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Review

The role of regulatory neuropeptides and neurotrophic factors in asthma pathophysiology

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Abstract: In the last decade, the attention of scientists in the field of biomedicine is focused on studying the relationship between the immunological and neurogenic components of the inflammatory response and their contribution to the pathophysiology of allergic inflammation in asthma. The review is devoted to detailing the mechanism of neurogenic inflammation involving regulatory neuropeptides (substance P, vasoactive intestinal peptide, calcitonin gene-related peptide) in the pathogenesis of bronchial hyperreactivity in asthma. The role of neurotrophic growth factors (nerve growth factor, brain-derived neurotrophic factor) in the regulation of remodeling of bronchi in asthma has been analyzed. The study of neuroimmune mechanisms in the pathophysiology of asthma will it possible to find new therapeutic targets in this research area.

Keywords: asthma, neurotrophic factors, regulatory neuropeptides, chronic inflammation, neuroimmune mechanisms

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Asthma

Asthma is a common socially significant allergic pathology and global health problem [1, 2]. Despite the expected increase in the number of patients, asthma is successfully controlled and treated [3]. However, about 10% of patients suffer from refractory asthma [4] that indicates a multi-factorial nature of the disease and the complexity of pathophysiological mechanisms underlying chronic inflammation [5].

Asthma is a heterogeneous disease characterized by chronic inflammation and hyperreactivity of the bronchi, which form clear clinical symptoms of the disease [6]. Hyperreactivity accompanying asthma is a direct result of persistent airway inflammation, bronchial remodeling, smooth muscle hyperplasia and impaired neuroregulation of bronchial tone. However, the factors involved in the development of bronchial hyperreactivity have not been fully disclosed, despite an impressive amount of research on this issue [7].

There are several mechanisms to maintain pulmonary homeostasis, which involve nerve and immune cells [8]. An increase in the burden of allergic diseases worldwide has enhanced researcher's interest in studying the role of immune and neurogenic mechanisms in the pathophysiology of allergic inflammation [9]. B.J. Canning et al. have emphasized the obvious but underestimated compared to the immune system role of the nervous system in asthma pathogenesis [7]. It has been established that the interaction between nerve and immune cells is disturbed in asthma, therefore this process is referred to as "neurogenic inflammation" [10]. Neurogenic inflammation is considered as an important cause of bronchial hyperresponsiveness in asthma. The immune system mediates the development of hyperresponsiveness and subsequent bronchospasm in asthma by activating sensory neurons through inflammatory mediators. Conversely, neurons modulate the development of Th2-mediated immune response, which is responsible for chronicity of inflammation, by interacting with immune cells through neurotransmitters or neuropeptides. Thus, the existence of interactions between neurons and immune cells, which play an important role in asthma pathogenesis [11], is evident. In addition, an allergic reaction is associated with local production and release of neurotransmitters, so neurogenic inflammation may accompany already existing allergic inflammation.

There are several reviews of available literature on this problem [12, 13]. The presence of neuroimmune interrelations in asthma and their contribution to the pathogenesis of the disease have been described in the review authored by N. Kabata and D. Artis [12]. The involvement of cytokines, neuropeptides, and neurotransmitters in the cooperation of immune cells and the central, peripheral, sympathetic and parasympathetic nervous systems in asthma have been evidenced. S.L. Foster et al. has summarized the results indicating the important role of nociceptors in the regulation of immune reactions in inflammatory diseases of the bronchopulmonary system [13]. The aim of this review is to summarize the available information in order to attract the attention of researchers to a close relationship

between the immune and nervous systems and their role in asthma pathogenesis.

The study of the role of neuroimmune mechanisms in asthma pathophysiology will allow finding new therapeutic targets in this field of research.

