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ENDOCRINE MECHANISMS OF BRONCHIAL CONTROL IN PATIENTS WITH BRONCHIAL ASTHMA

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The analysis of works published according to the results of studies by foreign and domestic authors on the role of the pulmonary neuroendocrine system in the functioning of the bronchi is carried out. Modern ideas about the endocrine mechanisms of bronchial control in patients with bronchial asthma are presented. A brief description of pro-inflammatory and anti-inflammatory peptide substances produced in the bronchopulmonary system is given. The possibilities of using some peptide substances as drugs in the treatment of patients with bronchial asthma are indicated.

Keywords: pro-inflammatory peptides, anti-inflammatory peptides, bronchopulmonary system, bronchial asthma.

Introduction. According to GINA (2018), bronchial asthma (BA) is a heterogeneous disease characterized by chronic inflammation of the airways and the presence of respiratory symptoms (wheezing, shortness of breath, congestion in the chest, cough), which vary in time and intensity and occur along with variable airway obstruction [16]. At the same time, the neurogenic and immune mechanisms of the development of BA are described in detail in the literature; at the same time, the role of the endocrine system in the development of this disease has not been studied enough.

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The active study of the role of the endocrine system in the development of lung diseases, including bronchial obstruction, began at the end of the 20th century. The impetus for their active study in pulmonology was the confirmation by a number of scientists of the influence of gastrointestinal peptides previously detected in the gastrointestinal tract (GIT) on the bronchopulmonary system (BPS) [1]. Later, endocrine cells secreting similar peptides were also detected in the BLS. One of the first to be identified was the Klara and Kulchitsky cells. By the beginning of the twenty-first century, a large number of endocrine-active cells were synthesized in the BPS, synthesizing peptides similar to gastrointestinal peptides: the tachykinin family, bradykinin, a peptide related to the calcitonin gene (PRCG), bombesin, a vasoactive intestinal peptide (VIP), peptide-histidine-methionine (PHM), adrenomedullin, neuropeptide "Y" and others. It was found that the effect of peptide substances on the functioning of the lungs is carried out by means of receptors located throughout the BPS [12, 22, 23]. Their functional activity was manifested in the blockade of the parasympathetic and sympathetic nervous systems, in connection with which non-adrenergic and non-cholinergic, i.e. peptidergic system of functioning of the lungs.

Later it was proved that certain immune competent cells (mast cells, macrophages, neutrophils, eosinophils and lymphocytes), as well as neurons, also have the ability to secrete peptides [22]. The presence of receptors for neuropeptides on the surface of the cell membranes of immune-competent cells, as well as neurons, was found [12]. It has been found that neuropeptides, acting through different types of receptors, can lead to different pharmacological effects, i.e. possess multidirectional pharmacological activity. The latter was the theoretical justification for a more in-depth study of the pro- and anti-inflammatory effects of various peptide substances on BPS in animal experiments and in patients with BA. It was found that the pro-inflammatory effect on the bronchi has: a family of tachykinins (substance P, neurokinins, chemokinin-1), bradykinin, PRCG, endothelin-1, bombesin, granin. The anti-inflammatory peptides included: VIP, neuropeptide "Y", neuropeptide pituitary adenylate cyclase-activating polypeptide-38 (PACAP-38), PHM, adrenomedullin, atrial natriuretic peptide (ANP).

Pro-inflammatory peptides and their role in the development of inflammatory diseases of the lower respiratory tract

Tachykinins play an active part in the development of inflammatory processes in many organs, including the gastrointestinal tract and BPS [23, 29, 30]. They

are produced in the central nervous system and peripheral tissues, including in the BPS. They are synthesized in the BPS by epithelial cells of the mucous membrane of the bronchi, endothelial cells, endocrine and endocrine-active immune-competent cells of the lamina of the bronchial mucous membrane (mast cells, eosinophils, neutrophils, lymphocytes, monocytes, macrophages), bronchial smooth muscle cells, neurons. It has been established that the BPS of BA patients is more sensitive to tachykinins than the BPS of healthy individuals [22].

