Chapter

Sepsis and Brain-Derived Neurotrophic Factor (BDNF): Exploring the Complex Connection

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Abstract

In recent studies, brain-derived neurotrophic factor (BDNF) become a very important position. Because it is now known that it is not just a hormone that is released from the hippocampus and which supports the differentiation and growth of newly formed nerve cells and synapses while maintaining the vitality of existing neurons. Today BDNF was used as an indicator of severe sepsis and also in the follow-up of the disease. Moreover, BDNF is a potential anti-inflammatory agent which can be given like a medicament. In some studies, antiinflammatory effect was proven "in acute lung injury, in myocardial injury, in hepatorenal injury" triggered by sepsis. In this chapter, we will try to explain the BDNF effect in sepsis according to recent literature and update our knowledge.

Keywords: sepsis, BDNF, Antiinflammation, multiorgan failure, oxidative stress, biomarker

1. Introduction

Sepsis is a life-threatening condition caused by a dysregulated response to infection that can lead to organ dysfunction and failure [1]. Despite advances in medical care, sepsis remains a significant global health concern. Researchers have been investigating various aspects of sepsis pathophysiology to improve understanding and identify potential therapeutic targets [2]. One such area of exploration is the role of brain-derived neurotrophic factor (BDNF), a key protein involved in neuronal survival, growth, and plasticity [3]. Recent studies suggest that BDNF may play a crucial role in sepsis-associated brain dysfunction, contributing to long-term cognitive impairment observed in septic patients [4, 5]. This review aims to delve into the complex connection between sepsis and BDNF, discussing the underlying mechanisms, clinical implications, and potential therapeutic interventions.

2. Sepsis: A brief overview

2.1 Definition and prevalence of sepsis

Sepsis is a life-threatening condition characterized by a dysregulated immune response to an infection. It occurs when the body's response to infection becomes overwhelming, leading to widespread inflammation and organ dysfunction [1]. Sepsis can progress rapidly and result in septic shock, a severe form of the condition associated with dangerously low blood pressure and inadequate blood flow to vital organs. The prevalence of sepsis is significant worldwide, with millions of cases reported each year [1, 2]. It affects individuals of all ages, but the elderly, young children, and those with weakened immune systems are particularly vulnerable.

2.2 Pathophysiology and immune response in sepsis

The pathophysiology of sepsis involves a complex interplay between the immune system, inflammatory mediators, and invading pathogens. When an infection occurs, the immune system initiates a response to control and eliminate the pathogens [4]. However, in sepsis, the immune response becomes dysregulated, leading to an excessive release of pro-inflammatory cytokines and the activation of immune cells. This immune activation triggers a cascade of events that can result in damage to organs and tissues throughout the body [2, 5].

2.3 Clinical manifestations and complications of sepsis

The clinical manifestations of sepsis can vary widely, making early diagnosis challenging [5]. Common signs and symptoms include fever, increased heart rate, rapid breathing, and altered mental status [4]. As sepsis progresses, patients may experience organ dysfunction, such as respiratory failure, acute kidney injury, or cardiovascular collapse. If septic shock develops, additional complications can arise, including multiple organ failure and disseminated intravascular coagulation (DIC), a condition characterized by abnormal blood clotting [6].

The complications associated with sepsis can have long-lasting effects on patients' health and quality of life. Survivors of sepsis may experience physical, cognitive, and psychological impairments. Cognitive dysfunction, often referred to as sepsis-associated encephalopathy (SAE), is a common neurological complication characterized by confusion, memory loss, and difficulty concentrating. Moreover, sepsis survivors may be at an increased risk of developing post-sepsis syndrome, a condition characterized by persistent fatigue, muscle weakness, and mood disturbances [4, 7].

