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The role of neurotrophic growth factors in the pathophysiology of bronchial asthma associated with obesity

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ABSTRACT

Bronchial asthma (BA) and obesity are common diseases with a tendency to a steady and progressive increase in the number of patients. A combination of these diseases is one of the major problems of modern medicine, requiring close attention due to a decrease in the quality of life, poor control over the course of the primary disease, and an increase in the frequency and duration of hospitalization. The association between asthma and obesity is obvious. However, detailed mechanisms underlying it require further investigation. In the last decade, in the formation of the phenotype of BA combined with obesity, much attention has been paid not only to the immune, but also to the neurogenic mechanisms of inflammatory response. It is known that the functioning of all parts of the nervous system can be controlled by neurotrophic growth factors due to their ability to influence many signaling mechanisms. Currently, there is evidence that neurotrophic factors are involved in the pathogenesis of bronchopulmonary and metabolic diseases. The review is devoted to detailed investigation of the mechanisms of neurogenic inflammation in obesity and asthma with participation of neurotrophic factors that may play a significant role in the formation of the obese–asthma phenotype. The study of new mechanisms involved in the pathogenesis of asthma and obesity will make it possible to find common therapeutic targets for this asthma phenotype.

Key words: obesity, bronchial asthma, neurotrophic factors.

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Роль нейротрофических факторов роста в патофизиологии бронхиальной астмы, сочетанной с ожирением

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РЕЗЮМЕ

Бронхиальная астма (БА) и ожирение являются широко распространенными заболеваниями с тенденцией к неуклонно прогрессирующему увеличению числа больных. Сочетанное течение данных заболеваний представляет собой одну из серьезных проблем современности, требующих пристального внимания в связи со снижением качества жизни, ухудшением контроля течения основного заболевания, повышением частоты и длительности госпитализации. Если взаимосвязь между БА и ожирением очевидна, то детализация данных механизмов находится в стадии изучения. В последнее десятилетие в формировании фенотипа БА, сочетанной с ожирением, пристальное внимание уделяется не только иммунным, но и нейрогенным механизмам воспалительной реакции. Известно, что контроль над функционированием всех отделов нервной системы способны осуществлять нейротрофические факторы роста благодаря их способности влиять на множество механизмов сигнализации. В настоящее время имеются данные об участии нейротрофических факторов в патогенезе бронхолегочных и метаболических заболеваний. Обзор посвящен детализации механизма нейрогенного воспаления при ожирении и БА с участием нейротрофических факторов, которые могут играть существенную роль в формировании фенотипа БА, сочетанной с ожирением. Изучение новых механизмов, вовлеченных в патогенез БА и ожирения, позволит найти общие терапевтические мишени для данного фенотипа БА.

Ключевые слова: ожирение, бронхиальная астма, нейротрофические факторы.

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ASTHMA AND OBESITY

Asthma is a widespread disease with a tendency to a steady increase in the number of patients, which is a serious medical and social problem. Globally, about 300 million people suffer from asthma, which accounts for 4–8% of the world population [1]. The number of asthma patients in the world is expected to increase to 400 million within the next five years. High prevalence of this pathology is associated with a decrease in the quality of life of patients, difficulties in controlling the symptoms of the disease, and high treatment costs [2]. According to the International Primary Respiratory Group (IpCRg), one of the reasons for the lack of asthma control is the presence of concomitant pathology, in particular obesity [3].

According to M. Ng et al., more than 600 million adults are obese (BMI ≥ 30 kg / m^2) and about 2.1 billion are overweight (BMI ≥ 25 kg / m^2) [4]. It is predicted that obesity will be diagnosed in 18% of working age population by 2025 [5]. The growing prevalence of obesity and overweightness [6] is observed in both developed and developing countries [7], which harms the global economy. The prevalence of adult obesity has increased from 15.1% in 1980 to 20.7% in 2015; the prevalence of childhood obesity has increased from 4.1% to 4.9% over the same period. In 2015, 417,115 deaths and 14,448,548 disability-adjusted life years (DALYs), years of life changed or lost due to disability, associated with obesity were registered, which accounts for about 10% of the total number of deaths and 6.3% of DALYs among people of all age groups [8]. Despite the progress in studying the etiopathogenesis of obesity and development of new approaches to its treatment, this pathology remains one of the most serious modern problems that resulted in the World Health Organization (WHO) statement on the need to stop the pandemic by 2025 [9].