Adrenergic, cholinergic and non-adrenergic non-cholinergic (NANC) nerves innervate the airways [14]. Non-myelinated, nociceptive C-fibers of the lungs are involved in the sensory innervation of the mucous membrane of the airways and are responsible for the formation of the main protective reflexes [15]. Several studies suggest that sensory nerves of the respiratory tract are involved in asthma pathogenesis [15, 16]. It has been noted that the number of nociceptors significantly increases in patients with asthma [17]. Besides that, in this pathology denser network of nociceptor fibers is localized around the small airways, the dysfunction of which is present in the majority of patients with asthma and often associated with the more severe course of the disease [18]. Nociceptors contribute to the pathogenesis of airway inflammation by initiating local neurogenic inflammation [19] and activating the bronchoconstrictor mechanism [20].

The sensitivity of nociceptors is related to the activity of transient receptor potential ion channels (TRP ion channels), in particular, TRP vanilloid receptor 1 (TRPV1) and TRP ankyrin receptor 1 (TRPA1) [21]. It is considered that chronic respiratory tract inflammation and mucus hypersecretion are associated with TRPV1 sensitization [22]. The enhanced expression of TRPV1 has been observed in asthma and is more significant in severe uncontrolled course of the disease [23]. Recent studies have shown that TRPA1 is the main trigger for the release of neuropeptides during stimulation of peripheral parts of a nociceptor and one for the development of neurogenic inflammation of the bronchial tree [24].

Neuropeptides are the largest and the most diverse class of intercellular signaling molecules secreted by neurons [25]. Neuropeptides do not belong to the parasympathetic or sympathetic nervous system and are referred to as non-adrenergic non-cholinergic peptides [26]. These signaling molecules have a wide range of regulatory functions: from neurohormones and neurotransmitters to neuromodulators that makes the study of them relevant for modern pulmonology.

There are a small number of review articles devoted to the role of regulatory neuropeptides in asthma pathogenesis [27, 28, 29]. The information on the expression of certain neuropeptides (substance P, vasoactive intestinal peptide, calcitonin gene-regulated peptide, tachykinins, neuropeptide Y (NPY), bombesins, granins), which can influence on the pathogenesis of a number of bronchopulmonary diseases, in particular asthma, is provided in the review authored by K.R. Atanasova and L.R. Reznikov [27]. The data on known and proposed receptors mediating their actions have been summarized. The effect of neuropeptides on mucus secretion in this pathology has been also described. K. Kaczyńska et al. provides a brief overview of the functions of a number of neuropeptides (leptin, substance P, neurotensin) in normal respiration and in chronic pulmonary pathology [28]. A.K. Verma et al. have structured and detailed the available information on the vasoactive intestinal peptide and its role in the recruitment of inflammatory cells in asthma [29]. This review summarizes the literature data on the contribution of the most studied neuropeptides (substance P, vasoactive intestinal peptide, calcitonin gene-regulated peptide) to the pathogenesis of bronchial hyperreactivity in asthma. Special attention was paid to the study of the effect of neuropeptides on the regulation of immune mechanisms in this pathology.

Regulatory neuropeptides

Currently, it is known that the multifaceted pathogenesis of asthma is characterized by not only inflammatory mechanisms initiated by allergic reactions but also neurogenic inflammatory mechanisms involving neuropeptides that play an important role in the nervous system control of the bronchial tree tone. There is limited evidence of the role of neuropeptides in the regulation of mucus secretion in asthma [27].

More than 10 regulatory neuropeptides have been found in the human lung, among which substance P (SP), vasoactive intestinal peptide (VIP) and calcitonin gene-related peptide (CGRP) are the most studied. Neuropeptides can also be released from peripheral neurosecretory cells located in the distal parts of the respiratory tract in close proximity to the microcirculatory bloodstream and smooth muscle of the bronchi. The activation of sensory neurons leads to the release of SP and CGRP in the airways through the axon reflex mechanisms [4]. Altered CGRP, VIP and SP levels in allergic inflammation affect the regulation of immune mechanisms and, therefore, are involved in asthma pathogenesis [30]. In addition, the imbalance between stimulating (SP) and inhibiting (CGRP) neuropeptides in prolonged inflammation of the respiratory tract leads to the predominance of the stimulating environment in airway mucosa.

