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Original article

Nasal reactivity to capsaicin in patients with seasonal allergic rhinitis during and after the pollen season

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Key words: allergic rhinitis; capsaicin; neurogenic inflammation.

Background: We aimed to study the participation of neurogenic mechanisms in nasal allergic inflammation by assessing the effect of neurogenic stimulation on the secretory and cellular responses of nasal mucosa in patients with allergic rhinitis.

Methods: A group of patients suffering from seasonal allergic rhinitis was challenged intranasally with incremental doses of capsaicin (0.3, 3, 12 µg) during and after the pollen season. Clinical symptoms after provocations were monitored, and unilateral nasal lavages were obtained. The nasal lavage fluid (NAL) was assayed for concentration of total protein, albumin, lactoferrin, and number of leukocytes, following by differential count.

Results: Capsaicin challenge during the pollen season produced greater congestion ($P<0.01$) and rhinorrhea ($P<0.05$) than after the season. The intensity of burning sensation (pain) was similar on both occasions. Capsaicin failed to increase albumin content in NAL both during and after the season. Total protein was increased only after the highest dose of capsaicin ($P<0.03$) after the season. The number of eosinophils in basal lavages was higher during the season. During the season, the total number of leukocytes at least doubled in 7/12 patients and the percentage of eosinophils increased in 6/12 patients after the capsaicin challenge.

Conclusions: Our study demonstrated that during the symptomatic period the nasal mucosa of allergic patients is more susceptible to neurogenic stimulation, showing enhanced secretory and inflammatory (cellular) responses.

Allergic rhinitis, which is characterized by the presence of sneezing, nasal congestion, and rhinorrhea in response to allergen exposure, is associated with inflammation of the nasal mucosa. The involvement of different inflammatory

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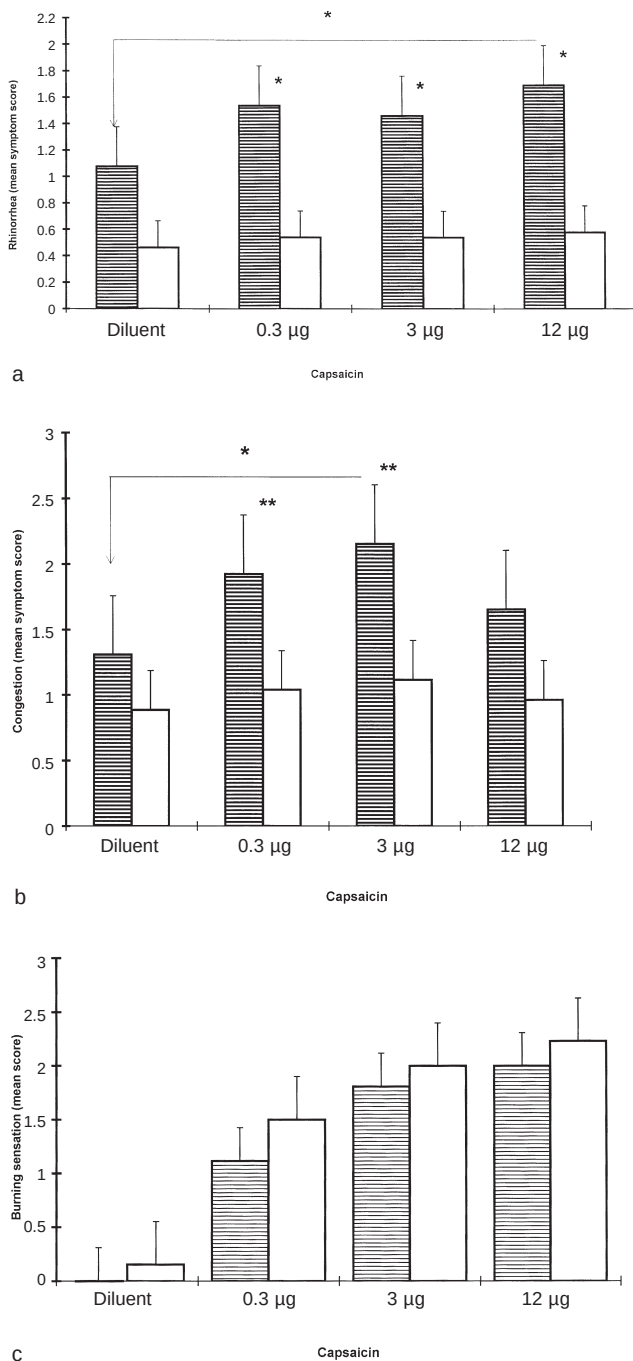


