

Intranasal capsaicin is lacking therapeutic effect in perennial allergic rhinitis to house dust mite. A placebo-controlled study

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Summary

Background In a recent placebo-controlled study we demonstrated that capsaicin is an efficacious substance in the treatment of non-allergic non-infectious rhinitis. In this study the therapeutic effect lasted more than 9 months. This effect was not based on modulation of inflammation.

Objective To evaluate the effect of repeated application of capsaicin to patients with a nasal allergy to house dust mites (HDM), using the same treatment protocol as recently introduced in the treatment of non-allergic patients.

Methods Twenty-six patients with rhinitis, 15 females and 11 males (range: 20–46 years; mean 30.5), allergic to HDM were treated with either capsaicin or placebo in a double-blind, placebo-controlled, parallel group design. Nasal reactivity to HDM expressed as nasal symptoms, albumin and leukotriene levels in nasal lavage fluid and responsiveness to histamine, assessed as symptoms before and 6 weeks after treatment, were used to compare both treatment groups. In addition, visual analogue scales and rhinitis quality of life (RQL) assessment before, 6 weeks after and 3 months after treatment were used as outcome variables.

Results No significant effect of capsaicin on nasal challenge tests with HDM (nasal symptoms, albumin and leukotriene levels), on VAS or RQL outcome 6 weeks or 3 month's after treatment, was demonstrated. Capsaicin did have a small effect on the area of the curve (AUC) of histamine dose response curves ($P = 0.03$).

Conclusion Desensitization with capsaicin in doses sufficient to control symptoms in patients with severe non-allergic rhinitis is lacking therapeutic effect in perennial allergic rhinitis.

Keywords: allergic rhinitis, nasal provocation, capsaicin, house dust mites

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Introduction

In animals, capsaicin peptide stimulates sensory C-fibres with the resultant release of substance P (SP) and calcitonin gene related peptide (CGRP). After several stimulations, this is followed by depletion of these fibres and this results

in nerve destruction, desensitization to capsaicin and other stimuli [1,2]. In man, nasal insufflation with capsaicin leads to plasma extravasation due to airway sensory nerve activation [3]. This sensory nerve activation goes with a cellular influx at 4 h after challenge [4]. The observation that capsaicin may desensitize C-fibres has been used in the treatment of non-allergic rhinitis [5–7]. It was shown in open studies that repeated stimulation of the nasal mucosa with capsaicin leads to improvement of nasal

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symptomatology. In a recent placebo-controlled study, it was demonstrated that capsaicin is an efficacious substance in the treatment of non-allergic non-infectious rhinitis [8]. In this study the therapeutic effect lasted more than 9 months. This effect was not based on modulation of inflammation [9].

The aim of the present study was to evaluate the effect of repeated application of capsaicin to patients with a nasal allergy to house dust mites (HDM), using the same treatment protocol as recently introduced in the treatment of non-allergic patients. It was hypothesized that the use of a treatment protocol with capsaicin, validated in the treatment of non-allergic rhinitis, would provide information about the role of the peptidergic innervation in allergic rhinitis. To explore the effect of capsaicin, clinical scores (i.e., visual analogue scores and quality of life questionnaires), and nasal responsiveness to house dust mite and histamine, were used as outcome variables.

Materials and methods

Subjects

Twenty-six rhinitis patients, 15 women and 11 men, aged 20–46 years (mean 30.5 years) participated in this study. They fulfilled the following criteria: a history of perennial rhinitis; intradermal skin reaction of at least 1 plus-sign to 3 BU/mL HDM extract (ALK Benelux, Groningen, the Netherlands), according to the standardized plus-sign scoring system defined by Norman [10]. Patients with concomitant allergy to pets were only included when they had no contact with pets. In case of a concomitant seasonal allergic rhinitis, patients were tested outside the season.

