

Original article

Cough provocation with capsaicin is an objective way to test sensory hyperreactivity in patients with asthma-like symptoms

Background: A group of patients with asthma-like symptoms and sensitivity to chemical irritants, but without bronchial obstruction, has been found among subjects referred for suspected asthma. They have no well-defined diagnosis, and no objective diagnostic method has previously been available. These patients are more sensitive to inhaled capsaicin than are patients with asthma or healthy controls. The aim was to study cough and other capsaicin-induced symptoms and to test the effect of a drug (lidocaine) that inhibits nerve transmission in sensory nerves.

Methods: Twelve patients were provoked with three different concentrations of inhaled capsaicin solutions in a randomized, double-blind order. They all had asthma-like symptoms and were sensitive to chemical irritants, but had no IgE-mediated allergy or demonstrable bronchial obstruction. Before the provocations, the patients inhaled lidocaine or placebo (saline), also in a double-blind, randomized order. The results were expressed as the number of coughs and scores of various symptoms.

Results: The patients reacted in a dose-dependent way with cough, airway, and eye symptoms, which were significantly reduced after preinhalation of lidocaine.

Conclusions: A drug that inhibits transmission in sensory nerves successfully blocked the number of coughs and other symptoms provoked by inhalation of capsaicin. This indicates that the mechanisms underlying chemical sensitivity in these patients may originate in the sensory nervous system, and we call this condition “sensory hyperreactivity”.

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Key words: asthma; asthma-like; capsaicin; cough; hyperreactivity; multiple chemical sensitivity.

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Accepted for publication 4 February 2000

Patients with an asthma-like condition are commonly seen in clinical practice. Two syndromes that masquerade as asthma are vocal cord dysfunction with asthma-like symptoms that are mainly induced by exercise (1, 2) and reactive airways dysfunction with asthma-like symptoms after one or more exposures to a high concentration of a chemical irritant (3, 4). Other patients suffer asthma-like symptoms after exposure to chemical irritants in daily life, but have no history of any acute exposure to irritating vapors (5–9). They complain mainly of cough, dyspnea, heavy breathing, stuffy nose, and eye irritation. Some of them also have hoarseness, itching in the mouth and ears, sweating, headache, vertigo, and fatigue. Their symptoms are induced not only by agents such as perfume, strong scents, and cigarette smoke, but also by exercise and cold air. Although the clinical features resemble those of asthma and allergy, the objective findings, that is, lung-function and bronchial methacholine tests, are normal, and skin prick tests show no evidence of allergy.

In previous studies, provocation with perfume caused

symptoms in these patients, even when they were not able to smell the perfume (6, 9). In one setup, the patients used a noseclip and a carbon filter to prevent the perfume from reaching the olfactory receptors, yet they could distinguish perfume and placebo in controlled recordings (6). In another study, when we provoked the airways (with blocked nose) or the eyes, the patients developed most symptoms from the eye provocations (9). These results strongly indicate that the symptoms were induced by the sensory nervous system.

Capsaicin, the pungent ingredient in red (capsicum) pepper, is known to stimulate the unmyelinated slow C-fibers of the sensory nervous system, and it has been used to induce cough in provocation models (10–12). Patients with asthma-like symptoms, but not bronchial obstruction, cough more after inhalation of capsaicin than do those with asthma and healthy controls (8). The hypothesis is that cough provocation with capsaicin is an *objective* way to demonstrate nonasthmatic airway hyperreactivity that originates in the sensory nervous system. The aim of this study was to determine whether

cough and other symptoms induced by capsaicin inhalations could be blocked by local anesthesia, and whether there was a dose-response relationship in the number of coughs, even if the provocations were done in a randomized, double-blind order.

Material and methods

Twelve nonsmoking patients took part in the study, 10 women and two men (23–60 years old, mean age 48 years), when they were examined 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 other symptoms induced by chemical irritants such as cigarette smoke, house paint, flower scents, and perfume. None had a history of any acute exposure to a high concentration of an irritant substance. All had normal lung function and a normal bronchial methacholine test (13). 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; i.e., muscular problems in two patients). Eight of them were taking β_2 -agonists and/or inhaled corticosteroids regularly, but had obtained little if any subjective relief from this therapy. The demographic data are shown in Table 1. Before any test, the patients were asked to take no medication for a minimum of 4 h. Long-acting bronchodilators were withheld for at least 48 h and antihistamines for 5 days.

The patients visited the center on two occasions, in a double-blind, randomized order, for provocation with capsaicin, with or without pretreatment with lidocaine or placebo. They started each time by gargling with 15 ml of lidocaine solution (5 mg/ml), which they then spat out. The gargling induced local anesthesia of the mouth and throat, which was an effective way to prevent the patients from distinguishing between the lidocaine and placebo inhalations. After 5 min, 1 ml of nebulized lidocaine (40 mg/ml) or saline was inhaled (Pariboy 36, Paulritzau Pari-werk KG, Starnberg-am-See, Germany). After a rest for another 5 min,

nebulized capsaicin was inhaled in three concentrations: 0.4, 2, and 10 μ M in a 1-ml solution. The choice of the concentration sequence was also randomized and administered double-blind. Each dose was inhaled to completion for 6 min to induce a cough, followed by a rest of 4 min. The number of coughs was counted for 10 min from the start of the provocation, and registered with a tape recorder. Symptoms were registered by a score after each provocation on a 0–3 scale (0=no symptoms, 1=mild, 2=moderate, and 3=severe symptoms). Three main symptoms were analyzed: dyspnea, stuffy nose, and irritation of the eyes. FEV₁ was measured with a spirometer (Vitalograph, Buckingham, UK) directly 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).