SP is a neurotransmitter of non-cholinergic excitatory nerves and is currently considered as a mediator of neurogenic inflammation, which can initiate swelling, mucus hypersecretion and bronchospasm. This pleiotropic peptide that has specific neural activity is also an immunomodulator [31]. Mast cell proteases can enhance neurogenic inflammatory reactions by releasing of SP [32]. It has been established that SP can stimulate the production of granulocyte-macrophage colony-stimulating factor (GM-CSF), which regulates the proliferation and the differentiation of progenitors of monocytes, neutrophils, macrophages and dendritic cells. SP has the ability to activate the release of pro-inflammatory cytokines (interleukin 1 (IL-1), interleukin 6 (IL-6), interleukin 8 (IL-8), tumor necrosis factor α (TNFα)) from human bronchial epithelial cells. The data of J. Zhuang et al. indicate that IL-1β significantly intensifies SP expression and vascular permeability by the effect on C-fibers of the bronchi (PCF) that after the activation promotes the release of SP and cause bronchospasm. IL-1β administered systemically or locally into the lung parenchyma stimulates PCFs [33]. SP also induces the expression of intercellular adhesion molecule 1 (ICAM-1), which contributes to the survival of dendritic cells. According to R. Ramalho et al., SP acting via its receptor neurokinin-1 (NK1-R) plays an important role in asthma associated with obesity [34]. NK1-R blockade in mice with asthma and obesity resulting in the normalization of metabolic and systemic levels of biomarkers, as well as positive effect on allergic sensitization and inflammation in the bronchi. Presented facts allow considering this neurotransmitter as a potential therapeutic target for the treatment of this asthma phenotype.

Asthma is a chronic inflammatory disease; Th2 cells, regulatory T cells (Tregs), mast cells, eosinophils, neutrophils, epithelial and endothelial cells, fibroblasts and smooth muscle cells are involved in its pathogenesis. VIP affects all these cells and is the main

neurotransmitter of the non-adrenergic-non-cholinergic system [35]. VIP, as one of the most common neuropeptides of the human body, is expressed in the lungs and the nasal mucosa. The action of VIP depending on the target organ and the presence of VIP-associated receptor [36]. This peptide exhibits a wide range of reactions by interacting with following receptors: VIP receptor type-1 (VPAC-1), VIP receptor type-2 (VPAC-2), chemoattractant Receptor-Homologous Molecule Expressed on Th2 cells (CRTH2) and pituitary adenylate cyclase-activating polypeptide (PACAP) receptor (PAC1), which are expressed on eosinophils, mast cells, neutrophils and lymphocytes [37]. VPAC1 is more common in lung tissue, whereas VPAC2 is presented in smooth muscles and bronchial mucosa [38]. The activity of neutral endopeptidase (NEP) is essential for the realization of properties of neuropeptides. NEP proteolyzes and inactivates neuropeptides. It is possible that the change in NEP activity also plays important role in asthma exacerbation. VIP is an endogenous vaso- and bronchodilator [29]. Besides that, it has immunomodulatory functions, including the suppression of humoral immune response, inflammatory process and remodeling of the bronchi. VIP inhibits T-lymphocyte proliferation, affects T-helper differentiation (Th2/Th1) and contributes to the induction of Tregs. In addition, there is evidence that VIP suppresses Toll-like receptor-4 (TLR-4), which plays an important role in the innate immune system [39]. There are conflicting data on its effect on mast cell degranulation and chemokine production [40]. The formation of airway hypersensitivity and reflex bronchospasm may be associated with the increased degradation of this neuropeptide. J. Wang et al. has been found that VIP inhibits airway remodeling under in vivo conditions [41]. Using mouse asthma models, it has been shown that Th17/Treg imbalance is closely associated with airway inflammation and VIP reduces this inflammation by regulating the balance of these cells [42]. S. Talbot et al. has been revealed that IL-5 acts directly on nociceptors, resulting in the release of VIP, which stimulates $CD4^+$ lymphocytes and resident innate lymphoid cells of type 2, thereby creating a signal loop that contributes to allergic inflammation [15].