Tachykinins act through neurokinin receptors: NK1 (substance P), NK2 (neurokinin-A, neurokinin B) and NK3. Tachykinins are important in the regulation of the peptidergic mechanisms of asthma and are by far the most studied neuropeptides in pulmonology.

Allergic sensitization of the respiratory tract of guinea pigs leads to the induction of tachykinins (substance P, neurokinin A) and a peptide related to the calcitonin gene (PRCG) by sensory neurons, which is one of the pathogenetic mechanisms of inflammation in the bronchi and bronchoconstruction [30]. Through NK1 receptors, tachykinins lead to the development of powerful inflammation in the mucous membrane of the bronchi causing vasodilation, an increase in vascular permeability, hypersecretion, stimulation of mast cells, lymphocytes, and chemotaxis of neutrophils and eosinophils, and through NK2 receptors they cause bronchospasms. Bronchial hyperreactivity (BGR) develops as a result of the isolation of tachykinins from capsaicin-sensitive centripetal nerves via the NK1/NK2 receptors [30].

The substance P, which was discovered in 1931, is the most studied of the tachykinin family. Substance P is encoded by the preprotachikinin-A gene and is expressed predominantly in sensory neurons sensitive to capsaicin. Receptors, through which substance P functions, were found in the lamina propria of the bronchial mucosa, the smooth muscles of the bronchi, near blood vessels, ganglia and nerve bundles of the submucosa. They are absent in the submucous glands and alveolar septa [12].

The substance P is actively synthesized in various immune inflammatory processes in the bronchi. It has been established that the content of substance P increases in serum, sputum, bronchoalveolar lavage, endocrine and endocrine-active BPS cells and sensory neurons of patients with BA [5, 22, 27]. The latter implies the direct participation of substance P in the development of the inflammatory process in the bronchial wall. Substance P affecting the vessels causes their dilatation, affecting the goblet cells of the respiratory tract and submucosal cells causes hypersecretion and stimulation of mucociliary clearance, affecting the smooth muscles of the bronchi causing bronchospasm. Substance P activates inflammation of the bronchi through the activation of immune-competent cells (mast cells, eosinophils, neutrophils, lymphocytes, monocytes, macrophages), chemotaxis of lymphocytes, neutrophils and eosinophils, as well as degranulation of target cells of allergies, predominantly mast cells [5, 22, 23].

Neurokinin-A, which has been actively studied in recent years, is a product of the preprotakhinin-A gene. As well as substance P, it is synthesized by immune, inflammatory, endothelial and epithelial cells, as well as by the smooth muscle cells of the bronchi in various immune inflammatory processes in the bronchi. It participates in the activation of immune cells, prolonging the inflammatory process in the bronchi [22]. There is an increase in its content in sensory neurons, as well as in endocrine and endocrine-active BPS cells of patients with BA. It causes contraction of smooth muscles, mainly in the BPS and gastrointestinal tract [13, 23, 31].

In patients with physical asthma, exercise-induced sputum was collected at the beginning and 30 minutes after exercise. In the induced sputum, secreted mucin 5AC, eicosanoids, cysteinyl leukotrienes, 15S-hydroxyethylisatetraenoic acid and tachykinins (neurokinin-A, substance P) were determined. At the same time, there was a twofold increase in the induced sputum of asthma patients in the physical effort of mucin 5AC, as well as tachykinins: neurokinin A and substance P. The authors assumed that the release of mucin 5AC after exercise may occur through activation of sensory nerves of the respiratory tract associated with cysteinyl leukotrienes tachykinins and the development of bronchial obstruction. Exercise-induced pathogenesis of bronchial obstruction involves the release of mediators (including tachykinins) in response to physical exertion. However, the mechanism that prevents airflow obstruction during exercise is not fully understood [28].

