Effect of seasonal allergic rhinitis on airway mucosal absorption of chromium-51 labelled EDTA

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Abstract

Background—Hyperpermeability of the airway mucosa is thought to be characteristic of allergic rhinitis and asthma. Nine subjects with seasonal rhinitis caused by birch pollen were studied and the nasal mucosal absorption of chromium-51 labelled EDTA was examined both in an asymptomatic period before the season and late into the season when significant allergic rhinitis symptoms were present.

Methods—A nasal pool device was used to keep a concentration of the absorption tracer in contact with a large part of the mucosa of the ipsilateral nasal cavity. Absorption was allowed for 15 minutes and measured as the radioactivity appearing in the 24 hour urine sample.

Results—The nasal absorption of ^{51}Cr -EDTA in subjects with seasonal allergic rhinitis was less during active disease than before the season.

Conclusions—An airway epithelial barrier that is subject to prolonged eosinophilic inflammation may not be disrupted but may rather increase its functional tightness.

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Mucosal barrier dysfunction is considered an important feature of allergic and inflamed airways. The question of an increased ability for absorption has been advanced as a pathogenetic factor and used to explain airway hyperresponsiveness in asthma and rhinitis. The available data, however, do not uniformly support the association between asthma and rhinitis and a non-tight epithelial lining of the airway. Although Ilowite *et al*¹ have reported that asthmatic subjects absorb inhaled tracer molecules more readily than control subjects, other reports suggest that absorption rates of inhaled tracers (small polar solutes) may not correlate with asthma or hyperresponsiveness.² This apparent controversy remains unresolved partly because neither the exposed mucosal surface area nor the surface concentration of absorption tracers were measured in these studies and, indeed, may not be easily controlled in human bronchial *in vivo* studies. Buckle and Cohen³ used iodine-125 labelled albumin as

an absorption tracer in subjects with allergic rhinitis and asthma and reported that the airway (nasal) mucosa showed increased absorption in these patients. Although this latter work is frequently cited, the findings may not be entirely valid. In a separate study⁴ we have shown that radioactivity appearing in plasma after nasal application of ^{125}I -labelled albumin probably reflects the fact that a small fraction of the nasal solution is swallowed (in our study < 1% of the instillate would have sufficed). In the gastrointestinal tract ^{125}I is dissociated from albumin and readily absorbed.⁴

We have developed methods by which mucosal absorption and exudation processes can be examined in some detail in animal tracheobronchial and human nasal airways^{5,6} and have shown that plasma exudates enter the airway lumen in response to inflammatory stimuli—such as allergens—applied to the mucosal surface. Furthermore, the acute mucosal exudation of bulk plasma has not been associated with epithelial damage, nor has any change in the absorption ability of the mucosa been induced.^{5,6} *In vitro* data suggest that the unidirectional exudation process may involve a hydrostatic pressure operated valve-like function of epithelial junctions.⁷ This dissociation between exudation and absorption permeabilities means that the abundant presence of plasma proteins on the mucosal surface of asthmatic and rhinitic airways⁸ may no longer be interpreted as a sign of a general “airway hyperpermeability” in these diseases.¹⁵

During the Swedish birch pollen season subjects with allergic rhinitis develop sustained mucosal plasma exudation and eosinophilia together with increased symptoms and increased responsiveness. These symptoms are controlled with topical glucocorticoids, confirming the inflammatory nature of the condition.^{9,10} In the present study the absorption capacity of the nasal mucosa was assessed before the start of the pollen season and 10 weeks later at its end.

Methods

Nine men aged 19–47 years (mean 30 years) with clear seasonal allergic rhinitis (positive history and skin prick test to birch pollen; other allergens not examined) were included after giving informed consent. No drugs were allowed during the study which was approved

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Figure 1 (A) Daily birch pollen counts in the south of Sweden from 8 April (day 1) until 26 May (day 49). (B) Mean (SE) composite nasal symptom scores in nine patients (based on daily diary entries of blockage, secretions, itching, and sneeze scores^{9,10}) during the birch pollen season. Absorption of ^{51}Cr -EDTA was examined before the season (outside the graph) and late into the season (↑).

by the ethics committee of the University Hospital of Lund. A nasal pool device (compressible plastic container with a nasal orifice adapter) was used to gently fill the unilateral nasal cavity with a solution of ^{51}Cr -EDTA (5 MBq/14 ml kept at room temperature, 20–22°C). By keeping the device compressed and the head flexed forward 60° from the upright position, the tracer solution was maintained in contact with a large and constant nasal mucosal surface area for 15 min.¹¹ The instillate was then drained back into the device and the mucosal surface was irrigated twice with saline to prevent further absorption.⁶ The quantity of absorbed ^{51}Cr -EDTA was determined by collecting and analysing urine passed during the subsequent 24 hours.⁶ Swallowing of tracer is minimised by this method and, as previously assessed,⁶ any contribution of gastrointestinally absorbed ^{51}Cr -EDTA is negligible.

