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Exudative hyperresponsiveness of the airway microcirculation in seasonal allergic rhinitis

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Summary

Background Mucosal exudation of plasma is a non-injurious, physiological response of the airway microcirculation to different inflammatory processes. The exudative response is similar in the nose and bronchi and exudation occurs in both allergic asthma and rhinitis. The exudative response is a specific end-organ function of the mucosal microcirculation that may be altered in airway diseases.

Objective This study examines the hypothesis of altered responsiveness of the superficial airway microcirculation to vascular permeability-increasing challenges in sustained allergic inflammation.

Methods Fourteen patients with birch-pollen induced allergic rhinitis were studied for 7 weeks during a Swedish birch-pollen season. Nasal symptoms (itching, sneezing, blockage, and discharge) were recorded and the occurrence of pollen was determined. The plasma exudation response was examined by topical histamine challenges at the end (May) and well out of (December) the season. Challenge and lavage were carried out concomitantly using a 'nasal pool'-device. The unilateral nasal cavity was filled for consecutive 10 minute periods with saline and two concentrations of histamine (80 μg/mL and 400 μg/mL). The lavage fluid levels of different-sized plasma proteins (albumin-66 000 D, fibrinogen-340 000 D, and α_2-macroglobulin-725 000 D) were determined.

Results The pollen season was mild resulting in only minor nasal symptoms. Histamine produced exudation of all plasma proteins across the microvascular epithelial barriers with particularly strong correlation between the levels of albumin and α_2-macroglobulin ($r = 0{\cdot}98$; $P < 0{\cdot}001$). The exudative response to histamine was concentration-dependent ($P < 0{\cdot}05$) and, furthermore, it was significantly greater late into the season compared with outside the pollen season (albumin: $P < 0{\cdot}05$, fibrinogen; $P < 0{\cdot}05$, α_2-macroglobulin: $P < 0{\cdot}01$).

Conclusion We conclude that histamine produced concentration-dependent nasal airway exudation of bulk plasma in subjects with seasonal rhinitis and that this response is abnormally great during the pollen season. Whether angiogenesis or increased responsiveness of the microvascular endothelium may explain this phenomenon now remains unknown. We suggest that a microvascular exudative hyperresponsiveness may characterize allergic airway disease.

Keywords: allergic rhinitis, airway hyperresponsiveness, airway hyperreactivty, airway inflammation, histamine, plasma exudation, albumin, fibrinogen, α_2-macroglobulin

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Introduction

Acute inflammatory challenges produce several physiological effects in the airways. Increased blood-flow, increased secretion, altered mucociliary activity, increased microvascular permeability, and cough/sneezes may be produced. Most of these are not specific to inflammation since they can be produced by irritants that merely evoke neural activity. However, one tissue response that is rather specific to inflammation is increased vascular permeability [1,2]. This effect is produced by allergen, occupational agents, viral infections, and select mediators [3–6]. It is not produced by methacholine [4,7] nor is it, in human airways, produced by potent neural agents such as capsaicin [8] and nicotine [9].

At mucosal inflammatory challenges or processes the profuse superficial airway microcirculation releases bulk plasma. The plasma exudate distributes in the lamina propria. It moves readily across the epithelial basement membrane and then up between individual epithelial cells. At this latter site only a very small increase in the hydrostatic pressure (about 5 cm H_2O) [10,11], most likely caused by the exudate itself, will create valve-like paracellular pathways for prompt luminal entry of almost non-sieved bulk plasma. (The plasma exudate increasingly contains newly formed oligoproteins, peptides, and, perhaps, more fluid.) The permeability of the subepithelial microcirculation can thus be monitored by the amount of exudative indices appearing on the mucosal surface per unit time [4].

At sustained inflammatory processes specific endorgans of the airway mucosa, such as the innervation, the secretory apparatus, and the microcirculation, may develop an altered responsiveness. We have speculated that specific endorgan hyperresponsiveness may characterize rhinitis and asthma or sub-groups of patients suffering from these inflammatory diseases [2]. The clinical experimental techniques currently available seem to allow specific measurements of end-organ functions in the nasal airways whereas the bronchial response is frequently recorded as a 'black box' sum effect of partly unknown components. Furthermore, it is possible that inflammatory disease mechanisms may be similar in nasal and bronchial mucosa [2]. For example, in both nasal and bronchial airways of allergic subjects, topical allergen challenge induces mucosal exudation of bulk plasma [2,12,13]. Additionally, we have previously demonstrated that an exudative hyperresponsiveness develops during a coronavirus-induced common cold [14].