To prevent interference with capsaicin treatment, symptomatic medication for rhinitis had to be withdrawn. Oral corticosteroids were withdrawn 2 months, astemizole 6 weeks, nasal or inhaled corticosteroids, cromoglycate and nedocromil 3 weeks and antihistamines 3 days before entering the study. Patients with nasal polyposis, nasal surgery less than 3 months before the study and nasal infection during the 2 weeks before the study were excluded.

Study design

Twenty-six patients with perennial rhinitis were randomized into a placebo and capsaicin treatment group. The study was designed as a double-blind, placebo-controlled parallel study. Immediately before treatment, baseline VAS (visual analogue scale) scores and rhinitis quality of life scores (RQL) were obtained from the patients. In addition, a nasal challenge with house dust mite and 24 h later, a nasal challenge with histamine, was performed. After the

last provocation, with an interval of a few days, capsaicin or placebo was applied into each nostril as previously described [8].

Six weeks after treatment with capsaicin or placebo, VAS and RQL scores were obtained and a second nasal challenge with house dust mite extract and histamine was performed. Three months after treatment, patients were asked to fill in questionnaires. On that occasion, nasal challenges were not carried out.

The study was performed during the period January–August to minimize natural exposure to HDM. The study was approved by the Medical Ethical Committee of the University Hospital Rotterdam-Dijkzigt, and all patients gave written informed consent.

Capsaicin or placebo treatment

Three applications of xylometazolinehydrochloride 0.1% (Otrivin R 1 mg/mL; Zyma, Breda, Holland; nebulizator) were given for decongestion in each nostril. The nasal airway was anaesthetized by three applications (10 mg/puff) of lidocainebase (100 mg/mL; Xylocaine R 10% spray; Astra, Rijswijk, Holland) in each nostril. To ensure good anaesthesia, a pause of 15 min was introduced. Lips, columella and philtrum were covered with a petrolatum/lanolin/glycerin salve. Patients were instructed to inhale deeply before, hold their breath during, and exhale after substance application. The capsaicin solution (0.1 mmol/L) consisted of pelargonic acid vanillylamide (Fluka, Buchs, Germany) dissolved in 3 mL alcohol (96%) and diluted in 1 L NaCl solution (0.9%) [Wolf, personal communication]. For 'placebo therapy' the dissolvent of capsaicin was used. During provocation, 0.5 mL solution was sprayed into each nostril (0.15 mg capsaicin). In 14 days, seven applications of capsaicin or placebo were given at 2-day intervals.

Rhinitis quality of life questionnaire

The rhinitis QOL questionnaire developed by Juniper *et al.* [11] was used. Patients had to score 25 items subdivided into the following domains: sleep ($n = 3$), nasal symptoms ($n = 5$), practical problems ($n = 3$), emotions ($n = 4$), activities ($n = 3$) and non-rhinitis symptoms ($n = 7$). They were asked how much they were troubled in each item as a result of their nasal symptoms during the previous week. The score of these items ranged from 0 (not troubled) to 6 (extremely troubled). With respect to the items concerning emotions, patients were asked how often they were troubled in each of the items as a result of their nasal symptoms. The score also ranged from 0 (never troubled) to 6 (constantly troubled). In the analysis, the mean score of the items in each domain was used. In addition, the average of the mean scores of the six domains was used to calculate the overall

QOL score. The subjects scored their quality of life over a 2-week period.

Visual analogue scale

The subjects rated overall nasal symptoms over a 2-week period on a visual analogue scale (VAS) (0–10 cm, 0 representing absence of symptoms and 10 representing a high intensity of symptoms) [8].

Nasal challenge with HDM and histamine

Challenges were performed in accordance with methods previously described [12]. On each occasion the patients waited for 30 min before the test to give the nasal mucosa time to acclimatize.

