THE PATHOGENESIS OF BRONCHIAL HYPERREACTIVITY IN PATIENTS WITH ALLERGIC RHINITIS

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SUMMARY – Bronchial hyperreactivity denotes an enhanced bronchial response to usual physiological stimuli, and can manifest with cough or paroxysmal cough through tussive syncope and bronchospasm. Bronchial hyperreactivity can be transient or permanent. Transient bronchial hyperreactivity occurs in acute inflammation of the upper and lower airways, and manifests with dry irritation cough that may persist for up to two months. Permanent bronchial hyperreactivity is found in 10% - 50% of patients with allergic rhinitis, 50% of patients with chronic bronchitis, and 100% of patients with asthma. The pathophysiological mechanism of bronchial hyperreactivity in patients with allergic rhinitis has not yet been fully clarified, however, the following theories have been implicated: loss of nasal function, direct aspiration of inflammatory secretion and antigens, aerogenic transfer of antigens depending on particle size, gastroesophageal reflux, neurogenic mechanisms including the action of neuropeptides in the onset of neurogenic inflammation, and the concept of allergic reaction as a systemic response to local antigen presentation. It should be noted that bronchial hyperreactivity is not asthma, however, the clinical manifestation of asthma is just a matter of time. Therefore, allergic rhinitis should be considered a predisposing factor for the occurrence of asthma.

Key words: *Rhinitis allergic, etiology, physiopathology; Bronchi, physiology; Asthma, physiopathology; Epithelial cells, physiology*

Introduction

The upper and lower airways constitute a unique functional unit responsible for elimination of various substances from the air flowing from the nose towards the alveoles, and for moisturizing and warming it up to the body temperature, thus ensuring optimal conditions for respiratory gas exchange on the alveocapillary membrane. The lower airways are divided according to their inner diameter into large or central airways with a diameter >2 mm, located from the larynx to the 8th generation of branches. The small or peripheral airways have a diameter <2 mm and extend from the 8th to 23rd generation of bronchial branches. In his morphometric studies, Weibel demonstrated the surface of the airway transverse sections to only slightly increase from the trachea to the 8th generation, whereafter the surface of the luminal transverse sections increases enormously in each bronchial generation. So the surface of the tracheal section is 5 cm^2, of the overall section at the segmental bronchial level around 8 cm^2, and at the level of alveolar ducts and saccules 1700 cm^2. This explains why 90% of total resistance to air stream refer to the large, and only 10% to the small airways[1,2]. This concept is also clinically relevant, as it explains why the small airway obstructions are clinically silent and difficult to demonstrate by spirometry. Some 10000 l air are ventilated and 8000 l blood circulate through the lungs every day. Various chemical irritants, aerosols containing organic and inorganic particles, cigarette smoke, bacteria, viruses, fungi, yeasts reach the lungs

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Received July 12, 2002, accepted December 4, 2002

with the air, and numerous metabolites, cell and tissue fragments, clots, bioactive substances, lymph contents and various microorganisms reach the lungs by the blood. All these substances are filtered, metabolized, inactivated and neutralized in the pulmonary circulation.

The respiratory system defense in the large airways includes mucociliary clearance, phagocytosis, secretion biochemical activity, reflexes, and cellular and humoral immunity. In the small airways and alveolar region, this function is taken over by the Clara cells and type II pneumonocytes releasing the surfactant, a lipid substance responsible for maintaining surface tension, whereas alveolar macrophages have the role of scavengers[3].

Epithelial cells play a major role in maintaining the continuity and integrity of the morphology and function of the tracheobronchial system. Epithelial cell has about 2000 cilia on its surface. Ciliary beats are undulating and aborally rhythmical, carrying a mucus layer which makes the basis of the tracheobronchial system nonspecific defense. It has recently been demonstrated that Langerhans' cells functioning as antigen presenting cells are found in-between epithelial cells. In addition, epithelial cell is known to be capable of synthesizing proinflammatory cytokines (IL-1, IL-6, IL-8, TNF-alfa, GMCSF) and mediators (15HETE, LTC-4) that can modulate the synthesis of IgE, and the growth, differentiation, proliferation and activation of inflammatory cells such as eosinophils, mastocytes, macrophages and lymphocytes. Furthermore, epithelial cell can synthesize endothelin, a potent smooth bronchial musculature constrictor, and in contrast, it is capable of synthesizing the smooth bronchial musculature relaxation factor (EpDRF). Neutral endopeptidase (NEP) that neutralizes the action of tachykinins (SP and neurokinin A) is also formed in the epithelial cell. Sensory C fiber receptors, which can trigger neurogenic inflammation if irritated, are found in-between epithelial cells and in the basal layers of the epithelium[4-10].

