EDITORIAL

Improving asthma treatment: the physiological message

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During the past decade, there has been an enormous growth in the understanding of the fundamental abnormalities in the airways of patients with asthma. In particular, this relates to the allergen-driven inflammation within the airway wall. The safe application of fibre-optic bronchoscopy in asthma has allowed pathologists, immunologists and molecular biologists to investigate the interaction among the various resident cells and the inflammatory infiltrate in the mucosa and lamina propria [1]. At present, this approach seems to offer the best prospect for a gradual clarification of the pathogenesis of asthma. In addition, it can be envisaged that monitoring cellular presence [2], and activity [3], during therapeutic interventions will provide a rationale for the development of a more causal treatment of the disease. Hence, there is little doubt that the major improvements in future asthma therapy and prevention will be based on respiratory cell and molecular biology.

Acute or chronic pathophysiology?

It is remarkable that in contrast to a better understanding of the genesis and modulation of airway inflammation in asthma, it is still largely unclear which are the main effector mechanisms causing the enhanced airways obstruction in the disease. This is rather unexpected, since it has been an area of physiological research for many decades. Airways obstruction remains the functional characteristic that is responsible for the clinical expression of asthma [4]. Even though the degree and variability of airways obstruction appear to be associated with many markers of inflammation in the airways of asthmatics, the physiological factors determining the severity of airway narrowing are far from being clarified.

The currently available models of asthma are almost invariably based on acute or subacute pathophysiology, caused by various inducers of airway inflammation [5]. This applies for animal models as well as experimental human models of asthma. Such an approach is presently leading to the development of potentially powerful drugs in the prevention and reversal of acute inflammatory changes in the airways [6]. However, asthma is a chronic disease, and its pathophysiology might not be fully covered by these models.

Many tissue components appear to be able to contribute

to the excessive and potentially life-threatening airway narrowing in asthma, including smooth muscle, airway nerves, bronchial vessels, connective tissue elements, mucosal or luminal exudates, and secretions [7]. Each of these can potentially be triggered by the various inflammatory pathways involved, but it has yet to be determined which of the effector mechanisms predominate in the various clinical presentations of asthma.

As a result of careful morphometry and physiological experiments, the functional importance of the chronic structural changes within the airways in asthma is now becoming apparent.

Airway connective tissue elements

In the "hypothesis" article in the present issue of the European Respiratory Journal, BRAMLEY *et al.* [8] strengthen the contribution of structural components within the airway wall, in particular of connective tissue, to the end-organ hyperresponsiveness in asthma. This is an area of great interest, particularly with regard to the long-term sequelae of the disease process. The very limited availability of tissue specimens obtained from patients with asthma has hampered rapid progress in this field. Indeed, the supportive evidence of BRAMLEY *et al.* [8] is only derived from data obtained in a single asthmatic subject. However, it is interesting, in view of hypothesis development, that the results presented provide an example of chronic abnormalities in structure of the airways in asthma.

The potential importance of the extracellular matrix may not be surprising, since chronic inflammation is associated with fibrosis and elastolysis [9]. This may alter the mechanical behaviour of the airways by changing the stiffness of the airway wall, which affects the load of the contracting smooth muscle [8] and the folding of the mucosa into the airway lumen [10]. In well-designed human *in vivo* experiments, BRACKEL *et al.* [11] have recently shown that there is, indeed, a difference between normal and asthmatic subjects in the compliance of the central airways. They concluded that the airways in asthma are relatively stiff, which might be due to oedema and/or fibrotic changes resulting from chronic inflammation. The results obtained with these indirect physiological techniques seem to contrast with those from the direct *in vitro* measurements by BRAMLEY *et al.* [8]. This might be due to the distinct methodologies, the limited number of experiments, or differences in stage of the disease process.

It should be emphasized that these mechanical events

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are not only of pathophysiological interest, since there is some recent evidence that therapeutic intervention can have beneficial effects on the nonmuscular components in asthma. Using bronchial biopsy specimens, DAVIES *et al.* [12] demonstrated by computer image analysis that the area of staining with a monoclonal antibody against collagen 3 in the subbasement membrane reticular layer was reduced after 4 months of inhaled steroid intervention. These observations warrant further attempts to develop strategies to prevent and reverse the structural changes in the airways in asthma.