Nasal challenges with HDM extract (100 BU/mL, 1000 BU/mL, 10 000 BU/mL; ALK Benelux, Groningen, the Netherlands) were performed at 10 min intervals after challenge with phosphate-buffered saline (PBS) containing human serum albumin 0.03% and benzalkonium chloride 0.05% (ALK Benelux, Groningen, the Netherlands). The HDM extract was sprayed into each nostril by means of a nasal pump spray delivering a fixed dose of 0.125 mL solution. Nasal response was monitored 10 min after each challenge. Nasal responsiveness was monitored by a symptom score according to Lebel [13]. The AUC was calculated as the sum of the three scores.

Nasal challenge with histamine phosphate (0.25, 0.50, 1.0, 2.0 and 4.0 mg/mL) was performed at 5 min intervals after challenge with PBS. The symptom score according to Lebel [13] was used as nasal response indicator. The AUC was calculated as the sum of the five scores.

Symptom score

Symptoms were recorded using a scoring system according to Lebel *et al.* [13]. Symptom scores were graded in points (pt): three to four sneezes = 1 pt; five or more sneezes = 3 pt; anterior rhinorrhoea = 1 pt; posterior rhinorrhoea = 1 pt; difficult nasal breathing = 1 pt; one nostril blocked = 2 pt; both nostrils blocked = 3 pt; pruritus of the nose = 1 pt; pruritus of palate or ear = 1 pt; and conjunctivitis = 1 pt (total score ranges from 0 to 11 pt).

Nasal lavage

Nasal lavages were performed as previously described [12]. This protocol comprises four pre-challenge washings with isotonic saline solution to clear the nose from secretions and to obtain baseline levels of mediators. In order to prevent nasal congestion due to allergen challenge, oxymetazoline 0.1% (two 0.125 mL puffs) was applied in both

nostrils. After 5 min the oxymetazoline was washed out just prior to the nasal challenge with PBS. A nasal lavage was performed 10 min after PBS and after each allergen challenge, immediately before the following challenge. Subsequently, lavage fluid was obtained hourly from 0.5 to 9.5 h after the last allergen challenge. Nasal lavages were performed with 10 mL isotonic saline solution (0.9%) pre-heated to 37 °C. In each nostril, 5 mL saline was instilled with a pipette while the subject gently flexed his/her head backwards. After 10 s, the lavage fluid was expelled and collected in plastic tubes. This procedure has been shown to produce a recovery of 7.7 ± 1.2 mL.

Mediator assays

Lavage fluid was stored on ice and centrifuged for 5 min at 400 g. The supernatant fluid was stored at -20 °C. Albumin was determined by automatic kinetic nephelometry using the Array analyser (Beckmann, Mijdrecht, the Netherlands) according to the manufacturer's instructions (sensitivity 2 mg/L).

The level of LTC₄/D₄/E₄ was measured by Biotrak® (Amersham, UK). The limit of sensitivity was 3.1 pg/100 µg.

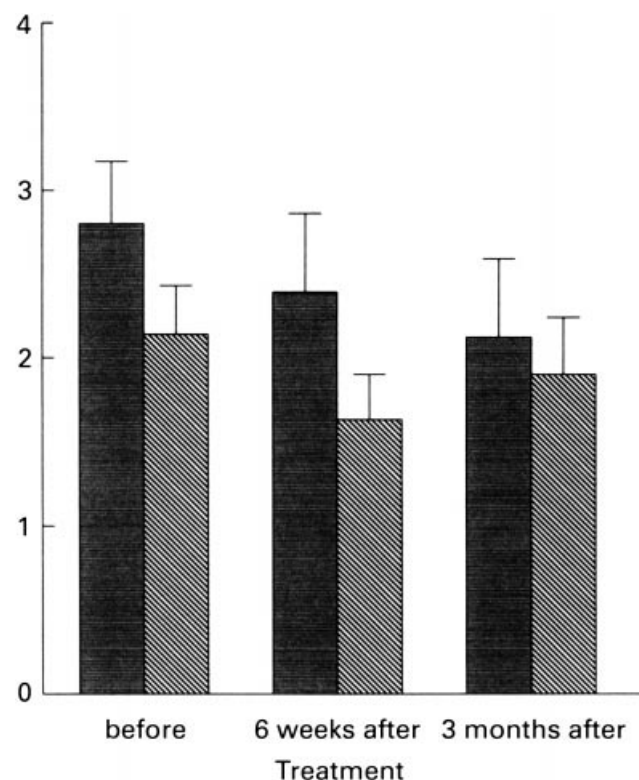


Fig. 1. Mean (SEM) rhinitis quality of life scores. (□), Capsaicin; (▨), placebo.