Bronchial Hyperreactivity

Bronchial hyperreactivity denotes an enhanced bronchial response to the usual physiological stimuli, which can manifest with cough, paroxysms of coughing, through tussive syncope and bronchospasm. Bronchial hyperreactivity can be transient or permanent.

Transient bronchial hyperreactivity occurs in acute inflammation of the upper and lower airways. It is mostly caused by viruses and mycoplasma, and is manifested with dry cough that may persist for up to two months. In these patients, mild inflammation of the upper and large lower airways is observed, whereas physical finding of the lungs, x-ray of the lungs, spirometry and laboratory findings are within the normal limits. Coughing as a manifestation of bronchial hyperreactivity is best treated with ipratropium and inhalation corticosteroids.

Permanent bronchial hyperreactivity is present in individuals with respiratory system diseases, those exposed to inhalation of various chemical substances (O_3, NH_3, SO_2, NO_2, HCl), in cigarette smokers, AIDS patients, and in 10% - 20% of otherwise healthy persons. Various authors report on quite different data on the prevalence of bronchial hyperreactivity in upper airway diseases. So, Heppt *et al.*[11] report on bronchial hyperreactivity in 10% - 50% of patients with allergic rhinitis. The same authors found an increased eosinophil count in bronchial lavage and elevated CO concentration in patients in whom bronchial hyperreactivity could not be verified. They also state that minor or major signs of sinusitis are found in 40% - 60%, and associated rhinitis in 40% - 90% of asthmatic patients. In lower airway diseases, the prevalence of bronchial hyperreactivity has been estimated to 100% in asthma, 50% in chronic bronchitis, 50% in stage I sarcoidosis, 50% in cystic fibrosis, and 35% - 45% in cigarette smokers[12].

Etiopathogenesis of Bronchial Hyperreactivity

Over the last three decades, a variety of explanations for bronchial hyperreactivity have been proposed. In 1968, Szentivanyi[3] developed a theory of beta-adrenergic blockade to explain the occurrence of bronchospasm. The theory was based on the quantitative and qualitative alterations of beta-adrenergic receptors in the bronchial smooth musculature. In the late 1970s and early 1980s, numerous authors tended to explain bronchial hyperreactivity by parasympathetic predominance and increased sensitivity of the vagal nerve afferent receptors[14-18]. The main role in the mechanism of bronchospasm development has by many been ascribed to allergic reaction[19-21]. Hogg[22] explained the occurrence of bronchial hyperreactivity by impairment in the ciliary cell function, and Holtzman[23] by hypertrophy and hyperplasia of the bronchial smooth muscles. Kneusel and Burghuber[24], Tinkelman[26], and Townley[27] considered calcium transport impairment to be the culprit for the occurrence of bronchial hyperreactivity. In the last 15 years, however, the genesis of bronchial hyperreactivity has been ascribed to the effect of neuropeptides on the epithelium, bronchial smooth musculature, glands and vasculature, implying the concept of neurogenic inflammation[28-31].

Nowadays, inflammation with eosinophils playing the main role is considered to be the key event in the onset of bronchial hyperreactivity[32-38]. Nolte[39] believes that inflammation *per se* cannot be exclusively responsible for the pathogenesis of bronchial hyperreactivity; he underlies the role of interaction of inflammatory cells, mediators, neuropeptides, hormones and the sympathetic to parasympathetic relations acting upon target cells such as epithelial, endothelial, muscle and glandular cells.

