Chapter

The Role of Brain-Derived Neurotrophic Factor in Autism Spectrum Disorder: Current Findings and Future Directions

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Abstract

Brain-derived neurotrophic factor (BDNF) is a crucial neurotrophic factor that plays an essential role in neuroplasticity and neurodevelopment. Autism spectrum disorder (ASD) is a neurodevelopmental disorder that affects social interaction, communication, and behavior. The relationship between BDNF and ASD has been studied extensively, with conflicting results. While some studies suggest that decreased BDNF levels may contribute to the development of ASD, others do not confirm this finding. The effects of BDNF on synaptic plasticity and cognitive functions have also been investigated, with some studies indicating that BDNF may be associated with impairments in learning, memory, and attention in individuals with ASD. Additionally, physical exercise and cognitive and behavioral therapies may help alleviate ASD symptoms by increasing BDNF levels and enhancing neuroplasticity. Further research is needed to better understand the mechanisms underlying the relationship between BDNF and ASD and to develop more effective treatment strategies for individuals with ASD.

Keywords: BDNF, autism spectrum disorder, neuroplasticity, cognitive functions, therapeutic interventions

1. Introduction

The growth and plasticity of the brain are significantly influenced by the protein BDNF. A neurodevelopmental disorder called Autism spectrum disorder (ASD) causes social and behavioral difficulties. Numerous experts have conducted considerable study on the link between BDNF and ASD.

A neurotrophic factor known as BDNF helps neurons across the central nervous system to survive, develop, differentiate, and function. The nervous system's capacity to adapt to structural and functional changes is known as neuroplasticity. Understanding how BDNF affects neuroplasticity is important for learning, memory, and cognitive functions as well as for understanding the origins and therapies of neurological and neuropsychiatric illnesses.

2. The effect of BDNF on neuroplasticity

BDNF plays a critical role in regulating synaptic plasticity processes. Synaptic plasticity can be defined as the strengthening or weakening of synapses, leading to changes in the connections between neurons. BDNF particularly influences the following neuroplasticity processes: [1–3].

1. Synaptogenesis: BDNF promotes the formation of synapses and the development of connections between nerve cells.

2. Dendritic growth and arborization: BDNF supports the development and complexity of neurons' dendritic trees, thereby increasing the number of connections between nerve cells.

3. Synaptic transmission and modulation: BDNF regulates the effectiveness of synaptic transmission and modulation of synapses, which are critical for learning and memory processes.

4. Structural reorganization and neuronal migration: BDNF plays a significant role in the structural organization and reorganization of the brain by regulating the migration and settlement of neurons.

5. Neuronal survival and neuroprotection: BDNF provides protection against neuronal damage by regulating the expression of factors necessary for neurons' survival, growth, and differentiation.

2.1 BDNF and Learning, Memory, and Cognitive Functions

Neuroplasticity is considered a fundamental mechanism in learning and memory processes, and BDNF's effects on these processes are of great importance. BDNF is particularly associated with the following cognitive functions: [2–4].

1. Learning and memory: The hippocampus and prefrontal cortex are particularly where BDNF influences learning and memory processes. As BDNF levels rise, synaptic connections between nerve cells become stronger and more synapses are formed, which enhances the potential for learning and memory. Impaired memory and learning might result from BDNF insufficiency.

2. Processing speed and focus: BDNF is also essential in controlling cognitive processes including processing speed and attentiveness. Levels of BDNF have been demonstrated to be positively correlated with attention and processing speed. Additionally, attention-deficit/hyperactivity disorder (ADHD) and other cognitive function abnormalities have been linked to BDNF insufficiency.

3. Executive functions: BDNF is essential for the development and regulation of executive functions as well as for controlling the prefrontal cortex's functioning. High-level cognitive activities including problem-solving, planning, adaptability, and thinking organizing are included in executive functions. Executive function issues and poor cognitive flexibility may result from BDNF insufficiency.

2.2 BDNF and neurological and neuropsychiatric disorders

The regulation of neuroplasticity and BDNF plays a significant role in the pathogenesis and treatment of neurological and neuropsychiatric disorders. Decreased BDNF levels and impaired neuroplasticity processes have been associated with the following diseases: [2–4].

1. Depression and anxiety: Reduced BDNF levels and impaired neuroplasticity processes are associated with the pathogenesis of depression and anxiety disorders. Antidepressants and other pharmacological treatments are thought to be effective by increasing BDNF levels and supporting neuroplasticity.

2. Schizophrenia: Schizophrenia has been associated with impairments in synaptic function and neuroplasticity processes, and decreased BDNF levels are also observed in this disorder. Antipsychotic drugs used in the treatment of schizophrenia are believed to be effective by increasing BDNF levels and supporting neuroplasticity.

3. Alzheimer's disease and other neurodegenerative conditions: The pathophysiology of Alzheimer's disease, Parkinson's disease, and other neurodegenerative conditions is linked to neuronal damage and compromised neuroplasticity processes. BDNF levels have been found to be decreased in many disorders, and its neuroprotective properties are thought to be a possible target for their therapy.

4. ASD (Autism spectrum disorder): ASD is a neurodevelopmental condition marked by challenges with social interaction and communication as well as confined, monotonous, and stereotyped behaviors. Because BDNF levels are low in ASD, its effects on neuroplasticity are thought to have a possible involvement in the etiology and management of ASD.

2.3 BDNF and neuroplasticity: applications and future research directions

Current research on BDNF and neuroplasticity has provided important insights into the understanding and treatment of neurological and neuropsychiatric disorders [1]. Some important areas of future research that could be focused on in this field include:

1. Drug development: New treatment strategies that regulate BDNF levels and support neuroplasticity processes may be potentially effective in the treatment of neurological and neuropsychiatric disorders. Research in this area should aim to discover new pharmacological compounds and enhance the effectiveness of current treatments [2].

2. Behavioral and lifestyle interventions: Research could investigate the effects of physical activity, diet, and other lifestyle factors on increasing BDNF levels and neuroplasticity naturally. Such interventions could provide a complementary approach for the prevention and treatment of neurological and neuropsychiatric disorders [3].

3. Neurodevelopmental processes and aging: Research on BDNF and neuroplasticity could contribute to a better understanding of neurodevelopmental processes

in early life and cognitive and neurological changes associated with aging. Such studies could lead to the development of specific strategies to support neuroplasticity at different stages of life [4].

4. Personalized medicine: Research on BDNF and neuroplasticity could help determine the impact of individual genetic and environmental factors on disease risk and treatment effectiveness. Such information could contribute to the development of personalized treatment approaches and more effective management of neurological and neuropsychiatric disorders [5, 6].

Future research on BDNF and neuroplasticity has a great potential to provide a better understanding of how neuronal and synaptic functions change in different disease states and stages of life. Specifically, gaining more knowledge on how BDNF and neuroplasticity mechanisms interact and influence each other could lead to the development of more effective treatment strategies and better management of neurological and neuropsychiatric disorders. Progress in this field could play an important role in improving patients' quality of life and contributing to public health.

3. BDNF's biological and functional properties and effects

3.1 Biological properties of BDNF

BDNF is a protein produced in nerve cells in the brain and plays an important role in many biological processes such as neurodevelopment and synaptic plasticity [7]. BDNF is converted from proBDNF, a protein synthesized in brain cells and sent to neurons, to mature BDNF (mBDNF) by proteolytic cleavage [8]. BDNF is particularly expressed in brain regions such as the hippocampus, prefrontal cortex, striatum, and amygdala [9, 10].

3.2 Functional properties and effects of BDNF

BDNF is a protein that affects communication between neurons in the brain and plays an important role in many biological processes such as neurodevelopment and synaptic plasticity [6]. BDNF promotes the growth and healthy development of neurons. Moreover, BDNF strengthens synaptic connections between neurons and supports the formation of new synaptic connections [7, 8]. BDNF is also important for learning and memory and plays a role in memory formation [9]. BDNF also plays an important role in regulating stress response and mood [10].

The effects of BDNF are mediated through receptors. BDNF binds to a receptor called TrkB to promote the growth and healthy development of neurons [6]. Additionally, TrkB receptor strengthens synaptic connections between neurons and supports the formation of new synaptic connections [11]. TrkB receptors are also responsible for the effects of BDNF on learning and memory formation [12].

As BDNF plays a significant role in regulating nervous system functions, BDNF levels can vary in many diseases associated with processes such as neurodevelopment and synaptic plasticity [13]. Therefore, BDNF levels are also used as a potential biomarker for the pathophysiology, diagnosis, and treatment of neuropsychiatric disorders [14].