Cross-reactivity (50% B/B₀) was LTC₄ (100%), LTD₄ (100%), LTE₄ (70%) and LTB₄ (0.4%).

Statistical analysis

Between-group differences were tested with the Mann-Whitney *U*-test, or the *T*-test whenever appropriate. Treatment effects were tested with analysis of covariance (ANCOVA) using the baseline measurement of the outcome variable as covariate. A *P*-value < 0.05 (two-sided) was considered significant.

ANCOVA was also performed on the AUC of the albumin and leukotriene levels. The AUC was calculated as the sum of the three albumin (or leukotriene) levels after log-transformation, as the distribution of albumin and leukotriene levels in nasal lavage fluid was skewed to the right. In the text, levels of albumin and leukotrienes are summarized by median values.

Results

Thirteen patients were treated with capsaicin, 13 with placebo. One patient treated with capsaicin was lost to follow-up because of a long-lasting stay abroad. One patient in the capsaicin group could not complete the

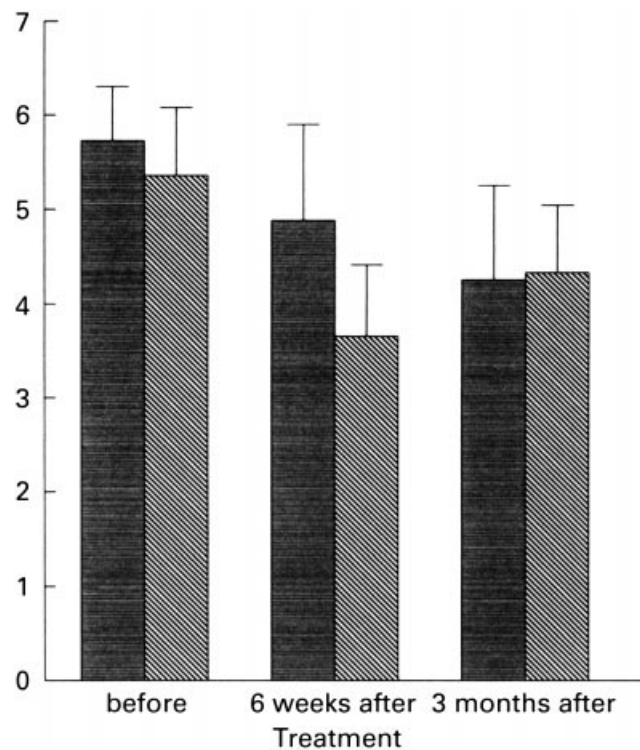


Fig. 2. Visual analogue scores (SEM). (■), Capsaicin; (▨), placebo.