The bronchoconstrictive effect of neurokinin-B has also been proven. This peptide is derived from the preprotachikin-B gene and is acted upon by the NK3 receptors. Neurokinin-B and NK3 receptors are predominantly found in the central nervous system, as well as on the periphery, mainly in the respiratory tract and gastrointestinal tract [19, 23].

Among proinflammatory neuropeptides, the peptide of the tachykinin families, chemokinin-1, has been actively studied in recent years, which, like substance P, interacts through NK1 receptors. It is synthesized predominantly by leukocytes, as well as by immunocompetent cells of the bronchial mucosa, including macrophages and causes a reduction in the bronchi in humans. In experimental mice, it has been established that it is generated by activated mast cell allergens and contributes to experimental chronic allergic inflammation of the airways [34]. Chemokine-1-induced bronchial contraction can be mainly associated with NK2 receptors in humans and with NK1 receptors in the guinea pig [15]. Chemokinin-1 800 times more powerful effect on the bronchi of people than neurokinin-A [22]. It has been established that chemokine-1 increases in patients with asthma and causes mast cell degranulation, an immune inflammatory process in the bronchial mucosa and bronchospasm [34].

As can be seen from the literature data presented, tachykinins are considered as possible mediators of asthma, and tachykinin receptor antagonists can be considered as a new class of drugs in the treatment of patients with asthma [13, 23]. For example, it was established that bronchospasm induced by inhalation of neurokinin-A in patients with BA is blocked by the double antagonist of NK1/NK2 receptors of the tachykinin DNK333 [13] and the antagonist of NK2 receptors of the tachykinin MEN11420 (nepadutant) [32]. It has been proven that dual NK1/NK2 receptor antagonists (DNK-333, AVE-5883 and MEN11420) have the property of weakening bronchial hypersensitivity (BHS) [13, 14, 32].

The NK2 receptor antagonist SR 48968 (saredutant) also prevents bronchoconstriction caused by neurokinin-A in patients with BA [5]. The NK2 receptor antagonist SR 144190 selectively inhibits the binding of neurokinin A to NK2 receptors in humans and various animal species. It prevented BHS in guinea pigs caused by citric acid to acetylcholine [6].

The NK3 receptor antagonist osanetant (SR142801) reduces the level of TNF-α and interleukin-6, as well as the activity of matrix metalloproteinase-9 in the inflammation of the respiratory tract caused by mouse endotoxin. A high anti-inflammatory activity in airway inflammation was observed in the combination of the NK1 receptor antagonist SR140333 and NK2 SR48968 [19].

The bronchoconstrictive effect of chemokine-1 is blocked by the NK2 receptor antagonist SR 48968, while the receptor antagonist SR 140333 only slightly reduced the effects of chemokinin-1 [22].

The triple antagonist of the NK1/NK2/NK3 receptor CS-003 reduced BGR and bronchoconstriction caused by neurokinin-A in BA patients [31].

The presented data are convincing evidence of inhibition of bronchoconstriction by selective antagonists of tachykinin receptors in patients with BA, and open up broad prospects for their use.

The role of nonapeptide bradykinin in the development of inflammation has also been studied. It is established that he is one of the mediators of inflammation in asthma. Its content increases in the bronchoalveolar lavage of patients with BA. Bradykinin affects vascular tone and permeability, causes hypersecretion and reduces the smooth muscles of the bronchi through cholinergic mechanisms. By activating fibroblasts, it is directly involved in the remodeling of the bronchi. It has been proven that NK2 (SR48968) and NK3 receptor antagonists (SR142801 or SB223412) suppress cough caused by bradykinin in guinea pigs [25].

PRCG also belong to pro-inflammatory peptides. The main sources of PRCG in the respiratory tract are believed to be unmyelinated and fine myelin sensory nerve fibers and neuroendocrine cells. PRCG receptors, as well as substance P, are found in the lamina propria of the bronchial mucosa, near blood vessels, as well as in the ganglia and nerve bundles of the submucosa [12]. In its own plastic of the bronchial mucosa, PRCG is localized predominantly on CD3 + / CD4 + and CD68 + cells [4]. In the smooth muscles of the bronchi, in contrast to substance P, very few PRCG receptors are detected, and in the glands and alveolar septa they are absent [12].