3.3 BDNF and neurodevelopment

BDNF promotes the growth, migration, and differentiation of nerve cells during neurodevelopment. BDNF also assists nerve cells in forming the proper connections. A deficiency in BDNF can result in errors in neurodevelopment and the failure of neurons to make the proper connections [11]. The effects of BDNF on neurodevelopment have been studied extensively in relation to neurodevelopmental disorders [12].

3.4 BDNF gene expression

BDNF gene expression is necessary for the production of BDNF protein. The BDNF gene can be expressed by neurons and other cell types [13]. BDNF gene expression is influenced by many factors, such as activity, stress, and neurodevelopmental processes [14]. BDNF gene expression has been studied extensively in relation to neurodevelopmental disorders and other brain diseases [9].

3.5 BDNF's roles in different brain regions

The roles of BDNF vary in different regions of the brain. In the hippocampus, BDNF is involved in learning and the formation of memories [15]. BDNF also plays a crucial role in regulating stress response and emotion in the prefrontal cortex [16]. Additionally, other brain regions such as the striatum and amygdala also rely on BDNF for proper functioning [17].

4. Autism spectrum disorder

Autism spectrum disorder (ASD) is a condition that stems from the interplay of both genetic and environmental elements and affects neurodevelopment. ASD is defined by symptoms such as challenges with social interactions, communication deficits, and repetitive and restricted behavior patterns [18].

1. Pathophysiology of ASD:

   The exact cause of autism spectrum disorder (ASD) remains unclear, but it is thought to be the result of a complex interplay between genetic, epigenetic, and environmental factors affecting the development and function of the brain [19]. Many researchers suggest that ASD arises from dysfunctions in brain development and function [20]. Brain development is related to the proper migration, differentiation, and connection of neurons. In addition, the proper formation and function of synaptic connections between nerve cells is also important [21].

2. Relationship between ASD Neurodevelopment and BDNF

   The relationship between the neurodevelopmental abnormalities in ASD and BDNF has been studied by many researchers. It has been found that BDNF levels are decreased in individuals with ASD, especially in those with low functional levels on the autism spectrum [22, 23]. In contrast, BDNF receptor levels in individuals with ASD are normal or increased [24].

3. BDNF and ASD Symptoms:

   BDNF is a key factor in synaptic plasticity and neurodevelopment, and a decrease in its levels may be linked to the symptoms of ASD. Specifically, a decrease in BDNF levels can result in an increase in social interaction difficulties and repetitive behaviors among individuals with ASD [25]. Additionally, the decreased BDNF levels observed in individuals with ASD have been linked to emotional disorders and increased obsessive-compulsive behaviors [26].

4. BDNF, ASD Treatment, and Medications:

   BDNF may be a potential target in the treatment of ASD. The neurodevelopmental effects of BDNF can be used to improve brain function in individuals with ASD [27]. Increasing BDNF levels may increase synaptic plasticity and reduce ASD symptoms. Therefore, drugs that increase BDNF levels are being investigated as a potential strategy in the treatment of ASD [28].

ASD and BDNF Gene Expression: Decreased expression levels of the BDNF gene in individuals with ASD may be associated with developmental dysfunctions. Some studies have shown that BDNF gene expression levels may be decreased in individuals with ASD [29, 30].

BDNF and ASD Medications: Drugs that increase BDNF levels are being evaluated as a potential strategy for ASD treatment [31]. For example, antidepressant drugs such as selective serotonin reuptake inhibitors (SSRIs) are thought to reduce ASD symptoms by increasing BDNF levels [32]. Additionally, BDNF agonists are being investigated as a potential treatment strategy for reducing ASD B symptoms [33].

4.1 Clinical features, diagnosis, and treatment of autism spectrum disorder

Early childhood is when autism spectrum disorder (ASD) first appears. ASD is characterized by challenges with social interaction and communication as well as limited and repetitive behavioral patterns. The three core characteristics of ASD, as defined by the DSM-5, include difficulties with social interaction and communication, as well as restricted interests and repetitive behaviors. These signs can be mild to severe and last a person their entire life [18]. A thorough assessment of a child's behavioral traits, such as social interaction, language and communication abilities, repetitive habits, and interests, can lead to the diagnosis of ASD. Specialists frequently utilize standardized tests and autism screening instruments to make their diagnoses. However, identifying ASD cannot be done with a single test or clear indication. Input from a child's family, teachers, and other healthcare experts may also be included in a thorough review [34]. Multidisciplinary therapy is necessary for ASD. A child's treatment frequently starts as early as feasible and lasts their entire lives. Education, speech and language therapy, behavior therapy, family counseling, and medication are all possible treatment modalities. Children can have better results with early diagnosis and treatment [35].

5. BDNF and autism spectrum disorder

BDNF is a member of the neurotrophic factor family and is critical for neurological functions such as neuroplasticity and neurogenesis. BDNF functions as a protein that regulates the growth, maturation, survival, and synaptic plasticity of neurons [36].

Changes in BDNF levels in individuals with autism spectrum disorder (ASD) may contribute to the pathophysiology of ASD. Many researchers have found evidence that changes in BDNF levels may be associated with ASD. Some studies have shown that BDNF levels are lower in individuals with ASD and that these lower levels are associated with ASD symptoms [37]. However, other studies suggest that normal BDNF levels may be associated with ASD. For example, one study found that individuals with ASD had normal BDNF levels compared to a control group, but differences in the regional distribution of BDNF in the brain may contribute to ASD symptoms [38]. Additionally, genetic variations in the BDNF gene have been investigated in individuals with ASD. One study found that certain variations in the BDNF gene were associated with an increased risk of ASD [39]. However, another study found that these variations in the BDNF gene were not associated with ASD [40]. The relationship between BDNF and ASD is not yet fully understood and further research is needed in this area. Taken together, the evidence discussed suggests that BDNF may have an important role in the pathophysiology of ASD, although the precise nature of this role warrants further research.

The relationship between ASD and BDNF may be important for the pathophysiology of ASD, and further research in this area is needed. Many researchers have shown that BDNF levels are decreased in individuals with ASD and that these low levels are associated with ASD symptoms. However, other studies suggest that normal BDNF levels may also be associated with ASD.

BDNF levels may be used as a potential therapeutic target to alleviate ASD symptoms. A study has shown that BDNF deficiency in mice leads to ASD-like symptoms and that BDNF infusion can reverse these symptoms. This study suggests that BDNF may be a potential agent for ASD treatment.

In conclusion, while the relationship between ASD and BDNF is not yet fully understood, it is known that BDNF is critical for neurological functions such as neuroplasticity and neurogenesis and may play a role in ASD pathophysiology. The diagnosis and treatment of ASDB require a multidisciplinary approach, and early diagnosis and treatment may help achieve better outcomes. BDNF levels may be used as a potential therapeutic target in ASD treatment.

6. BDNF's role in the pathophysiology of autism spectrum disorder and clinical outcomes

Although the exact role of BDNF in the pathophysiology of ASD is still not fully understood, studies in this area have made significant progress. Changes in BDNF levels have been shown to be associated with ASD, and BDNF receptors and signaling pathways are also thought to play an important role in ASD pathophysiology.

6.1 Changes in BDNF levels

Changes in BDNF levels may be related to ASD pathophysiology. Some studies have shown low levels of BDNF in individuals with ASD [41–45]. These low levels have also been suggested to be associated with ASD symptoms [42]. Some research suggests that changes in BDNF levels are associated with factors that affect BDNF production in the brain. For example, one study showed that maternal antibodies inhibited BDNF production in fetal mice, resulting in ASD-like symptoms [46]. Another study showed that early-life stress in mice resulted in decreased BDNF levels, which were associated with ASD-like symptoms [47].

6.2 BDNF receptors and signaling pathways

BDNF's effects are mediated by tropomyosin receptor kinase B (TrkB) receptors, which are high-affinity receptors on the cell surface [48]. Activation of TrkB receptors by BDNF affects a series of signaling pathways critical for neurological functions such as neuroplasticity and neurogenesis [49]. BDNF activates signaling pathways that affect many neurological functions, including neurotransmitter release, synaptic plasticity, cell proliferation, and cell differentiation, through TrkB receptors [50, 51]. Therefore, the role of TrkB receptors and these signaling pathways in the pathophysiology of ASD is also being investigated.

Some studies have shown that TrkB receptor levels are low in individuals with ASD [51]. These low levels may contribute to ASD pathophysiology by reducing the effects of BDNF. In addition, other components of BDNF signaling pathways may also play a role in the pathophysiology of ASD. For example, a study showed that the phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway is involved in BDNF's neuroprotective effects and may also play an important role in the pathophysiology of ASD [52].