Figure 1. Symptoms induced by capsaicin challenge during pollen season (hatched bars) and after pollen season (open bars). Data presented as mean symptom score $\pm$ SEM ($n=13$). A) rhinorrhea; B) congestion; C) burning sensation. * $P<0.05$; ** $P<0.01$ as compared to postseasonal values.

cells (mast cells, eosinophils, neutrophils, monocytes, and lymphocytes) in this process has also been demonstrated. Although it is clear that histamine is a major mediator of acute allergic rhinitis, other mediators such as leukotrienes (LTC_4), prostaglandins (PGD_2), kinins (bradykinin), cytokines (tumor necrosis factor- α [TNF- α], interleukin

[IL]-3, IL-4, IL-5, IL-6, IL-8, IL-9, IL-10, IL-13, platelet activation factor [PAF], and GM-CSF), and chemokines (RANTES, MIP1 α , etc.), seem to play a pivotal role in the development of persistent symptoms in the human airway mucosa (1–3). It has been suggested that in addition to parasympathetic nerves participating in bronchoconstrictor and secretory responses sensory nerves are also involved in the development of allergic inflammation. The presence of sensory fibers containing neuropeptides, such as substance P (SP), neurokinin A (NKA), calcitonin gene-related peptide (CGRP), and vasoactive intestinal peptide (VIP), in the human nasal mucosa formed the anatomic and physiologic basis of the involvement of the nonadrenergic noncholinergic (NANC) system in the nasal response (4). Animal studies demonstrated that neuropeptides released from sensory nerves have a great biologic potential and may have a role in inflammatory mechanisms in the airway mucosa (5–7). It is possible that sensory nerves and the NANC mechanism are also engaged in the allergic reaction; however, the evidence is so far circumstantial. Previous studies showed that allergen challenge releases SP, CGRP, and VIP into nasal lavages in allergic rhinitis patients (8). The administration of exogenous tachykinins (SP and NKA) in allergic rhinitis patients was reported to provoke nasal airway congestion, microvascular leakage (increase in albumin content in nasal washes), and recruitment of inflammatory cells (neutrophils and, in some cases, eosinophils) (9, 10).

New information on the role of neurogenic mechanisms in allergic processes in the nasal mucosa was obtained when nasal challenges with capsaicin were performed. Capsaicin is a specific neurotoxin capable of activating sensory nerve endings. In rodent airways, capsaicin releases neuropeptides and evokes neurogenic inflammation (i.e., vasodilation and plasma extravasation) (11, 12). However, most studies in the human nasal mucosa have demonstrated that capsaicin provokes mainly a secretory response without increasing vascular permeability (13, 14). There is also no direct evidence of the release of neuropeptides (SP, CGRP, and VIP) by capsaicin in the human nose (15). The capsaicin nasal challenge procedure remains an interesting method to determine neural nasal airway reactivity and may be useful for studying the role of neural mechanisms in the nasal mucosa. Since allergic inflammation developing in the nasal mucosa during the pollen season may change mucosal reactivity to several stimuli (e.g., histamine, methacholine [16, 17]), we aimed to determine whether nasal reactivity to neurogenic sensory stimulation is affected by allergic inflammation. Therefore, a group of patients with seasonal allergic rhinitis was challenged intranasally with capsaicin

Table 1. Proteins in basal nasal washes during and after pollen season ($n=13$; mean $\pm$ SEM)

Substance in basal lavage	Season	After season	P-value
Total protein (TP) ($\mu\text{g/ml}$)	45.4 ± 22.5	48.6 ± 15.8	NS
Albumin (Alb) ($\mu\text{g/ml}$)	15.3 ± 26.9	13.7 ± 26.8	NS
Lactoferrin (LF) ($\mu\text{g/ml}$)	20 ± 7.5	13 ± 5.7	* <0.05
NS: not significant.			

during the pollen season and ongoing allergic inflammation. The challenges were repeated outside the season when no inflammation was present in the nasal mucosa and symptom scores, and cytologic and biochemical parameters were assessed on both occasions.

