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Hungry brain: about the possible contribution of neurotrophic factors to anorexia nervosa

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Abstract

Introduction: Anorexia nervosa (AN) is an eating disorder characterized by restricted energy intake leading to weight loss below the healthy range. It is accompanied by anxiety and distorted body perception. While the disorder often manifests during adolescence, there is a noted decrease in the average age of onset, with an increasing number of cases in childhood. Successful treatment and maintenance of healthy body weight require an understanding of the complex etiology of AN, encompassing both psychosocial and specific biological factors.

Material and methods: For the review, databases PubMed, Cochrane, and Google Scholar were utilized, searching for the following keywords: anorexia nervosa, neurotrophins, neurotrophin 3, neurotrophin 4, BDNF, nerve growth factor, from the inception of the databases until September 2023.

Discussion: In the biological context, neurotrophic growth factors such as neurotrophin 3 (NT-3), neurotrophin 4 (NT-4), brain-derived neurotrophic factor (BDNF), and nerve growth factor (NGF) may play a significant role in the etiopathogenesis of AN. These substances are involved in processes such as neuroprotection, proliferation, maturation, and survival of neurons in both the central and peripheral nervous systems. They regulate neuronal plasticity, impact the production of neurotransmitters, and control synaptic activity. BDNF and neurotrophin 3 influence the serotoninergic and noradrenergic systems, which may be associated with neurobiological processes responsible for anxiety and mood disorders.

Conclusions: Understanding the role of neurotrophins in AN has the potential to lead to more effective and personalized therapies, enabling a better comprehension of the biological mechanisms of this disorder and the development of targeted pharmacological interventions.

Keywords: anorexia nervosa, bdnf, neurotrophin 3, neurotrophin 4, nerve growth factor

Streszczenie

Wstęp: Jadłowstręt psychiczny (AN) to zaburzenie odżywiania, charakteryzujące się ograniczeniem podaży energii, prowadzącym do utraty masy ciała poniżej poziomu prawidłowego. Towarzyszą mu zaburzenia postrzegania własnego ciała i lęk przed wzrostem masy ciała. Choroba najczęściej występuje w okresie dojrzewania, jednak obserwuje się także obniżanie średniego wieku zachorowań AN, a liczba przypadków w dzieciństwie rośnie. Mimo postępów w badaniach, nadal brakuje skutecznych terapii dla AN, a wskaźnik śmiertelności związany z tym zaburzeniem jest najwyższy wśród chorób psychicznych. Skuteczne leczenie i utrzymanie prawidłowej masy ciała wymagają zrozumienia złożonej etiologii AN, która obejmuje zarówno czynniki psychospołeczne, jak i specyficzne czynniki biologiczne.

Materiał i metody: W celu przeglądu literatury użyto elektronicznych baz danych PubMed, Cochrane i Google Scholar, przeszukując je przy użyciu następujących słów kluczowych: anorexia nervosa, neurotrophins, neurotrophin 3, neurotrophin 4, BDNF, nerve growth factor, od momentu utworzenia bazy danych do września 2023 roku.

Dyskusja: W kontekście biologicznym istotną rolę w etiopatogenezie AN mogą odgrywać neurotroficzne czynniki wzrostu, takie jak neurotrofina 3 (NT-3), neurotrofina 4 (NT-4), czynnik neurotroficzny pochodzenia mózgowego (BDNF) i czynnik

wzrostu nerwów (NGF). Te substancje biorą udział w procesach neuroprotekcji, proliferacji, dojrzewania i przeżycia neuronów zarówno w ośrodkowym, jak i obwodowym układzie nerwowym. Regulują plastyczność neuronów, wpływają na produkcję neuroprzekaźników i regulują aktywność synaptyczną. Dodatkowo, BDNF i neurotrofina 3 wykazują wpływ na układ serotoninergiczny i noradrenergiczny, co może być związane z procesami neurobiologicznymi odpowiedzialnymi za zaburzenia lękowe i nastroju.

Wnioski: Poznanie roli neurotrofin w AN ma potencjał prowadzenia do bardziej skutecznych i spersonalizowanych terapii, umożliwiając lepsze zrozumienie biologicznych mechanizmów tego zaburzenia i rozwijanie celowanych interwencji farmakologicznych.

Słowa kluczowe: jadłowstręt psychiczny, bdnf, neurotrofina 3, neurotrofina 4, czynnik wzrostu nerwów

Introduction

Anorexia nervosa (AN) has the highest mortality rate among mental disorders and illnesses [1]. It is an eating disorder that is characterized by a limited energy supply compared to energy requirements and leads to reduced body weight. Patients exhibit a fear of weight gain and obesity, counteract weight gain, and show disturbances in the perception and experience of their weight and body shape [2]. Successful treatment of AN still remains a challenge - regardless of intervention, only about half of patients maintain a normal body weight over the long term [3].

