Dean&Francis
ISSN 2959-409X

Role of BDNF in the Pathogenesis of Central Nervous System Diseases and Targeted Therapy

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Abstract:

Central nervous system diseases are associated with high morbidity and mortality. Existing treatments are mostly symptomatic and hardly alter disease progression, so new therapeutic approaches are urgently needed. Brain-derived neurotrophic factor (BDNF) is of great significance for the survival of neuronal as well as synaptic plasticity, and its functional abnormalities are related to many central nervous system (CNS) diseases, making it a potential therapeutic target. This article first elaborates on the biological functions and action mechanisms of BDNF, then reviews its action mechanisms, expression changes, and advances in targeted therapy in traumatic brain injury, Parkinson's disease, Alzheimer's disease, and depression, covering relevant studies on intervention methods such as drugs, electroconvulsive therapy, and acupuncture. At present, there are problems in this field such as unclear mechanisms in some aspects and the need for further verification of some therapeutic approaches. In the future, in-depth research on BDNF-related mechanisms and therapeutic methods is required to promote the development of BDNF-targeted therapy for central nervous system diseases towards a more effective and safe direction, which thereby provides new strategies for disease treatment.

Keywords: BDNF; TrkB signaling pathway; CNS; Synaptic plasticity; Neurotrophic therapy

1. Introduction

CNS diseases like Alzheimer's disease, depression, Parkinson's disease, depression, as well as traumatic brain injury have high morbidity and mortality all over the world. In the year 2016, there were approximately 330,000 new cases and 227,000 deaths of such diseases, with an incidence rate 17.3% higher than that in 1990. Regions with lower sociodemographic indexes bear a more significant disease burden, with disability-adjusted life years increasing by more than 22% [1]. These data highlight the signif-

icant impact of such diseases on global health and social economy, and also indicate an urgent need to develop new therapeutic methods. Currently, treatments for central nervous system diseases are mostly limited to drugs, surgery, and physical therapy, and most are symptomatic, which make it difficult to change the trajectory of disease progression. BDNF, a significant neurotrophic factor which is a significant role in synaptic plasticity and neuronal survival, with its functions mediated primarily through the p75NTR and TrkB receptors. It has been observed in studies that irregularities in BDNF function are intimately connected to the manifestation and worsening of a variety of CNS, including Alzheimer's, Parkinson's, and depression, pointing to its potential as a therapeutic objective. This review examines BDNF's role in major central nervous system diseases, with a focus on new therapeutic directions, alterations in expression, and its mechanism of action.

2. Biological Functions and Action Mechanisms of BDNF

BDNF, a key member of the family of the neurotrophic factors, exhibits complex mechanisms of action and broad biological functions. BDNF is initially synthesized as a precursor form (proBDNF), which is hydrolyzed by proteases to generate mature BDNF (mBDNF). The two forms mediate completely opposite biological effects by binding to different receptors. proBDNF tends to promote cell apoptosis and weaken synaptic connections, while mBDNF dominates the survival, differentiation, growth of neurons, and synaptic plasticity [2]. The realization of BDNF functions highly depends on its binding to the specific receptor TrkB, which triggers receptor dimerization and autophosphorylation, thereby activating multiple key downstream signaling pathways. Among them, the mainly responsible one for regulating cell survival and metabolism is the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, while the Ras/MAPK pathway focuses more on mediating cell differentiation and the formation of synaptic plasticity. In addition, BDNF can also affect synaptic transmission efficiency through the PLCγ pathway.

In the central nervous system, BDNF is widely expressed in important brain areas,including the hippocampus and the cortex. The induction and maintenance of long-term potentiation (LTP) represent key mechanisms through which BDNF critically supports learning and memory processes. Beyond its roles in neural plasticity, BDNF regulates the release and synthesis of neurotransmitters and influences a range of physiological processes including sleep, mood, and appetite. Studies have shown that its dysfunction is highly related to the development of several neurological disorders, especially epilepsy, Alzheimer's disease, and depression. Consequently, advancing therapeutic strategies for related disorders relies heavily on a deeper exploration of the molecular mechanisms and biological functions of BDNF [3].

3. Research Progress of BDNF-Targeted Therapeutic Approaches for Different CNS Diseases

All central nervous system diseases have abnormal neuroplasticity. As a key molecule regulating neuronal survival and synaptic function, BDNF is a common factor connecting stress, synaptic plasticity, and neurodegenerative susceptibility. In recent years, the development of BDNF-targeted drugs and the implementation of targeted therapy have become important directions in the research of CNS disease treatment.

3.1 Depression

Reduced BDNF levels in individuals diagnosed with Major Depressive Disorder (MDD) have been repeatedly confirmed. Clinical studies and imaging studies indicates that patients with depression have hippocampal atrophy and weakened BDNF signaling pathway, and stress models further confirm that neural activity can downregulate BDNF expression [4]. Conversely, antidepressant treatment has been shown to upregulate BDNF expression. Consistent evidence proving by studies and researches for animal and people, indicates that prolonged antidepressant use elevates mRNA and protein levels of BDNF in the hippocampus. Direct infusion of BDNF can produce antidepressant-like behavioral effects. The above findings support the "neurotrophic factor hypothesis of depression", which believes the impaired BDNF signaling pathway leads to abnormal hippocampal function, and restoring the function of this pathway is the key mechanism for the efficacy of antidepressant treatment. This theoretical framework also provides a basis for understanding the abnormal regulation of BDNF in other CNS disease, such as Alzheimer's disease.