Amount of smooth muscle

The most notable progress in understanding the increased severity of airway narrowing in asthma has been the recognition that the amount of smooth muscle is likely to be its major determinant. Certainly, enhancement of intrinsic contractility has also been observed in some, but not all, *in vitro* preparations of patients with asthma [13]. This might be due to elevated actomyosin adenosine triphosphatase (ATPase) activity within the smooth muscle cells, leading to an increase in shortening velocity and in maximum shortening capacity [14]. However, based on morphometric data of small airways in asthma and chronic obstructive pulmonary disease (COPD), detailed mathematical model studies by LAMBERT *et al.* [15] have indicated that the increased muscle mass is by far the most important abnormality responsible for excessive airway narrowing in these two disease entities. Taking the hypothesis of BRAMLEY *et al.* [8] into account, that the smooth muscle itself contributes to a relatively high compliance of the airway wall, it can be envisaged that smooth muscle hypertrophy or hyperplasia is, potentially, one of the major effector mechanisms determining the severity of airways obstruction in asthma.

These findings imply that further morphometric studies on the quantification of the amount of smooth muscle in the airway wall are needed, using various pathological techniques [8]. At present, the data indicate that investigation of the factors inducing airway smooth muscle hyperplasia and/or hypertrophy is a prerequisite for the development of successful therapeutic intervention in patients with excessive airway narrowing [16]. These factors may include a variety of cytokines and growth factors (interleukin-1 β , platelet-derived growth factor) [17], but also mediators such as: histamine, platelet-activating factor, endothelin-1, thromboxane-A₂, and leukotriene-D₄ [18, 19]. In this respect, much is to be learnt from cardiovascular research, in which the inducers of myointimal hyperplasia and its inhibitors have already been explored in more detail [20]. This kind of approach has already led to successful inhibition of airway smooth muscle proliferation *in vitro*, *e.g.* by heparin [21].

Vessels and parenchyma

Apart from smooth muscle mass and connective tissue elements within the airway wall, the severity of

obstruction is also determined by the degree of submucosal and adventitial swelling, and by the mechanical interdependence between the airways and the lung parenchyma [15]. This concerns the microvasculature, with the capacity for angiogenesis [22], and microvascular leakage and congestion [23], during the chronic and acute inflammatory events in asthma. In particular, adventitial swelling can augment airway narrowing, by reducing the effectiveness of the elastic load on the smooth muscle provided by the lung parenchyma [24]. This mechanical interdependence between airways and parenchyma appears to be clinically relevant, since the elastic forces limit smooth muscle shortening in normal subjects [25], which might be disturbed not only in emphysema [26] but also in patients with asthma [27].

Finally, the traditional view that contractile elements in the lung are restricted to the airways has recently been challenged by the observations of LUDWIG *et al.* [28]. They showed that aerosol bronchoconstrictor stimuli in dogs not only increase airway resistance, but also elevate the tissue viscance, which accounts for a large proportion of the increase in overall lung resistance. The acute changes in tissue viscance can either be due to parenchymal distortion [29], or to contractile elements within the lung parenchyma, *e.g.* in the interstitium or the peripheral vasculature. Again, the behaviour of these elements seems to be of clinical importance, since BRUSASCO *et al.* [30] recently demonstrated that this can be one of the determinants of excessive airway narrowing in man *in vivo*.

Conclusion

The availability of new techniques has facilitated rapid progress in the understanding of the cellular and molecular abnormalities in asthma. Hopefully, this will eventually lead to clarification of its pathogenesis and, subsequently, to strategies in the prevention of the disease. However, the development of new treatment modalities for patients already suffering from asthma requires the knowledge of the effector mechanisms in the end-organ determining the severity of airways obstruction.

Recent physiological studies have provided new information about the tissue elements that are responsible for disease severity. The results of these studies indicate that chronic structural changes within the lung are the main determinants of the excessive and potentially life-threatening airways obstruction in asthma. These structural changes could be sequelae of chronic inflammation. However, their prevention and reversal will not necessarily be obtained by anti-inflammatory therapy with the currently available corticosteroids. This can be illustrated by the limited capacity of steroids to normalize the functional abnormalities in asthma, such as airway hyperresponsiveness [31].

Consequently, remodelling of the airways requires new approaches, that are only just being explored. This issue has recently been addressed by PAGE and BLACK [32]. The present challenge is to combine the new knowledge on physiology, morphology and the molecular basis of asthma, in order to develop rational therapeutic interventions.

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