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Research Progress on Brain-Derived Neurotrophic Factor (BDNF) in the Sequelae of Stroke

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Abstract

The research progress of brain-derived neurotrophic factor (BDNF) in the treatment of sequelae of stroke is an important topic. Stroke is among the diseases with the highest mortality and disability rates among the elderly in China. BDNF plays an important role in the development and functional maintenance of the nervous system. In recent years, the application value of BDNF in rehabilitation therapy has gradually received attention. This study has adopted a systematic literature review method, searched Chinese and English databases, screened relevant studies, and conducted data extraction and quality evaluation. This review systematically introduced the research progress of BDNF in the correlation with post-stroke sequelae, with special attention to its application in post-stroke depression, motor dysfunction, and cognitive dysfunction. The results showed that a decrease in BDNF levels is closely related to the exacerbation of depressive symptoms, limited recovery of motor dysfunction, and the occurrence of cognitive dysfunction. BDNF, as a key neurobiological factor, has shown significant potential in the rehabilitation treatment of stroke. By exploring the potential of BDNF as a therapeutic target to prevent and treat sequelae of ischemic stroke, the current research bottlenecks, and the development trends of future treatment strategies.

Keywords

Brain-Derived Neurotrophic Factor, Sequelae of Stroke, Neurorehabilitation

1. Introduction

Stroke is one of the leading causes of death and disability among adults in China. With the aging of the population in China, the incidence rate of stroke is on the rise. According to the epidemiological survey, the incidence rate of stroke in China is higher than the global average, which brings a huge burden to the social and public health system [1]. Stroke is mainly divided into two categories: ischemic stroke and hemorrhagic stroke. Among them, ischemic stroke accounts for about 80% of all strokes [2]. The best period for rehabilitation is within 3 to 6 months after stroke, and implementing rehabilitation can reduce the conversion of ischemic stroke disability to disability [3]. Modern rehabilitation theory and practice have proven that effective rehabilitation training can alleviate patients' functional disabilities [4]. Brain-derived neurotrophic factor (BDNF) is a key neurotransmitter that plays a crucial role in the development and functional maintenance of the nervous system. In recent years, with the deepening of research on BDNF, its application value in the rehabilitation of therapy has gradually received attention. This article aims to review the application progress of BDNF in the rehabilitation treatment of post-stroke sequelae and propose future research directions.

2. Relationship between BDNF and Ischemic Stroke

2.1. BDNF and Ischemic Stroke

Brain-derived neurotrophic factor (BDNF) is mainly synthesized and secreted by neurons and glial cells and is widely distributed throughout the adult brain. It plays a crucial role in neuron survival and differentiation, axonal growth, synaptic plasticity, and angiogenesis, as well as in promoting learning, regulating emotions, and memory [5]. Significant progress has been made in the study of BDNF in animal models of ischemic stroke. Numerous studies have demonstrated that BDNF levels in the brain are significantly elevated post-stroke [6]. This finding suggests that BDNF plays a pivotal role in promoting neural plasticity following brain injury. Overall, the long-term rehabilitative effects of BDNF on ischemic stroke are achieved through diverse mechanisms, including anti-ischemic actions, promotion of structural repair in damaged areas, stimulation of angiogenesis and neurogenesis, and enhancement of synaptic plasticity [7]. These effects are of great therapeutic significance for the management of post-stroke depression, motor dysfunction, and cognitive impairment.

2.2. Biological Mechanism of BDNF

After binding to the specific receptor TrkB on the axon terminals of neurons, brain-derived neurotrophic factor (BDNF) initiates a series of intracellular signaling processes. This process includes the retrograde transport of BDNF from axon terminals to the cell body, where it activates key signaling pathways such as phosphatase C γ (PLC), the Ras MAP kinase pathway, and phosphatidylinositol 3-kinase (PI3K) [8]. Additionally, BDNF can be transported to the axon terminals and released there, where it is taken up by adjacent neurons and participates in the regulation of synaptic plasticity. These biological effects underscore the multifaceted role of BDNF in the nervous system, which not only acts on local neurons but also influences the overall function of neuronal networks. The bidirectional transport mechanism of BDNF provides robust evidence for its significance in neuroprotection and nerve regeneration. These effects may hold potential application value in the treatment of neurological diseases, particularly in promoting recovery after nerve injury and alleviating symptoms of neurodegenerative diseases.