The hypothesis tested in this study concerns the possibility that the superficial airway microcirculation may change its responsiveness to vascular permeability-increasing challenges during sustained allergic inflammation. To examine this potential disease characteristic histamine-challenges were carried out outside and late into the Swedish birch pollen season in subjects with seasonal allergic rhinitis. Based on our previous experience with histamine, we have selected two concentrations of this amine to produce the plasma exudation response [15]. Furthermore, we have used a nasal pool-device that applies, for defined periods of time, the selected histamine concentration on a large and reproducible mucosal surface area. The pool-device then gently, efficiently, and selectively lavages the exposed airway surface [15].

Material and methods

Study design

Fourteen patients with birch pollen induced allergic rhinitis were studied for 7 weeks during the birch pollen season of 1991 (from April 8 until May 26). Histamine challenges and nasal lavages were performed at the end of the pollen season (May 26, i.e. day 49) and well out of the season (December 1991) when the patients were asymptomatic. The levels of albumin, fibrinogen, and α_2-macroglobulin were determined in the lavage fluids.

Patients

Nine men and five women between the ages of 19 and 47 years (mean age 26 years) participated in this study. All patients had a history of birch pollen-induced allergic rhinitis, positive skin-prick test, and a positive reaction to nasal challenge with birch pollen. The patients had no other organic manifestations of their allergic disease. No drugs were permitted during the study or during a 3 week period before entering the study. All participants gave their informed consent before entering the study which was approved by the Ethics Committee at Lund University.

Nasal lavage and histamine challenge procedure

Histamine provocation and nasal lavages were performed concomitantly using the 'nasal pool' device method as previously described [15]. Isotonic saline solution (0·9%) at room temperature was used for lavages and challenges. Histamine hydrochloride was added to the saline solution to reach a final histamine concentration of 80 μg/mL (H80) and 400 μg/mL (H400), respectively. While the patient was positioned with the head flexed forward (60°), the unilateral nasal cavity was gently filled by compressing the nasal pool containers (Volume 15 mL). After two quick saline

lavages (duration: 30 s each) the different solutions were kept in the nasal cavity for consecutive 10 min periods and then returned back into the containers (0–10 min: saline; 10–20 min: H80; 20–30 min: H400). The weight of the fluid filled containers was recorded before (W_b) and after (W_a) the lavages. The weight of the empty plastic container (W_e) was subtracted and then the recovery (Rec) was calculated: $Rec = (W_a - W_e)/-(W_b - W_e) \times 100$. The lavage fluid was thereafter immediately centrifugated (650 ***g*** for 10 min) and frozen (−20°C) until analysed.

Analytical assay

Albumin Albumin was measured using a radioimmunoassay, sensitive to 6·25 ng/mL, with antiserum (rabbit anti-human albumin) (Dakopatts, Copenhagen, Denmark) and commercial standard (Calbiochem, San Diego, CA, USA). Iodination was performed using a lactoperoxidase method [16] to a specific activity of 2 mCi/nmol. Tracer and standards (or samples) were mixed with antiserum before adding goat anti-rabbit antiserum (Astra Draco, Lund, Sweden). The bound fraction was measured in a gamma counter (Clinigamma) (Pharmacia Diagnostica Norden, Uppsala, Sweden) and the data evaluated using RIA CALC (Pharmacia Diagnostica Norden, Uppsala, Sweden). The intra- and inter-coefficient of variation was 5% and 10%, respectively.

Fibrinogen Fibrinogen was measured with a radioimmunoassay sensitive to 2 ng/mL. Iodination was made with the lactoperoxidase method [16]. Rabbit anti-human fibrinogen (UCB-Bioproducts SA, Braine-L'allerud, Belgium) and human fibrinogen (reference substance) (Sigma, St Louis, Missouri, USA and Calbiochem, San Diego, CA, USA) were used. The samples were treated on a ultrasonic bath for 15 min and centrifuged at 2250 ***g*** for 10 min. Standards and samples, respectively, were mixed with tracer and antiserum. Separation was accomplished by adding diluted normal rabbit serum and goat anti-rabbit IgG (Astra Draco, Lund, Sweden). The bound fraction was measured in a gammacounter (Clinigamma, Pharmacia Diagnostica Norden, Uppsala, Sweden) and the results were calculated using RIA CALC (Pharmacia Diagnostica Norden, Uppsala, Sweden). The intra- and inter-assay coefficient of variation were 7% and 12%, respectively.