It has been established that the content of PRCG increases in bronchoalveolar lavage, sputum, peptidergic nerves and sensory neurons of the lower respiratory tract of patients with asthma [27]. PRCG may contribute to the late phases of asthmatic reactions after provocation by respiratory allergens [5]. This peptide enhances the effect of substance P, causes potent vasodilation, hypersecretion, bronchial edema and bronchial smooth muscle spasm, more pronounced than in substance R. In addition, it contributes to the release of inflammatory mediators, including histamine from mast cells, which increases inflammatory reaction of the bronchi and bronchospasm. It has been established that in this case the bronchospasm is not blocked by histamine, acetylcholine and leukotriene antagonists [4].

Endothelin-1, refers to peptides with pro-inflammatory, profibrotic, broncho-and vasoconstrictive effects. It plays an important role in the development of airway inflammation and remodeling in asthma [17].

Bombesins are synthesized by the nervous system, as well as various types of neuroendocrine cells, including lung cells. In the lungs, bombesins contribute to the differentiation of epithelial cells and play an important role in modulating the physiology of the respiratory tract. They cause hypersecretion of mucus and marked bronchial obstruction and are one of the main mediators of inflammation in patients with asthma. Bronchospasm develops due to the direct effect of Bombesin on the receptors of the smooth muscles of the bronchi. At the same time, bronchial obstruction caused by Bombesin is not affected by atropine, hexametonium, propranolol, triprolidine, methysergide, Ro 19-3704 [10].

In recent years, interest in facets has revived, mainly chromium granules A and B. The study of serum granules today is used to diagnose lung tumors. Some researchers have reported that chromogranin A is increased in patients with broncho-obstructive diseases, including those with asthma. The relationship between the amount of serum chromogranin A, smoking, respiratory symptoms and spirometry indicators has been studied. Studies were conducted on smokers with normal lung function and bronchial obstruction. At the same time, high figures of serum chromogranin A were detected in smokers with bronchial obstruction confirmed spirometrically, in contrast to smokers with a normal spirogram. At the same time, the increase in chromogranin A correlated with the degree of bronchial obstruction. The latter, according to the authors, suggests neuroendocrine activation in inflammatory and remodeling processes in the lungs [18].

The role of anti-inflammatory peptides in the functioning of the bronchopulmonary system

Among the anti-inflammatory peptides, the most studied is the VIP, which causes vasodilation, has a pronounced bronchodilatory effect, has a positive effect on bronchial secretion and mucociliary clearance. The bronchodilation activity of the latter is 100 times higher than that of isoproterenol. It has been proven that VIP has a powerful anti-inflammatory effect and inhibits the migration of eosinophils [5, 11]. It is detected in the intestine, in the central and peripheral nervous system, cardiovascular, respiratory, urogenital and immune systems, as well as in the thyroid gland. VIP receptors are found in the smooth muscles of the pulmonary vessels, large bronchi, on the surface of epithelial and glandular cells, and are practically absent in the bronchi of small caliber. The latter is due to the lack of its influence on their tone. Their receptors are also present in the nerve fibers of normal lungs [8, 11]

In order to determine the VIP in the lungs in patients with BA, the lung tissue obtained during autopsy and lobectomy in 5 patients with BA and 9 without BA was examined. Conducted immunohistochemical staining of lung tissue for the detection of VIP and histological examination of at least 80 sections of lung tissue of each patient. VIP was detected in more than 92% of the sites from the lungs of patients without BA. It was not found in any of the 468 sections of lung tissue of patients with BA. It was noted a significant decrease in the number of VIP in the nerves in the tissue from the lungs in all patients with asthma. According to the authors, patients with asthma have a loss of VIP from the pulmonary nerve fibers. At the same time, it is unclear whether this loss is a cause or a result of BA [2].