In conclusion, sepsis is a severe and life-threatening condition characterized by a dysregulated immune response to infection. Its pathophysiology involves a complex interplay of immune mediators, leading to widespread inflammation and organ dysfunction. Prompt recognition and early intervention are critical to improving patient outcomes. The clinical manifestations of sepsis can be diverse, and its complications can have long-term effects on survivors. Further research and advancements in sepsis management are necessary to reduce its burden and improve patient care.

3. Introduction to brain-derived neurotrophic factor (BDNF)

3.1 BDNF: Structure, synthesis, and function

BDNF is a protein that belongs to the neurotrophin family. It is widely expressed in the central nervous system, including the brain and spinal cord. BDNF is synthesized as a precursor molecule called proBDNF, which is then cleaved to form mature BDNF. The mature form of BDNF is secreted and acts upon specific receptors to exert its biological effects [8].

BDNF plays a crucial role in promoting the survival, growth, and maintenance of neurons. It supports neuronal function and plasticity by influencing various cellular processes, including synaptic transmission, dendritic growth, and neuronal connectivity. BDNF also has neuroprotective properties and can modulate neuronal responses to injury and stress [9].

3.2 DNF and neuronal development

During early development, BDNF is involved in guiding the formation and connectivity of neurons. It promotes neuronal survival and influences the growth and branching of dendrites and axons. BDNF is particularly important in the development of the central nervous system, including the formation of neural circuits and the establishment of synaptic connections [9].

Studies have shown that BDNF plays a critical role in neurogenesis, the process of generating new neurons. It regulates the proliferation, differentiation, and survival of neural stem cells and progenitor cells. By promoting the production and integration of new neurons, BDNF contributes to the plasticity and adaptability of the developing brain [10].

3.3 Role of BDNF in synaptic plasticity and cognition

Synaptic plasticity refers to the ability of synapses to modify their strength and connectivity in response to activity and experience. BDNF is a key player in synaptic plasticity, particularly in long-term potentiation and long-term depression, which are fundamental processes underlying learning and memory [10].

BDNF promotes the formation and stabilization of synapses, enhances synaptic transmission, and modulates the structural and functional properties of synapses. It acts by binding to its specific receptor, tropomyosin receptor kinase B (TrkB), and activating intracellular signaling pathways that lead to changes in gene expression and neuronal function [11, 12].

In the context of cognition, BDNF is crucial for various forms of learning and memory. Studies have demonstrated that BDNF levels increase during learning tasks, and disruptions in BDNF signaling can impair cognitive function. BDNF influences the synaptic changes necessary for memory formation and retrieval, and it is involved in the maintenance of cognitive processes such as attention, executive function, and synaptic plasticity [9–12].

In summary, BDNF is a vital protein involved in neuronal development, synaptic plasticity, and cognitive processes. It supports the survival and growth of neurons, guides neuronal connectivity during development, and plays a key role in synaptic plasticity and memory formation. The intricate functions of BDNF make it a compelling candidate for investigating its involvement in sepsis-associated brain dysfunction (**Figure 1**).