There are large differences in the prevalence of AN around the world, to which socio-cultural and genetic diversity contributes [3]. Based on a study by Micali and co-authors of AN among 5658 women from western countries, the lifetime prevalence of AN in women was estimated at 3.64% [4]. The peak incidence is during adolescence and in both males and females it is 15-19 years [1,5]. In turn, there is preliminary evidence that the age of onset of AN in adolescents has decreased over the past decade. In many countries, the incidence of AN in childhood is on the rise, however, there is no specific treatment strategy for children, there is a lack of data in this area, so research is needed on strategies for treatment and achieving sustained remission [6].

The etiology of AN is complex and multifactorial. Research in recent years has contributed to a better understanding of the psychobiological factors associated with AN. Genetic factors increase the risk of the disorder; psychosocial and interpersonal factors can lead to its onset, whereas changes in neural networks can sustain AN symptoms [6]. In order to effectively combat AN, it is necessary to understand the specific biological and psychosocial mechanisms affecting its onset and persistence. Understanding these processes can result in more effective treatment targeting and, consequently, support overcoming this disorder by patients.

Physiological factors hypothesized to be involved in the development and maintenance of AN symptoms are neurotrophins, or neurotrophic factors, signaling molecules essential in the long-term formation of synapses in the brain [7]. They may be a potential biomarker indicative of brain health and function, due to their crossing the blood-brain barrier and their ability to be detected in peripheral blood [8]. The focus on neurotrophins in the context AN in this review is substantiated by findings from various studies. Initial investigations using animal models have established a connection between neurotrophins and an increased susceptibility to AN. Specifically, brain-derived neurotrophic factor (BDNF) and its receptor neurotrophic tyrosine receptor kinase type 2 (NTRK2) have been implicated in body weight regulation, eating behavior, and energy balance [9-11]. Studies have also highlighted the role of BDNF as an anorectic factor, influencing appetite suppression through the regulation of the melanocortin signaling pathway in the ventromedial hypothalamus [12].

Moreover, observations suggest that a restrictive diet contributes to enhanced hippocampal neurogenesis, along with increased expression of both BDNF and neurotrophin 3 (NTF3) [13]. Another study using a neurotrophin 4/5 (NTF4/5) knockout mouse model demonstrated that these mice exhibit reduced food satiation and hyperphagic behavior, leading to obesity when fed ad libitum. Interestingly, the infusion of NTF4/5 into the third ventricle of the brain reversed the obese phenotype, indicating the involvement of NTF4/5 in the activation of signaling cascades in hypothalamic nuclei responsible for the control of food intake and energy expenditure [14].

The rationale for focusing on neurotrophins in this review stems from the significant impact of these factors on body weight regulation, eating behavior, and energy balance, as demonstrated in both animal models and genetic research exploring associations between neurotrophin genes and AN. These insights underscore the crucial role neurotrophins play in the intricate mechanisms underlying AN, providing a comprehensive perspective on their involvement in the regulation of food intake and related behaviors [9-14].

Brain-derived neurotrophic factor

BDNF is a factor belonging to the family of neurotrophins that is involved not only in neuroprotection (also during cerebral ischemia, glutaminergic stimulation, hypoglycemia, neurotoxicity), central nervous system (CNS) development and maturation, connectivity, synaptic plasticity [15], synaptic strengthening, but also in the regulation of food intake in humans and animals [16], and plays important role in neurocognitive functions, particularly psychomotor speed. BDNF is significant for proliferation (it stimulates and controls new neurons to growth, differentiation and preservation of neurons. Moreover it is important in energy homeostasis [16,17]. Peripheral tissues, such as skeletal muscles, internal organs, and adipose tissue, in along with neurons in the CNS, are responsible for producing BDNF, however 80% of BDNF blood levels are of brain origin [15].

BDNF acts via the TrkB receptor and is involved in activation of signal transduction cascades such as IRS1/2, PI3K, Akt [17]. The expression of this neurotrophin and receptor are present in areas that are associated with eating behavior, control appetite: Ventromedial nucleus (VMN), lateral hypothalamic area (LHA), paraventricular nucleus (PVN), dorsomedial nucleus (DMN). They are also found in dopaminergic neurons in the VTA (ventral tegmental area), which is part of the mesolimbic system (which functions as a pleasure and reward sensation pathway) [15]. BDNF is produced in regions in the brain, which are responsible for cognitive and executive functions, for example in the hippocampus. BDNF is also involved in activity-dependent forms of synaptic plasticity. It increases the level of NMDA receptors and intracellular calcium concentrations, which impact on synaptic activity [18]. Several studies found that in mutant mice, with deleted the BDNF gene, long-term potentiation (LTP) and hippocampus-dependent learning are greatly reduced. When TrkB and BDNF are lower, there is a reduction in LTP induction. Peripheral BDNF participates in providing signals from the endocrine system, immune system and nervous system. Researchers found that BDNF can be as a mediator in inflammation and cause neuronal changes connected to allergic asthma [17].