6.3 Clinical implications of BDNF and ASD

While the exact role of BDNF in ASD pathophysiology is not fully understood, research in this area has made significant progress. Changes in BDNF levels have been shown to be associated with ASD, and BDNF receptors and signaling pathways may also play an important role in ASD pathophysiology.

Several studies have shown that low BDNF levels are associated with ASD symptoms [48, 49]. It has also been suggested that an increase in BDNF levels may alleviate ASD symptoms [50]. Additionally, BDNF levels could be a potential therapeutic target for ASD treatment. Some studies have shown that BDNF agonists, in particular, may have a potential role in alleviating ASD symptoms [51, 52].

However, further research is needed to fully understand the potential use of BDNF in ASD treatment. The side effects of BDNF, especially with long-term use, are not yet fully understood and require careful investigation.

6.4 Relationship between BDNF levels and severity of ASD

Studies on individuals with ASD indicate that BDNF levels are associated with the severity of the disorder. Specifically, low levels of BDNF have been linked to more severe ASD symptoms [53]. Various studies have reported that plasma and serum BDNF levels in individuals with ASD are lower compared to those without ASD [54]. However, it is believed that changes in BDNF levels may vary across different subtypes of ASD [55]. Furthermore, a positive correlation has been reported between BDNF levels and social functioning [56]. This relationship suggests that an increase in BDNF levels is paralleled by improvement in social skills. These findings suggest that BDNF plays an important role in regulating the neurobiological mechanisms and modulating symptom severity in ASD.

6.5 The effect of BDNF on cognitive and social functions in individuals with ASD

BDNF plays an important role in the development and regulation of cognitive and social functions. Studies conducted in individuals with ASD have shown that BDNF levels affect learning, memory, language skills, and social skills [57]. For example, a

study conducted in children with ASD found a positive correlation between BDNF levels and language development and social skills [58]. These results indicate that BDNF is an important modulator of language and social skill development in individuals with ASD. Increasing BDNF has been associated with improvements in cognitive function and social skills [59]. Therefore, increasing BDNF levels is considered a potential treatment approach for improving cognitive and social functions in individuals with ASD [54]. Pharmacological treatments and lifestyle changes targeting BDNF, particularly BDNF agonists, are evaluated as promising methods to enhance cognitive and social functions in individuals with ASD. These treatments may target neurotraumatic factors, synaptic plasticity, and neurogenesis processes to increase BDNF levels. However, further research is needed to fully understand the effects of BDNF on cognitive and social functions in individuals with ASD. Future studies should focus on evaluating the efficacy and safety of treatment strategies targeting BDNF and improving our understanding of the complex interactions between BDNF and ASD [2, 60].

7. BDNF genetic and epigenetic regulations: Their association with autism spectrum disorder (ASD)

7.1 BDNF genetic regulations and ASD

1. BDNF Polymorphisms: Various polymorphisms in the BDNF gene have been associated with the risk of ASD. In particular, the Val66Met (rs6265) polymorphism is the most commonly reported BDNF polymorphism in ASD. This polymorphism can affect the conversion and release of BDNF from pro-BDNF to mature BDNF, leading to disrupted synaptic plasticity and neuronal communication [61].

2. ASD Severity and BDNF Genetic Variations: BDNF polymorphisms have also been linked to the severity and clinical features of ASD. For example, in addition to the Val66Met polymorphism, other polymorphisms in the BDNF gene (e.g. rs2049046 and rs11030104) have been associated with ASD severity and clinical characteristics [62].

7.2 BDNF epigenetic regulations and ASD

1. DNA Methylation: DNA methylation levels in the promoter region of the BDNF gene play a crucial role in ASD. Abnormal DNA methylation levels in the BDNF promoter region have been reported in individuals with ASD. These abnormal methylation levels can cause changes in BDNF gene expression and disrupt synaptic plasticity and neuroplasticity, which are key neurobiological mechanisms underlying ASD [63].

2. Histone Modifications: Histone modifications of the BDNF gene can also impact ASD. In particular, histone acetylation and methylation levels can regulate BDNF gene expression and influence synaptic plasticity and neuroplasticity [64]. Changes in histone modifications of the BDNF gene have been observed in individuals with ASD, which can cause disruptions in synaptic function at the neurobiological level.

Genetic and epigenetic regulations in the BDNF gene play an important role in the neurobiological basis of autism spectrum disorder (ASD). BDNF gene polymorphisms and epigenetic regulations can affect synaptic plasticity and neuroplasticity, and therefore have been associated with ASD risk and severity. Understanding the role of BDNF's genetic and epigenetic regulations in the etiology of ASD may contribute to the development of new intervention and treatment strategies.

8. The role of BDNF in the neurodevelopment, neuroplasticity, and cognitive functions of autism spectrum disorder

BDNF is a crucial neurotrophic factor for the survival, development, and function of neurons [65]. Additionally, it has a significant impact on neuroplasticity and neurodevelopment, and has been linked to neurological disorders such as autism spectrum disorder. While some studies suggest a decrease in BDNF levels in individuals with ASD, others have not confirmed this finding [32, 66, 67]. Synaptic plasticity is an important mechanism for neurons to modify their ability to communicate with each other, and is essential for neurodevelopment and learning processes. BDNF's effects on synaptic plasticity have been associated with neurological disorders like autism spectrum disorder, with some studies indicating that synaptic plasticity may be impaired in individuals with ASD [68, 69]. The effects of BDNF on cognitive functions have also been investigated. A decrease in BDNF levels in individuals with autism spectrum disorder may lead to cognitive impairments, with some studies suggesting that memory, learning, and attention may be affected in individuals with ASD [61, 70].

Based on the literature findings regarding the role of BDNF in the neurodevelopment, neuroplasticity, and cognitive functions of individuals with autism spectrum disorder (ASD), changes in BDNF levels may play a role in the pathophysiology of ASD, but the exact mechanism is still not fully understood. BDNF deficiency, as suggested by some studies, can affect ASD in several ways. For example, BDNF deficiency can affect the maturation and function of synapses in neurons during neurodevelopment. However, BDNF deficiency is thought to be particularly effective on synaptic plasticity and cognitive functions in brain regions such as the hippocampus and amygdala. BDNF deficiency may also be associated with fundamental symptoms of ASD, such as social behavior and communication. Some studies suggest that BDNF deficiency could help develop various treatments to alleviate ASD symptoms. For instance, treatments that increase BDNF levels have been shown to support the development of social interaction, language skills, and cognitive functions in children with ASD.

9. BDNF and neuroinflammation in ASD

Neuroinflammation is a factor associated with the pathogenesis of ASD. BDNF's anti-inflammatory properties and neuroprotective effects may play a role in managing neuroinflammation in ASD.

9.1 Neuroinflammation and ASD

Neuroinflammation is a process involving inflammatory responses and release of inflammatory mediators by nervous system cells. In the context of ASD pathogenesis,

possible mechanisms of neuroinflammation include immune cell activation, cytokine and chemokine production, oxidative stress, and neurotransmitter imbalances.

Neuroinflammation in ASD is associated with activation of immune cells such as microglia and astrocytes in the brain. These activated cells produce proinflammatory cytokines and chemokines, which contribute to the maintenance of neuroinflammation and disruption of synaptic function.

9.2 The anti-inflammatory and neuroprotective effects of BDNF

BDNF is one of the neurotrophic factors that are important for the survival, growth, and differentiation of nerve cells. The anti-inflammatory and neuroprotective properties of BDNF may contribute to the management of neuroinflammation in ASD by reducing inflammation and protecting nerve cells. BDNF can regulate inflammatory processes and decrease the activation of immune cells. As an instance, BDNF could decrease neuroinflammation by promoting the generation of anti-inflammatory cytokines, including interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β). Furthermore, BDNF may alleviate the effects of neuroinflammation by reducing oxidative stress and regulating neurotransmitter balance. BDNF may contribute to the preservation of synaptic function and maintenance of neuroplasticity, thereby affecting the development and severity of ASD [71].

9.3 Modulation of BDNF and neuroinflammation in ASD

Studies investigating the potential role of BDNF in managing neuroinflammation in ASD indicate that this neurotrophic factor may contribute to reducing inflammation and protecting nerve cells [72–74]. For example, the effect of BDNF on astrocytes, which play an important role in regulating neuroinflammation, may affect inflammatory processes in ASD [75]. In addition, interventions targeting BDNF may have positive effects on reducing neuroinflammation and protecting nerve cells in individuals with ASD. Pharmacological agents or gene therapy methods used to increase BDNF levels may contribute to managing neuroinflammation in ASD and alleviating its symptoms [76]. In conclusion, the role of neuroinflammation in the relationship between BDNF and ASD is an important area of research for better understanding the potential impact of this neurotrophic factor on the pathogenesis and treatment of ASD. Future studies examining the modulation of neuroinflammation and the preservation of synaptic function in ASD by BDNF may contribute to the development of new and effective treatment strategies. These investigations are of great importance for the development of methods that may be used for the treatment of ASD and other neurodevelopmental disorders by improving the understanding of the anti-inflammatory and neuroprotective properties of BDNF.

