

Hay fever: in the laboratory and at natural allergen exposure

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INTRODUCTION

Recent years have given us several new laboratory techniques for monitoring different parts of the response of the nasal mucosa to stimulatory events. Several of these are summarized in a recent monograph (7). These instruments have given us new possibilities for dissecting pathophysiological events taking place in the nasal mucosa as responses to allergen exposure. These include new techniques for the a-traumatic harvesting of cells from the nasal mucosa for quantitative and qualitative studies, techniques for measuring the release of inflammatory mediators, and techniques for monitoring different parts of the vascular response (7). Changes in the tone of blood vessels in the nasal mucosa can now be measured for the resistance as well as the capacitance vessels (6). Another, to a great extent neglected aspect of the defence mechanisms of the mucous membrane is the induced leakage of plasma through the endothelial-epithelial barrier. Through repeated nasal lavages it is now also possible to monitor this part of the vascular response of the nasal mucosa as well.

Most of the work utilizing these techniques has been performed as laboratory challenge experiments (7). However, some techniques are very useful also for the monitoring of changes occurring at natural allergen exposure. By combining information obtained in challenge experiments with those obtained during natural allergen exposure it is possible to evaluate the relevance of findings obtained at challenge experiments. Moreover, additional information concerning the timing and symptom-relationships of certain findings can be obtained.

Laboratory hay fever

Most laboratory studies have focused on different events associated with an early phase allergic reaction. After an appropriate allergen challenge the immediate response which takes place after a few minutes has an interesting time sequence. The patients start to sneeze within 2-5 minutes after a challenge, thereafter the secretory response starts to emerge and as the last part the nasal blockage is evident and maximal after 10-15 minutes. During recent years several investigators have utilized the nasal cavity for the study of allergen-induced mediator release (7). It has been shown that challenge with allergen induces the release of a whole array of different mediators (7). Besides histamine these include a variety of lipoxigenase and cyclooxygenase products, and also mediators of vascular and neurogenic origin. The precise role of these individual mediators in the pathogenesis of the allergic response is unclear. The redundancy of the systems involved will also make any precise evaluation on the contribution of each mediator to the allergic response very difficult, even when specific antagonists for each of the mediators become available.

Studies of allergen-induced changes in vascular tone has previously mainly focused on the capacitance vessels of the nasal mucosa since they are responsible for the regulation of the nasal patency. Thus it is well known that a nasal challenge with allergens induces a decrease in the tone of this part of the vascular bed, leading to an increase in blood content of the nasal mucosa. Utilizing the ^{133}Xe washout