Results

The daily pollen count and daily symptom scores indicated a relatively mild but significant season (fig 1 A and B). About five weeks before the beginning of the season, when all subjects had no symptoms of allergic rhinitis, mean (SD) absorption of ^{51}Cr -EDTA (calculated as absorbed volume of instillate) was 0.21 (0.05) ml (fig 2) which is comparable to that observed in healthy volunteers.⁶ At the end of the season the absorption was reduced (fig 2) to 0.04 (0.01) ml ($p < 0.01$, Student's two tailed t test for paired observations).

Discussion

It was important that the absorption study was carried out during a period of high pollen count when the symptom score was raised (fig 1). It seems unlikely, however, that the nasal symptoms could have had a major influence on the absorption data found. The mean score for the four symptoms was low, corresponding to about 1 on a scale for each symptom from 0 to 3 (fig 1). We have also shown in a separate study that the nasal absorption of ^{51}Cr -EDTA was unchanged in the presence of histamine that produced very marked symptoms including blockage⁶ (swelling of the mucosa largely due to dilatation and pooling of blood in venous sinuses).⁶ Sneezing is largely avoided when the nasal pool device is used and did not occur during the present measurements.

Because of its polar and hydrophilic nature ^{51}Cr -EDTA (MW 372) is thought to traverse the mucosa by paracellular epithelial routes after which it readily enters the profuse subepithelial microcirculation. It is possible that airway surface secretions and exudations may affect absorption but the role of this variable is reduced in the present study where the surface liquid was mixed with the pool fluid during the entire absorption period. Furthermore, we have previously shown that histamine, which is a potent exudative agent,¹¹ has no effect on nasal absorption of ^{51}Cr -EDTA.⁶ The nasal instillate contained a great excess of the absorption tracer, reducing the possibility that non-specific binding of ^{51}Cr -EDTA could have influenced the measurement of absorption. Moreover, mucociliary transport in the fluid filled cavity would be very inefficient. The nasal pool technique further ensures that a virtually constant concentration of tracer is kept in contact with a large area of the mucosa and will not change when a degree of blockage is induced.¹¹ The present findings suggest that the tightness of epithelial junctions is increased rather than reduced in allergic rhinitis.

During active allergic inflammation there is exudation of bulk plasma into the subepithelial tissues and into the airway lumen. It has been speculated that a paracellular flux of plasma across the epithelium may focally reduce the mucosal absorption of polar solutes.⁵ Exudation of the large plasma proteins¹⁰ may, through formation of fibrin-fibronectin gels, increase the tightness of

Figure 2 The absorption of ^{51}Cr -EDTA across the nasal mucosa before (first week of March) and late into the birch pollen season (23 May). Individual patient data are connected by solid lines.

mucosal barrier functions (J Erjefält, I Erjefält, CGA Persson, unpublished observations). A plasma exudative process or other unknown factors may have contributed to the reduced absorption in this study.

Allergic rhinitis characteristically is associated with hyperresponsiveness to different topical challenges. Thus methacholine has revealed a secretory hyperresponsiveness,⁹ histamine an exudative hyperresponsiveness, and allergen a complex hyperresponsiveness of cellular and mucosal end organ effects.¹² The present observations seem to exclude the possibility that increased mucosal penetrability can explain these increased responses. Indeed, in cases when the challenging agent exclusively affects subepithelial end organs the actual responsiveness of these structures may be underestimated because, according to the present findings, a reduced amount of the topical provoking agent would reach the target.

Our findings suggest that the airway absorption barrier is not more, but less, permeable in seasonal rhinitis and the nasal and tracheobronchial mucosa may be similar in this respect.¹² The present findings therefore raise the question whether absorption of inhaled material is reduced in allergic airway diseases. This question is not novel. It was raised in 1930 by Cohen *et al*¹³ who applied allergenic material to the nasal mucosa and found that Prausnitz-Küstner reactions developed much faster and much more frequently in healthy subjects than in patients with allergic rhinitis.

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