Material and methods

Patients and study design

Thirteen atopic subjects (six men/seven women) suffering from seasonal allergic rhinitis were included in the study. They all had at least a 2-year past history of sneezing, secretion, and nasal obstruction during natural exposure to grass-pollen allergens and positive skin prick tests (SPT) to relevant seasonal allergens. During the seasonal part of the study (May–June), the patients had nasal symptoms, and were allowed to use a nasal decongestant (oxymethazoline hydrochloride) and/or clemastine, which were stopped at least 3 days before the challenge day. The patients had received no anti-inflammatory treatment for at least 1 month before the capsaicin challenge, and no patient had received specific immunotherapy before the season. The patients were studied again outside the season (October–December), and the capsaicin provocation procedure was repeated.

Symptom scores, nasal airway resistance (NAR), and cytologic and biochemical changes in unilateral nasal lavage fluids were evaluated before and after nasal provocations with capsaicin.

Protocol of capsaicin provocation

Capsaicin (Sigma Co, USA) was diluted in ethanol and saline and delivered intranasally with a spray pump (120 μl per

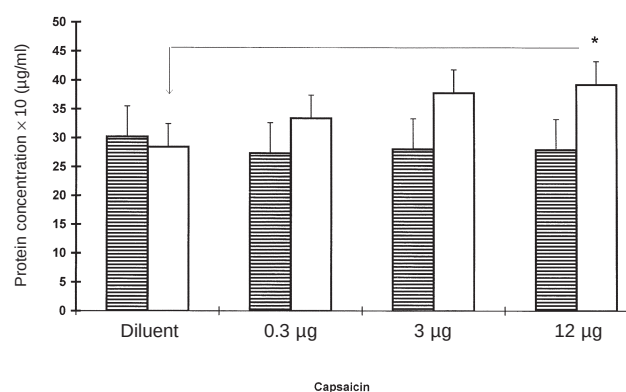


Figure 2. Total protein concentration in nasal washes after capsaicin challenge. Hatched bars: during season; open bars: after season. * $P<0.03$.

actuation). Diluent and three incremental doses of capsaicin (0.3, 3, and 12 μg) were sprayed into one nostril at 15-min intervals. Ipsilateral nasal washes were obtained before the provocations, after diluent instillation, and then 10 min after each dose of capsaicin.

Clinical symptoms and nasal resistance

Clinical symptoms during capsaicin challenges were recorded on a scale grading the responses as follows: none=0, mild=1, moderate=2, and severe=3 for symptoms such as burning sensation, nasal congestion, secretion, sneezing, and lacrimation.

Nasal airway resistance (NAR) was measured before and then 5 min after each capsaicin application by anterior rhinomanometry (Rhinomanometer Chest M.I. Inc., Japan).

Nasal lavages

Unilateral nasal lavages were performed by the “nasal pool” method of Greiff et al. (18). Patients were seated in a forward-flexed neck position (60° from the upright position), and a specially prepared syringe (with soft nozzle adapter) containing normal saline (5 ml) was inserted into the right nasal opening. The fluid was introduced into the nasal cavity and maintained for 5 min. Washing procedure was ended by aspiration of the instillate, and the lavage was collected. In 156 specimens that were analyzed, an average of 2.75 ml of lavage fluid was recovered (55% recovery).

The sample was centrifuged and the supernatant was immediately frozen at -20°C for biochemical analysis. The cell pellet was resuspended and the leukocytes were counted. Cytospin preparations were made, stained with May-Grünwald-Giemsa or Chromotrope b, and inspected by light microscopy.

