification substance of neural network to regulate mood [6].

2. Overview of Depression

"Melancholia" was first used to describe depression by Hippocrates, the Ancient Greek doctor who put forward the theory of Humours, arguing that the human body is made up of four bodily fluids, mucus, blood, gallbladder and melancholia, and that physical differences between people are caused by the different cooperation of these four bodily fluids [7]. He believed that people with more black bile and mucus had a depressive system, characterized by vulnerability and slowness of movement. The word "melancholia" has been in use for many years, not until the 12th century, when Moses Maimonides [8], a Jewish doctor, saw depression as a separate illness whose causes could not simply be explained by differences in "bodily fluids". But it was not until the 19th century that scientific research on depression began to unfold. Depression is a common chronic disease and its treatment is expensive. A community population in the United States in 1994 Survey data show that the lifetime prevalence of depression is 4.9% to 17.1%. The prevalence of major depression is 6% - 8% in primary care Settings. Longitudinal surveys of depression show that approximately 80% of individuals with major depression will experience at least one depressive episode in their lifetime, with relapse rates increased by the occurrence of short-term or below-threshold symptoms. The physical and mental harm and social burden caused by depression are huge. Suicide is the most serious outcome of the de-

velopment of depression. The incidence of suicidal behavior was about 3.5 percent among severely depressed patients, rising to 15 percent among depressed patients requiring hospitalization. The risk assessment for suicide due to depression is 12 - 20 times higher than the probability of suicidal behavior in the general population. In 1990, the World Health Organization defined major depression as the fourth most disabling disease in the world, with a higher rate of disability than ischemic heart disease or cerebrovascular disease. Simple depressive episodes are projected to become the second leading cause of disability worldwide by 2020. At the same time, depression has higher morbidity and mortality than cardiac diseases [9]. The two primary factors contributing to the increasing severity of depression are chronic course and recurrence of symptoms. The more severe and prolonged a depressive episode is, the more likely it is to become chronic. Therefore, early diagnosis and treatment of depression can not only reduce the damage caused by the disease, but also have the opportunity to reduce the incidence of chronic depressive episodes.

3. BDNF

BDNF is a small molecule dimer protein, which is one of the molecules most closely related to depression. In 1982, German biologist Brade *et al.* first extracted BDNF from pig brain [10]. BDNF is widely distributed in all parts of the brain, especially in the hippocampus, prefrontal cortex and amygdala, which are related to emotion. BDNF plays an important role in the growth and survival of neurons, the differentiation of other cells (such as neural stem cells) and the regulation of synaptic plasticity. It works by binding to specific tyrosine kinase receptor B, thereby activating its downstream related pathways and further producing neuroprotective effects. Current studies have positively supported the involvement of BDNF in the pathophysiological process of depression. Clinical evidence shows that the serum BDNF level of patients with major depressive disorder (MDD) is significantly lower than that of the normal population, and the brain BDNF level of such patients is also significantly lower than that of the healthy population in autopsy [11]. Studies have also shown that low plasma LEVEL of BDNF is associated with suicidal behavior in MDD patients, and the level of BDNF may serve as a biological marker for suicidal MDD patients [12]. It has also been reported that citalopram, one of the SSRI drugs, can not only improve the depressive symptoms of patients in the treatment of MDD, but also significantly increase the level of BDNF in their plasma. If combined with electro-convulsive therapy on this basis, plasma BDNF levels would be higher [13]. In addition, studies have found that combined use of some low-dose atypical antipsychotic drugs (such as quetiapine or risperidone, etc.) based on the effects of antidepressants (such as SSRIs or SNRIs) can not only improve the clinical symptoms of patients with depression, but also show an increase in plasma BDNF level [14]. However, some studies have shown that the level of serum BDNF is related to the duration of depression, but not to the severity and pres-