Overweightness and obesity occur twice more frequently in asthma patients than in the general population [10]. Asthma associated with obesity is one of the urgent medical and social problems requiring particular attention because of a decrease in the quality of life of patients, poor control over the course of the primary disease, and an increase in the frequency and duration of hospitalization [11]. A close relationship between obesity and asthma allows to consider their combination not only as a

comorbid condition but also as an independent phenotype of the disease [12]. This relationship is obvious; however, detailed mechanisms underlying it are still being studied [13]. Several concepts have been proposed to explain the existing relationship [14]. The leading ones are immunological and hormonal concepts revealing the role of systemic inflammation in obesity in the pathogenesis of asthma [15, 16]. At the same time, there has been a growing interest in the role of the nervous system in the pathophysiology of these diseases and its contribution to development of the obese-asthma phenotype.

In the vast majority of cases, asthma is an allergic disease and the immune system plays an important role in its development. A relevant and promising direction of modern research is the study of the neurogenic component of the inflammatory response in this pathology and the role of the nervous system in the development of allergic reactions in asthma [17, 18]. Bidirectional communication between neurons and immune cells was detected. An imbalance in the immune-neuronal communication results in the initiation of neurogenic inflammation. The immune system activates sensory neurons, thereby mediating bronchial hyperresponsiveness, while the interaction between neurons and immune cells results in the development of Th2-mediated immune response [19, 20].

There is increasing evidence that the association between obesity and neurological disorders affects both the peripheral (PNS) and central (CNS) nervous systems [21]. One of the new research directions is focused on studying the neural regulatory mechanism of metabolism in the white adipose tissue [22, 23]. Adipose tissue hormones are responsible for energy homeostasis in the body; therefore, excessive fat accumulation leads to impairment of metabolic processes in various organs and tissues [15, 24]. Obesity is associated with the development of non-insulin-dependent (type 2) diabetes [25], metabolic syndrome [26], neuropathy [27], and several other diseases. Using a mouse model of diabetic neuropathy (leptin-deficient BTBR ob/ob mouse) [21], the role of dyslipidemia accompanying obesity in the development of nervous system dysfunction was demonstrated [28]. Metabolic inflammation in CNS was observed in high-fat diet-induced obesity models [29]. The increased expression of microglia and astrocyte markers in the brain was demonstrated [30]. The same diet-initiated inflammation in the hypothalamus during the first day had persisted for a long period [31]. Currently, metabolic inflammation is being studied in close connection with neurological disorders in obesity [32–34].

Following the presented data, it is clear that the study of new mechanisms in the pathophysiology of asthma and obesity will make it possible to find promising therapeutic targets for treatment of asthma associated with obesity. Neurotrophic factors (NTFs) control the functioning of all parts of the nervous system due to their ability to modulate many signaling mechanisms [35]. Currently, there is evidence that neurotrophic factors are involved in the pathogenesis of neurodegenerative, skin, cardiovascular, psychiatric, bronchopulmonary, and metabolic diseases. Detection of neurotrophins and their receptors in the lungs attracted great attention of researchers to the study of their role in asthma pathophysiology [36, 37]. The involvement of NTF-signaling in the innervation of airways, epithelium, and smooth muscles as well as its presence in immune cells was established. A large body of data emphasizes the key role of sensory neurons in NTF-mediated bronchial hyperresponsiveness. At the same time, studies on the role of neurotrophic factors in the pathophysiology of obesity are few and focused mainly on their role in maintaining energy balance [38].

The review is devoted to detailed investigation of the mechanism of neurogenic inflammation in obesity and asthma with the participation of neurotrophic factors that can play a significant role in the development of asthma associated with obesity.

NEUROTROPHIC GROWTH FACTORS

Neurotrophic factors are a large group of polypeptide compounds. These factors play an important role in the development and functioning of the central and peripheral nervous systems, as well as the immune system. NTFs are involved in regulation of cell growth and differentiation by activating mitogen-activated protein kinases (MAP kinases).

Neurotrophic factors include several families and biomolecules with common properties. The main classification system is based on amino acid sequence homology of neurotrophic factors and in-

cludes four families (neurotrophins, the CNTF (ciliary neurotrophic factor) family, the MANF (mesencephalic astrocyte-derived neurotrophic factor) family, and the GDNF (glial cell line-derived neurotrophic factor) family). However, there are differences in the existing classification among some authors, which makes it possible to differentiate a larger number of families and biomolecules that also belong to neurotrophic factors [39].

