

Commentary

Impact of rhinitis on airway inflammation: biological and therapeutic implications

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Abstract

There is increasing evidence for a close link between the upper and the lower respiratory tracts and the fact that rhinitis has an important impact on asthma. Several clinical and experimental observations suggest a similar immunopathology between the upper and lower airways in allergic subjects. The common inflammatory process that develops in the respiratory tract explains some of the complex interactions among different clinical diseases such as rhinitis, sinusitis, asthma, bronchial hyper-responsiveness and viral infections. There are also non-inflammatory mechanisms that may contribute to the link between rhinitis and asthma. Moreover, the outcomes of various pharmacological treatments of rhinitis have recently provided further support for the hypothesis of the united airways. We discuss some of the recent observations on the nose–lung interaction and some of the novel therapeutic approaches used to treat rhinitis and asthma that arise from this.

Keywords: asthma, inflammation, rhinitis, sinusitis, united airways

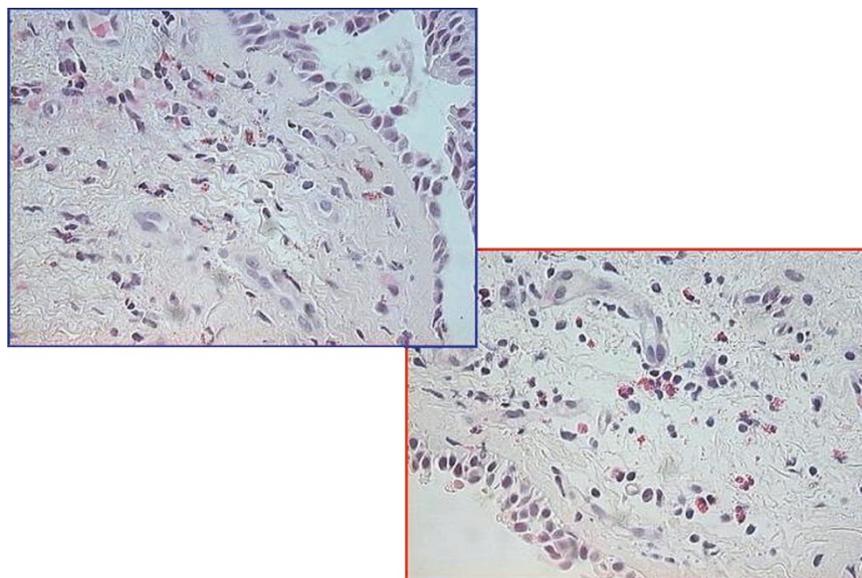
Introduction

The overall view of the pathophysiology of respiratory allergy has changed profoundly over the past 10 years. Increasing attention has been devoted to the relationship between rhinitis and asthma (i.e. between the upper and the lower respiratory airways) that was first noted in epidemiological studies. In addition, clinical observations provide compelling evidence for the following phenomena: the frequent co-existence of rhinitis and asthma, rhinitis as a risk factor for developing asthma, the occurrence of bronchial hyperresponsiveness in rhinitis, the association between upper respiratory infections and asthma exacerbations, the existence of a common pathogenic mechanisms between rhinitis and asthma, and the exacerbating role of sinusitis in asthma. More detailed knowledge of the mechanisms of inflammation (e.g. antigen presentation, cytokines, chemokines and adhesion molecules) has clarified, at least

in part, the functional relationships between the nose and bronchi. It is therefore reasonable to consider respiratory allergy as a disorder of the whole respiratory tract, which is manifest clinically as rhinitis and/or asthma, rather than as distinct diseases confined to specific organs. Consequently, some new terms have been introduced, including 'allergic rhinobronchitis', 'one airway one disease', and 'united airways disease' [1]. This approach of considering respiratory allergy as a disorder of the whole respiratory tract has relevant therapeutic implications because treating diseases of the upper airways can impact the lower airways, and drugs affecting the common pathogenic mechanisms can act on both compartments.