ence of psychotic symptoms [15]. Animal studies found that the expression level of BDNF mRNA in dorsal hippocampal dentate gyrus and ventral hippocampal CA3 regions of CUS rats was not decreased, but increased, indicating that depression-like behavior itself was not associated with the level of BDNF in rat brain. However, chronic antidepressant treatment (such as venlafaxine and imipramine) significantly increased the expression level of BDNF mRNA in the dentate gyrus of the dorsal hippocampus of rats, suggesting that the improvement of depression-like behavior of the rats by antidepressant treatment is strongly correlated with the expression of BDNF in the brain [16]. Other studies have found that the expression level of BDNF in each hippocampal region of chronic and unpredictable mild stress rats is reduced, which can be improved by different antidepressants including venlafaxine, fluoxetine or mirtazapine [17]. The difference between the results of the two studies may be related to the inconsistent rat model and the inconsistent detection indicators. It is worth mentioning that stress, as an important social environmental factor inducing depression, has been reported to reduce hippocampal neurogenesis and brain BDNF expression for many times [18]. At the same time, antidepressant treatment can promote the expression of neurogenesis and neurotrophic factor genes1 [19]. For example, injection of BDNF into the hippocampus of rats can improve depression-like behaviors including forced swimming and learned helplessness in depressed rat models [20], and peripheral administration of BDNF can also produce antidepressant effects similar to those of brain administration [21]. One of the reasons may be that antidepressants can promote the release of platelet BDNF in the blood of rats (related to the type and dose of antidepressants), making BDNF an important candidate predictor to evaluate the effect of antidepressants [22]. What is the mechanism by which BDNF exerts its antidepressant effect? BDNF has been found to promote the regeneration and survival of damaged hippocampal neurons. In vitro studies have shown that BDNF can promote the survival, proliferation and differentiation of hippocampal neural stem cells [23]. In animal studies, BDNF localized injection into the dentate gyrus of the hippocampus promoted the regeneration of the dentate gyrus of normal rats [24]. After injection of BDNF into the lateral ventricle, the regeneration of neurons in the inferior ventricle and the number of new neurons in the olfactory bulb were significantly improved [25]. In addition, studies have found that there is a close relationship between BDNF and 5-HT energy neurons, which can regulate each other to maintain dynamic balance. Evidence suggests that BDNF or NT-3 infusion into the adult brain can promote the growth of 5-HT-energetic neurons and regeneration of nerve fibers [26]. Other studies have shown that depressive episodes are associated with decreased activity of the CAMP-response element-binding protein brain-derived neurotrophic factor-tyrosine kinase B (CREB-BDNF-TRKB) pathway, which can be activated by antidepressant therapy (including drug therapy and physical therapy) for its antidepressant effects [27]. Related evidence included that the proliferation and differentiation abilities

of hippocampal dentate gyrus cells in TrkB receptor knockout mice were lower than those in wild-type mice, while depression-like behavior was not improved significantly after chronic antidepressant treatment, and the proliferation and differentiation abilities of neurons were not significantly increased. These results suggest that TrkB receptor is related to the regeneration of hippocampal neurons and the behavioral changes of mice after antidepressant treatment [28]. BDNF can also exert its biological effects through the PLC-R-IP3-Ca2 + pathway by increasing neuronal excitatory glutamate signal transduction [29] In addition, some studies have found that BDNF is an important part of the BDNF/MAPK/ERK/Bcl-2 cascade pathway. Activation of this pathway can exert a neuroprotective effect and thus play an antidepressant role [30].