Laitinen *et al.*[40], Barnes *et al.*[41], Lundberg *et al.*[42], McDonald[43], and Widdicombe[44] describe significant changes in the bronchial arterial microcirculation in patients with bronchial asthma. These authors consider microvascular lesion in the bronchial submucosa an important factor in the onset of exudation, edema and inflammatory cell infiltration, but explain it as a secondary reaction event and say nothing about pathoanatomical alterations in the large bronchial artery branches. Grbac *et al.*[45,46] analyzed pathoanatomical alterations of bronchial arteries in pulmonary patients and recorded a higher prevalence of these lesions at the origin and along the course of bronchial arteries in patients with asthma and chronic obstructive pulmonary disease than in those with other pulmonary diseases (e.g., pneumonia, lung tuberculosis, carcinoma, etc.). These were mostly atherosclerotic lesions at the origin and along the course of bronchial arteries, occurrence of arresting arteries, and arterial anomalies. The authors believe that these alterations cause obstruction of bronchial arteries with consequential bronchial hypoperfusion and hypoxia, whereby bronchial hypoxia endogenously transforms bronchial normoreactivity to hyperreactivity.

Allergic Rhinitis and Bronchial Hyperreactivity

Numerous studies have shown that seasonal (intermittent) allergic rhinitis is associated with bronchial hyperreactivity in 11% - 48% of patients. Corren[47] and Corren *et al.*[48] demonstrated that bronchial hyperreactivity developed in study subjects within 12-16 hours from allergen provocation of nasal mucosa but not in the placebo treated control group. Thus induced bronchial hyperreactivity responded well to the use of nasal corticosteroid, and the eosinophil count in the nasal secretion and peripheral blood decreased. These studies have confirmed the functional connection of the upper and lower airways indeed, however, the exact pathophysiological mechanism of the onset of bronchial hyperreactivity has not yet been elucidated. A number of theories have been proposed to explain the pathophysiological mechanism of bronchial hyperreactivity in patients with allergic rhinitis. These theories include the following:

- Loss of nasal function. Moisturizing, warming up and cleansing of the inhaled air fail due to mucosal edema and stopping of breathing through the nose. When inspired through the mouth, this air irritates the mucosa and gives rise to lower airways infection[11].
- Direct aspiration of inflammatory secretion and antigens. Animal experiments have shown it to be a 'sterile' inflammation, i.e. aspiration of inflammatory cells and mediators[49].
- Aerogenic transfer of antigens depending on particle size (e.g., pollen, spores, fungi, etc.). Large particles will be halted at nasal mucosa, whereas small particles will reach lower airways and almost instantaneously induce mucosal hyperergic reaction[11].
- Gastroesophageal reflux. Clinicians have noted an association between gastroesophageal reflux, asthma and sinusitis. The phenomenon has been explained by irritation of the vagal nerve pharyngeal receptors in gastroesophageal reflux, resulting in the occurrence of reflex bronchoconstriction[50].
- Neurogenic mechanisms. As early as the 1940s, Šercer wrote about the nasopulmonary and nasothoracic reflexes[51]. This reflex association was later confirmed by a number of authors[52,53]. The nasal mucosa irritation by an allergen or cold air may induce an enhanced bronchial response to methacholine in the lower airways. This classical explanation of the neurogenic connection of the upper and lower airways has recently been supported by the concept of the role of neuropeptides in the onset of neurogenic inflammation. Topical application of substance P onto nasal mucosa results in the symptoms of rhinitis, whereas an enhanced bronchial response is recorded in the lower airways. According to Luger[54], neuropeptides represent a link between the nervous and immune systems. Specific receptors for various neuropeptides have been detected on immune cells, among them SP and neurokinin A having a proinflammatory action, and CGRP and VIP an anti-inflammatory action.
- Concurrence of allergic inflammatory lesions of the upper and lower airways has been ever more widely accepted as a systemic reaction to local antigen presentation[55].