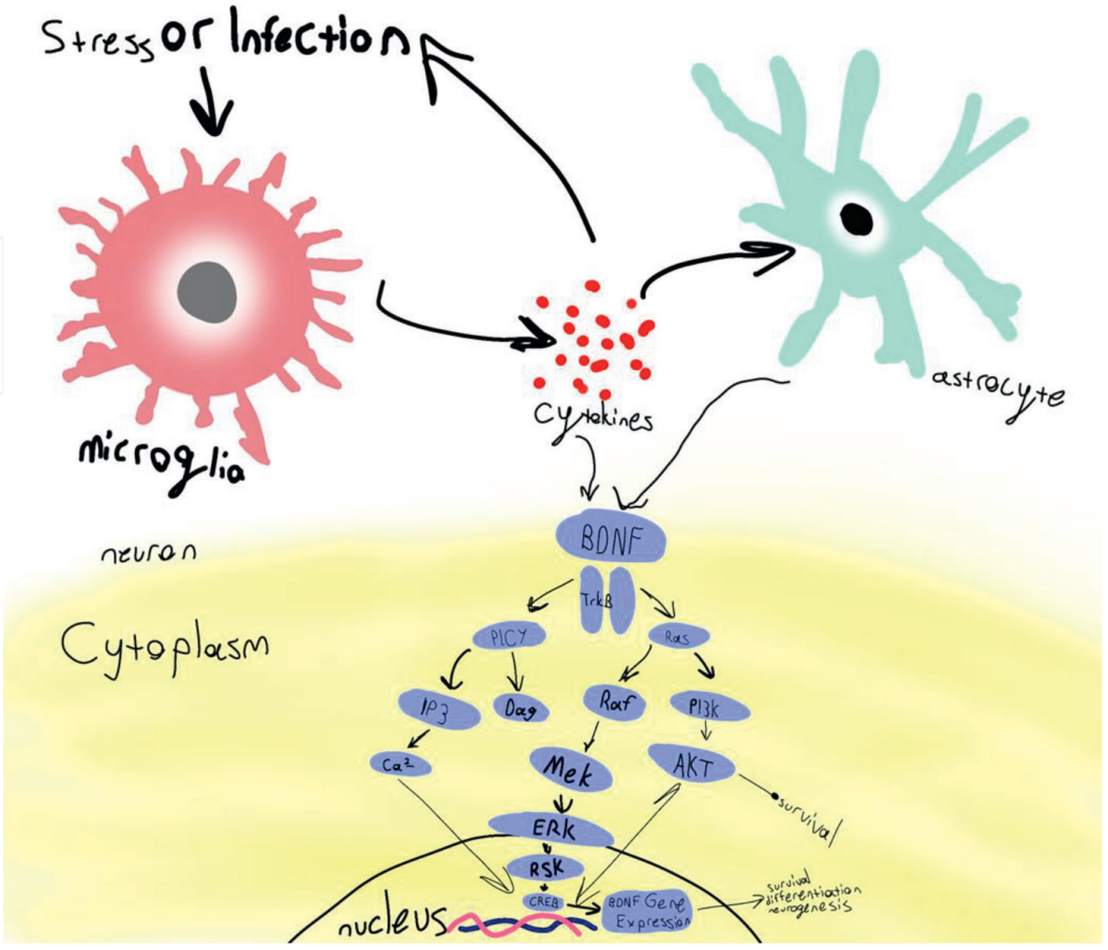

Figure 1.
The role of BDNF in the Neuroimmune Axis regulation (thank you to Derin Mavi bora for her support in this figure).

4. Sepsis-associated brain dysfunction

4.1 Understanding sepsis-associated encephalopathy (SAE)

SAE refers to the neurological dysfunction and cognitive impairment observed in patients with sepsis [13]. It is a common complication of sepsis, affecting a significant proportion of patients. SAE is characterized by a range of cognitive deficits, including confusion, delirium, memory impairment, attention deficits, and alterations in consciousness [13, 14]. It can have a significant impact on patient outcomes and contribute to long-term cognitive impairment.

The exact mechanisms underlying SAE are not fully understood, but several factors likely contribute to its development. These include the direct effects of the infectious agents or their byproducts, the systemic inflammatory response, and the impact of altered cerebral blood flow and oxygenation [14, 15]. The multifactorial nature of SAE makes it a complex condition to study and manage effectively.

4.2 Mechanisms of brain injury in sepsis

Sepsis can lead to brain injury through various mechanisms. The systemic inflammatory response in sepsis triggers the release of pro-inflammatory cytokines

and other inflammatory mediators, which can cross the blood-brain barrier and induce neuroinflammation [15]. Neuroinflammation contributes to the disruption of normal brain function and can lead to neuronal damage and death.

Another mechanism of brain injury in sepsis is the dysregulation of cerebral blood flow [16, 17]. Sepsis can result in abnormal vascular function, including microvascular dysfunction and impaired autoregulation. These alterations in blood flow can lead to hypoxia and ischemia in the brain, causing neuronal injury.