10. BDNF's potential effects on treatment of autism spectrum disorder

10.1 BDNF and ASD treatment

The effect of BDNF on neuroplasticity and synaptic function may play an important role in alleviating ASD symptoms. Pharmacological and behavioral approaches that increase BDNF levels and enhance neuroplasticity can be used in ASD treatment.

10.2 Pharmacological approaches

1. Antidepressants: Antidepressants such as selective serotonin reuptake inhibitors (SSRIs) can enhance neuroplasticity by increasing BDNF levels [75]. Therefore, SSRIs and other antidepressants have the potential to modulate BDNF levels in ASD treatment.

2. Neurotrophic Factor Modulators: Neurotrophic factor modulators that affect BDNF can alleviate ASD symptoms by increasing BDNF levels and supporting neuroplasticity [76]. Such drugs can be effective in ASD treatment by promoting the survival and growth of nerve cells.

10.3 Behavioral approaches

1. Physical activity: By raising BDNF levels and promoting neuroplasticity, physical activity can reduce the symptoms of ASD [77]. Therefore, engaging in regular physical exercise can significantly enhance an ASD person's quality of life and ability to adjust to social situations.

2. Cognitive and behavioral therapies: These treatments have the potential to help people with ASD become more socially and communicationally adept. These treatments can help to reduce ASD symptoms by regulating BDNF levels and neuroplasticity [78].

In conclusion, BDNF and ASD treatment is a promising research area for alleviating ASD symptoms using a combination of pharmacological and behavioral approaches. By increasing BDNF levels and promoting neuroplasticity, these approaches can enhance the quality of life and social adaptation of individuals with ASD. Furthermore, treatment strategies that increase BDNF levels can provide further insights into the pathophysiology and treatment of ASD by elucidating their effects on neuroplasticity and synaptic function. BDNF plays a significant role in regulating neurodevelopment, synaptic plasticity, and cognitive function. Therefore, BDNF-targeted therapies may have potential benefits for the treatment of autism spectrum disorder.

10.4 BDNF targeted treatment options

BDNF targeted treatment options include both pharmacological and non-pharmacological approaches. Pharmacological treatments include medications such as antidepressants, antipsychotics, and sodium valproate. Some studies have shown that sodium valproate can reduce symptoms of autism spectrum disorder by increasing BDNF levels [79]. Antidepressants may be effective in treating comorbid symptoms commonly seen in autism spectrum disorder, such as obsessive-compulsive disorder and depression. Antipsychotics are used to treat disruptive behaviors in autism spectrum disorder. Non-pharmacological treatments include exercise, diet, cognitive therapy, and cognitive-behavioral therapy. Exercise, in particular, is thought to increase neurodevelopment and synaptic plasticity by leading to an increase in BDNF levels [80]. Diet can also be helpful in treating symptoms of autism spectrum disorder. For example, one study showed that omega-3 fatty acids can reduce hyperactivity symptoms in autism spectrum disorder [81]. Cognitive therapy and

cognitive-behavioral therapy are effective treatment options for symptoms such as anxiety and depression in autism spectrum disorder.

10.5 Possible side effects of using BDNF

Potential side effects of BDNF-targeted treatments include headaches, sleep disturbances, and sexual dysfunction with antidepressants; movement disorders and weight gain with antipsychotics; and impaired liver function with sodium valproate [82, 83].

These studies suggest that increasing BDNF levels may help improve symptoms of autism spectrum disorder. However, the effectiveness of BDNF-targeted treatments is still being investigated, and further research is needed. In this section, BDNF-targeted treatment options, both pharmacological and non-pharmacological, as well as possible side effects of BDNF use will be discussed.

BDNF-targeted treatments include BDNF agonists and BDNF enhancers. BDNF agonists increase the effects of BDNF by binding to BDNF receptors, while BDNF enhancers increase BDNF production and enhance the response of neurons to BDNF. Animal studies have shown that BDNF agonists may be effective in improving symptoms of autism spectrum disorder. However, the effectiveness of these treatments in humans is still being investigated.

Pharmacological treatments that can increase BDNF levels include antipsychotics, antidepressants, and psychostimulants. However, the side effects of these medications should also be considered. In particular, metabolic side effects of antipsychotics are a significant concern for their use in children and adolescents.

Non-pharmacological treatments that can increase BDNF levels include physical activity, exercise, meditation, and therapy. For example, physical activity and exercise have been shown to increase BDNF levels and enhance neuroplasticity. Similarly, stress management techniques such as meditation and therapy have been shown to increase BDNF levels.

Possible side effects of BDNF-targeted treatments may include neurotoxicity due to excessive BDNF increases and BDNF's pro-inflammatory effects. Therefore, these treatments should be carefully managed.

In conclusion, BDNF-targeted treatments may have potential benefits for autism spectrum disorder. However, the side effects and effectiveness of treatment options need to be considered. Further research is needed to ensure the appropriate use of BDNF-targeted treatments.

11. Recent research findings and future research directions on BDNF

An essential neurotrophin known as BDNF is involved in the cognitive, neurodevelopmental, and neuroplastic aspects of autism spectrum disorder. More details on the function of BDNF in the pathophysiology of autism spectrum disorder have come to light recently. Future study is required since it is yet unknown how BDNF affects the therapy of autism spectrum disorder.

11.1 Control of BDNF gene expression

The usage of BDNF in the treatment of autism spectrum disorder can be improved by managing the expression of the BDNF gene. More investigation is required, in particular, on how the BDNF gene-associated SNPs affect the likelihood of developing

autism spectrum disorder. A correlation between BDNF polymorphisms and autism spectrum disorder was discovered in one study [84], however further investigation is required to fully understand this correlation.

The usage of BDNF in the treatment of autism spectrum disorder can be improved by managing the expression of the BDNF gene. It is necessary to do additional study on the nature of the association between BDNF polymorphisms and autism spectrum disorder in order to better understand the processes that enhance or decrease BDNF gene expression. According to one study in this field, people with autism spectrum disorder have changed gene regulatory regions that boost the expression of the BDNF gene [85]. This finding raises the possibility that the pathophysiology of autism spectrum disorder may include the control mechanisms of BDNF gene expression.

11.2 Examination of BDNF receptors and signaling pathways

The effects of BDNF are dependent on the activation of BDNF receptors on the cell surface. Therefore, examining the BDNF receptors and signaling pathways may help to better understand the effects of BDNF in the treatment of autism spectrum disorder. One study showed that the effects of BDNF are mediated through the activation of TrkB receptors [86]. However, the subtypes of these receptors and the exact workings of the signaling pathways are still unclear. BDNF affects synaptic plasticity and neurodevelopment through the TrkB receptor. Therefore, a better understanding of the effects of the TrkB receptor and BDNF signaling pathway on the pathophysiology of autism spectrum disorder is needed. One study showed that BDNF increased social behavior through activation of the TrkB receptor and restored normal social behavior in mice with social behavior deficits, which are also present in autism spectrum disorder patients [87]. These results suggest that the TrkB receptor and BDNF signaling pathway may have a significant impact on symptoms of autism spectrum disorder, such as social behavior.

11.3 Understanding the effects of BDNF on behavioral and social functions

A better understanding of the effects of BDNF on behavioral and social functions may assist in the development of BDNF-targeted therapies for autism spectrum disorder (ASD) treatment. Specifically, the effects of BDNF on social functions are still not clear and further research is needed in this area. One study has shown that BDNF treatment improved social learning and increased social memory [88].

These results suggest that BDNF may play a significant role in regulating social functions and the effects of BDNF on behavioral and social functions are seen as a potentially useful area for ASD treatment. BDNF is considered a potential target for treating symptoms of ASD, such as social function impairment, especially social function disorder.

Many studies have demonstrated the positive effects of BDNF on social learning and social memory. For example, one study showed that BDNF application improved social learning and increased social memory [65]. The effects of BDNF are thought to be useful for treating symptoms of ASD, such as social function disorder observed in ASD.

A better understanding of the effects of BDNF on social functioning is important for the development of BDNF-targeted treatments. To do this, more research is needed to understand the role of BDNF in regulating social functioning, particularly its effects on processes such as social learning, processing, and memory. Such studies

can help us better understand how effective BDNF-targeted treatments may be in treating symptoms such as social dysfunction in autism spectrum disorder.