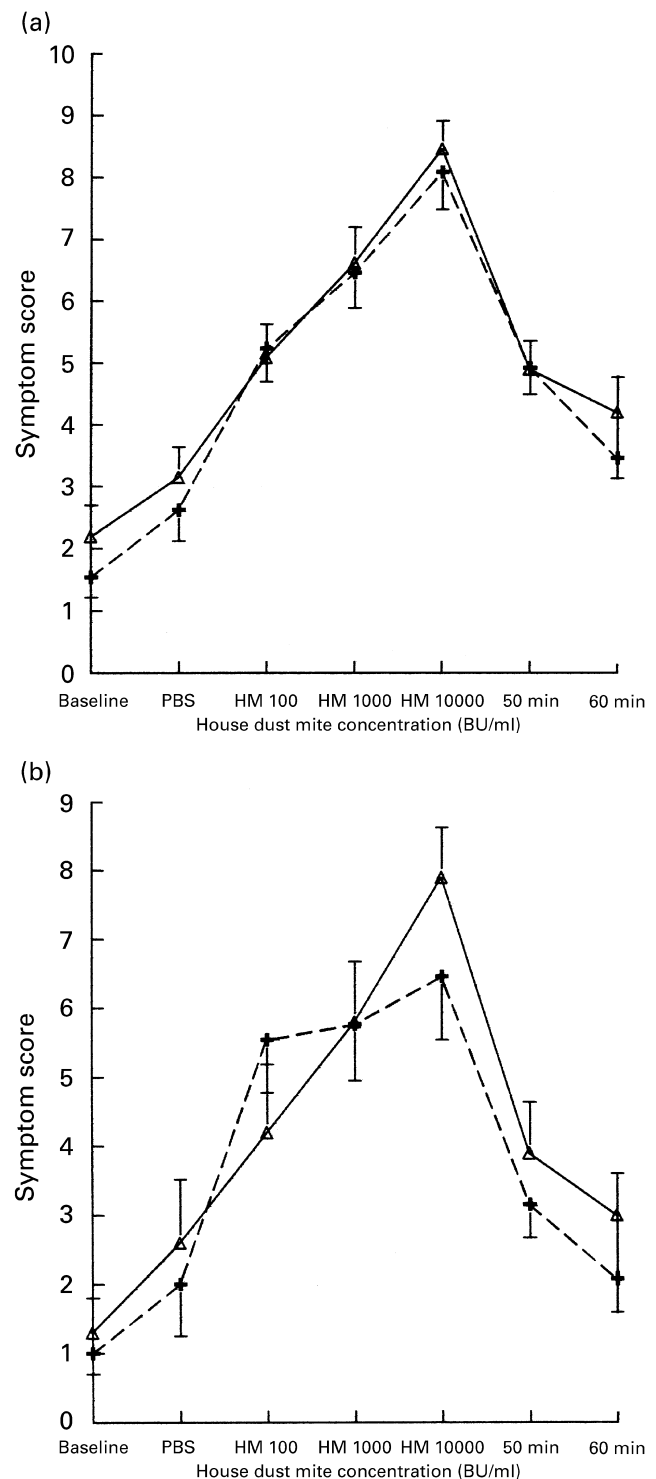


Fig. 3. Nasal challenge with house dust mite. Dose response curves (a) before and (b) after treatment with capsaicin (Δ) or placebo (+).

