Determinants and Regulating Processes in Bronchial Hyperreactivity

H. J. Neijens

Department of Pediatrics, subdivision of Pediatric Pulmonary Medicine, Erasmus University and University Hospital Rotterdam/Sophia Children's Hospital, Rotterdam, The Netherlands

Abstract. Bronchial hyperresponsiveness (BHR) can be considered as a feature of asthma, although only a loose relationship is present with symptoms and severity of the disease. Epidemiology of BHR may inform about determining factors in BHR and its role as a risk factor. BHR is found already at a young age, mostly diminishes with age, and increases in many asthmatic patients after midlife. Genetic determinants are suggested by familial segregation and twin studies. Allergy, respiratory infections, and cigarette smoking are found to induce increase in BHR and to modify its degree at the long run. The mechanisms in BHR are being unraveled gradually. A chronic inflammation with an important role for eosinophils, mast cells, and others, is thought to modify bronchial mechanisms, such as smooth muscle, epithelium, and autonomic systems. Growing evidence supports that T lymphocytes are implicated and may determine many of the inflammatory cells, such as eosinophils, neutrophils, and mast cells.

Key words: Bronchial hyperreactivity—Epidemiology—Mechanism, T-cell system.

Introduction

The majority of asthmatic patients are found to have bronchial hyperreactivity (BHR) and this phenomenon is clearly a central feature of the pathophysiology of asthma. BHR is related to the occurrence and severity of asthmatic symptoms in general and to the bronchial reaction after various stimuli such as allergens, exercise, and cold air. A wealth of information has been accumulated about clinical aspects of BHR, but still relatively modest knowledge is present

about factors that influence BHR and about basic regulating processes. This presentation aims to consider the rapidly growing information about these aspects.

Epidemiologic Studies

The relationship of BHR with age and various variables may inform us about factors that determine or influence BHR.

BHR is found to be present already in very young children. Infants seem to have pronounced BHR. Le Souef et al. [1] found bronchial obstruction after relative low doses of histamine, using a chest squeezing technique. Similar findings have been found by Tepper [2]. These findings are consistent with the concept that infants are born with BHR or develop it soon after birth. The course of BHR from infancy into adulthood has been considered by Australian investigators. It was estimated that BHR decreased, but largely persisted and that about 60% of the subjects who had ceased wheezing still had BHR [3]. Gerritsen et al. [4] found a decrease in BHR in about two thirds and an increase in about one third of the patients in their adulthood as compared to BHR in their childhood (between 6.14 years of age). BHR in adulthood was related to lung function values in childhood and age of onset of respiratory symptoms. They concluded that the outcome of childhood asthma was primarily predicted by the initial degree of bronchial obstruction and BHR.

BHR appears to decline with age during childhood and early adulthood until reaching its lowest level during the fifth decade according to a study by Hopp et al. [5]. Subsequently, BHR increases with age during the sixth and seventh decades. Rijcken et al. [6] concluded from a large Dutch population study that BHR increased with age.

In a study of adults between 18 and 64 years of age BHR was found to increase strikingly with age among cigarette smokers, but actually decreased in atopic nonsmokers, perhaps reflecting the waning of atopy in advancing years. Adjustment for the level of pulmonary function is necessary for comparison of a wide range of BHR values, which is not well taken care for in most epidemiologic studies. This seriously compromises the conclusions and comparison between studies.

A concept may be constructed implying a high degree of BHR in young children which decreases slightly in part of them into adulthood. In the second half of life an increase in BHR can be observed in association with smoking and possibly other factors. Along with atopy, BHR actually decreased with age.