Table 2. Cells in basal nasal washes during and after pollen season ($n=13$; mean $\pm$ SEM)

Cells in basal lavages	During season	After season	<i>P</i> value
No. of leukocytes ($10^3/\text{ml}$)	2.5 ± 2.7	3.7 ± 3.5	NS
Percentage of neutrophils	19 ± 6.5	32 ± 7.6	NS
Percentage of epithelial cells	62 ± 9.6	65 ± 8.6	NS
Percentage of eosinophils	11.3 ± 13.8	0.1	* <0.03

NS: not significant.

Biochemical analysis of nasal washes

Total protein in each sample was measured by Lowry et al.'s method (19). Albumin in the lavage samples was assayed by noncompetitive ELISA with anti-human serum albumin (HSA; Cappel, USA) and peroxidase-conjugated anti-HSA (Cappel, USA), as described by Kaulbach et al. (20). Lactoferrin (LF) levels were measured by noncompetitive ELISA by the standard procedure with rabbit antibody to human lactoferrin (Dako, Denmark) and rabbit anti-human lactoferrin conjugated to horseradish peroxidase (Cappel, USA) (21).

Statistical analysis

Analysis of variance was used to detect statistically significant differences between the repeated observations. A further analysis was made by Student's *t*-test (two-tailed) and the chi-square test. $P < 0.05$ was considered statistically significant.

Results

Symptoms

On the day of the seasonal challenge, all patients were symptomatic. On the day of the postseasonal challenge, despite the fact that the second study was performed after the pollen season, two patients reported weak nasal congestion and rhinorrhea and one patient reported nasal congestion in the morning. Prechallenge mean symptom scores for rhinorrhea, congestion, and lacrimation during the season were significantly higher than after the season ($P < 0.001$, $P < 0.001$, and $P < 0.05$ for rhinorrhea, congestion, and lacrimation, respectively; data not shown). Reported prechallenge symptoms, were mostly nasal congestion and rhinorrhea. The diluent did not increase prechallenge

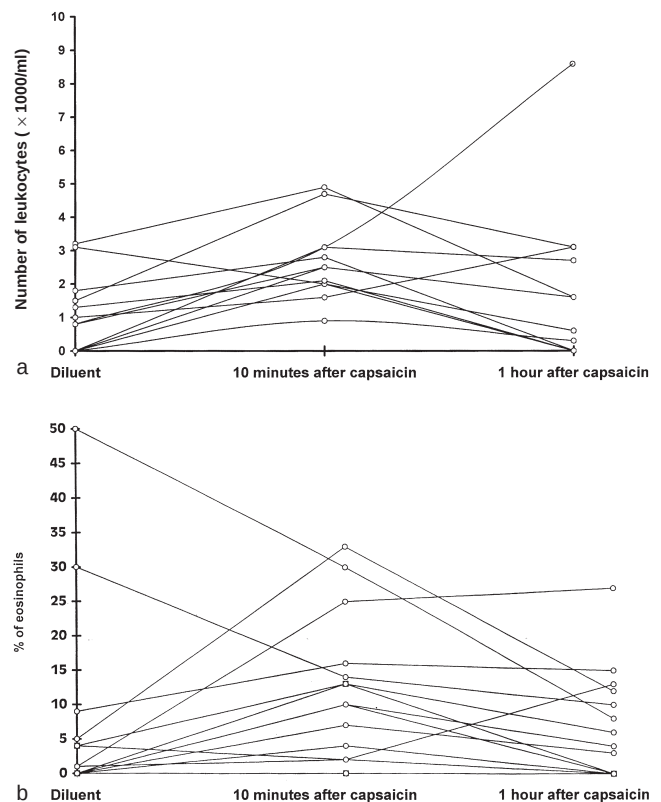


Figure 3. Effect of capsaicin challenge on cell number in individual washes during pollen season. a) Total number of leukocytes in individual nasal washes ($n=12$); b) number of eosinophils ($n=13$).

symptoms during either the first or the second part of the study. Capsaicin provoked significant increases in nasal congestion and rhinorrhea ($P < 0.05$), as compared to diluent, only during the season, but not afterward (Fig. 1A and B). Mean symptom scores for congestion and rhinorrhea after capsaicin were significantly higher during the season than afterward ($P < 0.05$). Capsaicin (at the maximal dose) increased the mean score for lacrimation only after the season ($P < 0.01$). Intranasal challenges with capsaicin both during and after the season induced a burning sensation in all patients in a dose-dependent fashion, but the intensity of the burning sensation was similar on both occasions (Fig. 1C). Additionally, dyspnea (in one patient), cough (in two patient), and headache (in one patient) were recorded after capsaicin challenge performed during the pollen season. NAR was not influenced by capsaicin challenge either during or after the season (data not shown).