α_2-macroglobulin α_2-macroglobulin was measured with a radioimmunoassay sensitive to 7·81 ng/mL. Rabbit anti-human α_2-macroglobulin (Prod.nr AO33, Dakopatts, Copenhagen, Denmark) was used as antiserum and standard human serum (Prod.nr. 679308, Behringwerke AG Diagnostica, Marburg, Germany) as standard. Human α_2-macroglobulin (Prod.nr 32632, Cappel/Organon Teknika, Turnhout, Belgium) was iodinated using the lactoperoxidase method [16]. Tracer and standards (or samples) were mixed with antiserum before adding goat anti-rabbit antiserum (Astra Draco, Lund, Sweden). The bound fraction was measured in a gamma counter (Clinigamma) (Pharmacia Diagnostica Norden, Uppsala, Sweden) and the data evaluated using Multi CALC (Wallac OY, Åbo, Finland). The intra- and inter-assay coefficient of variation were 3·8–6·0% and 3·1–7·2%, respectively.

Pollen count

The birch pollen occurrence was estimated by a Burkhard pollen trap located in the study area and expressed as the mean daily number of birch pollen grains per cubic meter of filtered air.

Assessment of symptoms

The participants were equipped with a score chart and estimated daily their nasal symptoms (blockage, itching, sneezing and secretion) from 0 to 3 (0 = no symptoms, 1 = mild, 2 = moderate and 3= severe symptoms) giving a total daily score range from 0 to 12 during the pollen season. At the histamine challenges, blockage and secretion were estimated from 0 to 3 and the number of sneezes were counted during each 10 min provocation.

Statistical analysis

Non-parametric statistics were used. Friedman test followed by Wilcoxon signed rank test. Spearman rank correlation test was used for calculations of correlation. A *P*-value less than 0·05 was considered significant.

Results

Pollen occurrence and daily nasal symptoms

All patients completed the study. Daily birch pollen counts and nasal symptom scores are presented in Fig. 1. The birch pollen occurrence was low to moderate and below average values for the region with only one peak above 100 grains/m^3 filtered air. Total birch pollen count (grains/m^3 filtered air/year) for the entire pollen season 1991 was only 1285 (mean value for the region during the years 1979–1991 is 2627). The nasal symptom scores were also low with some enhancement during the last weeks of the study period (in comparison with day 1 the total nasal symptoms were significantly increased on

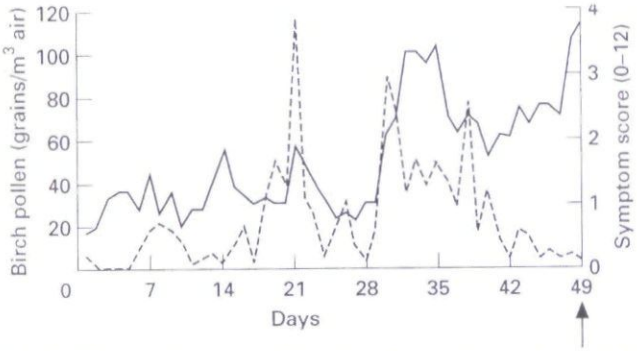

Fig. 1. Mean daily grains of birchpollen in the air during the 7 weeks' study period (8 April until 26 May 1991) and mean daily nasal symptom scores (sum of nasal blockage, secretion, itching, and sneezing; each symptom scored from 0 to 3 where 0 = no symptoms; 1 = mild; 2 = moderate and 3 = severe symptoms) experienced by the patients during the study period (in comparison with day 1 the total nasal symptoms were significantly increased on day 4, 7, 21, 30–39, 41–44, and 46–49; $P < 0{\cdot}05$; Wilcoxon signed rank test). Histamine challenges were made at the end of the seventh week (day 49; indicated with an arrow) and well out of the season (December). - - - . Pollen. — . Symptoms.

days 4, 7, 21, 30–39, 41–44, and 46–49; $P < 0{\cdot}05$; Wilcoxon signed rank test).