A number of authors have established that IL-5, which is a key cytokine for BA, acts directly on the nociceptors of the respiratory tract and causes the release of VIP. VIP, in turn, stimulates CD4+ lymphocytes, resulting in a Th2 response and allergic inflammation of the bronchi. Nociceptors are believed to enhance pathological adaptive immune responses [29].

It has been established that immune-competent cells involved in the development of inflammation in the mucous membrane of the bronchi (eosinophils, mast cells, macrophages, neutrophils) have the ability to release peptide substances that block the secretion of VIP [11]. Some authors suggest that in patients with BA, active peptidases, released in a BPS, result in the destruction of some peptides, including VIP. It has also been proven that persistent respiratory syncytial infection causes significant changes in the peptidergic innervation of the respiratory tract, namely, in this category of patients, VIP-reactive nerve fibers decreased [27].

VIP may be considered as a new anti-asthma drug due to its bronchodilating activity, vasodilation and immunomodulating and anti-inflammatory effects [9, 11]. When systemic injection of VIP has its drawbacks, such as hypotension, heart rate reduction. There have been attempts to use VIP as a drug in patients

with asthma, however, its only and serious drawback, restraining its use in these patients, is a very short half-life after intravenous administration [9]. These peptide effects are minimized by inhalation administration. The development of highly active analogues of VIP and systems for their delivery to the respiratory tract is a promising direction for the pharmacotherapy of broncho-obstructive diseases, including BA. Confirmation of the latter is the successful use of inhalation administration of the powder derivative VIP - [Arg 15, 20, 21, Leu17] - VIP-GRR (IK312532). The drug showed its high anti-inflammatory efficacy on the bronchi in the experiment [8].

PACAP-38 as well as VIP has anti-inflammatory and bronchodilating effects. Its effects are mediated by three receptors associated with G-protein: PAC1R, VPAC1 and VPAC2, which have similarities with VIP. PACAP-38 and its receptors are present in the central nervous system and peripheral organs, including the endocrine system (adrenal glands, pancreas, ovaries, testicles), gastrointestinal tract, BPS, cardiovascular system, urinary system, and immune competent cells [21]. In the BPS, it is localized in the nerve fibers innervating the lungs. PACAP-38 released from peripheral nerve endings with neurogenic inflammation. Plays an important role in the functioning of the lungs. It is a powerful bronchodilator and causes marked dilatation of the pulmonary vessels. It plays the role of the regulator of respiration with the catecholaminergic system in the medulla oblongata [21]. It has been established that PACAP-38 reduces the release of inflammatory neuropeptides from nerve endings. Agonists PACAP-38 can also be considered as possible drugs for the treatment of asthma.

The effect of PHM on BPS was studied. It resembles the action of VIP. However, its bronchodilating activity is several times higher than that of the VIP, the vasodilating activity is somewhat weaker. Secretory function is more pronounced as well. This peptide can also be considered as a drug for the treatment of BA.