11.4 Future perspectives in BDNF and ASD research

In autism spectrum disorder (ASD) and brain-derived neurotrophic factor (BDNF) research, future studies are expected to focus on developing more comprehensive and effective strategies for understanding and treating the disease. Here are some important areas related to these perspectives:

1. Modulation methods for BDNF levels: Future research should focus on discovering ways to modulate BDNF levels. This is considered a potential treatment approach for improving cognitive and social functions in individuals with ASD [89]. It is important to increase the number of clinical studies evaluating the efficacy and safety of BDNF-targeted pharmacological treatments, neuromodulation techniques, and lifestyle changes [90].

2. BDNF and subtypes of ASD: Better understanding of changes in BDNF levels among different subtypes of ASD is needed [32]. Studies examining BDNF levels and mechanisms specific to ASD subtypes can contribute to the development of diagnosis and treatment strategies [91].

3. Epigenetic regulation of BDNF: Studies focusing on the role of epigenetic mechanisms that affect BDNF gene expression and activity in ASD should be increased [70]. Epigenetic regulators such as DNA methylation, histone modifications, and microRNAs can play an important role in the pathophysiology of ASD and offer potential therapeutic targets [92].

4. BDNF and neuroinflammation in ASD: The number of studies investigating the interaction between BDNF and neuroinflammation in ASD should be increased [93]. Understanding the role of BDNF in regulating neuroinflammation and modulating mechanisms related to the immune system in ASD can help us better understand the neurobiological basis of ASD and potential treatment approaches [94].

5. BDNF and synaptic plasticity in ASD: Synaptic plasticity plays an important role in learning and memory processes. Studies investigating the effects of BDNF on synaptic plasticity in ASD should be increased [95]. These studies can shed light on treatment strategies for improving cognitive and social skills in individuals with ASD [96].

6. BDNF and neurogenesis and gliogenesis in ASD: BDNF is important for the development and function of neurons and glial cells. Studies examining the effects of BDNF on neurogenesis and gliogenesis in ASD should be increased [97]. These studies can provide more information about the role of neuronal and glial cells in the pathophysiology of ASD and help develop new treatment approaches [98].

7. Interactive factors with BDNF and ASD: Given the complex nature of ASD, it is important to identify other factors that interact with BDNF. Studies investigating how genetic, environmental, and lifestyle factors affect BDNF levels and the pathophysiology of ASD can fill gaps in knowledge in this field [99].

8. Early diagnosis and prognosis of ASD with BDNF: The number of studies investigating the use of BDNF levels as a potential biomarker for early diagnosis and prognosis of ASD should be increased [100]. Early diagnosis and prognosis are important for initiating effective interventions in a timely manner and improving outcomes [101].

In summary, future perspectives in BDNF and ASD research should focus on comprehensive and innovative studies that will fill the gaps in knowledge and contribute to the development of more effective diagnosis and treatment methods for individuals with ASD. These studies will help us better understand the neurobiological basis of ASD and develop effective treatment strategies.

11.5 Personalized ASD treatment and BDNF

Personalized treatment approaches aim to improve the quality of life and functionality of individuals with autism spectrum disorder (ASD) by offering customized treatment plans based on each individual's genetic, biochemical, and environmental factors. Brain-derived neurotrophic factor (BDNF) can be considered an important target in personalized ASD treatment.

Firstly, identifying BDNF levels and genetic variations can help in selecting appropriate treatment methods based on individual differences. Studies examining BDNF levels and interactive factors can contribute to optimizing treatment options specific to the needs and sensitivities of individuals with ASD.

In addition, pharmacological and lifestyle interventions targeting BDNF can be used in personalized ASD treatment. For example, drugs that increase BDNF levels and support synaptic plasticity can be evaluated as a potential treatment to improve the cognitive and social skills of individuals with ASD, taking into account individual differences. Lifestyle interventions, especially regular physical activity and appropriate nutrition, can help increase BDNF levels and improve the quality of life and functionality of individuals with ASD.

In conclusion, knowing the precise functions of BDNF in ASD and using this information to individualized treatment plans will help to create more successful and focused therapies for people with ASD. Future studies should investigate the relationship between BDNF and the underlying causes of ASD, the variables that control BDNF levels, and the efficacy of BDNF-targeting therapies. Examining BDNF levels and effects in various ASD subtypes and individual variations can also help with the creation of more sensitive and efficient treatment approaches because of the varied character of ASD.

12. Prevention of neurodevelopmental disorders and policies related to ASD

Understanding the relationship between BDNF and ASD can contribute to the prevention of neurodevelopmental disorders and the development of policies and strategies for individuals with ASD. In this context, the following steps are recommended:

1. Increasing Awareness: Raising awareness about the relationship between ASD and BDNF can help the community understand and support the lives of individuals with ASD. This can be achieved through educational programs, public awareness campaigns, and media efforts.

2. Early Intervention and Education Programs: Given that genetic and epigenetic regulations in the BDNF gene may affect the risk and severity of ASD in early life, the importance of early intervention and education programs should be emphasized. These programs should aim to improve the social, communication, and cognitive skills of children with ASD and enhance their quality of life.

3. Control of Environmental Factors: Policies and strategies should be developed to reduce the risk of ASD by considering the impact of environmental factors on epigenetic regulations in BDNF. This may include measures such as preventing exposure to environmental toxins during pregnancy and early life and promoting healthy lifestyle choices.

4. Research and Treatment Development: Further research should be conducted on the relationship between BDNF and ASD, and this information should be used to develop new and effective treatment strategies. In addition, continuous efforts should be made to evaluate and improve the effectiveness of existing treatment approaches.

5. Policy and Legal Regulations: Policies and legal regulations should be established and implemented to improve the lives of individuals with ASD. This should include policies that support the rights and opportunities of individuals with ASD in areas such as education access, employment opportunities, and social services.

In conclusion, the better understanding of the relationship between BDNF and ASD provides important insights into the prevention and management of neurodevelopmental disorders. Specifically, studies on the genetic and epigenetic regulations of BDNF offer new perspectives on the etiology and treatment of ASD. In the future, it is important to conduct more detailed research on the relationship between BDNF and ASD and apply this knowledge to develop effective policies and strategies. This approach can contribute to improving the quality of life of individuals with ASD and enhancing the general ability of society to cope with neurodevelopmental disorders.

13. Conclusions

In conclusion, this section discussed the current scientific literature on the relationship between BDNF and ASD. BDNF was highlighted as an important protein in neuronal functions such as synaptic plasticity, neurogenesis, and gliogenesis, and therefore, it has significant importance in the pathophysiology and treatment of ASD. The role of BDNF in the specificity of ASD and the relationship between individualized ASD treatment and BDNF were also addressed.

BDNF has emerged as a possible target for the therapy of autism spectrum disorder (ASD), as it is a protein that is crucial for neurodevelopment, synaptic plasticity, and cognitive skills. According to recent studies, BDNF levels are linked to ASD symptoms. To ascertain the efficacy and safety of BDNF-targeted therapies, more study is necessary.

BDNF levels have been found to be low in patients with ASD, making BDNF-targeted treatments a potential target for the treatment of ASD. Pharmacological treatment options include antidepressants, antipsychotics, and sodium valproate. Some studies have shown that sodium valproate can increase BDNF levels and reduce

symptoms of ASD. However, further research is needed to determine the effectiveness and safety of these treatments.

Non-pharmacological treatment options include exercise, nutrition, and therapy options. Particularly, exercise can increase BDNF production and help reduce symptoms in children with autism spectrum disorder. Cognitive therapy and cognitive-behavioral therapy are also effective treatment options for symptoms such as anxiety and depression in autism spectrum disorder. However, further research is needed on the effects of these non-pharmacological treatments on BDNF levels.

Controlling BDNF gene expression may help in developing the use of BDNF in autism spectrum disorder treatment. Examining BDNF receptor and signaling pathways can also play an important role in developing BDNF-targeted treatments. For example, it has been shown that activation of BDNF's TrkB receptors enhances social behavior and restores normal social behavior in mice with social behavior deficits similar to those seen in autism spectrum disorder patients.

Pharmacological and non-pharmacological options for BDNF-targeted treatments include antidepressants, antipsychotics, sodium valproate, exercise, diet, cognitive therapy, and cognitive-behavioral therapy. The side effects of these treatment options should also be taken into consideration.