Nasal lavage fluid recovery

Recovery (percentage of the instilled lavage fluid volume ± SEM) in December and May, respectively, was: out of season 79 ± 2 (saline), 80 ± 3 (H80), 80 ± 2 (H400), and late in season 77 ± 3 (saline), 78 ± 3 (H80), 79 ± 3 (H400).

Concentration-response to histamine

Lavage fluid levels of albumin, fibrinogen, and α_2-macroglobulin are presented in Fig. 2. The levels of the plasma proteins were in all lavages clearly above the detection limits of the assays. Except for fibrinogen levels in December, histamine induced a dose-dependent increase in the lavage fluid levels of all three plasma proteins both outside and late into the pollen season (Table 1).

Increased responsiveness to histamine

There were no significant seasonal changes in the levels of albumin, fibrinogen or α_2-macroglobulin in the saline

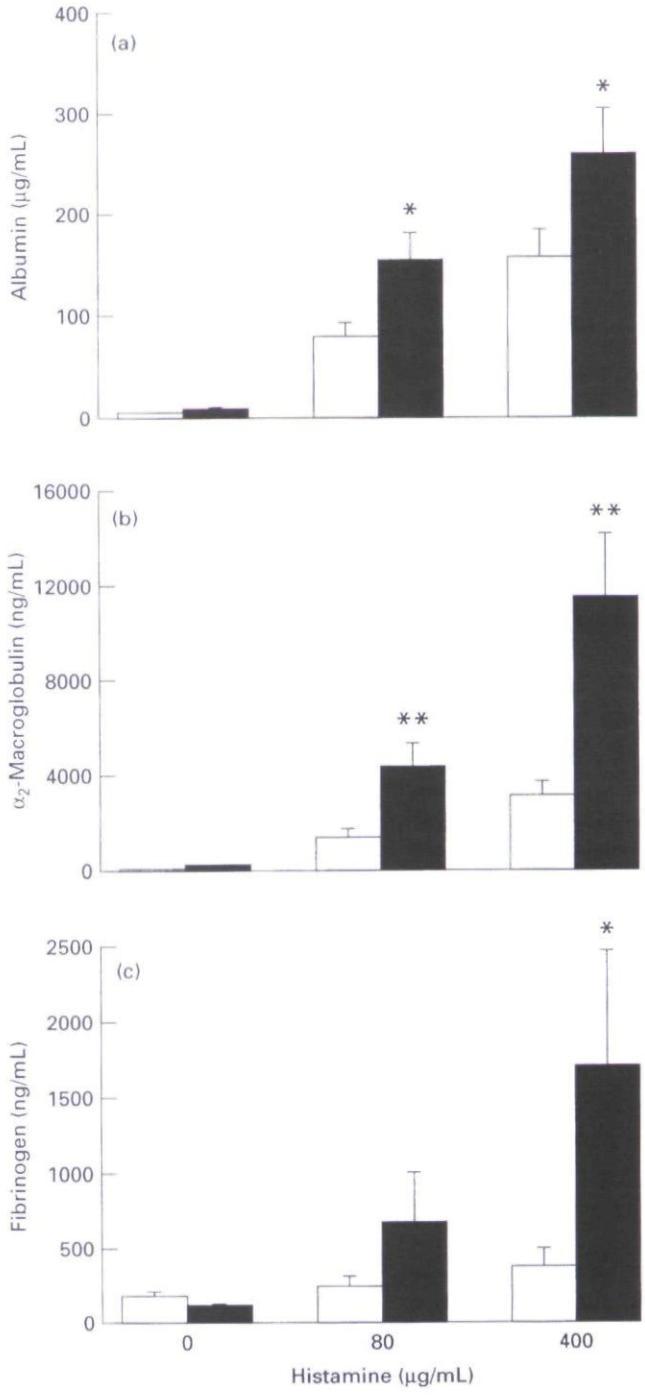

Fig. 2. Mean levels (± SEM) of albumin (a), α_2-macroglobulin (b) and fibrinogen (c) in the returned lavage fluids after consecutive 10 min provocation periods with saline and histamine, 80 µg/mL and 400 µg/mL, in the nasal pool lavage fluid. □. Out of season (December). ■. Late in season (May). Histamine-induced plasma exudation was concentration-dependent at both occasions. There were no changes in the baseline levels (saline challenge) of the plasma proteins, while significantly greater levels were found after histamine challenge during seasonal pollen exposure (*$P < 0{\cdot}05$ and **$P < 0{\cdot}01$; out of season vs late in season; Wilcoxon's signed rank test).