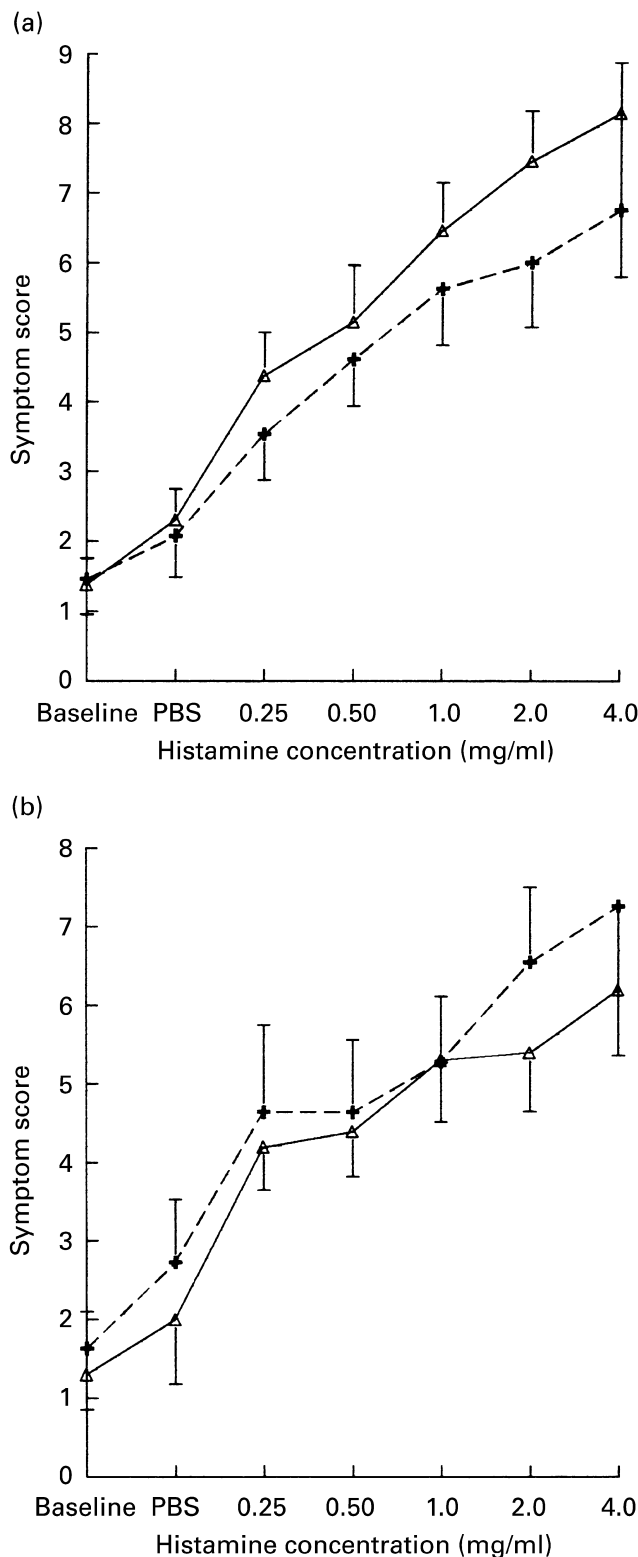


Fig. 4. Nasal challenge with histamine. Dose response curves (a) before and (b) after treatment with capsaicin (Δ) or placebo (+).

second series of nasal challenges because of a concomitant infection, and one other because of an exacerbation of rhinoconjunctivitis. One patient in the placebo group experienced a nasal infection during the second challenge. Another patient in the placebo group was not able to undergo the second histamine challenge because of major complaints due to the previous house dust mite challenge. All patients except the subject staying abroad were able to record VAS and RQL scores.

With ANCOVA using the baseline measurement of the outcome variable as covariate, a significant treatment effect on mean RQOL scores could not be detected at 6 weeks or 3 months (Fig. 1), on VAS scores at 6 weeks or 3 months (Fig. 2), or on AUC-HDM at 6 weeks after treatment (Fig. 3). In contrast, a significant effect of capsaicin on the AUC for histamine at 6 weeks (Fig. 4) was demonstrated using the outcome of the first histamine challenge as covariate ($P = 0.03$).

Albumin in nasal lavage increased from 3.4 $\mu\text{g/mL}$ at baseline to 17.1 at 10 000 BU/mL HDM challenge in the placebo group, and from 5.3 $\mu\text{g/mL}$ at baseline to 23.6 at 10 000 BU/mL HDM challenge in the capsaicin group before treatment. After treatment, albumin levels increased from 2.4 $\mu\text{g/mL}$ at baseline to 5.9 at 10 000 BU/mL HDM challenge in the placebo group, and from 5.9 $\mu\text{g/mL}$ at baseline to 18.1 at 10 000 BU/mL HDM challenge in the capsaicin group. With ANCOVA, after log-transformation, no significant treatment effect of capsaicin on the area of the curve could be demonstrated ($P = 0.169$). Leukotrienes in nasal lavage increased from 83.1 pg/mL at baseline to 453.8 at 10 000 BU/mL HDM challenge in the placebo group, and from 85.3 pg/mL at baseline to 110.6 at 10 000 BU/mL HDM challenge in the capsaicin group, before treatment. After treatment, leukotriene levels increased from 144.7 pg/mL at baseline to 194.3 at 10 000 BU/mL HDM challenge in the placebo group, whereas levels did not increase in the capsaicin group (baseline: 92.7; 10 000 BU/mL: 66.6). Again, no significant treatment effect of capsaicin on the AUC was found ($P = 0.705$).