The first concept on the effect of BDNF on appetite control was presented by P. A. Lapchak and F. Hefti in 1992. Research has demonstrated that long-term administration of BDNF to rats resulted in reduced body weight. The excision of the BDNF-encoding fragment in rats resulted in increased body weight [15,19]. Subsequently, numerous studies demonstrated lower serum BDNF levels in people diagnosed with AN, compared to those who are obese and also to those without obesity and AN. The researchers studied BDNF levels in 3 groups of women observing that BDNF levels decreased in AN patients and increased in obese patients [20]. In another study among AN patients, it has been shown that BDNF values are related to body weight and BMI but not to age, drugs, psychopathological indices. Moreover, researchers found rising levels of serum BDNF with weight recovery after AN [21].

Other factors have also been noted to interact with BDNF in controlling appetite. For example, leptin is one of the main hormones responsible for regulating body weight by inhibiting hunger. Leptin probably stimulates the translation in the dendrites of hypothalamic neurons of BDNF mRNA, which may affect the anorexic impact of BDNF [15]. BDNF acts on TrkB receptors, and this results in the inhibition of appetite. Researchers suggest that shortage of leptin causes decrease in BDNF gene expression [21]. Other examples of substances which are involved in enhancing the level of BDNF are glucose, CCK (cholecystokinin), CRH (corticotropin-releasing hormone). After ingestion of glucose, an increase in the expression of BDNF and the TrkB receptor is induced, which also suppresses appetite. Administration of CCK and CRH (corticotropin-releasing hormone) also increases serum BDNF levels [22].

Some studies have been conducted on animals that prove the impact of BDNF on their bodies. For example, pharmacological BDNF in rats induces decrease in food intake. One study showed that genetically modified rats with a change of BDNF/TrkB signaling develop hyperphagia and obesity [22]. Another study used genetically modified mice with deleted the BDNF gene. These mice had growth in activity, leptinemia, insulinaemia, glycaemia and linear growth [18]. Additional studies show an anorectic factor which is important in decrease of appetite by the downstream regulation of the melanocortin signaling in the hypothalamus. Several studies found that mice with lower levels of BDNF may cause rodents to have increased levels of anxiety and locomotor activity and food intake, which leads to obesity [23].

Serum levels of BDNF increase during weight recovery in AN, so this should improve the plasticity of neurons, which increases cognitive functions, such as learning and memorizing. Unfortunately, the anorexigenic effect of BDNF may promote relapse, by reducing appetite, when BDNF levels increase significantly during weight recovery [16]. High serum level of BDNF and a high level of self-directedness can be treated as protection from the development of AN [24]. Furthermore, BDNF probably plays an important role not only in AN, but also in autism, Alzheimer's disease, dementia, schizophrenia, type 2 diabetes mellitus, depression, Huntington's disease, Parkinson's disease, bipolar disorder [17].

Neurotrophins are also transcriptional regulators of neuronal genes, for example, BDNF is involved in regulating the expression of serotonergic markers. What

is more, they can induce a change in neurotransmitter function, including in noradrenergic and dopaminergic neurons, and thus can affect the behavior and mental state of a patient with AN. After their administration, there is modification of ion channels, easier release of neurotransmitters, and, even axons and dendrites can change their shape [25].

Nerve Growth Factor and Neurotrophins 3,4,5

The family of neurotrophins, along with BDNF, also includes nerve growth factor (NGF) and neurotrophins 3 (NTF3) and 4/5 (NTF4/5). Together with BDNF they play a role in the regulation of development, proliferation and survival of neurons in the CNS and peripheral nervous system. They control the plasticity of nerve cells as well as regulate the production of neurotransmitters and synaptic activity. In terms of AN, they primarily affect the regulation of food intake in both animals and humans. Neurotrophins action is mediated by high affinity tyrosine kinase receptors (NTRK1) activated by NGFB, NTRK2 by NTF4/5, and NTRK3 by NTF3 [26].

The results of experiments on animal models indicate that neurotrophins influence the regulation of food intake. For example, administration of NGF into the cerebral ventricles of non-obese mice causes central hypophagia and weight loss. In addition, in mice with limited food intake, increased synthesis of NTF3 and BDNF was observed [27]. Additionally, infusion of NTF4/5 into the cerebral ventricles of mice with the obese and hyperphagic phenotype transiently resulted in decreased appetite and therefore also weight loss [28].

