

Short communication

Sensory hyperreactivity – a possible mechanism underlying cough and asthma-like symptoms

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Background Investigations of patients referred for suspected asthma have revealed a little-known group with symptoms suggesting hyperreactive airways in whom provocation with methacholine does not lead to bronchial obstruction. The underlying mechanisms are not known, and no objective diagnostic method has been available.

Methods Provocations by inhalation of capsaicin solutions in stepwise increasing concentrations were used. Ten patients with asthma-like symptoms after exposure to nonspecific irritating stimuli, but without IgE-mediated allergy or demonstrable bronchial obstruction, were compared to 10 patients with verified bronchial asthma and 28 healthy controls.

Results The patients with asthma-like symptoms reacted with cough in a dose-dependent way. The number of coughs was significantly greater than in asthmatic patients and healthy controls. The latter two groups did not differ significantly.

Conclusions The capsaicin provocation test may be a valuable method for showing not only a greater cough sensitivity, but also asthma-like symptoms. The pathophysiology underlying the symptoms may be related to increased sensitivity of free, overactive nerve endings in the respiratory mucosa. Therefore, we suggest that this overreaction in the lower airways be called “sensory hyperreactivity”.

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In previous reports, we described a group of patients with asthma-like symptoms who were referred to our asthma and allergy outpatient clinic for investigation of suspected asthma (1, 2). The commonest symptoms were heavy breathing, difficulties in getting air, pressure or load over the chest, coughing, phlegm, hoarseness, stuffy nose, and eye irritation. Some also have more general symptoms, such as fatigue and headache. In most patients, the symptoms are induced by chemical irritants, cold air, or exercise. The patients have typical symptoms and negative asthma and allergy tests; e.g., normal pulmonary function tests but negative methacholine and skin prick tests. Patients have usually been on asthma medication, or have inhaled corticosteroids and β_2 -agonists, but most of them show no definite evidence of an objective or

subjective effect. Many of the patients cannot work and have been sick-listed for long periods or given disability pensions. No primary psychologic mechanisms exist, but secondary psychologic symptoms may develop, because the problems are difficult to deal with (1). In any case, the pathophysiologic mechanisms underlying this costly condition are not clear, and a reliable provocation model should be developed.

In our opinion, the asthma-like symptoms and the increased cough sensitivity in these patients are induced by a hyperreactive state of the sensory nerve system in the airways. Capsaicin, which is present in red pepper, excites certain afferent C-fiber nerves of the respiratory mucosa and has been used to induce cough in provocations (3). It has an immediate dose-dependent effect; the coughing

Table 1. Demographic data of patients with asthma-like symptoms

Patient no.	Sex	Age (years)	Profession	Baseline FEV ₁ % predicted	Duration of disease (years)	Cause
1	F	35	Veterinary assistant/ disability pension	115	15	Strong scents
2	F	59	Clerk/ disability pension	95	21	Strong scents, "sick buildings"
3	M	39	Clerk	106	5	Strong scents, airway infections
4	F	48	Nurse's assistant	102	10	Strong scents, airway infections
5	F	52	Nurse	77	25	Strong scents
6	F	23	Nursery schoolteacher	113	8	Strong scents
7	F	45	Clerk	97	3	Strong scents, cessation of smoking
8	F	57	Teacher/ sick-listed	110	11	Strong scents, "sick buildings"
9	M	45	Businessman/ sick-listed	99	10	Strong scents
10	F	52	Nurse's assistant	93	20	Strong scents

stops promptly after the provocation, and the reproducibility is good (4).

The present study aimed to test the sensory response to provocation with capsaicin inhalation by patients having asthma-like symptoms.

Material and methods

Ten nonsmoking patients were recruited for the study, eight women and two men between 23 and 59 years old (mean age 45 years) when they were seen at the asthma and allergy center because of symptoms suggestive of asthma. All of them had a history of at least 2 years of airway symptoms and sensitivity to chemical irritants, such as cigarette smoke, house paint, flower scents, and perfume. All except one (a woman with an isolated positive reaction to mugwort) had a negative skin test, with a standard panel of 11 allergens (*Dermatophagoides pteronyssinus*, *D. farinae*, *Aspergillus fumi-*

gatus, *Cladosporium*, dog, cat, horse, timothy, cocksfoot, mugwort, and birch), normal lung function, and normal bronchial methacholine test (5). All had a normal radiograph of the lungs within the last 5 years. Four of them had a pension for a disability or had been sick-listed for at least 1 year because of their symptoms, alone or together with other conditions (muscular problems in two patients). Seven of them were taking β_2 -agonists and/or inhaled corticosteroids regularly, but had obtained little or no subjective relief with this therapy. Demographic data are shown in Table 1. The patients were told to take no medication for a minimum of 4 h before any test. Long-acting bronchodilators were withheld for at least 48 h and antihistamines for 5 days.