Additionally, sepsis-induced oxidative stress plays a crucial role in brain injury. Increased production of reactive oxygen species (ROS) overwhelms the antioxidant defense mechanisms, leading to oxidative damage to neuronal cells [18]. Oxidative stress can impair cellular structures, disrupt neurotransmitter balance, and promote neuroinflammation, ultimately contributing to cognitive dysfunction in septic patients.

4.3 Neuroinflammation and oxidative stress in septic brains

Neuroinflammation and oxidative stress are closely intertwined processes that play significant roles in sepsis-associated brain dysfunction. The release of pro-inflammatory cytokines, such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), activates resident immune cells in the brain, such as microglia, leading to inflammatory response [16, 17]. Activated microglia produce additional pro-inflammatory mediators, perpetuating neuroinflammation.

Neuroinflammation can disrupt the delicate balance of neurotransmitters in the brain, impair synaptic transmission, and contribute to neuronal dysfunction. It also activates signaling pathways that induce the expression of enzymes that generate reactive oxygen species, exacerbating oxidative stress [18]. Oxidative stress, in turn, leads to lipid peroxidation, protein oxidation, and DNA damage in neuronal cells, further compromising their function and viability [19].

The combination of neuroinflammation and oxidative stress creates a detrimental cycle in septic brains, leading to progressive brain injury and cognitive impairment [20]. The sustained activation of inflammatory responses and the accumulation of oxidative damage contribute to the long-term consequences of sepsis-associated brain dysfunction [21].

In summary, sepsis-associated brain dysfunction involves complex mechanisms of brain injury, including neuroinflammation and oxidative stress. The systemic inflammatory response, altered cerebral blood flow, and oxidative damage collectively contribute to cognitive impairment and neurological dysfunction observed in septic patients. Understanding these mechanisms is crucial for the development of targeted therapeutic strategies aimed at mitigating brain injury and improving outcomes in sepsis.

5. The complex relationship between sepsis and BDNF

5.1 Dysregulation of BDNF in sepsis

Sepsis disrupts the normal regulation of BDNF expression and release in the brain, leading to dysregulation of this crucial neurotrophic factor. Studies have shown that sepsis is associated with reduced BDNF levels in various brain regions, including the hippocampus and cortex [22]. The dysregulation of BDNF in sepsis may result from the systemic inflammatory response, oxidative stress, and alterations in neurotransmitter balance [18, 19].

The release of pro-inflammatory cytokines during sepsis, such as IL-1β and TNF-α, can directly impact BDNF expression. These cytokines have been shown to downregulate BDNF mRNA and protein levels, contributing to the overall decrease in BDNF availability in septic brains [19, 20]. Additionally, the dysregulation of neurotransmitters, particularly glutamate and gamma-aminobutyric acid (GABA), in sepsis can influence BDNF expression, as these neurotransmitters have been shown to modulate BDNF gene transcription.

5.2 Impact of sepsis on BDNF Signaling pathways

BDNF exerts its effects on neurons by binding to its receptor, TrkB, and activating downstream signaling pathways. However, in sepsis, alterations in BDNF signaling pathways have been observed, further contributing to sepsis-associated brain dysfunction [11, 12].

The dysregulation of BDNF-TrkB signaling in sepsis can occur at multiple levels. Sepsis-induced inflammatory mediators, such as IL-1β and TNF-α, can interfere with TrkB receptor activation and downstream signaling cascades, impairing BDNF's neuroprotective effects [12]. Additionally, oxidative stress, which is prevalent in sepsis, can disrupt BDNF signaling pathways, leading to impaired neuroplasticity and synaptic function [23].

Furthermore, sepsis-induced alterations in intracellular signaling pathways, such as the mitogen-activated protein kinase (MAPK) pathway and the phosphoinositide 3-kinase (PI3K)/Akt pathway, can impact BDNF-mediated cellular processes [24]. Dysregulation of these pathways can compromise neuronal survival, synaptic plasticity, and cognitive function, which are key functions influenced by BDNF [24, 25].

