
Capsaicin cough sensitivity in allergic asthmatic patients increases during the birch pollen season

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Background: A change in neural responsiveness may occur as the result of allergic inflammation in the lower airways as well as in the upper airways. In the lower airways, capsaicin cough sensitivity is known to reflect sensory neural reactivity.

Objective: The aim of this study was to establish whether allergic inflammation changes airway neural sensory reactivity during prolonged allergen exposure.

Methods: Ten nonsmoking patients with birch pollen-allergic asthma performed a capsaicin inhalation challenge twice, once in the off-pollen season and once during the pollen season. The number of coughs and symptoms induced by capsaicin were recorded and compared with those of healthy control subjects.

Results: The response to capsaicin, expressed as number of coughs, increased in a dose-dependent manner during both tests. Before the season, the response was similar to that of healthy control subjects, but during the pollen season, the reactivity was significantly increased.

Variations in forced expiratory volume in 1 second were not significant before and after each challenge, and values did not change during the pollen season as compared with the winter season.

Conclusions: Sensory reactivity in allergic asthmatic patients may be increased during prolonged allergen exposure as during the pollen season. This finding suggests that allergic inflammation in the lower and/or upper airways may trigger neurogenic mechanisms of significant clinical importance.

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INTRODUCTION

Inflammation in allergic asthma is a frequently studied topic and is regarded as the key phenomenon behind lower airway hyperreactivity.^{1,2} Some studies indicate a change in neural responsiveness in connection with allergic inflammation, especially in the nose,^{3–8} but how and to what extent neurogenic inflammation plays a role in airway hyperreactivity in the lower airways has remained obscure.^{10,11} Capsaicin, the pungent ingredient in hot pepper, is known to stimulate the unmyelinated slow C-fibers of the sensory nervous system by means of the recently identified vanilloid receptor type 1 (VR1) receptors.⁹ In work published in 1999, it was shown that nasal reactivity to capsaicin and other chemical irritants changed in allergic patients during the pollen season.⁷ When inhaled, capsaicin provokes coughing. Capsaicin cough sensitivity has previously been used to estimate sensory neural reactivity of the lower airways.^{12–18} The capsaicin-induced cough is probably the result of activation of the C-fibers and/or rapidly adapting receptors of the A-fibers after release of neuropeptides from the VR1-receptors.¹⁹ Capsaicin is known to have little or no effect on the bronchial tone in humans, including those with asthma, in contrast to its known bronchoconstrictive effect in guinea pigs.^{12,13,20} However, capsaicin releases neuropeptides from sensory nerves, and inhaled neurokinin A has been shown to cause bronchocon-

striction in asthmatic patients, and therefore this relation remains obscure.^{21,22} Some studies have found a capsaicin-induced bronchodilation in humans, which may be one possible explanation.^{23–25}

Capsaicin cough sensitivity varies with sex and is influenced by respiratory infections.^{16,17} Some studies show a change in this sensitivity in chronic asthma and chronic obstructive pulmonary disease,¹⁸ whereas other studies do not report the same findings.¹⁵

One of the cardinal features of asthma is said to be bronchial hyperreactivity, which is defined as an abnormal fall in forced expiratory volume 1 second (FEV₁) after a standardized provocation with methacholine or histamine.^{1,2} Often, increased sensitivity to methacholine in asthmatic patients has been considered to reflect a general sensitivity to chemical agents, although this is poorly understood. It is a common clinical experience that patients with well defined asthma often complain that airway symptoms are triggered by exposure to perfumes or flowers with strong scents and chemical agents such as cigarette smoke and car exhaust fumes. However only a few articles report reactions to these stimuli.^{26,27} The symptoms triggered by chemical agents often seem to be independent of bronchial obstruction and usually do not improve with asthma therapy. In some allergic asthmatic patients, the clinical impression is that this kind of airway hyperreactivity is induced during ongoing allergic inflammation such as during the pollen season.

The same trigger factors may induce similar symptoms in nonasthmatic patients who have no immunoglobulin (Ig)E-

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mediated allergy, bronchial obstruction, or bronchial hypersensitivity to methacholine, but who have a sensory hyperactivity to chemical stimuli. A pathophysiologic cause related to overactive free sensory nerve endings in the respiratory mucosa is suggested, and a damaged epithelium may also contribute.^{28,29}

The present study was designed to investigate whether sensory (capsaicin) reactivity may be changed during prolonged allergen exposure in allergic asthmatic patients. Recordings during ongoing allergic inflammation as during the pollen season were compared with off-season values and with recordings in healthy control persons to gain an understanding of how allergic inflammation influences certain neurogenic expressions.