A volume of 1 ml of saline was nebulized (Pariboy 36, Paulritzau Pari-werk KG, Starnberg-am-See, Germany) and inhaled for 6 min to induce a cough, followed by a 4-min rest. The number of coughs was counted for 10 min from the start of the provocation, and registered with a tape recorder. Thereafter, the provocations were performed in the same way using increasing concentrations of capsaicin; i.e., 0.4, 2, and 10 μ M in 1 ml solution. FEV₁ was measured with a spirometer (Vitalograph, Buckingham, UK) before and after each dose, and the best of three trials was recorded. Pulse rate, O₂ saturation, respiratory rate, and CO₂ in exhaled air were determined with a pulse capnograph (Oscar Oxy, Dansjö Medical AB, Bromma, Sweden).

The controls comprised 28 nonsmoking, subjectively healthy, volunteers (23 women and five men, between 27 and 57 years of age, mean 43 years). None of them were taking any drug known to affect the lower airways. The provocations with capsaicin were performed as above, except that no lung-function tests or recordings with pulse capnograph were done.

Reproducibility was evaluated by repeating the above-described provocation in all patients with asthma-like symptoms and in nine of the healthy volunteers, after about 1 week.

In a second comparison, we studied 10 nonsmoking patients, five women and five men, between 23 and 59 years of age, mean 35 years, who had had verified asthma for at least 5 years. They had earlier shown an increase of $\geq 20\%$ in FEV₁ after inhaling a β_2 -agonist. Five of them were inhaling corticosteroids regularly, and all inhaled β_2 -agonists intermittently. Three patients were on inhaled, long-acting β_2 -agonists. On most days, they had no symptoms of asthma. Seven had positive skin tests to more than two allergens.

The patients with asthma were sensitive to methacholine, as judged by a provocation test

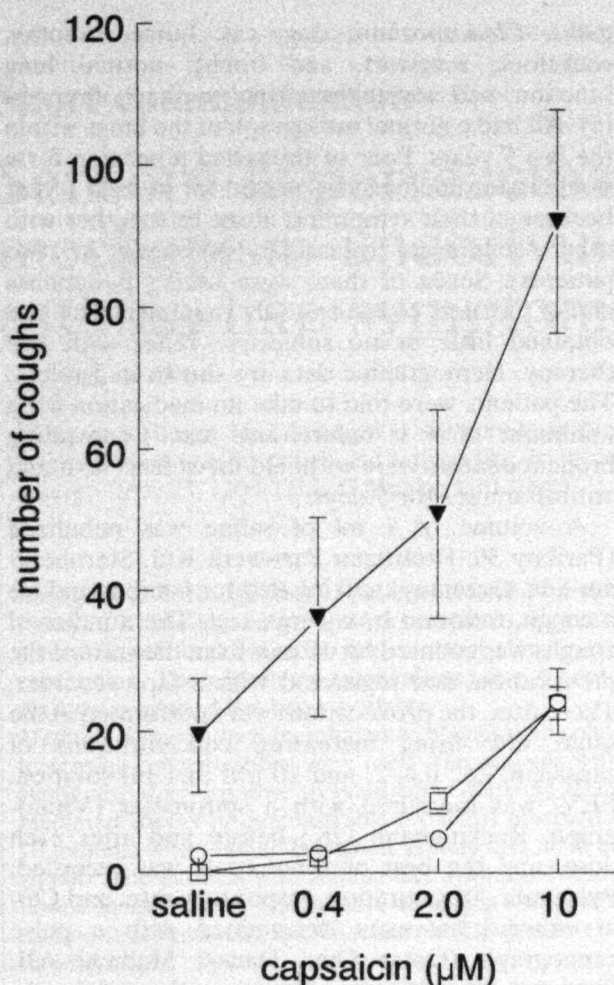


Fig. 1. Inhalation of capsaicin in increasing concentrations induces increasing number of coughs in healthy subjects (squares), patients with asthma (circles), and those with asthma-like symptoms (triangles). Last group differs significantly from others. Results are presented as $\pm$ SEM.

(5). Nine of them had a PC_{20} of <2 mg/ml (a fall in FEV_1 of $\geq 20\%$ after the inhalation of 2 mg methacholine or less), and one had a PC_{20} of <4 mg/ml. No change in medication was made in any of the patients for several months before starting the study, and, clinically, there had been no exacerbations of their symptoms.

In asthmatic patients, the provocations with capsaicin were performed in exactly the same way as in patients with asthma-like symptoms. They were told to take no medication for a minimum of 4 h before any test. Long-acting bronchodilators were withheld for at least 48 h and antihistamines for 5 days.

Statistical analyses of the results with different doses and between the different groups were performed with ANOVA. Reproducibility was tested with linear regression analysis.

The study was approved by the local ethics committee.

Results

The numbers of coughs was counted and registered on a tape recorder. One patient with asthma-like symptoms was unable to inhale the highest concentration of capsaicin and stopped after 50 coughs.

The asthma-like, nonallergic, nonmethacholine-sensitive patients reacted dose-dependently with cough during the capsaicin provocation. Even saline caused coughing. The healthy controls reacted in a similar way, but with less coughing and not at all to the saline provocation (Fig. 1). Asthmatic patients did not differ significantly from the healthy controls.