Functional and immunological aspects

The association between the upper and lower respiratory airways has been confirmed by numerous epidemiological

Figure 1

Bronchial biopsies obtained after allergen-specific bronchial challenge in an asthmatic subject (left) and in a rhinitic subject (right). The inflammatory responses are superimposable in the two subjects [20].

studies. Although the studies have some methodological limits, the data from the literature are quite consistent. Several cross-sectional trials have shown that the coexistence of rhinitis and asthma is extremely common: when a sufficiently detailed methodology is used, rhinitis is detected in more than 90% of asthmatic subjects [2]. Longitudinal studies have shown that subjects with rhinitis are more likely to develop asthma, and that rhinitis usually precedes asthma (see [3,4] for a review). This latter phenomenon also occurs in non-allergic rhinitis, as demonstrated in recent trials; Leynaert *et al* showed that rhinitis itself is a risk factor for developing asthma, even in non-atopic subjects [5].

The relationship between the nose and bronchi has been studied from several viewpoints, each elucidating a different aspect of the mechanism. In allergic subjects, allergen-specific nasal challenge can elicit both an immediate bronchoconstrictor response and an increase in airway responsiveness [6,7], as well as a bronchial inflammation, characterized by an influx of eosinophils [8]. Segmental bronchial challenge can also induce nasal symptoms, as well as nasal inflammation in patients with allergic rhinitis [9]. The inflammatory process is central to the allergic response [10], as clearly demonstrated by several experimental models including nasal and bronchial challenge [11]. When an allergic reaction takes place (i.e. allergen-IgE-mast cell), the so-called early phase occurs within minutes. This first step involves the release of histamine, vasodilation, increased permeability, and bronchoconstriction. This early phase is followed by a complex

network of inflammatory phenomena in which T lymphocytes, cytokines and adhesion molecules are involved. During the early phase, specific adhesion molecules are expressed *ex novo* or upregulated on the surface of the endothelium (selectins) and the epithelium (integrins). The adhesion molecules favour the rolling, extravasation, and migration towards the epithelium of inflammatory cells. The kinetics of inflammation following allergen exposure involve the migration of inflammatory cells to the mucosa within about 30 min. Inflammatory infiltration increases over the following 24 hours and then slowly subsides.

Using induced sputum, Polosa *et al* [12] showed that subjects with rhinitis alone have an increased number of eosinophils during the grass pollen season. Crimi *et al* [13] recently compared the bronchial inflammatory response following allergen-specific challenge in patients suffering from asthma alone or rhinitis alone. Utilizing bronchial biopsy and lavage, the authors found no morphological difference between the two groups: the bronchial inflammatory response (cell influx and basement membrane thickening) is the same regardless of which airway is affected by disease (Fig. 1), confirming that atopic subjects have a common inflammatory response.

When exposure to allergen is too low to provoke symptoms, a weak inflammatory infiltration occurs in the mucosa. This process is called 'minimal persistent inflammation' (MPI) and it has been demonstrated in both mite-induced and pollen-induced rhinitis [14]. MPI also involves

a weak and persistent expression of intercellular adhesion molecule-1 (ICAM-1), the major receptor molecule for human rhinoviruses. MPI and ICAM-1 expression in asymptomatic allergic subjects are important because asthma exacerbations in children are frequently related to upper respiratory viral infections [15], primarily due to rhinoviruses. Another functional systemic link between the nose and bronchi has recently been hypothesized, based on the observation that bone marrow can promptly and specifically respond to nasal challenge by increasing the rates of production and maturation of eosinophilic precursors [16] (Fig. 2).

Indeed, the association of rhinitis and asthma has also been observed in non-atopic subjects [5], in whom mechanisms other than allergic inflammation must be operative. The upper respiratory tract functions as a physical filter, resonator, heat exchanger, and humidifier of inhaled air. Failure of any of these functions could clearly alter the homeostasis of the lower respiratory airway tract [17]. When asthmatics orally hyperventilate with cold air, they suffer a decrease in forced expiratory volume, whereas their nasal resistance is increased [18].