Table 1. Statistic significance (*P*-values for Wilcoxon signed rank test) for comparisons of the exudative response (lavage fluid levels of plasma proteins) to nasal histamine challenge: concentration-response during seasonal pollen exposure

	Albumin *P*	α_2-Macroglobulin *P*	Fibrinogen *P*
Out of season			
Saline vs H80 vs H400 (Friedman test)	<0·001	<0·001	NS
Saline vs H80	<0·01	<0·001	NS
H80 vs H400	<0·05	<0·01	NS
Late in season			
Saline vs H80 vs H400 (Friedman test)	<0·001	<0·001	<0·001
Saline vs H80	<0·01	<0·001	<0·01
H80 vs H400	<0·01	<0·01	<0·05

challenge (baseline), while the exudative response to histamine was significantly increased during seasonal pollen exposure for all three plasma proteins (Table 2). Almost the same statistical significance was obtained if net changes were compared, i.e. saline lavage fluid levels (baseline) were subtracted from lavage fluid levels in H80 and H400 (Table 2).

Calculations of correlations between the lavage fluid levels of the plasma proteins were made on the three lavages (saline + H80 + H400) in December and May. The levels of albumin and α_2-macroglobulin demonstrated a strong correlation at both occasions ($r = 0{\cdot}92$ and $r = 0{\cdot}98$ for December and May respectively; $P < 0{\cdot}001$) (Fig. 3) while the levels of fibrinogen showed much weaker correlations with the other two proteins (values for December and May, respectively: $r = 0{\cdot}48$ ($P < 0{\cdot}01$) and $r = 0{\cdot}76$ ($P < 0{\cdot}001$) for fibrinogen-to-albumin; and $r = 0{\cdot}50$ ($P < 0{\cdot}01$) and $r = 0{\cdot}74$ ($P < 0{\cdot}001$) for fibrinogen-to-α_2-macroglobulin) (Spearman rank correlation coefficient).

Histamine-induced nasal symptoms

The nasal symptom scores increased concentration-dependent on histamine challenge at both occasions (number of sneezes: $P < 0{\cdot}05$, secretion score: $P < 0{\cdot}001$, blockage score: $P < 0{\cdot}001$; values for both occasions; Friedman test). However, neither sneezes, nor

Table 2. Statistic significance (*P*-values for Wilcoxon signed rank test) for comparisons of the exudative response (lavage fluid levels of plasma proteins) to increased responsiveness out of season vs late in season during seasonal pollen exposure

	Albumin *P*	α_2-Macroglobulin *P*	Fibrinogen *P*
Saline vs Saline	NS	NS	NS
H80 vs H80	<0·05	<0·01	NS
	(0·055)	(<0·01)	NS
H400 vs H400	<0·05	<0·01	<0·05
	(<0·05)	(<0·01)	(<0·01)

Within parenthesis are the *P*-values for comparison of net changes, i.e. saline lavage fluid levels being subtracted from lavage fluid levels in H80 and H400.
Saline. Saline challenge. H80. Histamine 80 μg/mL. H400. Histamine 400 μg/mL.