Biochemical findings

Total protein and albumin concentrations in basal nasal washes (before capsaicin challenge) were not significantly different during and after the pollen season. However, the

mean concentration of lactoferrin was significantly higher during the season (Table 1). Capsaicin challenge increased the total protein concentration by at least 25% as compared to placebo during the season in eight patients and afterward in 10 patients. The increase was significant ($P < 0.05$) only when the patients were challenged with the highest dose of capsaicin after the season; however, the mean increase of total protein in nasal washes after the season was not significantly different from during the season (Fig. 2).

The mean lactoferrin concentration increased during the first seasonal challenge only by 15%, but during the second, postseasonal challenge, it increased by 34%. Mean maximal change in lactoferrin concentration was 25% during the season and 38% afterward. However, none of these differences were statistically significant (data not shown).

Albumin levels in nasal washes were not influenced by capsaicin challenge either during or after the season (data not shown).

Cellular findings

Eosinophils were present in basal nasal washes of all but one patient during the season and in only one patient after the season; the mean number of eosinophils was significantly higher during the pollen season (Table 2). Neither the total number of cells nor the percentage of neutrophils or epithelial cells in basal nasal washes was different during and after the season.

Ten minutes after capsaicin challenge performed during the season, the number of leukocytes and percentage of eosinophils showed a tendency to increase, but the mean increase was not significant. The number of leukocytes and eosinophils in nasal washes obtained 1 h after capsaicin provocation showed a tendency to decrease below prechallenge values (Fig. 3A and B). Analysis of data from individual patients demonstrated that the number of total leukocytes in nasal washes obtained 10 min after seasonal capsaicin challenge increased significantly (i.e., at least double the postdiluent numbers) in seven patients; in four patients, it increased by at least 25%; and in one patient, it decreased (Fig. 3A). An increase in the percentage of eosinophils in the lavage fluid was detected in 6/13 patients (Fig. 3B). Capsaicin challenges performed after the pollen season did not induce an increase in the number of leukocytes in nasal washes in any of the 12 patients. Only in one patient were few eosinophils in a single wash detected after capsaicin challenge.

Discussion

Our study was performed during a relatively mild pollen season, as reflected by low symptom scores and also a lack of seasonal increase in total protein and albumin concentration in basal lavages. On the other hand, elevated basal levels of lactoferrin, as well as the presence of eosinophils in nasal washes, suggested the presence of allergic inflammation at some stable level.

Capsaicin challenge both during and after the pollen season evoked typical, clinical symptoms such as burning sensation, congestion, and rhinorrhea, and in a few patients also sneezing and lacrimation (22, 23). The mean symptom scores for rhinorrhea and congestion after capsaicin challenge were higher during than after the season, a fact which may reflect an enhanced response of either cholinergic or sensory nerve fibers. On the other hand, we did not observe significantly higher scores for burning sensation during the season. Since burning sensation (or pain) results exclusively from activation of sensory nerve fibers, our data suggest that these fibers were not hyperresponsive to stimulation during the season. Our observation contrasts with the study of Greiff et al., who observed an increased pain response to capsaicin during the season, suggesting sensory nerve hyperresponsiveness associated with allergic inflammation (24). Our findings instead suggest the upregulation of cholinergic pathways during the pollen season, as reflected by augmented rhinorrhea, congestion, and lacrimation in response to capsaicin. The discrepancies may reflect different challenge methods used: in our study, capsaicin was applied as a spray, and Greiff et al. delivered capsaicin by the nasal pool technique. It is possible that, depending on the method used, a different effective concentration of capsaicin may reach specific receptors in the mucosa, thus resulting in differential sensory or secretory response during the pollen season.