Genetic Factors

Duiverman et al. [7] studied groups of young children. A relatively high degree of BHR is present in asthmatic children, whereas a normal or slight degree was found in healthy children. Children without asthma who have borderline BHR

turned out to have a positive family history for asthma and asthmatic children with a relatively low degree of BHR had a negative family history. The study of Duiverman and others points to a genetic determinant in the occurrence of BHR. Heredity as a factor in BHR is also suggested by twins and family aggregation data. Konig and Godfrey [8] have demonstrated a greater intrapair correlation of exercise-induced bronchus obstruction in monozygotic than among dizygotic twins. Hopp et al. [9] confirmed this in a relatively large selected population of twins, which was not the case in a small study by Zamel and colleagues [10]. Familial aggregation of BHR has been assessed in families of persons with asthma. Healthy relatives of asthma patients and infants with wheezy bronchitis were found to have an increased occurrence of exercise-induced bronchus obstruction [11]. Also Townley et al. [12, 13] reached these conclusions. These human studies are in accordance with animal data involving rats [14] and dogs [15].

Thus, there is clearly an heritability component in BHR, but the genetic character is probably multifactorial and not likely to be dependent on a single gene. Longo et al. [16] found information to suggest them an autosomal-dominant pattern of inheritance.

Environmental Influences

A number of variables have been identified that are able to modify BHR, such as allergen reactions, viral infections, smoking, and polluted air. These factors are found to induce a temporarily increase in BHR, but their role in the generation of a persistent rise is less certain and awaits further study.

Allergy clearly has an effect on BHR, but the relationship between them is complicated. Allergen challenge and longitudinal studies with challenging and nonchallenging periods have indicated that BHR may increase due to an allergic late reaction in asthmatics. In population studies BHR is found to be associated with the presence of sensitization to common allergens [17–19].

Allergy and BHR may be connected either by genetically linked traits, or may interact by cellular and metabolic processes or both. Allergen-induced mediators, such as histamine and leukotrienes, as well as cell action by eosinophils and others, might well sensitize the bronchial mechanism to react in an augmented way.

Acute respiratory infections early in life (bronchiolitis, pneumonia) were found to be associated with the presence of BHR later on, in a study by Weiss and colleagues [20]. Those subjects who had croup or bronchiolitis or had repeated lower respiratory illnesses, had increased bronchial responsiveness as compared to those subjects who did not had such respiratory diseases. No clear relationship was detected between the presence of acute lower respiratory illness and atopy.

These and other observations suggest an interrelationship between infections, in particular bronchiolitis and BHR. This is not the case with aspecific lung injury in a random population. Several studies show that lung injury per se

is not sufficient for induction of BHR, and that a genetic predisposition is probably necessary.

Cigarette smoking may cause heightened airway responsiveness, but this relationship seems to be evident only among persons with a sufficiently high cumulative exposure. This could be concluded from Burney et al. [19], Woolcock et al. [21], and Sparrow et al. [22], but not by the group of Van der Lende [23] which might be explained by a relatively low dose of smoking and the young mean age in this study.

A number of plausible mechanisms can be proposed for a direct causal relationship between smoking and BHR, namely, chronic airway inflammation, airway epithelial damage, and smoking-induced reduction in lung function.

The susceptibility to induce an increase in BHR and the development of chronic lung disease by all those environmental variables seems to be dependent, at least partially, on host factors. These factors are still difficult to define. The initial degree of BHR has been found to reflect a risk factor by several studies. This is substantiated by the studies of Postma et al. [24], who provided evidence indicating that the degree of BHR is related to the gradual loss in lung function. The decline in lung function is greater along with a higher degree of BHR.

The following *concept of BHR* is supported by all this information. An endogenous component is present in BHR, which is probably largely genetically determined. In addition, certain environmental variables may induce a further augmentation in BHR. This susceptibility is probably dependent on host factors that are highly associated with the presence of asthma and probably linked to the genetic system.

Mechanisms of BHR

The causes of BHR are being unraveled step by step, although the responsible basic abnormality is still not elucidated. Along with research progress three stages can be considered.

Anatomic and Functional Modifications in Bronchial Systems

Anatomical and functional modifications in bronchial systems directly regulate bronchial diameter. Some reports produce evidence that airway smooth muscle from asthmatics exhibited increased contractile responses in vitro to agonists (histamine, methacholine and leukotriene C_4) as compared to that of healthy controls [25, 26]. However, few true asthmatics have been studied in this way.