3. Application of BDNF in the Sequelae of Ischemic Stroke

3.1. BDNF and Post-Stroke Depression

Post-stroke depression (PSD) is a common complication following stroke, with patients often developing depressive states during their recovery from stroke sequelae [9]. The pathological and physiological mechanisms underlying PSD are not yet fully understood; however, the prognosis of PSD significantly impacts the quality of life for patients. Consequently, identifying effective biomarkers to predict the occurrence of post-stroke depression is of paramount importance. Li *et al.* [10] utilized immunohistochemistry and reverse transcription polymerase chain reaction (RT-PCR) to detect the expression of BDNF and TrkB proteins and mRNA in the cerebellum of ischemic stroke rat models. The findings indicated that decreased expression of BDNF and TrkB was associated with the development of PSD and depressive-like behavior. BDNF also interacts with various neurotransmitter systems, including serotonergic, glutamatergic, and GABAergic systems, which are closely related to the pathophysiology of depression [11] [12]. BDNF can cross the blood-brain barrier, and the level of BDNF in the serum of patients with depression is significantly reduced. Based on this, it is postulated that lower levels of BDNF in the serum of PSD patients may signify a breakdown in the stress adaptation system, which is unable to protect the brain from stress-induced neuronal degeneration, thus providing a potential basis for the development of depression [13].

Serum BDNF levels in patients with post-stroke depression are significantly lower, and these levels tend to decrease further as the condition progresses. This suggests a correlation between peripheral blood BDNF levels and the occurrence and severity of depression. Conventional treatments for PSD include antidepressant medications, transcranial electrical stimulation therapy, and psychological counseling. Serum BDNF levels can effectively reflect the core symptoms of depression and may offer new therapeutic avenues for future treatments. However, the critical threshold of BDNF concentration that could assist in diagnosing PSD is not yet well-defined. Moreover, key issues regarding the dosage, timing, and route of administration for BDNF as a treatment need to be clarified through rigorous scientific research and clinical trials.

3.2. BDNF and Post-Stroke Motor Dysfunction

The expression of BDNF is closely related to motor dysfunction in patients after ischemic stroke. BDNF not only provides protection to neurons from further damage, but also promotes the survival of nerve cells and the growth of axons. Research has shown that BDNF can up-regulate the expression of markers related to axonal sprouting and synaptic development, such as MAP1/2 or synaptophysin [14]. These proteins play a crucial role in the process of neural repair. After a stroke, the level of BDNF in the brain typically decreases, which may lead to increased vulnerability of nerve cells and subsequently affect the recovery of motor function [15]. Zhu *et al*. evaluated the functional recovery of neural stem cells (nSCs) modified with BDNF after transplantation and found that BDNF not only promoted neurogenesis in vitro but also significantly enhanced functional recovery after transient middle cerebral artery occlusion in vivo experiments [16]. This suggests that BDNF may facilitate neural repair by promoting the formation of new neural connections. After stroke, BDNF levels near the injury area usually increase as part of a natural repair mechanism to compensate for the decreased levels of neurotrophic. However, if the intensity of this endogenous response is insufficient to support nerve regeneration and repair, the patient's motor function recovery may be limited. BDNF is crucial for motor function recovery after stroke by promoting neuroplasticity, which refers to adaptive changes in the brain's structure and function [17].

In summary, BDNF plays a pivotal role in the recovery process of motor dysfunction following a stroke. It offers a potential therapeutic pathway for the restoration of motor function in stroke patients by protecting and repairing neurons, promoting neurogenesis, and fostering neuroplasticity. Significant improvements in motor function can be observed in animal models after thrombotic stroke through intravenous injection of BDNF. Future research should focus on how to effectively utilize these characteristics of BDNF in order to provide more precise and effective rehabilitation treatments for stroke patients.

3.3. BDNF and Cognitive Impairment after Stroke

The prevalence of cognitive impairment following stroke is indeed significant, with incidence rates reaching up to 64% [18]. This has a profound impact on the patient's recovery and overall quality of life. BDNF, as a key neurotrophic factor, is crucial throughout various stages of nervous system development. It plays a critical role in maintaining synaptic plasticity, memory encoding, and cognitive function [19].