We did not observe an increase in total protein or lactoferrin concentration after capsaicin challenge, although the doses were comparable to other studies reporting release of these proteins. On the contrary, there was a tendency to decreased secretory protein response during the season. Such a discrepancy between clinical (symptoms) and biochemical (protein in nasal washes) responses is difficult to explain. However, a similar discrepancy was previously reported after nasal challenge with metabisulfate (MBS), which, like capsaicin, seems to act by sensory nerve stimulation (25). Albumin content in nasal washes was unchanged after capsaicin both during and after the season, a fact which is consistent with previous observations that capsaicin does

not increase vascular permeability in the nasal mucosa (14, 15, 24). It has been recently reported that capsaicin induces release of albumin into the nasal washes in patients with perennial rhinitis (26). However, even in this study, albumin expressed as a fraction of total protein apparently did not increase, a fact which argues against its vascular origin (15, 21).

Previous studies demonstrated that capsaicin challenges were followed by influx of inflammatory cells (mainly neutrophils but also eosinophils) in both normal and allergic patients (27, 28). Similarly, in most of our patients challenged with capsaicin during the season, a significant increase in the number of leukocytes in nasal lavages was observed. As opposed to Philip et al. (28), who could not find any selectivity in cell-type increase after capsaicin challenge, we observed a significant enrichment in eosinophil recovery from the nasal washes. However, an increase in the total number of leukocytes and eosinophils after capsaicin in our study cannot be unequivocally interpreted as recruitment of cells from the vascular compartments, since we did not observe an increase in albumin concentration in nasal washes, and this excluded the presence of increased vascular permeability in the nasal mucosa. The observation that eosinophils are recruited into the nasal washes after capsaicin during the season may reflect the fact that during this period eosinophils are present in the epithelial layer of the mucosa. Thus, the increased number of total leukocytes and eosinophils after seasonal capsaicin challenge may be due to one of the following:

- 1) direct action of capsaicin on migration of leukocytes (29)
- 2) epithelial cell desquamation provoked by capsaicin during allergic inflammation (27)
- 3) exudative hyperresponsiveness of the superficial microcirculation observed during the pollen season (30).

All the above mechanisms are capable of promoting transient influx of leukocytes present in the superficial layer of the mucosa. Capsaicin can release neuropeptides, which in turn may stimulate leukocyte activity (31–33). We can speculate that after capsaicin challenge eosinophils may

appear in nasal lavages as a result of exudative absorption of these cells without increased vascular permeability. Decrease in the total number of leukocytes and eosinophils observed 1 h after seasonal capsaicin challenges is consistent with the data of Philip et al., who reported the interesting phenomenon of the biphasic cellular response after capsaicin (28). In that study, increased leukocyte counts in nasal washes were present at 10 and 30 min, but not at 60 min, after capsaicin challenge, and the second, late influx of leukocytes was observed at 4 h. Interestingly, these authors demonstrated similar cellular influx in asymptomatic, allergic, and nonallergic patient populations.

Seasonal allergic rhinitis is characterized by a variability of nasal reactivity and different character of nasal responses to stimuli during and after the pollen season (34). Few studies were performed to evaluate the possible role of neurogenic mechanisms in human airways during allergic inflammation (22, 24–28). Most of the studies compared nasal reactivity in asymptomatic allergic rhinitis patients and in normals; only one study was performed under natural allergen exposure during and after the season (24). Although previous studies demonstrated enhanced sensory response to capsaicin, our study is the first to report cellular response of nasal mucosa to capsaicin application during the symptomatic pollen season.

In conclusion, we have demonstrated that intranasal challenge with capsaicin performed during ongoing allergic inflammation induces more intense symptoms including nasal congestion and rhinorrhea (but not burning sensation) than challenge performed in the same patient outside the season in the absence of inflammation in the mucosa. Moreover, seasonal challenge was accompanied by influx of leukocytes including eosinophils into the nasal lavage fluid.

Our data indicate that the presence of allergic inflammation changes the responsiveness of human nasal mucosa to neurogenic stimulation.

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