Airway smooth muscle hyperplasia is present even in relatively mild asthmatics, possibly as a result of various growth factors released from inflammatory cells, such as platelet-derived and macrophage-derived growth factors. It seems likely the hyperplasia of airway smooth muscle would contribute to airway hyperrresponsiveness, and may explain the persistence of bronchial hyperresponsiveness after inflammation has subsided.

Autonomic nervous control of the airways is complex and several studies have investigated the possibility that defects in autonomic control may contribute to bronchial hyperresponsiveness and the pathology of asthma. Several abnormalities of autonomic function, such as enhanced cholinergic and α-adrenergic responses or reduced β-adrenergic responses, have been proposed.

Current thinking suggests that these abnormalities are likely to be secondary to the disease, rather than primary defects. It is possible that airway inflammation may interfere with autonomic control by several mediators and mechanisms [27].

Airway epithelial damage may be a critical feature of BHR and may explain how several different mechanisms, such as allergen exposure, virus infection, and ozone exposure, can lead to its development, since all these stimuli may lead to epithelial disruption. Epithelial disruption may contribute to BHR in a number of ways. Mechanical removal of epithelial cells in vitro results in increased responsiveness of airway smooth muscle to spasmogens [28, 29] and suggests that epithelial cells may release a relaxant factor by analogy with endothelial-derived relaxant factor in vessels. Damage of epithelium would thus remove the protective effect of this relaxant factor, leading to exaggerated bronchoconstrictor responses. Epithelial cells themselves may release inflammatory mediators, such as leukotriene B_4 and 15-HETE, which is chemotactic for inflammatory cells [30]. Epithelial damage will also expose sensory nerve endings, which may be activated by inflammatory mediators, leading to inflammation via an axon reflex mechanism [31].

Inflammatory Processes in the Bronchi

There is now considerable experimental evidence that induced BHR is associated with inflammation in the airways [32]. Histopathologic studies from asthmatic patients who have died during asthma attacks show that there is marked inflammation in the airways, with infiltration of inflammatory cells, particularly eosinophils, disruption of airway epithelium and mucus hypersecretion [33]. Similar pathologic changes have also been found in bronchial biopsies from asthmatics who are relatively mild [34] and suggest that airway inflammation may underlie BHR.

By bronchoalveolar lavage (BAL) several cell types are found, especially after provocation; these cells are eosinophils, neutrophils, mast cells, and lymphocytes. Wardley et al. [34] found an inverse relationship between BHR (PC20) and the percentage of mast cells, eosinophils, epithelial cells, and the amount of MBP. It now seems likely that several different cells are involved in the pathogenesis of asthma, and that these cells produce a variety of mediators that interact in a complex way to produce a number of pathologic effects that, together, contribute to BHR.

Macrophages are present throughout the respiratory tract, and the recent demonstration that they may be activated by IgE-dependent mechanisms has suggested that they may be involved in asthmatic inflammation [36]. They have the potency to produce and release a variety of mediators. Macrophages from

asthmatics release increased amounts of mediators, such as thromboxane, pro-staglandins, and platelet-activating factor (PAF).

Histologic studies suggest that eosinophil infiltration is a feature of asthmatic airways and differentiates asthma from other inflammatory conditions. Allergen inhalation results in a marked increase in eosinophils in bronchoal-veolar lavage fluid at the time of the late reaction [37], and there is a relationship between peripheral eosinophilia and bronchial hyperresponsiveness [38].

Eosinophils release a variety of mediators, including leukotriene C_4 and PAF, and basic proteins such as major basic protein, eosinophil cationic protein and eosinophil-derived neurotoxin, that are toxic to airway epithelium and other structures.

Neutrophil infiltration is characteristic of some animal models of asthma [39]. Neutrophils are particularly related to provocation with toxic factors such as ozone [40] and industrial agents, but are also found shortly after allergen inhalation before the eosinophils arrive. Although neutrophils are found to produce factor(s) that may induce BHR [41], their role in human asthma is less certain [42].