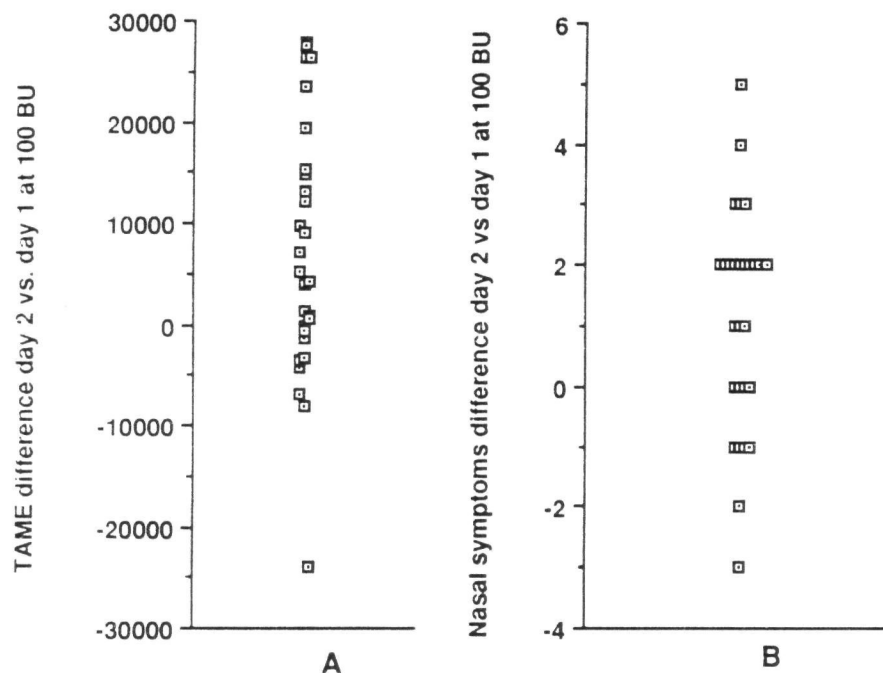


Fig. 1. Panel A. Individual differences in TAME-esterase activity in nasal lavages following nasal allergen challenges (100 BU) with 24 h interval in 28 hay fever patients (day 2-day 1). Panel B shows the differences in symptom scores at the same allergen challenges. From reference 1.

technique for the study of blood flow in the nasal mucosa we have recently shown that allergen induces a dose-dependent decrease in blood flow of the nasal mucosa, a phenomenon which to a great extent appears to be reflex-mediated (6). The response of other parts of the nasal mucosal vascular bed such as the AV-shunts and the interrelationship behind these different parts of the vascular response remains still to a great extent unknown.

Early and late phase allergic reactions

After appropriate allergen-challenges in the lower airways as well as the skin, a significant proportion of the patients exhibit a late phase allergic reaction. The late phase reaction includes a reappearance of symptoms and a local infiltration of the challenge site with inflammatory cells of vascular origin. The demonstration of late phase allergic reaction in the nose has been surrounded by controversy with some investigators being able to demonstrate a late phase whilst others have failed to do so. It is conceivable that the late phase, in terms of its inflammatory component, is not only apparent

in specific locations but more likely a general allergen-induced phenomenon which is more or less obvious at different locations. In similarity to other locations, the relationship of any nasal late phase to the size of an initiation early phase is unclear, and whether there are differences between early and late phase in which symptom is dominant and whether other allergen-related or individual-related factors contribute to the expression of a late phase in the nose is at present unknown.

Nevertheless the nasal mucosa has been utilized for the study of the flux of inflammatory cells at a time when such a late phase is apparent (3). It has thus been shown that there is an increase in the number of neutrophils, basophils and specifically eosinophils on the surface of the nasal mucosa 6–8 h after a strong allergen challenge. Interestingly, pre-treatment with prednisone in a dose which abolished the symptoms of a nasal late phase also abolished the increase in eosinophils but not neutrophils. On the other hand treatment with topical glucocorticosteroids abolished the influx of all inflammatory cells of vascular origin.

Hyperresponsiveness - a phenomenon of airway mucosa.²

One of the characteristics of the late phase of the lower airways is an increased responsiveness to unspecific and specific stimuli (4). A similar feature might also be found in the upper airways, although the correlation with the late phase remains to be clarified. The increase in responsiveness can be demonstrated in the laboratory, following nasal allergen challenges as well as during natural allergen exposure. This feature can be demonstrated in a majority of hay fever patients, but it has no clearcut relationship to the size of the initiating allergic response (1). The individual increase in response to a rechallenge 24 h after an initial challenge for 28 unselected hay fever patients is shown in Fig. 1. As shown, the majority of the patients had an increased responsiveness to a specific rechallenge. The pathogenesis of this increased responsiveness is still unclarified, although some interesting aspects have been demonstrated. In this context it is also of interest to point out that this feature of the allergic response, increased responsiveness, apparently is not a general phenomenon of the allergic inflammation, but limited to certain sites. Thus, immediate or late phase dermal allergic reactions are not followed by an increase in local responsiveness to rechallenge with specific or unspecific agents (2). On the contrary, the more likely response to dermal-rechallenges is a decrease in reactivity. It has also been shown that the specific increased responsiveness includes an increased generation of mediators, such as histamine, rather than an increase in responsiveness at the receptor level (8). The precise relationship between the allergen-induced specific and unspecific hyperresponsiveness remains still to be clarified. In terms of pathogenesis, it is conceivable that part of the changes in responsiveness is due to changes in the barrier function of the mucous membrane. This might include elements of a changed effector cell distribution, some being more superficial and changes in the penetrability of the mucous membranes to macromolecules such as allergens. The nose here offers a possibility to dissect such specific questions.