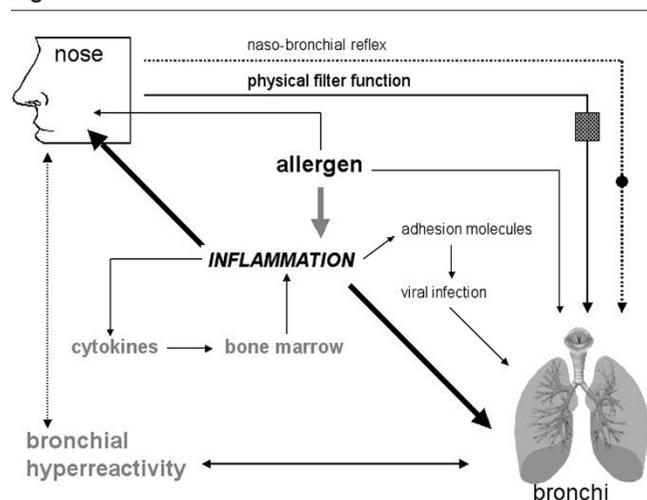
Therapeutic aspects

The connection between the upper and lower respiratory tracts can also be studied in terms of response to therapy. If we consider the functional link (inflammation in particular) existing between the nose and the bronchi, it is reasonable to expect that effective treatment of rhinitis may have some effect on the bronchi [1]. In this sense, the anatomical difference between the two compartments must be taken into account: nose and paranasal sinuses are rigid boxes where erectile sinusoids predominate, whereas bronchi are included in elastic parenchyma and are rich in smooth muscle tissue. In fact, β_2 agonists are highly effective against asthma but have no effect on rhinitis; conversely, H1 receptor antagonists treat rhinitis symptoms but are ineffective against asthma.

The use of intranasal corticosteroids significantly reduced concomitant bronchial hyperresponsiveness as well as asthma symptoms in asthmatic patients in several clinical trials (for a review see [19]). The same result was observed in patients with allergic rhinitis, where cetirizine significantly reduced non-specific bronchial hyperresponsiveness [20]. This synergistic effect was also demonstrated in patients with rhinitis and asthma, using a H1 receptor antagonist in association with a leukotriene receptor antagonist [21].

The link between upper respiratory disease and asthma is also evident in children, where allergic inflammation and viral infections seem to interact. The bronchodilator action of H1 receptor antagonists *per se* is weak and of negligible clinical relevance. The effect on the lower airways, previously demonstrated with ketotifen [22] and recently

Figure 2



Some of the possible functional interactions between the nose and bronchi, in which the inflammatory process plays a central role (see text).

demonstrated with some new compounds, seems to be due to their anti-allergic properties [23]. Continuous treatment for 1 year with terfenadine (versus placebo) reduced the occurrence of upper respiratory infections as well as nasal symptoms and local inflammation by approximately 50% [24]. Cetirizine treatment for six consecutive months similarly resulted in a significant global reduction of the need for asthma medications [25]. These observations, derived from small groups, have recently been confirmed by the large Early Treatment of Atopic Child study: early and continuous anti-histamine treatment reduces the subsequent onset of asthma in atopic children [26].

Conclusion

It is now recognized that allergic rhinitis and asthma are two clinical manifestations of a single disorder of the airways. This view is supported by numerous epidemiological, clinical and immunological observations suggesting that allergy is a systemic disorder of the respiratory tract.

Indeed, rhinitis and asthma share common pathogenetic mechanisms, a high prevalence in the population, negative effects on the quality of life, and certain therapeutic approaches. The strength of the considerations mentioned prompted the World Health Organization to publish an extensive position paper devoted to the relationship between rhinitis and asthma and its therapeutic implications [27], highlighting the concept of 'one airway one disease'.

Inflammation represents the most important link between the upper and lower respiratory tracts, as confirmed by the measurable effects of drug therapy. Obviously, some questions remain unanswered: in particular, the relative weight and role of allergy as compared with other possible mechanisms that are involved, for instance, in non-atopic subjects.

The united airways disease hypothesis is clearly supported by the data, and new therapeutic rationales in the management of respiratory allergy must be put forward.

Acknowledgements

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