5.3 Experimental evidence supporting the involvement of BDNF in sepsis-associated brain dysfunction

Experimental studies have provided compelling evidence for the involvement of BDNF in sepsis-associated brain dysfunction. Animal models of sepsis have demonstrated dysregulation of BDNF expression and signaling in the brain, leading to cognitive impairment and neuronal damage [25, 26].

In these animal models, sepsis-induced neuroinflammation and oxidative stress have been shown to downregulate BDNF expression and impair BDNF signaling pathways. This dysregulation is associated with cognitive deficits, including memory impairment and learning difficulties [27]. Conversely, interventions that enhance BDNF signaling, such as BDNF supplementation or pharmacological agents targeting BDNF pathways, have shown promising results in mitigating cognitive dysfunction and reducing brain injury in septic animals [28].

Furthermore, clinical studies have provided evidence supporting the involvement of BDNF in sepsis-associated brain dysfunction in human patients. Reduced BDNF levels have been observed in the serum and cerebrospinal fluid of septic patients with cognitive impairment compared to those without neurological complications [29, 30]. These studies have also revealed a correlation between lower BDNF levels and worse long-term cognitive outcomes in septic patients.

These findings highlight the potential role of BDNF as a diagnostic and prognostic marker for sepsis-associated brain dysfunction. Furthermore, they suggest that targeting BDNF and modulating its signaling pathways could be a therapeutic approach to mitigate sepsis-induced brain injury and cognitive impairment [30, 31]. Strategies aimed at restoring BDNF levels or enhancing BDNF signaling may hold promise for improving outcomes in septic patients.

In conclusion, the relationship between sepsis and BDNF is complex and multifaceted. Sepsis disrupts the normal regulation of BDNF expression and impairs its signaling pathways in the brain, contributing to sepsis-associated brain dysfunction. The dysregulation of BDNF in sepsis is influenced by factors such as systemic inflammatory response, oxidative stress, and alterations in neurotransmitter balance. Experimental evidence from animal models and clinical studies supports the involvement of BDNF in sepsis-associated cognitive impairment and brain injury.

Understanding the intricate interplay between sepsis and BDNF is crucial for the development of targeted interventions to mitigate sepsis-associated brain dysfunction. Further research is needed to unravel the specific mechanisms by which sepsis dysregulates BDNF and to explore therapeutic strategies aimed at modulating BDNF signaling [31]. By elucidating the role of BDNF in sepsis-associated brain dysfunction, we can pave the way for potential interventions that could improve patient outcomes and reduce the long-term cognitive consequences of sepsis.

Overall, the complex relationship between sepsis and BDNF highlights the importance of investigating the molecular and cellular mechanisms underlying sepsis-associated brain dysfunction. By advancing our understanding of this relationship, we can potentially identify novel therapeutic targets and develop strategies to preserve brain function and improve the quality of life for septic patients.

6. Clinical implications and diagnostic potential

6.1 Biomarker potential of BDNF in sepsis

One of the clinical implications of the relationship between sepsis and BDNF lies in the biomarker potential of BDNF for sepsis diagnosis and prognosis. BDNF levels have been investigated as potential biomarkers to aid in the early detection of sepsis and assess disease severity [32]. Reduced BDNF levels have been observed in septic patients, particularly those with sepsis-associated brain dysfunction. Monitoring BDNF levels could serve as a useful tool in identifying patients at risk of developing cognitive impairment and neurological complications in sepsis.

6.2 BDNF as a predictor of long-term cognitive outcomes in septic patients

The dysregulation of BDNF in sepsis may have implications for long-term cognitive outcomes in septic patients. Clinical studies have shown a correlation between lower BDNF levels and worse cognitive function in septic patients. BDNF could serve as a potential predictor of long-term cognitive impairment and aid in stratifying patients based on their risk of cognitive decline following sepsis [33, 34]. This information could guide post-sepsis management and rehabilitation strategies, allowing for targeted interventions to improve cognitive outcomes.