Based on the above pathological research results, a series of studies on intervening depression through BDNF-related pathways have been carried out. A meta-analysis confirmed that antidepressant treatment can significantly increase peripheral blood BDNF levels, and this change is related to the improvement of depressive symptoms [5]. Liu et al. subjected 80 male SD rats to unpredictable stress to establish models, then administered placebo, ketamine, TrkB receptor blocker K252a, and ketamine respectively,

ISSN 2959-409X

and subsequently detected behavioral and hippocampal-related molecular indicators. The outcomes indicate that the immobility time of rats in the stress ketamine group in forced swimming test was significantly shortened, the expression level of BDNF in the hippocampus was significantly increased, and the expressions of pCREB, GLT-1, PSD95 and other proteins in the hippocampus were also increased compared with the stress placebo group. However, after adding K252a, the improvement effects of ketamine on the above indicators were weakened, and the promotion effect of ketamine on the density of hippocampal neuron dendritic spines was also inhibited. This study clearly verified the important role of BDNF-TrkB signaling pathway in the antidepressant effect of ketamine [6]. In addition to drug treatment, Electroconvulsive Therapy (ECT) can also significantly increase serum BDNF levels in psychiatric patients going through severe depression.

3.2 AD

AD is marked by worsening cognitive decline and synaptic dysfunction, with alterations in BDNF playing a key role in this pathological process. The level of expressing the BDNF is extraordinary in the hippocampus and cortex, and is a key molecule for synaptic plasticity and memory formation [7]. Both post-mortem examinations and peripheral blood analyses consistently reveal that shows a markedly reduced serum BDNF content levels of Alzheimer's disease patients, and BDNF expression in relevant brain regions is also significantly lowered compared to healthy controls. A meta-analysis covering 15 studies and more than 2000 participants with AD confirmed that serum BDNF concentration is significantly reduced, while BDNF levels in patients with Mild Cognitive Impairment (MCI) show no significant changes, which suggests that the decrease in BDNF levels mainly occurs in the late stage [8]. Another study reported that in AD BDNF expression or TrkB receptor expression may be upregulated, which may be a compensatory mechanism of the body in response to neuronal damage. In addition, researchers also explored the association between the Val66Met polymorphism and AD, but large-sample cohort analysis failed to find a evident correlation between this polymorphism and AD susceptibility [7].

Li Shan et al. used male neonatal SD rats as subjects, constructed a depression model by subcutaneous injection of clomipramine from postnatal day 8 to 21, then intraperitoneally injected 7,8-dihydroxyflavone hydrate (7,8-DHF) into the model group from postnatal day 51 to 64 and set up a normal saline control group, respectively detecting the rats' social behavioral indicators, body weight, spleen index, and related factor expressions. The study found that the overall movement distance of rats in the depression model group showed a notably decrease compared to the normal saline control group and the treatment group, the expression level of IL-1β in their serum was significantly increased, and the expression of BDNF in the hippocampus was negatively correlated with serum IL-1β ($r = -0.784$), while long-term 7,8-DHF intervention could significantly reverse the above abnormalities. This study first used a three-chamber experimental box to detect the social behavior of SD rats, which clarifies the impact of BDNF in the depression pathogenesis and intervention effect of 7,8-DHF [9]. Zhan Jinqiong et al. constructed a model by administering $0.1mg \cdot kg^{-1}$ dizocilpine to SD rat pups on postnatal day 6, and intervened with 7,8-DHF ($5mg \cdot kg^{-1}$ intraperitoneal injection), then detected related indicators. The results demonstrated that the dendritic spine density of hippocampal neurons in the model group was notably reduced compared to the normal control group, and the 7,8-DHF group could restore this indicator to a level close to normal (13.5±1.7)/10μm. In addition, the 7,8-DHF group could also upregulate and restore the phosphorylation level of GluR1 protein to (97.5±9.3), which was greatly beyond that of the model group (47.9±10.8). This study focused on the BDNF/TrkB pathway and clarified the role and mechanism of 7,8-DHF through multi-indicator detection [10]. In addition, BrAD-R13, a derivative of BDNF receptor agonist, has also entered clinical trials for moderate AD treatments.