METHODS

Patients

Ten allergic, nonsmoking, asthmatic patients took part in this study. There were 4 women and 6 men aged 25 to 47 years (mean age 31 years). All patients had a history of rhinitis and asthmatic symptoms (dyspnea, wheezing, and coughing) during the birch pollen season, at least a 2+ reaction in the skin

prick test, and a radioallergosorbent test class 2 reaction to birch allergen. All had previously shown an increase of at least 15% in FEV₁ after inhalation of a β_2 -agonist, and this, in combination with asthmatic symptoms, was considered confirmation of the diagnosis of asthma. Six of the patients were sensitive to methacholine according to reactions to provocation tests within the past 3 years, and had a fall in FEV₁ of >20% after inhalation of 4 mg or less of methacholine.³⁰ Five patients used a stable dose of inhaled steroids all year round and five patients went without inhaled steroids. One of the patients using inhaled steroids also took oral steroids during the pollen season and two took nasal steroids during this period. All patients inhaled short-acting β_2 -agonists intermittently and two patients regularly used inhaled long-acting β_2 -agonists. Demographic data and ongoing medication are given in Table 1.

Patients were asked to take no medication for a minimum of 4 hours before any test. Long-acting bronchodilators were withheld for at least 48 hours. Patients allergic to furry animals were asked to avoid any close contact with animals. They had no ongoing asthmatic symptoms on the days of capsaicin provocation.

Table 1. Demographic data of patients with allergic asthma

Patient Number	Sex	Age	Predicted Baseline FEV ₁ %	PC20 mg/mL	Skin Prick Test Positive	ECP Winter μ g/L	ECP Pollen Season μ g/L	Regular Daily Medication	Intermittent Medication
1	f	29	91	1.5	Dogs, cats, horses, grass, birch, mugwort	13	20		β_2 -agonist, antihistamine, and nasal steroids, 400 μ g
2	m	25	87	1.2	Cats, grass, birch	18	34	Inhaled steroids, 800 μ g	β_2 -agonist intermittently
3	f	25	85	4.3	Birch	37	37	Inhaled steroids, 1600 μ g, and long-acting β_2 -agonist	β_2 -agonist
4	m	29	106	0.8	Dogs, cats, horses, grass, birch	28	83		β_2 -agonist
5	m	46	93		Birch	5	18	Inhaled steroids, 400 μ g, and long-acting β_2 -agonist	β_2 -agonist and antihistamine
6	m	26	111	>16	Dogs, cats, horses, grass, birch	19	23	Inhaled steroids, 800 μ g	β_2 -agonist, antihistamine, and oral steroids, 10 mg Prednisolone daily
7	f	37	80	1.7	Grass, birch, mugwort	16	27		β_2 -agonist, antihistamine, and nasal steroids
8	m	38	106	>16	Grass, birch	35	30	Inhaled steroids, 800 μ g	β_2 -agonist and antihistamine
9	m	26	89	0.3	Dogs, cats, grass, birch	4	10		β_2 -agonist
10	f	25	114	0.7	Cats, horses, grass, birch	12	9		β_2 -agonist and antihistamine

PC₂₀ fall in FEV₁ > 20%; ECP, eosinophilic cation protein; f, female; m, male.

Exclusion criteria included ongoing infection or any other illness during the preceding month, a chronic systemic disease, smoking, or pregnancy.

Control Group for Capsaicin Provocation

The control group consisted of 10 healthy, nonsmoking subjects, six women and four men, aged 24 to 48 years (mean age 36 years). None had a history of respiratory difficulties, asthma, or allergy, and none took medications regularly.