Monitoring seasonal disease

One should be aware of the fact that all challenge experiments are artificial situations which cannot mimic the continuous low grade exposure occurring during natural exposure regardless whether early phase, late phase or rechallenge experiments are performed. Thus certain important events may well only be apparent during natural allergen exposure. However an advantage of the human nose is that many of the techniques applied in the laboratory may well be applied to monitor changes occurring at natural allergen exposure as well. Thus, seasonal allergic rhinitis due to pollens offers a possibility to study events taking place in the mucous membrane with knowledge of the initiating stimulus, (pollen counts), and the symptoms experienced by the individual patient. A few such studies have been performed with simultaneous monitoring cellular as well as biochemical events (9, 10).

Signs of mast cell activation

Although challenge experiments and theoretical considerations point to the participation of mast cell in hay fever disease, the actual proof is scarce. Using new techniques for atraumatic cell-harvesting it has recently been possible to provide further evidence for the active involvement of mast cells in the pathogenesis of hay fever. Morphological studies have demonstrated a redistribution of mast cells from their normal habitat in the subepithelial layer towards the surface of the mucous membrane, with an increased proportion of these located intra-epithelially during pollen season (5). Recently, further evidence of their active participation has been provided. It has been demonstrated that there is a changed relationship between nasal mucosal mast cell density and histamine content from before to during the pollen season (9). Before pollen season there was a strong correlation between mast cell density and histamine content of the mucosa; a correlation which was not present during pollen season indicating an extracellular pool of tissue histamine. Interestingly the level of tissue histamine found dur-

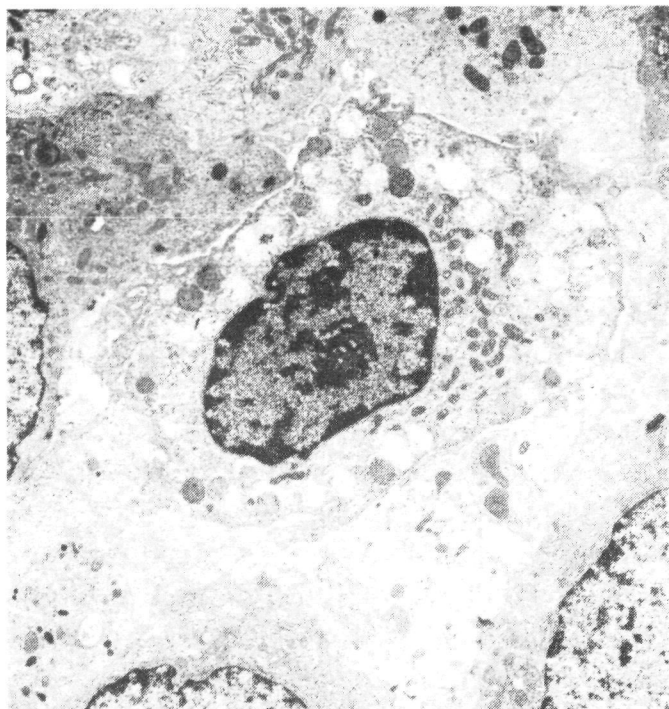


Fig. 2. Electron micrograph of a mast cell obtained in a specimen taken during pollen exposure. Several signs of secretory activity such as totally or partially empty mast cell granules and plasma membrane folds are shown. Original magnification $\times 12,000$.

ing pollen season in the nasal mucosa correlated strongly with the symptoms experienced by the patients. Signs of secretory activity of the mast cells during natural allergen exposure has also been provided by electron microscopy (Fig. 2).

Participation of eosinophils

The eosinophil is one cell type which besides the mediator cells shows consistent changes in number of following allergen challenge experiments. This is also true when it comes to natural allergen exposure and it has been shown that the number of eosinophils on the surface of the nasal mucosa strongly correlates with the degree of pollen exposure and symptomatology of the patients (10). Although the presence of the eosinophils during these conditions strongly indicates an active role for these cells, the specific role of the eosinophils is still at large.

CONCLUSION

The upper airways offer a possibility to continuously monitor allergic mucosal reactions not only in the laboratory but also during natural allergen exposure. Such studies will provide further insights in the pathogenesis of allergic disease; insights which might well be of a general nature and therefore relevant also for other parts of the airways.

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