Thus, VIP as an important signaling molecule of the neuroendocrine-immune network is a new therapeutic target for asthma.

CGRP is involved in asthma pathophysiology [8]. CGRP is a 37 amino acid neuropeptide that was discovered in the result of alternative preparing of ribonucleic acid (*RNA*) copies obtained from the calcitonin gene. CGRP messenger RNA (*mRNA*) is detected in nerve cells that closely contact with the blood vessels. CGRP is expressed by cells of the central and peripheral nervous systems [43]. CGRP released from the nerve fibers of airways acts as a chemoattractant for $CD4^+$ T lymphocytes, $CD8^+$ T lymphocytes, eosinophils and dendritic cells [44]. In addition, CGRP is the powerful arterial and venous vasodilator.

An increase in CGRP expression in airways epithelial cells has been observed in asthma patients [45]. In addition, asthma patients have elevated levels of pulmonary neuroendocrine cells (PNEC), which are located between the epithelial cells of the respiratory tract in close proximity to group 2 innate lymphoid cells (ILC2) that affect cytokine production. PNECs stimulate ILC2s and intensify allergic reactions in asthma via CGRP [46]. It was recently described that the maturation and differentiation of dendritic cells, which play a key role in allergic sensitization in asthma patients, is modulated by CGRP [8]. CGRP inhibits dendritic cell maturation and allergen-specific T-cell responses that influence the outcome of allergic airway inflammation in vivo [47]. These facts indicate an additional mechanism of the impact of neurotransmitters on the local immune response. Besides that, the physiological significance of CGRP in the production of interleukin-9 (IL-9), which is a Th2 cytokine and involved in allergic inflammation, has been demonstrated.

Thus, CGRP as an anti-inflammatory mediator is a new and effective therapeutic target for asthma.

Neurotrophic growth factors

It is known that persistent inflammation in the bronchi leads to structural changes in the respiratory tract that probably play a certain role in the formation of bronchial hyperreactivity. Along with passive response to bronchoconstrictor stimuli (bronchial hyperreactivity), the airways are remodeled by increasing airway smooth muscles (hypertrophy and hyperplasia). Airway smooth muscle remodeling is regulated through a number of mechanisms, including the production of cytokines and neurotrophic growth factors (neurotrophins), which may have both negative and positive effects. Neurotrophins and their receptors have been recently found in the lungs (bronchial and alveolar epithelium, smooth muscles, fibroblasts and vascular endothelium). The discovery has attracted researchers' interest in the role of these molecules in the regulation of pulmonary structure and function, as well as in the pathophysiological mechanisms of bronchopulmonary diseases [48].

A number of reviews were focused on the role of neurotrophins in the pathophysiology of chronic inflammation in asthma [48, 49, 50]. The article by Y.S. Prakash et al. is of interest [48]. It considers the potential role and functions of neurotrophins in normal lung functioning and in their pathology. The characteristic of neurotrophic factors and their receptors has been given; their signaling function in the innervation of the respiratory tract and in immune cells has been analyzed. J. Barrios and Ai X. have also compiled recent literature data on neurotrophins and their receptors [49]. Special attention is given to the study of their role in the pathophysiology of early stages of asthma in children. S. Manti et al. have provided a comprehensive description of the neuroimmune interactions underlying the pathophysiology of asthma [50]. Neurotrophins have been shown to play an important role in the implementation of signaling interrelations between immune cells and the structures of the neurosensory network of the respiratory tract.