Capsaicin Inhalation Test

Capsaicin inhalation tests were performed on two occasions in the patient group. The first test was done in the off-pollen season (December to the beginning of March), and the second test was done in May, when birch pollen counts were high. The control subjects were challenged on one occasion. Saline, 1 mL, was nebulized (Pariboy 36, Paulritzau Pari-werk KG, Starnberg-am-See, Germany) and inhaled through a mouthpiece to completion during 6 minutes to induce coughing, followed by 4 minutes of rest. The number of coughs was counted for 10 minutes from the onset of provocation, and tape-recorded. Thereafter, provocations were carried out in the same way by using the following increments of capsaicin: 0.4, 2, and 10 μ M in a 1-mL solution. With more than 70 coughs in reaction to one dose of capsaicin, the test was terminated out of consideration for the patient. A spirometer (Vitalograph, Buckingham, UK) was used to measure FEV₁ before and after each provocation, and the best of three trials was recorded. After each provocation, symptoms were registered on a scale of 0 to 3 (0 = no symptoms; 1 = mild symptoms; 2 = moderate symptoms; and 3 = severe symptoms). Twelve main symptoms were identified: coughing, dyspnea, nasal irritation, irritation of the throat, hoarseness, chest pain/pressure, production of mucus, irritation of the eyes, dizziness, headache, fatigue, and sweating.

Laboratory Tests

Eosinophilic cation protein in serum (serum-ECP, μ g/L) was analyzed in each patient in connection to the provocations to get an indication of eosinophil activation, believed to reflect the ongoing allergic inflammation in the respiratory mucosa.³¹

Pollen Registration

The number of birch pollen per cubic meter was obtained from the Botanic Institution at the University of Gothenburg, for the period in May when the patient group was challenged with capsaicin.

Statistical Methods

The effects of the provocations were analyzed using the Wilcoxon signed rank test, the Mann-Whitney *U* test, and confidence intervals for nonparametric analyses.³² Values of $P < 0.05$ were considered statistically significant. Mean values $\pm$ SE are shown in the Figures.

Informed consent was obtained from all patients and control subjects. The local ethics committee approved the study.

RESULTS

Coughing

All subjects were able to inhale the three doses of capsaicin and reacted with a dose-dependent increase in the number of coughs, in accordance with our earlier experience.²⁸ Before the pollen season, this increase was modest in the asthmatic group and was similar to the reaction of the healthy control subjects. During the pollen season, the mean number of coughs was significantly higher in the asthmatic group compared with preseason measures, as analyzed by Wilcoxon signed rank test ($P < 0.01$ for 2 μ M; 95% confidence interval [CI] = 3.5 to 14.0 more coughs; $P < 0.02$ for 10 μ M; 96% CI = 8, 40 (Fig 1, 2, and 3).

Pollen season measures in patients also differed significantly from those of healthy control subjects, as analyzed by Mann-Whitney *U* test ($P < 0.02$ for 2 μ M capsaicin) (Fig 1).

Patients who did not use inhaled steroids ($n = 5$) tended to cough more during the pollen season than during the off season, but the difference was not significant.

Airway Symptoms

In the off season, patients experienced few airway symptoms as the result of the capsaicin challenges (except for coughing) and their responses were not significantly different from those of the healthy control subjects. During the pollen season, there was a significant difference in the symptom score with regard to dyspnea and coughing using the highest concentration of capsaicin (10 μ M) compared with off-season recordings ($P < 0.05$; Wilcoxon signed rank test; Fig 4). The control subjects had no symptoms or few symptoms from the capsaicin challenges.

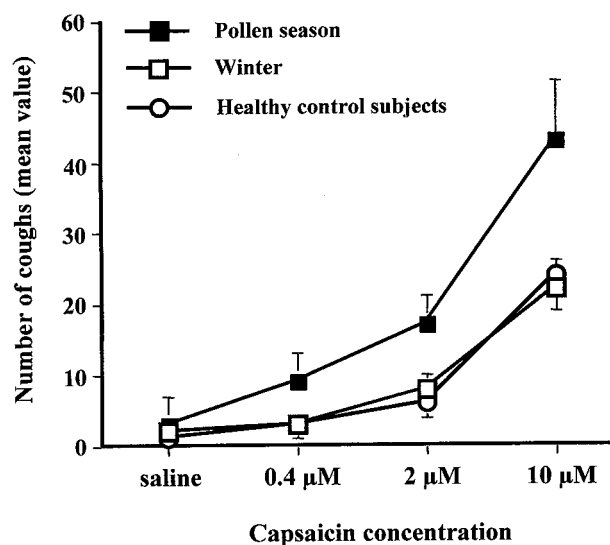


Figure 1. Mean number of coughs ($\pm$ SEM) in allergic patients ($n = 10$) during the pollen season and during winter and in healthy controls ($n = 10$) after provocation with three increments of capsaicin.