Discussion

Several investigators have shown that capsaicin is effective in the treatment of patients with non-allergic rhinitis [5–7]. Recently, it was demonstrated that capsaicin applied in an identical treatment protocol has a long-lasting therapeutic effect of at least 9 months [8,9]. From the study performed with non-allergic patients, it was concluded that the treatment protocol with capsaicin provided a validated tool to test the effects of capsaicin and thereby, the role of peptidergic nerves, in allergic rhinitis.

To explore this issue further, it was decided to use

patients and a set of outcome parameters which proved to be reliable in the evaluation of the effect of nasal corticosteroids. Patients allergic to house dust mites were selected according to previously described criteria. Nasal challenge tests with house dust mite extract and histamine were performed according to previously described methods [12].

Although levels of albumin and leukotrienes were lower than seen in earlier studies [12,14], the magnitude of the nasal response after HDM and histamine challenge, assessed in terms of nasal symptoms, was comparable with the reactions observed in an earlier study [12].

The effect of capsaicin on HDM challenge was not significant, and the effect on histamine challenge was statistically significant but small. This is in contrast to earlier findings with corticosteroids using the same outcome parameters. Nasal corticosteroids decreased the early nasal reaction to HDM by 76%, whereas the response to histamine was lowered by 34% [12]. The lack of therapeutic efficacy of capsaicin was also demonstrated by the absence of effect on visual analogue scores and RQL parameters.

The present findings contrast with the results of Stjärne *et al.* [15]. They showed, in an open non-randomized trial, that capsaicin decreased nasal responsiveness to allergen in five birch pollen allergic patients compared with placebo treatment in four patients. The protocol they used involved application of capsaicin-soaked cotton wool into the nose during two 15 min sessions. It is reasonable to suppose that this application induced a much stronger desensitization than the protocol we used. This assumption is in line with the observation of Stjärne, that it was impossible to anaesthetize the nasal mucosa of patients very well. All patients experienced considerable pain whereas in the present study, patients could not testify whether they had received capsaicin or placebo. The blindness for patients achieved in this study was the same as seen in the first study [8].

Stjärne showed that capsaicin does not affect nasal inflammation in allergic rhinitis [15]. Combining the present results with those of Stjärne's, it might be speculated that nasal symptoms and the response to HDM are mainly dominated by inflammatory events and thereby, not modified by interference at the level of C-fibres. It might be that modulations of C-fibres by capsaicin has a small effect on histamine responsiveness, indicating that histamine responsiveness is a sensitive marker for monitoring alterations in the peptidergic nerve system. The effect of capsaicin on histamine responsiveness corresponds with the study of Sanico *et al.* showing that capsaicin desensitization attenuates reflex nasal secretion after hyperosmolar saline challenge [16]. In this study, however, larger amounts of capsaicin were used. More extensive desensitization and

defunctionalization of nerve fibres may eventually modify the outcome of the allergic reaction, as demonstrated by Stjärne *et al.* [15].

Interestingly, capsaicin used in concentrations which do not modify nasal allergy had a marked clinical effect on non-allergic rhinitis [8]. Although baseline VAS scores in the patients with allergic and non-allergic rhinitis were of comparable magnitude, it is quite hazardous to compare diseases with different pathophysiological backgrounds. The non-allergic patients were highly selected, characterized by severe nasal disease [8] and the absence of inflammation [9]. It can be speculated that allergic rhinitis was not affected by capsaicin by domination of nasal inflammation, whereas the efficacy of capsaicin in non-allergic rhinitis may be due to domination of the peptidergic system in the absence of nasal inflammation.

In conclusion, desensitization with capsaicin using doses sufficient to control nasal symptoms in patients with severe, non-allergic rhinitis is lacking therapeutic effect in perennial allergic rhinitis.

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