Many different mediators have been implicated in asthma and they may have a variety of affects on the airways that account for many of the pathologic features of asthma. Thus, mediators such as histamine, prostaglandins, and leukotrienes contract airway smooth muscle, increase microvascular leakage, increase mucus secretion, and attract other inflammatory cells. It is therefore possible that interaction between inflammatory mediators might account for BHR.

PAF, like antigen, stimulates accumulation of eosinophils in lung [43] and in the skin of atopic subjects [44]. This selective attraction of eosinophils might explain how PAF can produce such a prolonged increase in responsiveness, since eosinophils may lead to damage and shedding of airway epithelium as discussed above. Since eosinophils themselves are a rich source of PAF [45], they can attract further eosinophils and there is the potential for a continued inflammation. PAF has other properties that may be relevant in asthma. In animals, PAF is a potent inducer of airway microvascular leak, being the most potent agent so far described [46]. This may lead to airway edema and plasma extravasation which may be involved in the creation of BHR [47].

Immunoregulating Factors

The study of immunoregulating factors is the final step in the elucidation of the mechanisms and this approach has just started. The concept is that immune factors related to T lymphocytes have an important role to regulate cellular responses by eosinophils and other aspecific cells and thus determine the occurrence and degree of bronchial inflammation.

Infiltration by T lymphocytes (CD_3^+/CD_4^+) together with T-cell activation (IL-2 receptor) was found in association with allergen-induced late-phase skin

reaction in human atopic subjects by Frew et al. [48]. These changes were accompanied by eosinophil infiltration and activation.

Bronchoalveolar lavage studies of the human late asthmatic reaction have revealed the presence of increased numbers of eosinophils and lymphocytes during the late response, whereas no such changes were seen in isolated early responders [49]. Gonzalez et al. [50] studied T-cell subsets in BAL and blood. BAL lymphocytes increased until 6–12% of the cells in both BAL and blood isolated early and dual responders after allergen challenge. In the dual responders CD_4 and CD_8 increased, whereas in the isolated early reactions no change in CD_8 and thus decrease in the 4 : 8 ratio was present in BAL. The absence of a CD_8 rise in late-phase responders raises the possibility that CD_8 T lymphocytes control the occurrence of late bronchial reactions.

Effects of T-cell activation have been found in several other cell types, namely, IL-2 and HLA-DR receptor activation on endothelial cells and CD_4 antigen on epidermal Langhans cells. Both provide indirect evidence of γ-interferon secretion from activated T cells. A strong association was detected linking CD_4^+ T lymphocyte numbers with the number of activated eosinophils in the study by Frew et al [48].

These findings suggest that CD_4^+ T lymphocytes are attracted to sites of allergic inflammation and that these cells and their products may contribute to the pathogenesis of chronic allergic inflammation. Cytokines such as γ-interferon have many actions, including activation of macrophages for subsequent elaboration of eosinophil activation factors. There have been several reports of a defect in suppressor cell function in asthma [51, 52]. CD_8^+ T cells produce a histamine-induced suppressor factor that inhibits lymphocyte proliferation and lymphokine production.

The clinical relevance of T lymphocytes in asthma is further supported by the observation showing that the number of T lymphocytes expressing HLA-DR and IL-2 receptors indicating cell activation, was increased with exacerbations [53].

A growing body of information suggests that eosinophil differentiation and proliferation is controlled by cytokines including IL-5- and T-lymphocyte-derived eosinophil colony stimulating factors both in humans and animals [54–56].

An action of T lymphocytes on neutrophil activation was put forward by Tsai et al. [57] who detected a lymphocyte-derived factor. After induction by anti-CD_4 antibodies, LTB_4 generation by neutrophils increased by 15%–350%.

Good evidence supports now that T lymphocytes are present and active in allergic reactions in the skin and in the bronchi. T lymphocytes are found to have the potency to induce eosinophil, neutrophil, and macrophage activation, for which actions in vivo evidence has been detected. Inadequate actions of CD_8^+ T lymphocytes, probably a specific subset, might also be critical in asthmatic reactions. Since the actions of T lymphocytes are under control of immunoresponse genes, genetic factors might well guide asthmatic reactions and BHR along this line.

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