The mean number of coughs after inhalation of the highest dose of capsaicin was 93 in the group of asthma-like cases and 23 in healthy subjects and asthmatics (Fig. 1). Asthma-like cases differed significantly ($P < 0.001$) from the control group of healthy subjects and from patients with asthma in the number of coughs as an effect of each concentration of capsaicin.

The reproducibility after the highest dose of capsaicin in patients with asthma-like symptoms and in controls was good (linear regression analysis, $r^2 = 0.92$, $P < 0.02$).

The values for FEV_1 , pulse rate, O_2 saturation, respiratory rate, and CO_2 in the expired air were entirely normal throughout, and no significant differences were found after the provocations with capsaicin in any of the patient groups. These values varied very little during the provocations.

In addition to coughing after capsaicin provocation, patients with asthma-like symptoms complained about their "other usual symptoms", such as heavy breathing, difficulties in getting air, pressure or "load" on the chest, phlegm, hoarseness, stuffy nose, and eye irritation.

Discussion

Patients with asthma-like symptoms coughed more after capsaicin provocation than did healthy subjects and patients with asthma. They complained of symptoms other than coughing, such as those after exposure to strong scents. This has also been shown in a previous study reporting asthma-like symptoms after perfume provocations (2).

Cough induced by a reflex of the respiratory tract is hard to control, but it is possible. However, it seems unlikely that patients with asthma-like symptoms tried to cough more, in view of the dose-response effect of the capsaicin provocation,

the good reproducibility, and the negative methacholine provocation. The patients had not been told that the doses of capsaicin would be increased during the provocation procedure.

No significant fall in FEV₁ was induced by capsaicin. This agrees with previous findings that capsaicin does not cause bronchial obstruction (6). Although cough is a common symptom in asthma, the patients with asthma did not differ from healthy controls in the cough response, unlike those with asthma-like symptoms. This indicates that the hypersensitivity to methacholine of many asthmatics is not related to sensitivity to all chemical agents. Five of the asthmatic patients were inhaling corticosteroids regularly. The cough response to capsaicin occurs via sensory nerve stimulation, and it is unlikely that inhaled steroids influence this. To ensure that inhaled corticosteroids had no effect, they were to be withheld for several weeks, but we felt that this influenced the patients' asthmatic condition too much.

The patients with asthma-like symptoms were carefully investigated, and asthma and allergy were excluded. No objective method has been available to separate patients with asthma-like symptoms from those with asthma and from healthy subjects. The cough response to capsaicin was increased in these patients and was dose-related. In clinical practice, a standardized method to determine the sensory sensitivity in patients with airway symptoms could be of value. As the patients in this study coughed more even after inhaling saline, the effort to find a "sensitivity threshold dose" is not meaningful, but the actual number of coughs should be recorded. More clinical studies are needed to determine suitable concentrations of capsaicin for a test that could be used in a standardized way.

Recently, a receptor was found for capsaicin (7). This receptor, VR1, binds capsaicin and vanilloid and probably also other chemical compounds that may be found in perfume, but this point has not been studied. In patients suffering from hyperalgesia, an increased response to noxious stimuli is believed to be due to an enhancement of VR1. Similar mechanisms could explain the increased cough response to capsaicin. It seems likely that the VR1 receptors of the C-fibers of the sensory nerve system are remodulated in the airways of these patients, or that the number of receptors has increased. Since the patients are sensitive to various chemical or physical stimuli and this sensitivity can be verified by capsaicin provocation, we suggest the term "*sensory hyperreactivity*" for this condition. However, even saline made the patients with asthma-like symptoms cough more, and this could not be ascribed to the VR1 receptors. It is possible

that there is also an increased sensitivity to tactile stimuli and a change in quickly activated A-fibers.

In the literature, mainly from the USA, there are several reports of *multiple chemical sensitivity* (MCS) (8–11). This syndrome, characterized by symptoms from various organs, not only from the airways, is induced by low concentrations of various chemical inhalants. The airways symptoms are similar to those described by our patient group, and they are also similar to those described in the *sick-building syndrome* (12). MCS has been classified as a psychologic disorder and has been rejected as an established organic disease by several institutions, because it has not been possible to provoke the symptoms (13). They are said to be set off by various agents and are manifested in various forms. It seems plausible that syndromes and disorders induced by chemical irritants or other environmental challenges may have the same pathophysiologic causes. Investigations depend on the nature of the symptoms and this may influence the physician. Therefore, patients with symptoms mainly of the lower respiratory tract will be referred to an asthma/allergy clinic and be considered either to have something like asthma or not to have asthma. These results should encourage studies of the effect of capsaicin in other unexplained conditions after environmental exposure; e.g., multiple chemical sensitivity and the sick-building syndrome.

It is of great clinical importance to demonstrate and verify the patients' symptoms by an objective test, and not only refer to the symptoms, which may then be regarded as merely psychologic. This new knowledge may also permit development of an effective treatment of the condition. In further studies, we shall try to block the capsaicin response and to develop capsaicin provocation as a diagnostic test.

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