Neurotrophins are the neurotrophic growth factor family that include neurotrophin-3 (NT3), neurotrophin-4/5 (NT4/5), brain-derived neurotrophic factor (BDNF), and nerve growth factor (NGF). The family of ciliary neurotrophic factors, or neurokines (neuropoietic cytokines), includes CNTF, leukemia inhibitory factor (LIF), interleukin-6 (IL-6), cardiotrophin-1, cardiotrophin-2, prolactin, growth hormone, leptin, interferons-α/β/γ, and oncostatin M. The MANF family includes MANF (arginine-rich, mutated in early-stage tumors (ARMET)) and cerebral dopamine neurotrophic factor (CDNF).

Another family of neurotrophic growth factors is called glial cell line-derived neurotrophic factors (GDNF-family ligands) and includes GDNF, neurturin (NRTN), artemin (ARTN), and persephin (PSPN). There is a family of neurotrophic factors that consists of epidermal growth factor (EGF), neuregulin, and transforming growth factors alpha and beta (TGFα and TGFβ). The ephrin family contains several members (ephrin A1, A2, A3, A4, A5, B1, B2, and B3).

In addition, some biomolecules were also identified as neurotrophic factors, such as insulin-like growth factor-I/2 (IGF1/2), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), interleukin-1, -2, -3, -5, -8 (IL-1, -2, -3, -5, -8) and a number of others.

This review summarizes the available literature data on neurotrophins, the most studied family of neurotrophic growth factors, and describes their role in the pathophysiology of asthma and obesity. Special attention is paid to insulin-like neurotrophic factors, the role of which in asthma and obesity is being actively studied today in connection with the emergence of new data on the mechanisms of their action. Based on analysis of the available literature data, it was shown that further study of neurotrophins and insulin-like neurotrophic growth factors is promising as a therapeutic target in asthma associated with obesity.

THE FAMILY OF NEUROTROPHINS AND THEIR ROLE IN THE PATHOPHYSIOLOGY OF ASTHMA ASSOCIATED WITH OBESITY

Neurotrophins (NTFs) are ligands for high-affinity protein tyrosine kinase receptors (TrkA, TrkB, TrkC) that interact with the low-affinity non-tyrosine kinase receptor p75NTR. The p75NTR receptor belongs to TNF receptors. The interaction of NGF with this receptor induces apoptosis at certain stages of cell development. Other functions of NTFs are realized through protein tyrosine kinase receptors. The Trk receptors impact on survival, differentiation, and functional properties of neurons. In particular, the TrkB receptor initiates phosphorylation processes, which leads to an increase in synaptic plasticity. Each of the receptors interacts with a specific site of the neurotrophin molecule triggering a respective signaling cascade [40].

Neurotrophins are produced by smooth muscle and neuroendocrine cells of the lungs. Therefore, NTFs can be involved in the asthma pathogenesis both through interaction with Trk receptors and through an alternative pathway modulating allergic inflammation and airway dysfunction by influencing airway innervation.

In addition to the known effect of neurotrophins on the nervous system, a wide range of regulatory effects of these growth factors on the immune system are described in the literature [35]. Immune cells synthesize NTFs that can bind to receptors expressed by the same cells, influencing the activity of immune system cells through autocrine and / or paracrine interactions [39]. Several types of immune cells (including dendritic cells, mast cells, eosinophils, macrophages, and T and B lymphocytes) are the main source of NTFs in the development of inflammation, in particular, allergic inflammation in asthma.

It is known that $CD4^+$ and $CD8^+$ T lymphocytes express NGF, BDNF, and their receptors. NTFs and their receptors are also found on T helper 1 and T helper 2 cells. It was shown that B lymphocytes synthesize NGF and NT3. Macrophages were reported to have the ability to produce NGF, BDNF, and NT4. It was found that monocytes are able to express protein tyrosine kinase receptors (TrkA), and

polymorphonuclear eosinophils in the bone marrow produce TrkB and TrkC receptors. Eosinophils can not only express neurotrophin receptors but also can store these mediators. The exposure to the allergen from bronchoalveolar lavage fluid (BALF) was accompanied by an increase in NTF receptor expression on eosinophils. In addition, members of the NTF family have the ability to increase the viability of endobronchial eosinophils [40]. Therefore, NTFs not only play an important role in the functioning of the central and peripheral nervous systems, but also have an immunoregulatory effect in allergic diseases, in particular, asthma.