The neuropeptide "Y" was first isolated from the pig hypothalamus in 1982. Its abnormal regulation is associated with the development of a wide range of diseases, including obesity, hypertension, atherosclerosis, epilepsy, metabolic disorders, and many cancers [26]. At the end of the twentieth century, began to be widely studied in pulmonology. It is synthesized both in the peripheral and central nervous systems. The content of neuropeptide “Y” increases in the peptidergic nerves of the lower respiratory tract and sensory neurons. In the smooth muscles of the bronchi, their number decreases. The effect of the neuropeptide "Y" is closely related to the sympathetic nervous system. In patients with asthma, an increase in serum adrenaline, norepinephrine and neuropeptide "Y" was detected. Apparently, this peptide having a neuronal origin leads to the release of vasopressors, which is accompanied by vasoconstriction and bronchodilation. It plays an important role in the regulation of airway blood flow, smooth muscle contraction and modulation of the immune response. Its content increases in the airways of patients with asthma. According to the authors, the neuropeptide "Y" can participate in the regulation of cytokines and the cellular activity of immune cells in asthma. At the same time, it remains unclear whether such an increase in it is a protective or compensatory mechanism [24]. Although some authors suggest a protective role of the peptide in patients with asthma. A decrease in its quantity contributes to the hypersecretion of mucus in patients with asthma. The content of neuropeptide "Y" is increased in the bronchoalveolar lavage. There was an increase in the content of neuropeptide “Y” in the serum of experimentally allergenic mice. An inflammatory reaction of the respiratory tract was detected in these mice, which was confirmed by an increase in the content of neutrophils and eosinophils in bronchoalveolar lavage. A direct strong correlation was noted between the content of neuropeptide “Y” in the serum and an increase in the bronchoalveolar lavage of experimental mice of neutrophils and eosinophils. An increase in the level of neuropeptide “Y” in peripheral blood was attributed by the authors to increased inflammation of the airways in allergenized mice [20].

In recent years, the role of ANP has been studied. Its receptors are found in the lung tissue, expressed by type II pneumocytes. Its concentration in the blood plasma increases with severe exacerbations of asthma. Intravenous administration of it to experimental animals significantly reduced bronchospasm provoked by inhalation administration of histamine. It has been proven that ANP has a powerful bronchodilator effect. The disadvantage of this peptide is the short half-life, in connection with which the possibilities of inhalation administration of ANP for the purpose of bronchodilation and bronchoprotection are considered [7, 33].

Adrenomedullin was isolated in 1993 from human pheochromocytoma cells. It belongs to the family of PRCG and is an effective vasoactive peptide. It is detected in the blood, heart, blood vessels, lungs, kidneys, endocrine glands, cerebrospinal fluid. Its main properties are: vasodilation, diuretic and natriuretic effects, positive inotropic effect, inhibition of endothelial cell apoptosis, induction of angiogenesis, inhibition of cardiomyocyte apoptosis, suppression of aldosterone formation, anti-inflammatory effect and antioxidant activity. The physiological effects of adrenomedullin are mediated by the participation of type 1 receptors - PRCG. The amount of peptide increases during an attack of asthma. The peptide also acts as a bronchodilator. The effect of adrenomedullin on bronchoconstriction induced by histamine and / or acetylcholine in anesthetized guinea pigs in vivo was studied. At the same time, the peptide inhibited bronchoconstriction caused by acetylcholine and induced a prolonged bronchodilation response [3].

Conclusion. As the literature data show, the connection between the nervous, endocrine and immune systems is carried out by means of neuropeptides [22]. The classical definition of neuropeptides has been changed in recent years, since they are not produced exclusively by neurons, but are also synthesized by endocrine and immunocompetent cells. They are considered as neuroendocrine immune modulators and play an important role in the functioning of the general neuroimmune-endocrine system [23]. Thus, the discoveries of recent years make it possible to isolate the neuroimmune-endocrine mechanisms of the development of BA, i.e. combine neurogenic, immune and endocrine mechanisms into one.

Many peptide substances in animal experiments have proven their anti-inflammatory and bronchodilation effects. This allows us to consider them as possible drugs for the treatment of BA. A number of proinflammatory peptides, lead to the activation of the inflammatory process in the bronchi and bronchial obstruction through exposure through various receptors. The search for antagonists acting on these receptors is a new direction of anti-inflammatory and bronchodilatory therapy of asthma.

It is known that many anti-inflammatory neuropeptides reduce the inflammatory response by reducing inflammatory and regulating anti-inflammatory mediators. Anti-inflammatory neuropeptide receptors can also be promising targets in the treatment of BA [23].

Sometimes contradictory, but encouraging data on the possibility of using peptides as drugs in pulmonology open

up broad horizons in the treatment of patients with broncho-obstructive pulmonary diseases, including asthma.

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