4. The Role and Mechanism of BDNF in Central Nervous System

BDNF is a kind of protein factor that plays an important role in the production and maintenance of central nervous system function. It is widely distributed in the body and plays an important role in the repair and regeneration of neurons, glial cells and even some immune cells. In recent years, a large number of studies have focused on the physiological effects of BDNF and TrkB and their changes in neurological diseases or injuries, and there have also been some reports on the changes of BDNF mrna expression during brain development [31]. Animal experiments have shown that the expression of BDNF and its receptor trkB mRNA is significantly increased after cerebral ischemia and hypoxia. The decrease in the volume of injured brain tissue can be reduced by 50% when BDNF is given in the ventricle, and 90% when BDNF is given before injury, suggesting that BDNF has a significant neuroprotective effect. BDNF combining trkB receptor's biological effects include: 1) The embryonic cells can maintain the midbrain dopaminergic neurons survive and to dopaminergic phenotypic differentiation, can induce differentiation of dopaminergic neurons form, such as increasing of cells, neuron dendritic branch makes half of Parkinson rats induced by amphetamine rotation behavior was significantly reduced, even in the dark BDNF was still effective after several weeks of damage to the dopamine system in the striatum. 2) Improve the biological activity of neurons and reduce the natural death of neurons after injury; 3) Maintain the functions of vestibular nucleus and trigeminal nerve sensory neurons and the survival of embryonic retinal ganglion cells [32]. During the development of the nervous system, BDNF can induce the directed differentiation of neural precursor cells, promote neuronal proliferation, accelerate neuronal migration, and promote the maturation and perfection of the nervous system. Animal experiments have confirmed that BDNF can also increase the activity of motor neurons in cultured embryonic rats and protect the damaged facial neurons in newborn rats [33]. Local application of BDNF can also save 92% of spinal motor neurons after the sciatic nerve is severed in newborn rats, indicating that BDNF affects the survival of developing motor neu-

rons. In adults, BDNF shows a wide range of neurotrophic and neuroprotective activities, which can promote the utilization of glucose and other energy substances by neurons and improve the activity of cellular enzymes. BDNF can prevent the natural death of motor neurons [34], and has positive significance for the survival and maintenance of normal physiological functions of neurons [35]. BDNF protects neurons, promotes the survival and regeneration of neurons after injury, which is a complex life process. The mechanism is as follows: Binding of BDNF to its specific receptor TrkB can further activate tyrosine kinase, leading to the phosphorylation of tyrosine proteins and various proteins (PLC, PI-3-K, etc.), thus playing different biological effects. For example, PLC can then activate ras-MAPK and other pathways, which are related to cell proliferation and differentiation. The activation of phosphoinositol 3 kinase (PI-3-K) not only plays a pro-survival role, but also plays a certain role in the establishment of axonal and dendrite polarity and neuronal migration of juvenile neurons. BDNF can also be transported to the end of axons and released by the cell body, which can be taken up and utilized by secondary neurons and participate in synaptic plasticity. Experiments have shown that BDNF and TrkB combine to achieve signal transduction reaction mainly through ras protein pathway encoded by oncogene RAS [36]. Neurotrophic factor protects neurons from the excitatory toxic effects of glutamate, Almeida [37] *et al.* found that Pi-3-K and Ras/MAPK signal transduction pathways play an important role in realizing this function. The morphological changes and caspase-3 activity of glutamate-induced apoptosis were decreased by preculture of hippocampal neurons with BDNF for 24 h, and the activities of PI-3-K and Ras/MAPK pathways were increased in the short term. Inhibition of PI-3-K and Ras/MAPK signaling pathways cancels the protective effect of BDNF against glutamate-induced neuronal death.

5. BDNF and the Pathogenesis of Depression

In depression, decreased expression of neurotrophic factor is involved in some pathophysiological processes and may be one of the basic pathological changes of depression. Cell matrix studies suggest that decreased BDNF levels are a phenomenon closely related to stress, especially in understanding stress-related depression. Experiments that induced depression-like behaviors in rodents showed that stress can regulate endogenous BDNF expression [38]. Psychological and physical stress can reduce hippocampal BDNF mrna, suggesting that stress-related depression is closely related to hippocampal BDNF [39]. Duzman *et al.* (1997) believed that stress-related depression, in particular, might be caused by atrophy or necrosis of hippocampal CA3 pyramidal nerve cells, and was partly related to the decreased ability of some neurons to acquire BDNF. Smith *et al.* reported that binding stress caused the decrease of BDNFmRNA in hippocampus. Chronic unpredictability stress method was used to make depression model of rats, and open-field scoring method was used to observe the behavioral changes of rats. Immunohistochemical method was used to detect the expression of