By binding to the tyrosine kinase receptor B (TrkB), BDNF activates a series of intracellular signaling pathways, which provide essential neuroprotection for the brain and central nervous system following damage [20]. The intracellular domain of TrkB possesses intrinsic tyrosine kinase activity. Upon binding with BDNF, it becomes activated, leading to enhanced autophosphorylation of TrkB and subsequent activation of the Ras MAPK pathway. This pathway is involved in promoting the widespread opening of receptors and is integral to the regulation of cognitive function [21]. Studies have also shown that certain proteins, such as protease B and FNDC5/irisin, can cross the blood-brain barrier and regulate the expression of BDNF in the hippocampus, thereby promoting neurogenesis and improving memory [22]. BDNF is equally essential for enhancing synaptic transmission efficiency and promoting long-term potentiation (LTP), which underpins learning and memory formation [23]. The deficiency of BDNF may lead to impaired synaptic function, which in turn affects cognition.

Research has demonstrated that cognitive impairment after stroke is closely associated with reduced levels of BDNF. Detailed assessments of the cognitive status of stroke survivors have revealed a significant correlation between cognitive impairment and decreased levels of BDNF in peripheral blood, independent of the patient's demographic characteristics [24]. Chen *et al.* further validated that serum BDNF levels in stroke patients are reduced and are positively correlated with mini-mental state examination (MMSE) scores, reinforcing the importance of BDNF in cognitive function [25]. In light of these findings, the development of treatment strategies targeting BDNF is seen as a promising approach to improving cognitive impairment in stroke patients. By enhancing BDNF levels or mimicking its effects, it may be possible to significantly improve the quality of life and rehabilitation prospects for these individuals.

In summary, BDNF plays a pivotal role in the rehabilitation process of cognitive impairment after stroke. It provides the critical biological foundation for the recovery of cognitive function through various mechanisms, including the promotion of neuronal metabolism, optimization of synaptic function, and maintenance of neurotransmitter balance. Future research should focus on translating these findings into effective clinical interventions that can help stroke patients regain cognitive abilities and improve their overall recovery outcomes. This may involve the development of BDNF-based therapies, such as targeted drug delivery systems or neurotrophic factor replacements, which could be tailored to individual patient needs. Additionally, research into the potential of combining BDNF enhancement with other rehabilitation strategies, such as cognitive training and physical therapy, could yield synergistic effects that further improve cognitive recovery.

In conclusion, the role of BDNF in cognitive rehabilitation after stroke is multifaceted and promising. By addressing the underlying mechanisms of cognitive impairment and leveraging the neuroprotective and neurorestorative properties of BDNF, there is potential to create novel and effective treatments that can make a significant difference in the lives of stroke survivors. As such, BDNF remains a key focus of scientific inquiry and a hopeful avenue for future clinical applications in the realm of stroke rehabilitation.

4. Summary and Prospect

This review systematically examines the advancements in research regarding brain-derived neurotrophic factor (BDNF) within the context of post-stroke rehabilitation therapy, with a specific emphasis on its applications in three critical areas: post-stroke depression, motor dysfunction, and cognitive impairment. The high prevalence and severity of cognitive impairment following stroke present significant challenges to both rehabilitation efforts and the quality of life for affected patients, highlighting the urgent need for effective treatment strategies. While the potential therapeutic role of BDNF in addressing post-stroke sequelae has been recognized, current research is still characterized by several shortcomings and challenges. Firstly, the majority of existing studies have focused on the correlation between BDNF levels and cognitive impairment, but they often lack in-depth exploration of the mechanisms underlying changes in BDNF levels. For instance, it remains to be fully elucidated whether the reduction in BDNF levels is a consequence of the stroke itself or a direct cause of cognitive impairment, necessitating further experimental research to clarify this fundamental question. Secondly, although BDNF is known to play a crucial role in cognitive function through the activation of TrkB receptors and their downstream signaling pathways, the complexity and interplay of these signaling pathways may introduce uncertainty regarding therapeutic efficacy. Additionally, the route of administration and dosing of BDNF present significant challenges, with ensuring its safe and targeted action in the affected area being a key focus of research.

Future research should delve into the mechanism of action of BDNF, develop personalized treatment strategies, investigate novel drug delivery methods, and evaluate long-term efficacy and safety. Discovering more convenient and feasible detection methods can promptly detect changes in BDNF concentration, providing a reference for clinical treatment. Interdisciplinary collaboration will help promote the application of BDNF therapy in clinical practice, providing stroke patients with more precise and effective treatment options, thereby significantly improving their rehabilitation prospects and quality of life.

In summary, BDNF has great potential in the treatment of cognitive impairment after stroke. By deepening research and overcoming current limitations, we are expected to provide more efficient treatment methods for stroke patients, thereby significantly improving their quality of life.

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Conflict of Interest

All authors declare that there has not been any commercial or associative interest that represents competing interests in connection with the work submitted.

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