3.3 Parkinson's Disease(PD)

PD is distinguished by the progressive degeneration osf dopaminergic neurons located in the striatum and substantia nigra. Changes in the BDNF signaling pathway are a common feature of PD. In PD patients and experimental models, BDNF levels in serum and the substantia nigra-striatum region are reduced. The reduction of BDNF levels is related to the loss of dopaminergic neurons, the decrease of tyrosine hydroxylase activity, and the impairment of dopamine synthesis, which indicates that BDNF deficiency plays an important role in the progression of PD. Experimental studies have confirmed that BDNF can promote the survival of dopaminergic neurons, regulate the function of dopamine transporters, and protect neurons from toxic damage induced by α-synuclein. Therapeutic strategies targeting this pathway include direct BDNF delivery and virus-mediated BDNF gene transfer. Both methods can improve neuron survival rate and partially restore motor function in PD models. In addition, studies have found that exercise can increase BDNF levels in the substantia nigra-striatum system of PD models, which thereby exert neuroprotective effects and improving motor

function [11].

Based on the above pathological research results, a series of studies on treating Parkinson's disease through BDNF-related pathways have been carried out. Zhu et al. first clarified that memantine improves cognition and synaptic plasticity in PD model mice through the BDNF-TrkB pathway. The experiment used C57BL/6 mice as subjects, constructed acute and subchronic PD models by intraperitoneal injection of MPTP, set up different doses of memantine pretreatment groups, and detected related indicators by combining behavioral tests, electrophysiological recordings, and molecular biology techniques. The results found that the hippocampal BDNF content in the MPTP model group was noticeably reduced, and could be restored after pretreatment with 10mg·kg^{-1} memantine. Memantine pretreatment could reverse the decrease in LTP amplitude induced by theta burst stimulation in the MPTP model group, and this effect could be blocked by the TrkB inhibitor TrkB-FC [12]. In the Parkinson's disease (PD) model, direct infusion of BDNF or BDNF gene delivery mediated by viral vectors can significantly reduce dopaminergic neuron damage [11]. The above research results bring considerable hope for the treatment method of Parkinson's disease targeting the BDNF pathway.

3.4 Traumatic Brain Injury (TBI)

Neuroinflammation after TBI is a key link in secondary injury. TREM2 has neuroprotective effects in neurodegenerative diseases, but its mechanism in TBI is not clear, and the Akt/CREB/BDNF pathway is closely related to neuroprotection. The experiment used WT and TREM2 KO mice as subjects, constructed a TBI model by controlled cortical impact (CCI), injected the TREM2 agonist COG1410 via tail vein 1 hour after CCI, and detected related indicators by combining behavioral tests, Western blot, immunofluorescence and other techniques. Based on the results, it is showed the expression of endogenous TREM2 peaked 3 days after CCI and 89.43% of it was localized in microglia. COG1410 treatment could significantly upregulate BDNF expression in the injured area and prolong the residence time of mice in the target quadrant in the Morris water maze. TREM2 KO could completely eliminate the upregulating effect of COG1410 on BDNF and the improving effect on neurological function. This study first confirmed that COG1410 can exert neuroprotective effects by activating TREM2 to regulate the Akt/CREB/BDNF pathway in microglia, which provides new experimental evidence and mechanism explanation for BDNF-targeted therapy of TBI [13].

Acupuncture, a traditional Chinese medicine technique, also has unexpected effects on central nervous system diseases. In recent years, it was found that acupuncture can treat TBI and promote the recovery of neurological function. Li et al. used SD rats as subjects, constructed a TBI model by lateral fluid percussion, selected Baihui, Renzhong, Hegu, and Zusanli acupoints for daily acupuncture intervention once a day for 14 days, and detected related indicators by combining behavioral tests and molecular biology techniques. The results showed that BDNF peaked 12 hours after TBI and then fell back to normal at 48 hours, while BDNF in the acupuncture group was still significantly increased at 168 hours. In addition, the acupuncture group showed prolonged time in the target quadrant and greater amount of platform crossings in the Morris water maze, as well as higher EPSP slope and PS amplitude of LTP. The above therapeutic effects of acupuncture could be blocked by K252a. This study first clarified that acupuncture improves neurological function after TBI by prolonging the activation of the BDNF/TrkB pathway and regulating downstream Akt and Erk1/2 signals, which provides BDNF-targeted molecular mechanism support for traditional acupuncture in the treatment of TBI [14].

4. Conclusion

This article integrates the current research progress on the biological functions, pathological changes, and therapeutic potential of brain-derived neurotrophic factor (BDNF) in central nervous system diseases. By elaborating on the dual signaling pathways of BDNF mediated by TrkB and p75NTR receptors, this article emphasizes how the balance between precursor BDNF (proBDNF) and mature BDNF (mBDNF) determines neuronal survival, synaptic remodeling, and cognitive function outcomes. Research evidence from depression, Alzheimer's disease, and Parkinson's disease shows that abnormal BDNF function is a common mechanism connecting neurodegeneration and impaired synaptic plasticity. This article further outlines a series of therapeutic strategies including BDNF receptor agonists, acupuncture, and electrical stimulation therapy. Although many strategies are still in the preclinical research stage, these studies collectively establish BDNF as a possible thread for the improvement of disease-modifying therapies. By integrating advances in molecular biology, pathology, and translational research, this article emphasizes that BDNF is not only a theoretical framework for understanding the mechanisms of central nervous system diseases but also a key target for formulating therapeutic strategies, providing a basis for future innovations in the treatment of central nervous system diseases.

ISSN 2959-409X

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