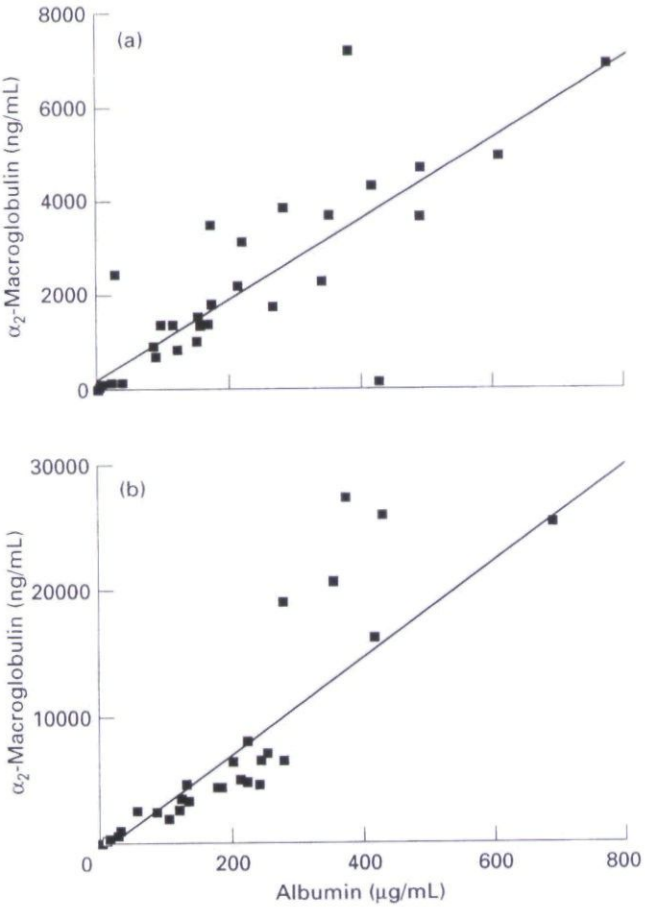

Fig. 3. Correlations between the lavage fluid levels of albumin (66 000 D) and α_2-macroglobulin (725 000 D) in (a) December and (b) May. Calculations made on the three lavages (saline + H80 + H400; $n = 42$ at both occasions; $P < 0{\cdot}01$ for both r-values; Spearman rank correlation coefficient). (a) $r = 0{\cdot}92$; (b) $r = 0{\cdot}98$.

scores for nasal secretion or blockage induced by saline (baseline) or any of the two histamine challenges were significantly increased late in season compared with values obtained out of season (Wilcoxon's signed rank test) (Fig. 4).

Discussion

The present study involving subjects with seasonal allergic rhinitis has demonstrated that topical histamine produced concentration-dependent exudation of different-sized plasma proteins (albumin-66 000 D; fibrinogen-340 000 D; and α_2-macroglobulin-725 000 D) into the airway lumen both outside and during the pollen season. Also, the correlation between albumin- and α_2-macroglobulin-levels in the lavage fluids was very high,