There were also scientific studies that reflected the real impact of neurotrophins on AN in humans. The concentration of neurotrophins in the serum of women suffering from AN was tested in the study including 60 hospitalized AN patients. The control sample consisted of 45 healthy women with no history of eating disorders. The results of the experiment indicate that the serum levels of NTF 4 in the AN group of patients were significantly lower than in the group of healthy women. In addition, in patients with the restrictive type of AN, this difference was more noticeable than in the group of patients with the binge-purgative type. Therefore, it can be concluded that a too low level of NTF 4 in the serum may be related to personality dimensions and executive functions [29].

This suggests that NGF, NTF3 and NTF 4/5 have a noticeable effect on the regulation of food intake. The increased release of the above-mentioned neurotrophins may therefore play a role in the pathogenesis of AN by reducing patients' appetite.

Recently, a great deal of attention has been paid to finding ways to treat anxiety and mood disorders which coexist with AN, in turn, to do this, an understanding of neurobiological processes is needed. NT-3 affects the release of serotonin and norepinephrine, and thus may have antidepressant effects. NT-3 is expressed mainly in the dentate bend of the hippocampus, and facilitates hippocampal plasticity. One of the AMPA receptor enhancers, S47445, stimulates NT-3 and BDNF gene transcription, resulting in the formation of new dendritic spikes and synapses [30]. The study by Hao P. presented the effect of NT-3 (loaded in biodegradable material-chitosan) on neural progenitor cells (NSCs) after traumatic brain injury (TBI). They found that chitosan with NT-3 stimulated NSCs to proliferate and form neural networks, as well as migrate to the area of brain damage and ultimately, restore brain function. By doing so, NT-3 has been shown to be responsible for neurogenesis and angiogenesis through the creation of an appropriate microenvironment [31].

Nerve Growth Factor and Neurotrophins 3,4,5

Several meta-analyses have demonstrated that AN causes structural changes in the brain. Reduced gray matter volume (GMV) was found in the hippocampal, cingulate, midbrain, cerebellar regions, and the lateral occipital cortex, according to a meta-analysis and qualitative review of morphological changes in the brain [32]. Another meta-analysis of voxel-based morphometry (VBM) studies (228 AN patients and 240 controls) revealed decreased GMVs in the left hypothalamus, left inferior parietal lobe, right lentiform nucleus, and right caudate [33]. Today, we know more about the changes taking place in patients' brains, attention is increasingly being paid to more than structural changes and a meta-analysis published in 2022 regarding neurotrophic factor among AN patients is another work summarizing these. Researchers have demonstrated a correlation between diminished blood BDNF levels and the presence of eating disorders (EDs) and they point out that the establishment of a causal link between these two factors warrants further investigation. Given the substantial burden associated with EDs as highlighted in prior studies and the potential involvement of disrupted BDNF levels in the initiation and advancement of EDs, interventions aimed at restoring BDNF levels to their normal range are considered advantageous for individuals affected by these conditions [34]. Moreover, another research team suggested that BDNF serum concentrations may be a state marker of AN [35]. Although during the preparation of this review, we found numerous studies describing the role of BDNF in AN, to date, research addressing the role of other neurotrophins is very limited, which, in the authors' opinion, should draw the attention of researchers in the field.

The significant weight loss associated with anorexia

damages practically each part of the body, including the central nervous system. However, some studies indicate that anorexia might be a condition that originates in an atypical brain structure [36].

Brain damage consequently gets worse as the eating disorder progresses. Understanding the underlying causes of anorexia might benefit researchers in developing new therapies. Additionally, for those who have frequently considered themselves responsible for habits they are unable to quit, knowing that the problem has a biological origin may be therapeutic.

To summarize, it can be said that neurotrophins have as many functions as potential side effects. They take part not only in weight modification, but also in long-term potentiation and therefore in memory formation and learning. They affect feelings of anxiety and locomotor activity. They stimulate NSCs to proliferate and migrate, restoring proper brain function after injury. They interact with many other substances in processes necessary for proper functioning. They are related to oxytocin, which increases the expression of neurotrophin genes in the hippocampus, therefore regulating brain plasticity at this level. The impact of neurotrophins is enormous – from regulation at the neuron level to changes in cognitive function and behavioral changes in the patient. Learning the exact mechanisms of neurotrophins presents many challenges, however efforts should be made to discover as precisely as possible the relationship between neurotrophins and AN, because each discovery may potentially be a breakthrough in the fight against this disorder.

Conflict of interest

The authors have declared no conflict of interest.

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20. Opposite Changes in the Serum Brain-Derived Neurotrophic Factor in Anorexia Nervosa and Obesity PALMIERO MONTELEONE, MD, ALFONSO TORTORELLA, MD, VASSILIS MARTIADIS, MD, CRISTINA SERRITELLA, MD, ANTONIO FUSCHINO, MD, AND MARIO MAJ, MD, PHD
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