The place of airway hyperresponsiveness in the asthma phenotype

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Introduction
Asthma is a common chronic disease, which can affect individuals from early childhood and towards elderly age [1]. As long as its pathogenesis remains unclarified the definition of asthma relies on describing the abnormalities at the clinical, physiological, pathological, immunological and cellular level. First, the disease is characterized by symptoms, such as periodic chest tightness and wheezing [1]. This is accompanied with variable airways obstruction as measured by peak flow rates or spirometry [1]. The variability in airways obstruction can be mimicked in the laboratory by administering either a bronchodilator, which reveals its reversibility [1], or by using a bronchoconstrictor stimulus, thereby measuring the so-called airway hyperresponsiveness [2].

Beside these clinical and physiological features, asthma is characterized by cellular and histological abnormalities at the airway level [3]. These include mucosal, submucosal, and adventitial inflammation, as demonstrated by epithelial shedding, collagen deposition in the sub-basement membrane reticular layer, infiltration by mononuclear cells, mast cells, granulocytes, and airway wall swelling by plasma extravasation and smooth muscle hyperplasia or hypertrophy [3]. There is increasing evidence that this pathology is associated with a specific profile in local cytokine and mediator synthesis [4]. Hence, it is highly likely that a fundamental change in the phenotypes of several resident and infiltrative cells in the airways underlies the pathogenesis of asthma [4].

At present, it has not been clarified as to whether such fundamental cellular changes in asthma are caused by genetic predisposition (associated with the expression of atopy), environmental influences (such as respiratory virus infections), or both. In search of these factors, it is essential that the diagnosis of asthma can be made without uncertainty. To that end many studies have relied on the presence of airway hyperresponsiveness to bronchoconstrictor stimuli [5,6], in order to distinguish asthma from upper respiratory tract disorders, such as allergic rhinitis. Indeed, it has been argued that the diagnosis of asthma in epidemiological studies can best be made based on the presence of wheezy episodes together with airway hyperresponsiveness [7].

The question arises whether airway hyperresponsiveness is an appropriate tool to define the asthma phenotype in studies on the genetics of asthma. If so, it can be employed in segregation and linkage analysis in family studies [8]. If not, the asthma-researchers should provide the geneticists with other markers that have high negative as well as positive predictive value for asthma.

Is airway hyperresponsiveness a single entity?
The pathophysiology of airway hyperresponsiveness is not fully understood. Normally, airway hyperresponsiveness is defined as an increased sensitivity to bronchoconstrictor stimuli, as measured by dose–response curves with pharmacological agents, such as histamine or methacholine, or by exposure to physical stimuli, such as exercise [2]. It has been shown that, apart from hypersensitivity to the stimuli, asthma is particularly characterized by an increase in maximal airway narrowing [9,10]. There is increasing evidence that these two abnormalities are determined by partly independent mechanisms. This indicates that the response of asthmatics to bronchoconstrictor stimuli has a complex pathophysiology.

There are multiple steps between encountering a stimulus and the increase in resistance to air flow within in the airways [11]. It requires agonist–receptor interaction leading to smooth muscle activation. Subsequently, actual shortening of the muscle is determined by mechanical factors, such as the amount and contractility of the muscle, and its pre- and after-load provided, e.g. by the surrounding parenchyma. Luminal narrowing is further dependent on submucosal and adventitial swelling and intraluminal secretions. And finally, geometry and flow regime in the lumen will determine the increase in resistance, as measured during a bronchial challenge test in vivo [11].
There is experimental evidence that each of the above steps can play an independent role in determining airway hyperresponsiveness in asthma [9,10,12]. This fits in with the observations that measures of airway hyperresponsiveness are only moderately correlated with the pathology at the airway level [3]. Even though hyperresponsiveness to methacholine appears to be stronger related to, e.g. eosinophilic inflammation, than clinical indices, such as symptoms, beta-agonist usage, peak flow rates and spirometry [13], unfortunately, the challenge test results do not allow discrimination of the predominant underlying mechanism. Therefore, it is unclear whether airway hyperresponsiveness in the individual patient is caused by, e.g. epithelial damage, axon reflexes, eosinophil activation, smooth muscle hyperplasia, or microvascular leakage. Hence, it appears that airway hyperresponsiveness is not a single entity, but a common physiological pathway of multiple mechanisms leading to an increase in the ease and degree of airway narrowing to bronchoconstrictor stimuli in vivo.

What is its distribution in the general population?