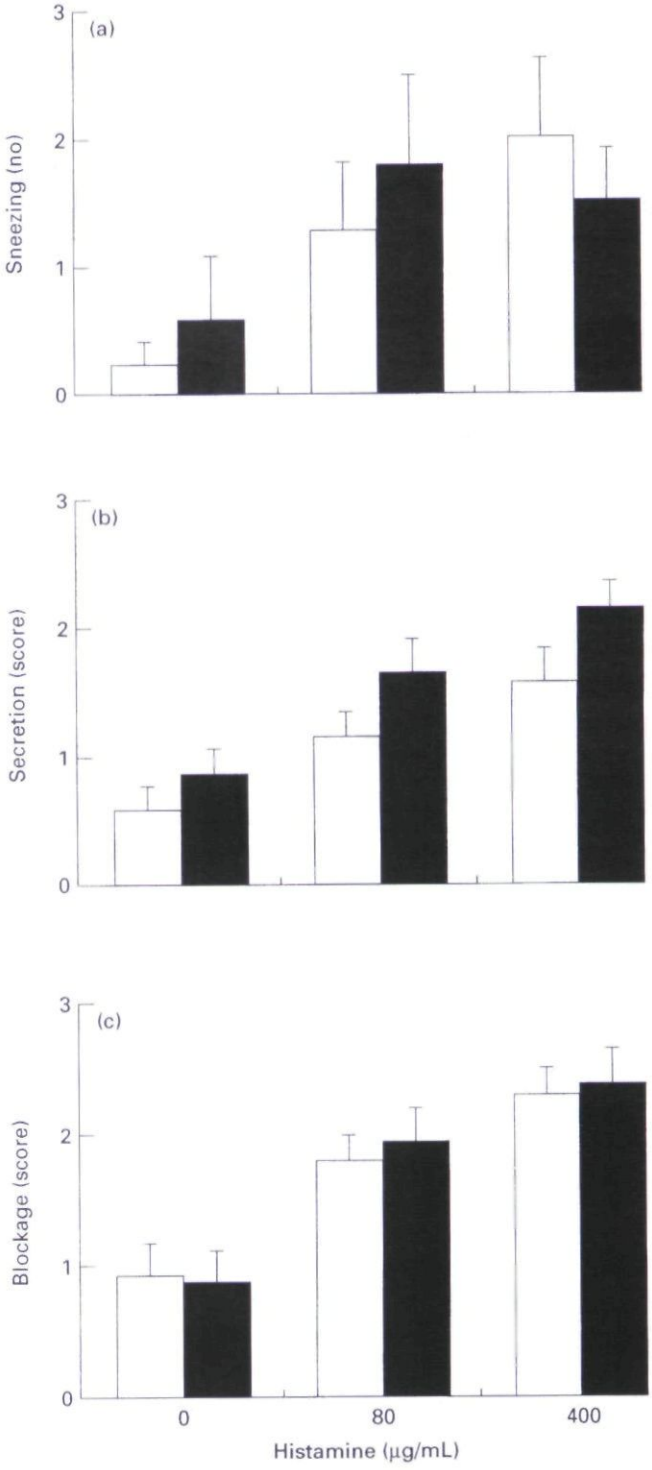

Fig. 4. Mean number of sneezes (± SEM) (a), and mean nasal symptom scores (± SEM) of secretion (b) and blockage (c) in December (out of season = □) and May (late in season = ■). The histamine-induced nasal symptoms were concentration-dependent on both occasions. There were no statistical significant changes in neither saline (baseline) nor histamine-induced symptoms during seasonal pollen exposure.

strongly supporting the notion that the acute exudation process is of a non-sieved nature [1,2,4]. Despite the mild pollen season, the exudative responsiveness to histamine was significantly increased at the end of the pollen season. This result thus suggests that a novel type of airway hyperresponsiveness, 'exudative hyperresponsiveness of the subepithelial microcirculation', may develop in allergic airway diseases.

In a series of studies involving human and guinea-pig airways we have examined the mechanisms of mucosal exudation (luminal entry) of plasma [1,2]. The epithelial lining and the subepithelial network of microvessels are key structures for this process. Topical stimulation with inflammatory mediators leads to active separation of endothelial cells in the post-capillary venules. Due to intravascular hydrostatic forces plasma is extravasated through open gaps in the venular wall. For isolated airway tissue experiments it appears that a hydrostatic pressure of about 5 cm H_2O, exerted on the basolateral aspects of epithelial cells, is sufficient to move the plasma macromolecules further across the epithelial lining [10,11]. The luminal entry of plasma is thus already produced by threshold inflammatory challenges, and it may occur without generation of oedema or increased lymph protein transport [17]. Since the movement of extravasated plasma into the airway lumen may not be much hindered by the normal epithelial lining the appearance of plasma exudation indices on the mucosal surface may promptly and specifically reflect the permeability of the subepithelial microcirculation.

The acute mediator-induced mucosal exudation of plasma is a unidirectional paracellular flux of differently-sized solutes. The increased outward-directed 'permeability' (exudation) is produced without changes of the mucosal inward-directed 'permeability' (absorption) [18,19]. We have even observed that the mucosal absorption permeability is reduced in a subgroup of the present patients (men) during the present pollen season (as assessed with ^{51}Cr-EDTA, a small polar solute similar in size to histamine) [20]. We therefore suggest that the increased responsiveness to histamine-challenge in the present study does not reflect increased mucosal absorption permeability but is due to an increased responsiveness of the subepithelial microcirculation. Furthermore, the magnitude of this vascular hyperresponsiveness is probably underestimated since, as a consequence of the previously demonstrated reduced mucosal absorptivity [20], it is anticipated that less histamine reaches the microcirculation at the end of the pollen season compared with out of the season.

In this study we have used the 'nasal pool'-device which permits concomitant provocation and lavage from a large and reproducible airway mucosal surface area. We chose two concentrations of histamine, one of which is known to be a significant threshold exudative dose. The other concentration was five times stronger but still submaximal on the steep slope of the concentration-response curve [15]. These concentrations of histamine were kept in direct contact with the nasal mucosa for 10 min which is a sufficient period for the exudative response to be fully or almost fully developed [15]. Although there were no changes in baseline levels of the proteins (saline challenge), the exudative response to both concentrations of histamine were significantly increased during seasonal pollen exposure. Subtraction of the baseline values from the histamine challenge values revealed similar results indicating that a shift to the left of the dose-response curve for topical histamine had occurred in seasonal allergic rhinitis. This exudative hyperresponsiveness of the airway microcirculation may reflect changes in the responsiveness of the vascular endothelial cells that regulate the permeability to plasma, or it may be a result of angiogenesis associated with prolonged allergic inflammation. However, whether these possibilities or other explanations are valid remains speculative. The histamine-induced nasal symptoms were not significantly increased during this rather weak pollen season. However, the recording of symptoms may be a much more coarse method than quantitation of plasma indices by employment of the nasal-pool device which offers well controlled challenge-lavage conditions.