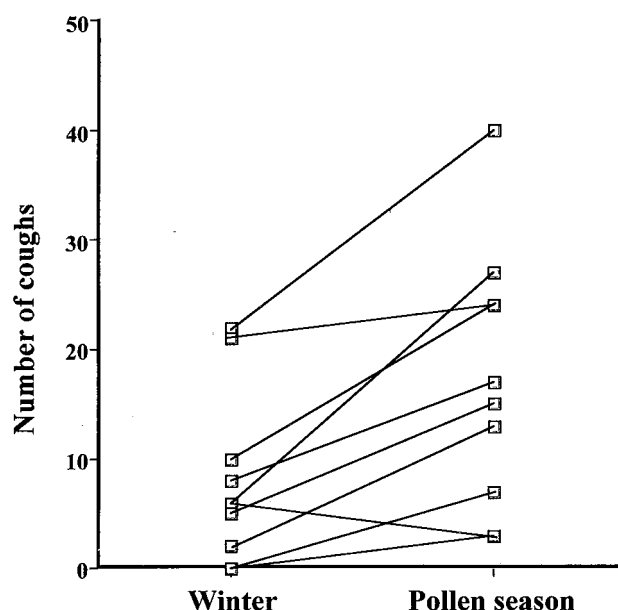


Figure 2. Number of coughs in allergic patients ($n = 10$), during the pollen season and during winter after the second dose of capsaicin ($2 \mu\text{M}$).

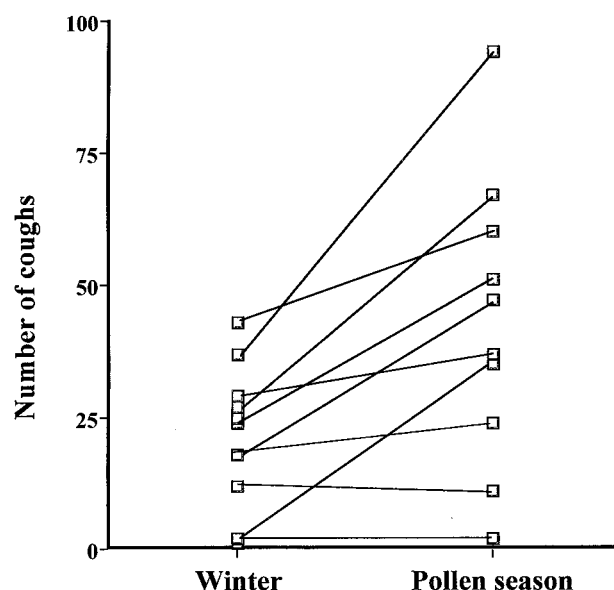


Figure 3. Number of coughs in allergic patients ($n = 10$), during the pollen season and during winter after the highest dose of capsaicin ($10 \mu\text{M}$).

Spirometry

Before the preseason capsaicin test, FEV_1 varied between 85% and 114% of predicted value (mean value 96%, 95% CI = 87, 104). After the preseason test, the mean value of FEV_1 was 97% of predicted (NS). Before the seasonal test, predicted FEV_1 varied between 81 and 117% (mean value

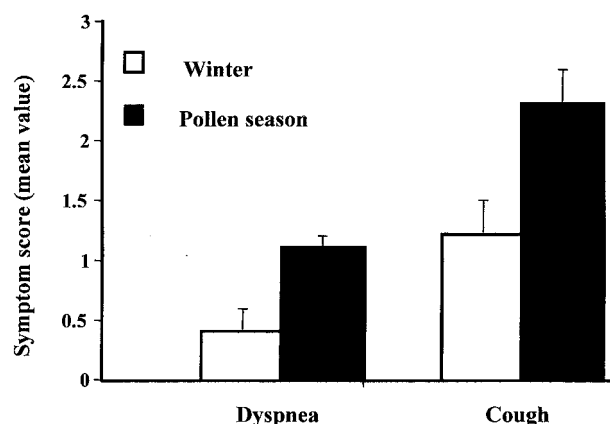


Figure 4. Mean symptom score of dyspnea and coughing during the pollen season and during winter ($\pm$ SEM) in 10 allergic patients after the highest dose of capsaicin ($10 \mu\text{M}$).

98%, 95% CI = 88, 109). After the seasonal test, the mean value of FEV_1 was 100% of predicted (NS).

Laboratory Tests

Serum-ECP ($\mu\text{g/L}$), calculated with Wilcoxon's signed rank test for paired samples, was statistically significantly higher during the pollen season, $P < 0.04$, with a corresponding 96% CI of 0.5, 30.5. The median ECP values were 25 during the pollen season and 17 during the winter season.