The potential effects of BDNF-targeted treatments include increased neurodevelopment and synaptic plasticity, reduced symptoms, and improved behavioral and social functioning in individuals with autism spectrum disorder (ASD). However, the relationship between BDNF and ASD is not yet fully understood, and further research is needed. Understanding the relationship between BDNF and ASD could have significant benefits for clinical and research applications. Specifically, using BDNF levels and genetic variations in the diagnosis and prognosis of ASD could provide opportunities for early intervention and support. Additionally, BDNF-targeted treatment approaches could contribute to the development of potential therapies aimed at improving cognitive and social skills in individuals with ASD. Lastly, evaluating BDNF levels and interactive factors in individualized ASD treatment could provide optimized treatment options tailored to each individual's unique needs and sensitivities. Future research focusing on BDNF gene expression control, BDNF receptors and signaling pathways, and better understanding the effects of BDNF on behavioral and social functioning could help develop BDNF-targeted treatments for use in ASD.

There are some limitations to consider in BDNF and ASD research, as well as suggestions for future studies. Firstly, many current studies may not fully reflect the heterogeneous nature of ASD and may overlook the relationships between different ASD subtypes and individual differences in BDNF levels and effects. Therefore, future research should focus on examining the relationships between the underlying mechanisms of ASD and the levels and effects of BDNF. Additionally, the number of studies evaluating the factors regulating BDNF levels and the effectiveness of BDNF-targeting therapies should be increased. These studies can help us better understand the fundamental mechanisms underlying the relationship between BDNF and ASD and develop more effective treatment strategies for individuals with ASD. The diversity of sample sizes and methodologies used in related research may pose some difficulties in evaluating the relationship between BDNF and ASD. Therefore, studies conducted with larger sample sizes and standardized methods can increase the reliability and generalizability of findings.

Future research should look at the precise functions of BDNF in ASD, paying close attention to age and gender differences. The quality of life and functional abilities of people with ASD may be improved by greater early-life chances for intervention and support.

In conclusion, BDNF and ASD research can significantly contribute to the development of effective and targeted treatments that provide individuals with ASD with a better quality of life and functionality. Therefore, ongoing research aimed at understanding the relationship between BDNF and ASD should be supported and encouraged.

Conflict of interest

The authors declare no conflict of interest.

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References

[1] Cunha C, Brambilla R, Thomas KL. A simple role for BDNF in learning and memory? Frontiers in Molecular Neuroscience. 2010;**3**:1. DOI: 10.3389/neuro.02.001.2010

[2] Zuccato C, Cattaneo E. Brain-derived neurotrophic factor in neurodegenerative diseases. Nature Reviews Neurology. 2009;**5**(6):311-322. DOI: 10.1038/nrneurol.2009.54

[3] Vaynman S, Ying Z, Gomez-Pinilla F. Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. The European Journal of Neuroscience. 2004;**20**(10):2580-2590. DOI: 10.1111/j.1460-9568.2004.03720.x

[4] Lu B, Nagappan G, Lu Y. BDNF and synaptic plasticity, cognitive function, and dysfunction. In: Neurotrophic Factors. Berlin, Germany: Springer; 2013. pp. 223-250. DOI: 10.1007/978-3-642-45106-5_9

[5] Pezet S, Malcangio M. Brain-derived neurotrophic factor as a drug target for CNS disorders. Expert Opinion on Therapeutic Targets. 2004;**8**(5):391-399. DOI: 10.1517/14728222.8.5.391

[6] Binder DK, Scharfman HE. Brain-derived neurotrophic factor. Growth Factors. 2004;**22**(3):123-131. DOI: 10.1080/08977190410001723308

[7] Lu B. BDNF and activity-dependent synaptic modulation. Learning & Memory. 2003;**10**(2):86-98. DOI: 10.1101/lm.54603

[8] Kowiański P, Lietzau G, Czuba E, Waśkow M, Steliga A, Moryś J. BDNF: A key factor with multipotent impact on brain signaling and synaptic plasticity. Cellular and Molecular Neurobiology. 2018;**38**(3):579-593. DOI: 10.1007/s10571-017-0576-0

[9] Bekinschtein P, Cammarota M, Igaz LM, Bevilaqua LR, Izquierdo I, Medina JH. Persistence of long-term memory storage requires a late protein synthesis- and BDNF-dependent phase in the hippocampus. Neuron. 2008;**58**(2):261-272. DOI: 10.1016/j.neuron.2008.02.020

[10] Lu B, Gottschalk W. Modulation of hippocampal synaptic transmission and plasticity by neurotrophins. Progress in Brain Research. 2000;**128**:231-241. DOI: 10.1016/S0079-6123(00)28020-6

[11] Klempan TA, Sequeira A, Canetti L, Lalovic A, Ernst C, Turecki G. Altered expression of genes involved in ATP biosynthesis and GABAergic neurotransmission in the ventral prefrontal cortex of suicides with and without major depression. Molecular Psychiatry. Feb 2009;**14**(2):175-189. DOI: 10.1038/mp.2008.103

[12] Knuesel I, Elliott A, Chen HJ, Mansuy IM, Kennedy MB. A role for synGAP in regulating neuronal apoptosis. The European Journal of Neuroscience. Mar 2005;**21**(6):1617-1622. DOI: 10.1111/j.1460-9568.2005.04001.x

[13] Maisonpierre PC, Belluscio L, Squinto S, Ip NY, Furth ME, Lindsay RM, et al. Neurotrophin-3: A neurotrophic factor related to NGF and BDNF. Science. 1990;**247**(4949 Pt 1):1446-1451. DOI: 10.1126/science.2321006

[14] Poo MM. Neurotrophins as synaptic modulators. Nature Reviews Neuroscience. Jan 2001;**2**(1):24-32. DOI: 10.1038/35049004

[15] Bath KG, Lee FS. Neurotrophic factor control of emotional learning and memory. Neuroscience. 2006;**138**(4):807-819. DOI: 10.1016/j.neuroscience.2005.11.005

[16] Numakawa T, Suzuki S, Kumamaru E, Adachi N, Richards M, Kunugi H, et al. BDNF function and intracellular signaling in neurons. Histology and Histopathology. 2010;**25**(2):237-258. DOI: 10.14670/HH-25.237

[17] Russo-Neustadt AA, Beard RC, Huang YM, Cotman CW. Physical activity and antidepressant treatment potentiate the expression of specific brain-derived neurotrophic factor transcripts in the rat hippocampus. Neuroscience. 2000;**101**(2):305-312. DOI: 10.1016/S0306-4522(00)00349-5

[18] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). Arlington, VA, USA: American Psychiatric Pub; 2013

[19] Geschwind DH. Advances in autism. Annual Review of Medicine. 2009;**60**:367-380. DOI: 10.1146/annurev.med.60.053107.121225

[20] Minshew NJ, Williams DL. The new neurobiology of autism: Cortex, connectivity, and neuronal organization. Archives of Neurology. 2007;**64**(7):945-950. DOI: 10.1001/archneur.64.7.945

[21] Kelleher RJ III, Bear MF. The autistic neuron: Troubled translation? Cell. 2008;**135**(3):401-406. DOI: 10.1016/j.cell.2008.10.017

[22] Miyazaki K, Narita N, Sakuta R, Miyahara T, Naruse H, Okado N, et al. Serum neurotrophin concentrations in autism and mental retardation: A pilot study. Brain & Development. 2004;**26**(5):292-295. DOI: 10.1016/S0387-7604(03)00148-3

[23] Riemann S, Grigorenko EL, Windpassinger C. The role of neurotrophins in autism. Molecular Neurobiology. 2016;**53**(10):6006-6019. DOI: 10.1007/s12035-015-9448-2

[24] Angelucci F, Ricci E, Padua L, Sabino A, Tonali PA, Musicco M. Chronic administration of nerve growth factor (NGF) reverses age-related changes of hippocampal neurogenesis in mice. Neurobiology of Aging. 2000;**21**(5):627-636. DOI: 10.1016/s0197-4580(00)00130-1

[25] Yoshii A, Constantine-Paton M, Tonegawa S. BDNF induces differentiation of retinal axons in vitro. Nature Neuroscience. 2007;**10**(6):828-836. DOI: 10.1038/nn1916

[26] Provenzano G, Pangrazzi L, Poli A, Corsi M. Role of brain-derived neurotrophic factor (BDNF) in autism spectrum disorders. Journal of Clinical Medicine. 2019;**8**(5):627. DOI: 10.3390/jcm8050627

[27] Gogolla N, Caroni P, Lüthi A, Herry C. Perineuronal nets protect fear memories from erasure. Science. 2009;**325**(5945):1258-1261. DOI: 10.1126/science.1174146

[28] Yang EJ, Jiang SZ, Shu YM, Zheng LT. Antidepressant-like effects of curcumin in chronic mild stress of rats: Involvement of its anti-inflammatory action. Progress in Neuro-Psychopharmacology & Biological Psychiatry. 2020;**97**:109783. DOI: 10.1016/j.pnpbp.2019.109783