BDNF in hippocampus and cortex, and ELISA method was used to detect the content of BDNF in cerebrospinal fluid, hippocampus and cortex. Results Compared with the normal control group, the number of BDNF positive cells in the hippocampus and cortex of the depressed model group was significantly reduced, indicating that the content of BDNF in the brain tissue of the depressed model group was significantly lower than that of the normal control group [40]. The hypothesis of impaired hippocampal neuroplasticity in depression can be summarized as follows: 1) Disruption of nerve regeneration plays an important role in the pathophysiological process of depression; 2) Antidepressants can normalize the damage. There is much doubt about this hypothesis. Transcranial magnetic stimulation (TMS) has been reported as an effective antidepressant treatment without increasing the rate of hippocampal neuron regeneration. There are also questions about how to look at the level of hippocampal neuron regeneration in depressed people. Therefore, more research is needed to confirm this hypothesis and explore the whole process of regeneration, *i.e.* the generation, differentiation and survival of new neurons. Clinical studies suggest that BDNF plays an important role in the pathogenesis of patients with major depression. The data of brain imaging and autopsy studies showed that some brain regions of limbic system were structure-altered and function-impaired in patients with depression, which provided clinical evidence for the involvement of neuroplasticity mechanism in the pathological changes of depression. Magnetic resonance imaging (MRI) showed atrophy of the hippocampus, frontal cortex, amygdala, ventral striatum and other brain areas in patients with depression [41]. The expression of BDNF and TrkB decreased in hippocampus. The expression of BDNF and TrkB was increased in the hippocampus of patients who received antidepressant treatment before death [42]. Further studies found that the serum BDNF level in living patients with depression decreased significantly and recovered after antidepressant treatment [43]. So far, many studies at home and abroad have attempted to further explore the correlation between BDNF gene coding variation and behavioral characteristics of depression. Although there is no clear gene that causes depression, many studies have found that BDNF gene Val66Met and other polymorphisms are associated with depression. Chen *et al.* reported that when the mouse BDNF gene homozygous (BDNF Met/Met) was replaced by the heterozygous Val/Met genotype, the biologically related release of BDNF decreased significantly, the anxiety-like emotions and behaviors increased, and the anti-anxiety efficacy of fluoxetine was delayed. This suggests that BDNF SINGLE nucleotide polymorphism plays an important role in the pathogenesis of depression [44]. Sen *et al.* [45] reported the study of depression susceptibility and BDNF5'-end SINGLE nucleotide polymorphism, which leads to the substitution of Val66Met at the 66th position of BDNF. Sen *et al.* selected 441 American caucasians as research subjects and found that the neuroticism score of Val allele population was significantly increased, suggesting that BDNF gene polymorphism may be positively correlated with depression [46]. A similar

study of 343 Germans also found that people with Val/Val had higher anxiety characteristics than Met/Met or Val/Met [47]. Schule *et al.* [48] showed that BDNF gene Val66Met polymorphism was correlated with dexamethasone test results in patients with depression. Hwang *et al.* [49] showed that the polymorphism of VAL66Met in BDNF gene was correlated with depression in the elderly (111 cases). Of course, there are studies that have not found a positive association. Three recent studies of Chinese and Korean populations found no association between BDNF gene polymorphism and depression, which may be due to small sample sizes and ethnic differences. Surtees *et al.* did not find positive results in a study of BDNF gene polymorphisms and mood states in 7389 older adults in the community [50].

6. Expectation

According to the World Health Organization (WHO), 350 million people worldwide suffer from depression, and by 2020, the disease burden of depressive disorders will rise to second only to ischaemic heart disease and become the second leading cause of disability and death. BDNF has been preliminarily confirmed to be involved in the pathogenesis and treatment of depression. However, most of the studies are preliminary, especially the mechanism of BDNF in the pathogenesis and treatment of depression has not been clearly understood. The future research direction is to further search for evidence to support BDNF as a biological marker of depression. In order to develop more effective treatment measures, it is necessary to clarify the pathogenesis and treatment of depression.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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