Pollen Registration

The seasonal capsaicin tests were performed between May 2 and 11, 2000. During this period, the birch pollen count was high, varying between 116 and 388 pollen/ m^3 .

DISCUSSION

The influence of neurogenic factors on allergic inflammation and vice versa is still unclear, although several studies indicate a close relationship.^{10,11} One of the most important symptoms in asthma is coughing, which is primarily a reflex to get rid of the excess secretion, another important, although varying, part of asthma. Coughing in asthma is not necessarily caused by obstruction and excessive airway secretion. It could also be the result of an increased cough reflex induced by enhanced neural sensory reactivity. A common complaint in asthmatic patients of sensitivity to various chemical stimuli such as strong scents may have the same cause. Scents and scenting chemicals are known to stimulate not only the olfactory system but also, normally with a higher threshold, the sensory C-fibers of the trigeminal nerve.^{33,34} These sensory C-fibers are also stimulated by capsaicin. Both an increased cough reflex and sensitivity to different chemicals may be the result of an enhanced sensitivity of sensory trigeminal and vagal nerve endings. The feeling of dyspnea triggered by a chemical stimulus does not always involve bronchial obstruction but could be another expression of asthmatic inflammation. In nonasthmatic, nonallergic patients, airway symptoms

induced by chemical stimuli are believed to be caused by a sensory hyperreactivity,^{28,29} and corresponding symptoms in asthmatic patients may reflect the same mechanisms. However, there is an important difference: in this group of asthmatic patients, the increased airway sensory neural reactivity was the result of an active allergic inflammation.

Patients with different airway diseases may have a reduced cough threshold to capsaicin. To our knowledge, it has not been studied how asthmatic patients with or without allergy react to capsaicin challenges during different phases of their asthma. It is possible that in connection with an asthmatic exacerbation, the neural sensory reactivity is also enhanced, in accordance with the increase in sensitivity to methacholine occurring in allergic asthmatic patients during the pollen season.³⁵ However, in a recent study, the capsaicin cough threshold (measured as C5) did not change during acute bronchodilation or during a histamine-induced reduction of FEV₁.¹⁸

All patients in this study had symptoms of rhinitis during the pollen season, and nasal reactivity to capsaicin is known to be increased under such conditions.⁷ Whether allergic patients with only rhinitis and no asthma also have an increased cough reflex is not known. The relationship between the upper and lower airways is often discussed from different perspectives.³⁻⁸ A further perspective could be the possible influence of the nose on the cough reflex and on sensory nervous mechanisms.

Patients not using inhaled steroids tended to cough more during the pollen season than during the off-season, but the difference was not significant.

This could indicate that when the allergic inflammation is adequately treated, the link to capsaicin sensitivity is not activated. However, the groups were too small to draw major conclusions.

We conclude that prolonged, ongoing allergic inflammation in patients with asthma who are allergic to birch pollen may induce an increased neurogenic reactivity followed by symptoms such as cough and dyspnea in the absence of bronchial obstruction. To our knowledge, there is no established way to treat neurogenic cough, but the results of this study emphasize the importance of treating the underlying allergic inflammation.

The findings suggest that respiratory symptoms triggered by chemical irritants do not necessarily involve obstructed airways, but a different mechanism (a sensory hyperreactivity) that causes similar (asthma-like) symptoms, like feelings of chest tightness and cough, is responsible. This may further explain why β_2 -agonists do not always help, why lung function in some contexts correlates poorly with respiratory symptoms.^{36,37} These findings are also in accordance with those of studies attempting to characterize the increased cough sensitivity after antigen challenge in guinea pigs. The findings support the theory that the antigen-induced increase in cough response to inhaled capsaicin is indeed independent of lung function but is correlated to the obtained eosinophils in bronchoalveolar lavage fluid.^{38,39}

Finally, this study indicates a link between allergic asthmatic inflammation and a hyperreactivity of the sensory nervous system in humans. The nature of this link, whether it is reflexogenic or mediator-dependent, and where it takes place, whether in the lower and/or upper airways, is not known. One way of further exploring these mechanisms may be to perform and compare allergen challenges in the upper and lower airways and monitor the time course of capsaicin cough response during both the early- and late-phase reactions. This approach could further be combined with measuring neuropeptide levels in bronchoalveolar and nasal lavage; which may also shed some new light on the interaction between upper and lower airways. Of great future interest is also to compare capsaicin cough sensitivity in patients with allergic and nonallergic asthma.

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