Brain-derived neurotrophic factors

BDNF is produced by epithelial cells, smooth muscle cells, sensory neurons, and some immune cells, such as T cells, macrophages, and mast cells [36, 40]. BDNF stimulates growth of neurons, axons, and dendrites and affects cell apoptosis. The action of this factor is mediated by the ERK signaling pathway (mitogen-activated protein kinase (MAPK) signaling pathway), which is named after ERK (extracellular signal-regulated kinase), the central MAP-kinase, and PI3K/AKT/mTOR signaling pathway, the components of which are enzymes phosphoinositide 3-kinase (PI3K), AKT, and mTOR kinases, that are responsible for proliferation of smooth muscle cells [41]. It was shown that BDNF interacts with TrkB and p75NTR receptors. TrkB expression was found on $CD45^+$ lymphocytes, mast cells, alveolar type 2 cells, and eosinophils [42].

Trigger factors of bronchopulmonary diseases increase BDNF expression by smooth muscle cells [43]. The expression of this factor was found in the airway epithelium [42]. The elevated expression of BDNF is observed in asthma [44], which suggests its involvement in the processes of bronchial remodeling and hyperresponsiveness. It was established that patients with severe asthma have higher levels of mature BDNF isoforms [45]. V. Aravamudan et al. found that type 2 cytokines can regulate the BDNF level in asthma [40]. The relevance of further study of BDNF effects in the airways is undoubted.

The neurotrophic activity of BDNF and its role in inflammation, metabolism, and pathogenesis of cardiometabolic diseases are summarized by the term "triact" that explains the interactions between the brain, the immune system, and the adipose tissue [46]. There is evidence that the level of this factor is closely associated with increased body weight, obesity, type 2 diabetes, and development of metabolic syndrome [47]. Under experimental conditions, it was demonstrated that the elevation of BDNF level improves metabolic regulation by influencing insulin sensitivity in hepatocytes and the function of pancreatic beta cells [48]. It was found that decreased activity of BDNF and its TrkB receptor in the hypothalamus leads to a significant increase in body weight in rodents [49]. However, some results indicate a complex and contradictory relationship between obesity and BDNF levels in children [50]. According to L. Sandrini et al., obesity is not associated with lower circulating BDNF levels [51]. It should be noted that the mechanisms of the development of neurological disorders in obesity are not completely understood. New strategies targeted at BDNF are being developed for treatment of obesity, diabetes, and neurological disorders [52]. It was shown that therapeutic interventions aimed at increasing BDNF expression can have a beneficial effect on the metabolic function, thereby improving neurocognitive parameters in patients with obesity or type 2 diabetes [53]. Obviously, BDNF may be a promising therapeutic target in asthma associated with obesity.

Neurotrophin-3 and neurotrophin-4

Recently, much attention has been paid to the role of NT3 and NT4 in the pathophysiology of bronchopulmonary diseases. Mast cells and eosinophils synthesize NT3. Alveolar macrophages constitutively express NT3 and produce BDNF and NGF in response to allergic stimuli, while interstitial macrophages constitutively express only BDNF. The NT4 factor is involved in the innervation of the lungs [42]. The TrkB receptor has the highest affinity for NT3 and NT4. The TrkC receptor is only activated by NT3. Both NT3 and BDNF, acting through TrkB and TrkC, are able to induce nitric oxide production, thereby facilitating bronchodilation. Patients with asthma exhibit an increased NT3 level in BALF [42, 54]. In a rodent model of allergic asthma, it was demonstrated that the use of NT3 results in switching from noncholinergic innervation to cholinergic one [55]. At the same time, the role of NT3 and NT4 in obesity as well as their contribution to the pathophysiological mechanism

of development of asthma associated with obesity has not been studied.

Nerve growth factors

NGF is one of the most studied members of the protein family of neurotrophic factors. The TrkA receptor has the highest affinity for NGF. The presence of p75NTR is necessary to increase the affinity of TrkA for neural growth factor. This factor is synthesized by astrocytes and has a neurotrophic effect. In addition to the ability of NGF to stimulate the survival of neurons and their repair after damage described by R. Levi-Montalcini [56], it is involved in the control of the main cellular processes, such as oxidative stress, apoptosis, and neurogenesis. Data are indicating that NGF regulates the survival and activity of immune cells, fibroblasts, cardiomyocytes, epithelial cells, mast cells, and adipose tissue cells [57], which makes the study of its role in the pathophysiology of asthma and obesity relevant.

The results of experimental studies carried out on rodent models indicate the relationship between the enhanced NGF level and the development of allergic inflammation. For example, exposure to tobacco smoke was accompanied by an increase in NGF expression [58]. Asthma patients are characterized by an elevated NGF level [59] that correlates with the level of eosinophils, the main effector cells in this pathology [60]. There is evidence of a simultaneous increase in the number of mast cells and NGF levels in chronic inflammation [61]. NGF is produced by both $CD4^+$ and $CD8^+$ T lymphocytes. Under experimental conditions, the role of NGF in modulating the balance of Th1 and Th2 responses of T cells in asthma was shown [62]. Enhanced NGF secretion by Th2 cells was identified, which may be directly related to allergic asthma. In addition, NGF is involved in airway remodeling in asthma [59]. Genomic studies revealed the relationship between NGF, rs6330, and TrkA rs6334 in asthma patients [54].