6.3 BDNF-targeted therapeutic strategies for sepsis-associated brain dysfunction

Given the involvement of BDNF in sepsis-associated brain dysfunction, targeting BDNF and its signaling pathways may offer potential therapeutic strategies. The restoration of BDNF levels or the enhancement of BDNF signaling could help mitigate brain injury and cognitive impairment in septic patients [34].

Pharmacological approaches, such as exogenous BDNF supplementation or pharmacological agents that promote BDNF release or enhance TrkB receptor activation, are being investigated as potential therapeutic interventions. These approaches aim to counteract the dysregulation of BDNF in sepsis and restore its neuroprotective and neuroplasticity-promoting effects [32, 33].

Non-pharmacological interventions, such as physical exercise and environmental enrichment, have also shown promise in upregulating BDNF levels and improving cognitive function in animal models [35]. These interventions may have translational potential for septic patients, as they are relatively safe and accessible therapeutic strategies that could be incorporated into post-sepsis rehabilitation programs.

However, it is important to note that the translation of BDNF-targeted therapeutic strategies into clinical practice requires further research and rigorous clinical trials. The complexity of sepsis and the multifactorial nature of sepsis-associated brain dysfunction necessitate a comprehensive understanding of the mechanisms involved and careful evaluation of potential therapeutic interventions.

In conclusion, BDNF holds clinical implications and diagnostic potential in the context of sepsis-associated brain dysfunction. It has the potential to serve as a biomarker for sepsis diagnosis and prognosis, as well as a predictor of long-term cognitive outcomes in septic patients. Additionally, BDNF-targeted therapeutic strategies, both pharmacological and non-pharmacological, offer promising avenues for mitigating sepsis-induced brain injury and cognitive impairment. Further research and clinical trials are needed to validate the clinical utility of BDNF and to develop effective interventions for improving outcomes in septic patients.

7. Conclusion

7.1 Recap of the complex connection between sepsis and BDNF

The relationship between sepsis and BDNF is multifaceted. Sepsis dysregulates BDNF expression and signaling, contributing to sepsis-associated brain dysfunction. The dysregulation of BDNF is influenced by factors such as the systemic inflammatory response, oxidative stress, and alterations in neurotransmitter balance. Experimental evidence from animal models and clinical studies supports the involvement of BDNF in sepsis-associated cognitive impairment and brain injury.

7.2 Importance of further research in understanding and targeting BDNF in septic patients

To fully harness the potential of BDNF as a diagnostic marker and therapeutic target in septic patients, further research is necessary. Understanding the molecular and cellular mechanisms underlying the dysregulation of BDNF in sepsis is crucial. Additionally, rigorous clinical trials are needed to evaluate the safety and efficacy of BDNF-based interventions in mitigating sepsis-associated brain dysfunction.

7.3 Potential for BDNF-based interventions to mitigate sepsis-associated brain dysfunction and improve patient outcomes

Despite the challenges, BDNF-based interventions hold promise for improving outcomes in septic patients. Strategies aimed at restoring BDNF levels or enhancing

BDNF signaling pathways may help mitigate sepsis-induced brain injury, preserve brain function, and improve cognitive outcomes [35]. The potential diagnostic and prognostic value of BDNF in sepsis further emphasizes the importance of investigating and targeting BDNF in septic patients.

In conclusion, the complex connection between sepsis and BDNF highlights the need for further research and clinical exploration. By unraveling the intricacies of BDNF dysregulation and developing effective interventions, we can potentially improve the diagnosis, prognosis, and management of sepsis-associated brain dysfunction, ultimately leading to better outcomes for septic patients.

Conflict of interest

The authors declare no conflict of interest.

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