The present results may be compared with observations reported by Majchel *et al.* [21] who examined histamine challenge-induced effects in ragweed-induced rhinitis. Based on their results of histamine-induced nasal symptoms, these authors concluded that hyperresponsiveness during the pollen season may be due to an increased baseline (i.e. seasonally induced 'baseline' nasal symptomatology) and not to increased sensitivity to histamine *per se*. Majchel *et al.* [21] also measured albumin levels in the nasal lavage fluids after the histamine challenge and made the interesting observation that the histamine response (albumin levels) was higher at the peak than at the end of the pollen season. This particular effect remains unexplained since the authors [21] were not able to find significant changes during any part of the pollen season compared with the histamine-induced albumin exudation/secretion out of the season. There are a number of aspects which need consideration when our study is compared with that of Majchel *et al.* [21]. Not only did we examine a weak birch pollen season with quite limited symptomatology, whereas Majchel *et al.* [21] worked with ragweed-allergic patients, who developed significant symptoms. The methodologies are also distinct. We applied specific concentrations of histamine on a large nasal mucosal surface area while Majchel *et al.*

[21] sprayed different doses of histamine into the nostril. The peak output of albumin in our study was also about fivefold greater than that reported by Majchel *et al.* [21]. We cannot exclude the possibility that this discrepancy in part reflects the efficient washing exclusively of the exposed mucosal surface that is carried out by the present nasal pool device. Furthermore, in the present study we analysed three plasma proteins and could, therefore, secure that the recorded albumin levels reflected mucosal exudation of plasma and not secretory processes.

The correlation between albumin and α_2-macroglobulin in the returned lavage fluid was excellent on both challenge occasions. This result agrees with the notion that histamine consistently produces mucosal exudation of bulk non-sieved plasma. The luminal entry of α_2-macroglobulin, well-known for its antiprotease activity, is of particular interest since this protein is highly capable of binding and targeting different cytokines [22,23]. In airway inflammatory processes, a considerable amount of subepithelial (lamina propria) cytokine production and release may thus be transported to the airway surface by the exudation process. Hence, sampling of airway surface material during active exudative phases may yield important possibilities to monitor also subepithelial cytokine patterns in inflammatory airway diseases [24,25].

It seems well established that a bronchial hyperresponsiveness to histamine challenges develops in subjects with seasonal rhinitis and asthma [26–29]. However, it is not known what mechanisms or, indeed, which endorgan responses, in addition to bronchial smooth muscle, that are involved in bronchial hyperresponsiveness to histamine challenges. As first calculated by Hutt and Wick [30], any increase in the thickness of tissue and surface layers between the bronchial smooth muscle and the free airway lumen will in theory result in increased obstructive responsiveness to any bronchial constrictor. The plasma exudation response might increase the thickness of the lamina propria by increasing its content of fluid and matrix macromolecules. Equally, the mucosal surface layer will be increased by a sticky and tenacious plasma exudate [31]. The exuded plasma also contains numerous proinflammatory peptides, oligoproteins, and proteins. An increased tendency for the exudative response may, therefore, be of significance whether it occurs in allergic airway disease (this study), common cold [14] or other forms of rhinitis, and in asthma.

We conclude that a microvascular exudative hyperresponsiveness may develop even in mild seasonal allergic rhinitis. Hence, exudative indices may be a more sensitive measure of airway inflammation in ongoing disease compared with acute inflammation. Furthermore, both the hyperresponsiveness and the maintained bulk nature of the mucosal exudation process (this study) strengthen the likelihood that all the multifactorial protein systems of plasma (e.g. coagulation and complement system together with immunoglobulins, fibronectin and other proteins) participate in airway mucosal inflammatory processes. We have previously demonstrated that also sensory nerve responsiveness (producing irritation and pain) may be increased in seasonal rhinitis [8]. The possibility that a number of specific mucosal endorgans have altered physiological responsiveness provides a novel concept of airway hyperresponsiveness with as yet unproven importance for characterization of airway diseases, their pathogenesis, and their pharmacotherapy.

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