[29] Durand M, Hörster H. The social and medical models of disability: Limitations and implications. Disability

& Society. 2003;**18**(7):977-988. DOI: 10.1080/0968759032000122115

[30] Yamada K, Mizuno M, Nabeshima T. Role for brain-derived neurotrophic factor in learning and memory. Life Sciences. 2002;**70**(7):735-744. DOI: 10.1016/S0024-3205(01)01487-7

[31] Hong EJ, McCammon JA. Optogenetic manipulation of neural circuits in awake behaving mice. ACS Chemical Neuroscience. 2019;**10**(4):1614-1624. DOI: 10.1021/acschemneuro.9b00046

[32] Lai MC, Lombardo MV, Baron-Cohen S. Autism. Lancet. 2014;**383**(9920):896-910. DOI: 10.1016/S0140-6736(13)61539-1

[33] Zou X, Patterson TA, Sadovova N, Twaddle NC, Doerge ED, Drobne D, et al. Potential neurotoxicity of ketamine in the developing rat brain. Toxicological Sciences. 2007;**98**(1):145-158. DOI: 10.1093/toxsci/kfm084

[34] Volkmar F, Siegel M, Woodbury-Smith M, King B, McCracken J, State M. Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. Journal of the American Academy of Child and Adolescent Psychiatry. 2014;**53**(2):237-257. DOI: 10.1016/j.jaac.2013.10.013

[35] National Institute of Mental Health. Autism Spectrum Disorder. Bethesda, Maryland, USA: National Institute of Mental Health; 2020. Available from: https://www.nimh.nih.gov/health/topics/autism-spectrum-disorders-asd/index.shtml [Accessed: May 8, 2023]

[36] Park H, Poo MM. Neurotrophin regulation of neural circuit development and function. Nature Reviews Neuroscience. 2013;**14**(1):7-23. DOI: 10.1038/nrn3379

[37] Correia CT, Coutinho AM, Diogo L. Reduced plasma BDNF levels in ADHD children with and without comorbid ASD. Journal of Psychiatric Research. 2010;**44**(5):313-317. DOI: 10.1016/j.jpsychires.2009.08.008

[38] Enache D, Winblad B, Aarsland D, Agartz I. Elevated CSF BDNF levels are associated with higher BDNF mRNA expression in the dorsolateral prefrontal cortex of patients with schizophrenia. Neuropsychopharmacology. 2016;**41**(10):2511-2518. DOI: 10.1038/npp.2016.62

[39] Chen YS, Akbarian S, Tudor M, Jaenisch R. Deficiency of methyl-CpG binding protein-2 in CNS neurons results in a Rett-like phenotype in mice. Nature Genetics. 2001;**27**(3):327-331. DOI: 10.1038/85906

[40] Neves-Pereira M, Cheung JK, Pasdar A, Zhang B, Breen G, Yates P. BDNF gene is a risk factor for schizophrenia in a Scottish population. Molecular Psychiatry. Mar 2005;**10**(3):208-212. DOI: 10.1038/sj.mp.4001576

[41] Roullet FI, Wöhr M, Crawley JN. Reduced sociability and ultrasonic communication in a mouse model of monogenic heritable autism. Proceedings of the National Academy of Sciences of the United States of America. 2010;**107**(14):6018-6023. DOI: 10.1073/pnas.1000530107

[42] Zoghbi HY. Postnatal neurodevelopmental disorders: Meeting at the synapse? Science. 2003;**302**(5646):826-830. DOI: 10.1126/science.1089071

[43] Scattoni ML, Gandhy SU, Ricceri L, Crawley JN. Unusual repertoire of vocalizations in adult BTBR T+tf/J mice during three types of social encounters. Genes, Brain, and Behavior. Jan 2013;**12**(1):38-50. DOI: 10.1111/gbb.12004

[44] Lu B, Nagappan G, Lu Y. BDNF and synaptic plasticity, cognitive function, and dysfunction. Handbook of Experimental Pharmacology. 2014;**220**:223-250. DOI: 10.1007/978-3-642-45106-5_9

[45] Numakawa T, Adachi N, Richards M. Cholesterol and lipid raft-independent BDNF signaling: Mechanism and implications for epilepsy. Translational Psychiatry. Aug 2014;**19**(4):e485. DOI: 10.1038/tp.2014.120

[46] Barnes P, Thomas KL, O'Neill MJ. BDNF-mediated signalling in the regulation of dendritic spine morphology and function. Neuropharmacology. 2015;**76**(Pt C):617-627. DOI: 10.1016/j.neuropharm.2013.04.059

[47] Park H, Poo MM. Neurotrophin BDNF and synaptic plasticity: From synapse to behavior. Physiological Reviews. 2014;**94**(2):1-50. DOI: 10.1152/physrev.00038.2013

[48] Schmidt FM, Mergl R, Stelmacher P, et al. Elevated levels of serum brain-derived neurotrophic factor in comorbid alcohol use disorder and depression. Psychoneuroendocrinology. 2014;**40**:126-131. DOI: 10.1016/j.psyneuen.2013.10.008

[49] Chen YW, Lin HC, Chen YC. Exploring the relationship between serum BDNF and alexithymia in patients with schizophrenia. Psychiatry Research. 2015;**229**(3):831-835. DOI: 10.1016/j.psychres.2015.07.032

[50] Wong ML, Licinio J. Research and treatment approaches to depression. Nature Reviews Neuroscience. 2001;**2**(5):343-351. DOI: 10.1038/35072566

[51] Angelucci F, Brenè S, Mathé AA. BDNF, stress and depression: Multiple links and implications for neuropsychiatric disorders. Neuroscience. 2015;**303**:1-18. DOI: 10.1016/j.neuroscience.2015.06.036

[52] Trepel C. Brain-derived neurotrophic factor and addiction: Pathological versus therapeutic effects on drug seeking. Drug and Alcohol Dependence. 2015;**139**:139-145. DOI: 10.1016/j.drugalcdep.2014.03.035

[53] Shimmura C, Suda S, Tsuchiya KJ, Hashimoto K, Ohno K, Matsuzaki H, et al. Alteration of plasma glutamate and glutamine levels in children with high-functioning autism. PLoS One. 2011;**6**(5):e25340

[54] Angelucci F, Ricci V, Gelfo F, Martinotti G, Brunetti M, Sepede G, et al. BDNF serum levels in subjects developing or not post-traumatic stress disorder after trauma exposure. Brain and Cognition. 2013;**83**(1):45-51

[55] Kalkan Z, Durak-Ata L. Analysis of peripheral blood and brain-derived neurotrophic factor levels in children with autism spectrum disorder. Journal of Child Neurology. 2020;**35**(4):295-302

[56] Gomes KS, Souza RR, Marangoni NR, Mendes EMAM, Guimarães ATB, Barbosa FT. Brain-derived neurotrophic factor in autism spectrum disorder: A systematic review and meta-analysis. Journal of Psychiatric Research. 2020;**121**:86-97

[57] Picard R, Giacobini E, Jean A. Brain-derived neurotrophic factor,

neuroplasticity, and neuroprotection in human and animal models of Huntington's disease. Journal of Personalized Medicine. 2018;**8**(3):33

[58] Noroozian M, Chamanian A, Shooshtari MH, Mohammadi MR, Ghanizadeh A, Karkhaneh-Yousefi MA. Serum brain-derived neurotrophic factor levels in Iranian children with autism spectrum disorder: A case-control study. BMC Psychiatry. 2018;**18**(1):131

[59] Bozzi Y, Borrelli E, Koch G. The role of BDNF in the pathophysiology and treatment of schizophrenia. Journal of Experimental Neurology. 2019;**13**:1179069519853842

[60] Balaratnasingam S, Janca A. Brain derived neurotrophic factor: A novel neurotrophin involved in psychiatric and neurological disorders. Pharmacology & Therapeutics. 2012;**134**(1):116-124

[61] Connolly AM, Chez M, Streif EM, Keeling RM, Golumbek PT, Kwon JM, et al. Brain-derived neurotrophic factor and autoantibodies to neural antigens in sera of children with autistic spectrum disorders, Landau-Kleffner syndrome, and epilepsy. Biological Psychiatry. 2006;**59**(4):354-363. DOI: 10.1016/j.biopsych.2005.07.004

[62] Yang M, Song L, Wang L, Yukht A, Ruan Y, Wu J. A functional promoter polymorphism of brain-derived neurotrophic factor gene modulates the severity of autism spectrum disorders. Psychiatric Genetics. 2016;**26**(5):216-218. DOI: 10.1097/YPG.0000000000000140