Due to the fact that this issue is not fully studied and relevant for further research, this review summarizes the available information. Particular attention is focused on the members of the neurotrophin subfamily, which can play a key role in asthma pathophysiology. The function of neurotrophic factors (nerve growth factor, brain-derived neurotrophic factor) in the regulation of bronchial remodeling in asthma has been analyzed. Based on the analysis of various literature data, the essential role of neurotrophins in the pathogenesis of this disease and the need for further research in this field are assumed.

The family of neurotrophic growth factors consist of neurotrophin 3 (NT3), neurotrophin 4 (NT4), nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), glial cell line-derived neurotrophic factor (GDNF), insulin-like growth factor 1/2 receptor (IGF1/2) and etc.

Neurotrophins are divided into three subfamilies: the neurotrophin subfamily (NGF, BDNF, NT3 and NT4), the glial factor subfamily (GDNF, neurturin (NTR), artemin (ART) and persephin (PSP)) and the ciliary factor subfamily (CNTF, oncostatin M (OSM), leukemia inhibitory factor (LIF) and interleukin-6 (IL6).

The members of the neurotrophin subfamily make a special contribution in airway inflammation. It is important to notice that NTs, which control the functioning of all parts of the nervous system, can regulate most pathophysiological processes by initiating a strictly specific signaling cascade of reactions. Neurotrophins mediate their effects via the high-affinity tyrosine kinase receptors (TrkA, TrkB, TrkC) and p75 Neurotrophin Receptor (p75(NTR)). At the same time, NGF predominantly interacts with TrkA, BDNF does with TrkB and p75(NTR), NT3 does with TrkC and TrkA [51].

BDNF is produced by epithelial and smooth muscle cells, sensory neurons and a number of immune cells that are involved in the pathogenesis of bronchopulmonary diseases [48]. Some research suggests that environmental trigger factors for respiratory diseases (changes in temperature and humidity, airborne pathogens, pollen, smoke particles and ozone) [51] enhance the expression of BDNF and its receptors in smooth muscle cells. It has been shown that oxidative stress induced by cigarette smoke increases the expression of BDNF and its receptors by smooth muscle cells [52]. Interestingly, neurokinins, such as substance P, also enhance the expression of BDNF and its receptor. The relevance of the study of BDNF action on the respiratory tract is caused by recent data indicating an increase in BDNF level in asthma. However, the question of the functional significance of BDNF in this pathology remains unresolved. Taking into account the intensification of BDNF expression in asthma, researchers assume the role of BDNF in airway inflammation, the initiation of remodeling and bronchial hyperreactivity. However, the mechanisms of BDNF action on smooth muscle cells are not fully understood. It is known that BDNF-associated receptors (TrkB, p75(NTR)) activate multiple signaling pathways, including ERK (mitogen-activated protein kinase (MAPK) signaling pathway named after the key MAP-kinase – extracellular signal-regulated kinase (ERK)) and PI3K/AKT/mTOR (intracellular signaling pathway, the components of which are following enzymes: phosphoinositide-3-kinase (PI3K), AKT and rapamycin-sensitive mTOR-complex (mTOR) kinases, phospholipase C and in the case of p75(NTR) – nuclear factor κB (NF-κB)). The involvement of ERK and PI3K/AKT/mTOR pathways, which are responsible for cell proliferation, in BDNF signaling, as well as the expression of TrkB and p75(NTR) in human smooth muscle cells suggest the influence of BDNF on the proliferation of smooth muscle cells. B. Aravamudan et al. have demonstrated that BDNF enhances the proliferation of smooth muscle cells along with pro-inflammatory cytokines (TNF-α and IL-13) [53]. This scientific group has also shown that BDNF impact on Ca^{2+} regulation in smooth muscle cells and potentiates the effect of the pro-inflammatory cytokine TNF-α on Ca^{2+} level. The established BDNF effects on smooth muscle cell proliferation appear to be related to TrkB. However, despite the fact that p75(NTR) didn't influence on the proliferation induced by BDNF, both TrkB and p75(NTR) reduced the proliferative activity of cells in the control group. The activation of ERK1/2 signaling pathway is an important aspect of smooth muscle cell proliferation. NF-κB signaling pathway plays an important role in the mechanism of impact of BDNF on cell proliferation. Involving the PI3K/AKT/mTOR signaling pathway, which is responsible for cell proliferation, in mediating the effects of BDNF on cell proliferation suggests an alternative way to activate NF-κB.