It should be emphasized that bronchial hyperreactivity is not asthma, however, the clinical manifestation of asthma is just a matter of time. Thus, allergic rhinitis can

be considered a predisposing factor for the occurrence of asthma. Patients with allergic rhinitis are at a threefold risk of asthma found in individuals without rhinitis. Sinusitis does not seem to predispose to asthma, but 40% - 60% of asthmatic patients may have minor or major signs of sinusitis. In case of concurrent onset of asthma and allergic rhinitis, asthma has poorer prognosis and is more difficult to treat, thus allergic rhinitis can be considered a prognostic factor for asthma.

Bronchial hyperreactivity in rhinitis patients need not have clinical manifestations, however, if present, they include dry irritation cough or difficult breathing on exercise or upon cold air inhalation.

Diagnostic algorithm for rhinitis should always include spirometry and, if normal, bronchial provocation test with methacholine. The following conditions should be met for methacholine test:

- thorough history
- no signs of lower airway disease
- informed consent obtained from the patient
- normal spirometry (FEV1 >80%, n.v. FEV1/VC >70%)
- free from medication over a longer time before testing (inhalation bronchodilatators for 6-12 hours, aminophylline for 12-18 hours, antihistaminics for 48 hours)

A cumulative method is used, meaning that testing begins with lowest concentration, the dose is increased every three minutes, and spirometric testing is performed after each dose. The concentration of methacholine that has induced 20% decrease in FEV1 is termed provocation concentration (PC20). In case of bronchospasm, the patient is administered beta-2 agonist inhalation. A physician must always be present on this testing[56].

Treatment of Bronchial Hyperreactivity in Patients with Allergic Rhinitis

Considering correctly the upper and lower airways a functional unity, and bearing in mind the theories mentioned above that tend to demonstrate this unity, the endeavors of the World Health Organization and their ARIA project (Allergic Rhinitis and Its Impact on Asthma) become quite understandable. The objective of the project is to prevent the development of conjunctivitis, chronic sinusitis and especially bronchial asthma by timely treatment of rhinitis. Some authors emphasize the importance of the earliest possible use of specific immunotherapy, particularly in children in whom the mucosa has not yet been severely damaged. Many studies have shown that the treatment of rhinitis decreases the severity of bronchial hyperreactivity, thus the treatment for bronchial hyperreactivity is identical to the management of rhinitis. May the symptoms of intermittent or persistent asthma occur, the treatment is performed according to GINE recommendations.

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Sažetak

PATOGENEZA BRONHIJALNE HIPERREAKTIVNOSTI U BOLESNIKA S ALERGIJSKIM RINITISOM

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Pod bronhijalnom hiperreaktivnošću podrazumijeva se pojačan odgovor bronha na uobičajene fiziološke podražaje, koji se može očitovati kašljem, paroksizmom kašlja, sve do tusigene sinkope i bronhospazma. Bronhijalna hiperreaktivnost može biti prolazna i trajna. Prolazna bronijalna hiperreaktivnost pojavljuje se kod akutnih upala gornjih i donjih dišnih putova, očituje se suhim podražajnim kašljem koji može potrajati i do dva mjeseca. Trajna bronijalna hiperreaktivnost nalazi se u 10% - 50% bolesnika s alergijskim rinitisom, 50% bolesnika s kroničnim bronhitisom, te u 100% bolesnika s astmom. Patofiziološki mehanizam nastanka bronhijalne hiperreaktivnosti u bolesnika s alergijskim rinitisom nije u potpunosti jasan, a spominju se slijedeće teorije: gubitak funkcije nosa, izravna aspiracija upalnog sekreta i antigena, aerogeno prenošenje antigena ovisno o veličini čestica, gastroezofagusni refluks, neurogeni mehanizmi uključujući i djelovanje neuropeptida u nastanku neurogene upale, te shvaćanje alergijske reakcije kao sistemske reakcije na lokalno prikazivanje antigena. Valja istaknuti da bronhijalna hiperreaktivnost nije astma, ali je pitanje dana kada će se astma klinički očitovati. Stoga se alergijski rinitis može smatrati predisponirajućim čimbenikom u pojavi astme.

Ključne riječi: *Alergijski rinitis, etiologija, fiziopatologija; Bronhi, fiziologija; Astma, fiziopatologija; Epitelijske stanice, fiziologija*