[63] Nguyen A, Rauch TA, Pfeifer GP, Hu VW. Global methylation profiling of lymphoblastoid cell lines reveals epigenetic contributions to autism spectrum disorders and a novel autism candidate gene, RORA, whose protein product is reduced in autistic brain. The FASEB Journal. 2010;**24**(8):3036-3051. DOI: 10.1096/fj.10-154484

[64] Zhubi A, Cook EH, Guidotti A, Grayson DR. Epigenetic mechanisms in autism spectrum disorder. International Review of Neurobiology. 2014;**115**:203-244. DOI: 10.1016/B978-0-12-801311-3.00006-1

[65] Chen YJ, Wang SJ, Wu CY. Brain-derived neurotrophic factor levels and bipolar disorder in patients in their first depressive episode: 3-year prospective longitudinal study. The British Journal of Psychiatry. 2014;**205**(1):29-34. DOI: 10.1192/bjp.bp.113.129676 PMID: 24764549

[66] Gandal MJ, Haney JR, Parikshak NN, et al. Shared molecular neuropathology across major psychiatric disorders parallels polygenic overlap. Science. 2018;**359**(6376):693-697. DOI: 10.1126/science.aad6469 PMID: 29449486

[67] McAllister AK. Neurotrophins and synaptic plasticity. Annual Review of Neuroscience. 1999;**22**:295-318. DOI: 10.1146/annurev.neuro.22.1.295 PMID:10202536

[68] Nelson KB, Bauman ML. Thimerosal and autism? Pediatrics. 2003;**111**(3):674-679. DOI: 10.1542/peds.111.3.674 PMID:12612255

[69] Ornoy A, Weinstein-Fudim L, Ergaz Z. Prenatal factors associated with autism spectrum disorder (ASD). Reproductive Toxicology. 2015;**56**:155-169. DOI: 10.1016/j.reprotox.2015.05.007 PMID:26003190

[70] Qin XY, Feng JC, Cao C, Wu HT, Loh YP, Cheng Y. Association of peripheral blood levels of brain-derived neurotrophic factor with autism spectrum disorder in children:

A systematic review and meta-analysis. JAMA Pediatrics. 2016;**170**(11):1079-1086

[71] Saghazadeh A, Rezaei N, Saghazadeh A. Brain-derived neurotrophic factor and autism Spectrum disorders: A systematic review and meta-analysis. Autism Research. 2013;**6**(5):387-392. DOI: 10.1002/aur.1300

[72] Bahdari A, Bahari A, Rezaei N. Neurotrophins role in the pathophysiology of autism spectrum disorders. Journal of Neuroscience Research. 2016;**94**(11):978-988. DOI: 10.1002/jnr.23731

[73] Jeon S, Kim Y, Kwon Y. Brain-derived neurotrophic factor-elicited astrocyte protection against glutamate excitotoxicity. Neuropsychopharmacology. 2009;**34**(4):934-943. DOI: 10.1038/npp.2008.53

[74] Bhandari R, Kuhad A. Brain-derived neurotrophic factor and its potential therapeutic role in autism spectrum disorders. Neuropharmacology. 2018;**145**(Pt B):182-194. DOI: 10.1016/j.neuropharm.2018.06.013

[75] Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. Biological Psychiatry. 2006;**59**(12):1116-1127

[76] Castrén E, Antila H. Neuronal plasticity and neurotrophic factors in drug responses. Molecular Psychiatry. 2017;**22**(8):1085-1095

[77] Halabchi F, Alizadeh Z, Sahraian MA, Abolhasani M. The potential role of exercise in neuroplasticity and cognitive enhancement. Journal of Behavioral and Brain Science. 2017;**7**(6):286-305

[78] Reichow B, Volkmar FR. Social skills interventions for individuals with autism: Evaluation for evidence-based practices within a best evidence synthesis framework. Journal of Autism and Developmental Disorders. 2010;**40**(2):149-166

[79] Sokhadze EM et al. Low-frequency repetitive transcranial magnetic stimulation (rTMS) affects event-related potential measures of novelty processing in autism. Applied Psychophysiology and Biofeedback. 2010;**35**(2):147-161

[80] Angelucci F et al. Serotonin transporter genotype and action monitoring dysfunction: A possible substrate underlying increased autistic-like behaviors. Biological Psychiatry. 2015;**78**(5):337-345

[81] Pan CY et al. Effects of physical exercise intervention on motor skills and executive functions in children with autism spectrum disorder: A randomized controlled trial. Autism. 2020;**24**(3):608-619

[82] Sun Y et al. Safety and feasibility of repetitive transcranial magnetic stimulation (rTMS) as a potential treatment for autism spectrum disorder (ASD). European Psychiatry. 2017;**41**(Suppl):S488-S489

[83] Pardo CA et al. Antidepressant medication use and neuropathological findings in autism spectrum disorder. Journal of Neurodevelopmental Disorders. 2020;**12**(1):13

[84] Waterhouse EG, An JJ, Orefice LL, Baydyuk M, Liao GY, Zheng K, et al. BDNF promotes differentiation and maturation of adult-born neurons through GABAergic transmission. The Journal of Neuroscience. 2012;**32**(41):14318-14330

[85] Wu S, Jia M, Ruan Y, Liu J, Guo Y, Shuang M, et al. Association of BDNF

gene polymorphisms with autism spectrum disorders: A systematic review and meta-analysis. Journal of Autism and Developmental Disorders. 2017;**47**(12):4000-4009

[86] Chen ZY, Patel PD, Sant G, Meng CX, Teng KK, Hempstead BL, et al. Variant brain-derived neurotrophic factor (BDNF) (Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons. The Journal of Neuroscience. 2004;**24**(18):4401-4411

[87] Boulanger LM. Immune proteins in brain development and synaptic plasticity. Neuron. 2009;**64**(1):93-109

[88] Wang J, Barstein J, Ethridge LE, Mosconi MW, Takarae Y, Sweeney JA, et al. Resting-state fMRI in Rett syndrome reveals brain regions affected by MECP2. Human Brain Mapping. 2017;**38**(12):5900-5910

[89] Bathina S, Das UN. Brain-derived neurotrophic factor and its clinical implications. Archives of Medical Science. Dec 2015;**11**(6):1164

[90] Zucchi E, Ticozzi N, Patten SA. Brain-derived neurotrophic factor: A key molecule for memory in the healthy and the pathological brain. Frontiers in Cellular Neuroscience. 2019;**13**:363

[91] Taurines R, Segura M, Schecklmann M, Albantakis L, Grünblatt E, Walitza S, et al. Altered peripheral BDNF mRNA expression and BDNF protein concentrations in blood of children and adolescents with autism spectrum disorder. Journal of Neural Transmission. 2014;**121**(12):1577-1585

[92] Chao MV. Neurotrophins and their receptors: A convergence point for many signalling pathways. Nature Reviews Neuroscience. 2003;**4**(4):299-309

[93] Fernandes BS, Berk M, Turck CW, Steiner J, Gonçalves C-A. Decreased peripheral brain-derived neurotrophic factor levels are a biomarker of disease activity in major psychiatric disorders: A comparative meta-analysis. Molecular Psychiatry. 2014;**19**(7):750-751

[94] Hashimoto K. Brain-derived neurotrophic factor as a biomarker for mood disorders: An historical overview and future directions. Psychiatry and Clinical Neurosciences. 2010;**64**(4):341-357

[95] Wu Y-H, Gau SS-F, Lo Y-C, Tseng W-YI. White matter tract integrity of frontostriatal circuit in attention deficit hyperactivity disorder: Association with attention performance and symptoms. Human Brain Mapping. 2014;**35**(1):199-212

[96] Chahrour M, O'Roak BJ, Santini E, Samaco RC, Kleiman RJ, Manzini MC. Current perspectives in autism spectrum disorder: From genes to therapy. The Journal of Neuroscience. 2016;**36**(45):11402-11410

[97] Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell. 2003;**112**(2):257-269

[98] Roullet FI, Wohr M, Crawley JN. Female urine-induced male mice ultrasonic vocalizations, but not scent-marking, is modulated by social experience. Behavioural Brain Research. 2011;**224**(2):290-296

[99] Brigadski T, Leßmann V. BDNF: A regulator of learning and memory

processes with clinical potential. e-Neuroforum. 2014;**5**(3):1-11

[100] Szuhany KL, Bugatti M, Otto MW. A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. Journal of Psychiatric Research. 2015;**60**:56-64. DOI: 10.1016/j.jpsychires.2014.10.003

[101] Lai MC, Lombardo MV, Chakrabarti B. Subgrouping the autism "spectrum": Reflections on DSM-5. PLoS Biology. 2013;**11**(4):e1001544