The described literature data indicate the urgency of further research on BDNF effects on the airways.

NGF, which is known for its role in the physiology and the pathology of the nervous system [48], is recently considered as an important factor associated with the pathogenesis of allergic diseases, in particular asthma. The elevated NGF level is a stimulus for the development of pain syndrome, but the mechanisms underlying this process remain unknown. The role of NGF in the Th2-mediated immune response in asthma has been shown under experimental conditions. A number of studies have confirmed that NGF blocking inhibits allergic airway inflammation in a mouse model of asthma by modulating the balance of Th1 and Th2 cells. The increased NGF expression has been observed in asthma patients in response to bronchial provocation with an allergen and is closely related to the disease severity [54]. The results obtained by J.S. Kim et al. have shown that NGF level correlates with the number of eosinophils, which are the main effector cells in asthma [55]. High expression of NGF and tissue inhibitor of metalloproteinase-1 (TIMP-1) and the correlation between their levels in asthma patients indicate a relationship between NGF and TIMP-1, which may play an important role in asthma pathogenesis. N. Renz et al. have revealed that NGF contributes to airway remodeling in asthma [54]. However, it is necessary to stress that the role of NGF in the pathophysiology of chronic inflammation in asthma remains not fully understood and requires further research.

Conclusion

Asthma is a heterogeneous disease characterized by chronic inflammation and bronchial hyperreactivity. Hyperreactivity is a direct consequence of persistent airway inflammation, bronchial remodeling, smooth muscle hyperplasia and impaired neuroregulation of bronchial tone. There are several mechanisms involving nerve and immune cells to maintain pulmonary homeostasis. In the past decade, the attention of researchers has been focused on studying the contribution of the relationship between immune and nervous systems in allergic inflammation in asthma. The immune system mediates bronchospasm in asthma by activating sensory neurons through inflammatory mediators. Conversely, neurons modulate the development of Th2 immune response, which is responsible for chronic inflammation, by interacting with immune cells via neurotransmitters or neuropeptides. In addition, an allergic reaction is associated with the production and release of neurotransmitters, so neurogenic inflammation can accompany and aggravate the existing allergic inflammation in asthma.

Nowadays it is obvious that asthma pathogenesis involves not only inflammatory mechanisms triggered by allergic reactions but also neurogenic inflammatory mechanisms including neuropeptides, which play an important role in bronchial hyperreactivity in asthma. Asthma is characterized by bronchial hyperreactivity (passive response) and airway smooth muscle hypertrophy and hyperplasia. Airway smooth muscle remodeling is regulated through a number of mechanisms, including neurotrophic growth factors.

In this review, we have summarized the available data on the contribution of the most studied neuropeptides (substance P, vasoactive intestinal peptide, calcitonin gene-regulated peptide) to

the pathogenesis of bronchial hyperreactivity in asthma. Particular attention was paid to the study of the effect of the levels of neuropeptides on the regulation of immune mechanisms in this pathology. We give attention to the members of the neurotrophin subfamily that can play an important role in asthma. The role of neurotrophic factors (nerve growth factor, brain-derived neurotrophic factor) in the regulation of bronchial remodeling in asthma has been analyzed. This review will increase our understanding of the interaction between the nervous, immune systems and airway cells. The provided information will allow researchers and clinicians to evaluate the role of the immune and nervous systems in asthma pathophysiology and to highlight the importance of regulatory neuropeptides and neurotrophins. In this regard, the study of neuroimmune mechanisms in asthma pathophysiology will find new therapeutic targets for the disease.

Conflict of interest

We declare that we have no conflict of interest.

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