Using a traditional measure, the provocative concentration causing a 20% fall in FEV1 (PC20) to inhaled histamine, it has been impossible to investigate whether there is a unimodal or bimodal distribution of airway responsiveness within the general population [14]. This is due to the fact that many normal individuals do not reach 20% fall in FEV1, even after inhaling large bronchoconstrictor doses [2]. One way to overcome this problem has been the calculation of other variables from the dose–response curve, such as the ‘two-point slope’ [15]. This is an overall index of position and shape of the dose–response curve, which can be measured in the vast majority of subjects in epidemiological studies. It has been shown that the ‘two-point slope’ is normally distributed within a random population of schoolchildren [16]. This seems to confirm that hyperresponsiveness is not due to a single abnormality. The question whether airway responsiveness should be considered as a dichotomous or a continuous variable in studies on genetics of asthma depends on the predictive value of various cut-off values for the presence and absence of asthma, which will be addressed.

Is its presence and severity constant within subjects?

Laboratory, clinical, and epidemiological studies have shown that the presence and severity of airway responsiveness can vary within subjects. First, this has been demonstrated after laboratory challenges: e.g. exposure to allergens [17] or experimental virus infection [18]. It is remarkable that such changes in airway hyperresponsiveness are dissimilar for different directly and indirectly acting bronchoconstrictor stimuli [19]. This fits in with the complex pathophysiology determining airway responsiveness. Second, it appears from follow-up studies in asthma that, in spite of the measurements being well reproducible [2], airway responsiveness can vary to a great extent over months [20]. Again, this may not be unexpected, in view of the variable disease state of the airways in asthma leading to transient changes in hyperresponsiveness.

Airway hyperresponsiveness not only varies spontaneously, but can also change as a result of therapeutic intervention [21]. For instance, regular use of inhaled steroids does improve airway hyperresponsiveness in asthmatics, but normalization cannot be accomplished in most of the patients [22]. This fits in with the observations that airway inflammation in asthma does not resolve completely after inhaled steroids [23]. Hence, there appears to be a reversible and a non-reversible component. It cannot be excluded that these components are being determined by distinct mechanisms, e.g. by acute and chronic inflammatory events, respectively [24]. In this respect it is of interest that asthma in children, who do not respond favourably to corticosteroids, appears to be associated with persistent or latent (adeno) virus infection in the airways [25]. Thus, airway hyperresponsiveness associated with virus infection might not be comparable to that associated with atopy only.

These observations not only indicate that single measurements are of limited value when using airway hyperresponsiveness in defining the asthma phenotype, but again underline the heterogeneous background of this physiological measure.

What is the predictive value of airway hyperresponsiveness for the presence of asthma?

When using airway responsiveness measurements in family studies on the genetics of asthma, simple and strictly standardized challenge tests should be used. Currently, histamine and methacholine challenges are most widely used [2]. However, it has been argued that a non-pharmacological challenge, such as exercise [2], might clinically be more relevant and more specific in distinguishing asthma from other causes of chronic airways disease, particularly in children [26].

When using histamine and exercise challenges in epidemiological surveys, it has been shown that the predictive value of the tests for asthma, as defined on basis of symptoms, doctor’s diagnosis, medication usage and hospitalization, is very limited. Even though the
commonly used criteria, such as PC20 < 8 mg/mL or an exercise response >10% fall in FEV\textsubscript{1}, lead to a high negative predictive value for the presence of asthma, the positive predictive value of these cut-off values is only 35 and 25%, respectively [27,28]. This indicates that the airway responsiveness measurements can at best exclude, but not confirm the presence of asthma in the general population.

Conclusion

In search of the genes for asthma, geneticists require unequivocal tools for segregation or linkage analysis in family studies. Measurements of airway hyperresponsiveness have been, and still are, of great value in describing the asthma phenotype, as long as difficult breathing is considered to be the basic problem in this disease. However, in unravelling the pathogenesis at the gene level, it seems to be inevitable that more specific markers of the disease are needed. In this respect, one might for instance think of adding cellular or soluble markers in (induced-) sputum [29].

In view of the above, it is even surprising that recent studies, as reported by Bleecker and Postma during this meeting, have successfully demonstrated linkage between airway hyperresponsiveness to histamine and chromosome 59 in asthma [30]. This illustrates that, at present, the asthma phenotype should be based on measures at the clinical, physiological, and cellular level.

At this stage, we can conclude that:

- airway hyperresponsiveness is a complex functional disorder, of which the multiple underlying cellular abnormalities have not been clarified;
- hyperresponsiveness has a variable and fixed component, being associated with signs of acute and chronic inflammation, respectively;
- the simple outcome measures (PC20, two-point-slope) are numerically continuous, with a unimodal distribution in the general population;
- when using standardized histamine, methacholine, or exercise challenges, the cut-off levels have low positive predictive value for asthma in a general population;
- hence, airway hyperresponsiveness per se is of limited use when defining the asthma phenotype, particularly when being based on a single determination;
- more fundamental, preferably non-invasive characteristics of asthma need also to be employed in future segregation or linkage analysis on asthma genetics.

References

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