It should be noted that the role of NGF in the pathophysiology of chronic inflammation in asthma remains to be investigated. The modulation of NGF level affecting the activity of immune cells will make it possible to correct intersystem relationships in asthma. It is one of the topical research fields focused on the search for a new strategy for treating this pathology.

Recent study results have shown that the levels of two neurotrophic factors, NGF and BDNF, are altered in cardiometabolic diseases (atherosclerosis, obesity, type 2 diabetes, metabolic syndrome). These observations have underlain the hypothesis of metabotropic deficiency of NGF/BDNF that plays an important role in the pathogenesis of cardiometabolic diseases [38, 46]. The concept of NGF metabotrophicity is based on the fact that two neurotrophic factors, NGF and BDNF, can act as metabotrophins due to their involvement in maintaining cardiometabolic homeostasis [38].

The data presented above confirm that further studies on the role of these factors in the development of asthma associated with obesity are required.

THE ROLE OF INSULIN-LIKE NEUROTROPHIC FACTORS IN THE PATHOPHYSIOLOGY OF ASTHMA ASSOCIATED WITH OBESITY

The system of insulin-like neurotrophic factors includes ligands (IGF-1 and IGF-2), high-affinity proteins (IGFBP 1–6) that bind them, and receptors. This hormonal network is involved in the processes of cell proliferation, differentiation, and apoptosis.

IGF-1 synthesized by hepatocytes is the most important mediator of the biological action of growth hormone. IGF-1 is one of the proinflammatory mediators involved in the pathogenesis of various diseases, in particular metabolic disorders, inflammatory bronchopulmonary pathology, and lung cancer [63, 64]. The expression of IGF-1 signaling components was observed in the cells of the respiratory tract, smooth muscles, lung parenchyma, and in alveolar macrophages. H. Lee et al. demonstrated that IGF-1 and IGFBP-3 signaling pathways contribute to the pathogenesis of asthma [65]. The mechanism of action of corticosteroids in asthma therapy appears to be associated with inactivation of IGF-1/IGF-1R signaling [66, 67]. Due to the existing relationship between IGF-1 and Th2 and Th17 cells involved in asthma pathogenesis, the immunoregulatory role of IGF-1 in this pathology is being actively studied [68]. S.R. Kim et al. showed that IGFBP-3 reduces allergic inflammation and airway hyperresponsiveness in asthma by inhibiting IGF-1 activity [69]. The role of IGF-1/IGF-1R in the regulation of phagocytic activity of airway cells in asthma was revealed [70].

IGF-1 has an insulin-like metabolic effect and does not affect lipolysis or lipogenesis. In contrast to insulin, the biological activity of IGF is regulated by high-affinity binding proteins that influence the metabolic homeostasis and can directly participate in the molecular regulation of insulin signaling. Currently, IGFBP-1 and IGFBP-2 are considered as biomarkers and promising therapeutic targets in obesity and diabetes [71]. Therefore, this proinflammatory mediator can be a novel promising target for therapeutic measures in asthma associated with obesity.

CONCLUSION

Asthma and obesity are common diseases and a combination of these diseases is one of the pressing global problems because of the decrease in the patients' quality of life and the increase in the frequency and duration of hospitalization. Detailed mechanisms underlying the relationship between these diseases and a pathogenetic target for their effective therapy have been actively studied. In the last decade, along with the immune component of the inflammatory response, attention of researchers has been focused on studying the role of the neurogenic component in the pathophysiology of asthma associated with obesity.

Over the past 30 years, the role of neurotrophic growth factors has been to the largest extent studied in diseases of the nervous system, and a search for a potential therapeutic target is extremely urgent at present. At the same time, NTFs are expressed by many cells and involved in the pathogenesis of bronchopulmonary and metabolic diseases. Therefore, these factors can play a significant role in the development of asthma associated with obesity. However, there are few research works regarding the role of neurotrophic factors in the pathophysiology of asthma and obesity; moreover, there are no data on their contribution to the development of asthma associated with obesity. We hope that this review will draw attention to the complex relationship between neurotrophins, nerve, and immune cells in respiratory diseases, in particular, asthma associated with obesity.

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