Statistical analyses of the differences with various doses and between lidocaine and placebo were done with ANOVA and the Wilcoxon signed rank sum test. The local ethics committee approved the study.

Results

The number of coughs was counted and registered on a tape recorder. Because of a severe cough, one patient was unable to inhale the highest concentration of capsaicin when the preinhalation was placebo. Therefore, in this patient, only the corresponding doses were analyzed when lidocaine was used.

The patients reacted dose-dependently with cough during the capsaicin provocations. This was significant ($P<0.05$) at all concentrations of capsaicin after preinhalations with placebo and at the two highest concentrations after preinhalations even with lidocaine. The mean number of coughs after inhalation of the highest concentration of capsaicin was 34 after preinhalation of lidocaine and 68 after placebo (Fig. 1). The recordings after inhalation with lidocaine differed significantly ($P<0.005$) from those after

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	45	Clerk	97	3	Strong scents, cessation of smoking
2	F	52	Nurse/sick-listed	77	25	Strong scents, cigarette smoke
3	M	47	Priest	82	7	Strong scents, cigarette smoke
4	F	51	Shop assistant	110	5	Strong scents, cessation of smoking
5	F	23	Nursery schoolteacher	113	8	Strong scents, cigarette smoke
6	F	48	Nurse's assistant	102	10	Strong scents, airway infections
7	M	56	Businessman	101	6	Strong scents
8	F	52	Nurse's assistant	91	20	Strong scents, cigarette smoke
9	F	59	Clerk/disability pension	95	21	Strong scents, cigarette smoke, "sick buildings"
10	F	52	Nurse	105	12	Strong scents, cigarette smoke
11	F	57	Teacher/sick-listed	98	11	Strong scents, "sick buildings"
12	F	35	Veterinary assistant/disability pension	115	15	Strong scents, cigarette smoke

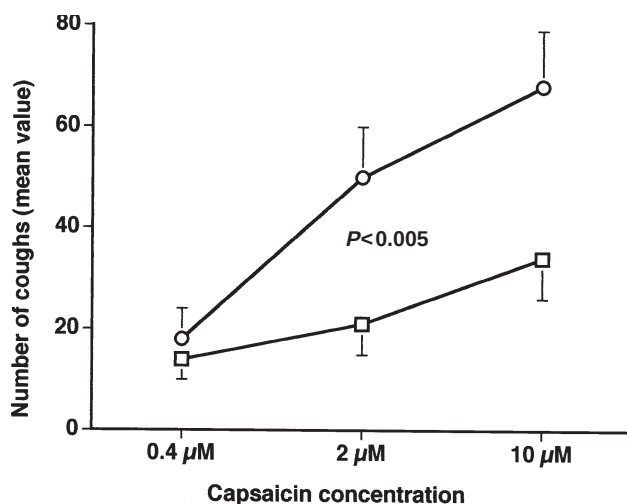


Figure 1. Inhalation of 1 ml of capsaicin in concentration of 0.4 ($n=12$), 2 ($n=12$), and 10 μ M ($n=11$) induced increasing number of coughs in patients with sensory hyperreactivity. Recordings after pretreatment with inhalations of lidocaine (squares) differed significantly from those after pretreatment with placebo (circles). Bars represent SEM.

inhalation of placebo for the number of coughs. All but one patient had less coughing when lidocaine rather than placebo was used (Fig. 2).

In addition to coughing after capsaicin provocation, the patients complained about their "other usual symptoms", such as heavy breathing, difficulties in getting air, pressure or "load" over the chest, phlegm, hoarseness, stuffy nose, and eye irritation. Recordings of the scores of the three most common symptoms are presented in Fig. 3.

The values for FEV₁, pulse rate, O₂ saturation, respiratory rate, and CO₂ in the expired air were entirely normal throughout, and no significant differences in any of the patient groups were found after the provocations with capsaicin.

Discussion

We have earlier shown that patients with asthma-like symptoms suffer more cough from capsaicin provocation than do patients with asthma or healthy controls. The patients in this study coughed intensively; in several cases, a patient coughed more than 100 times. The provocations were not pleasant, but most patients claimed that they suffered more from chemicals in their daily life. The number of coughs among subjects with asthma-like symptoms and the dose relationship to capsaicin concentrations were in accordance with our earlier results (8). This study confirmed that capsaicin provocation is an objective method to demonstrate airway sensitivity to chemical irritants in patients with asthma-like symptoms. This sensitivity may originate in the sensory nervous system and be due to an increase in sensory nerve

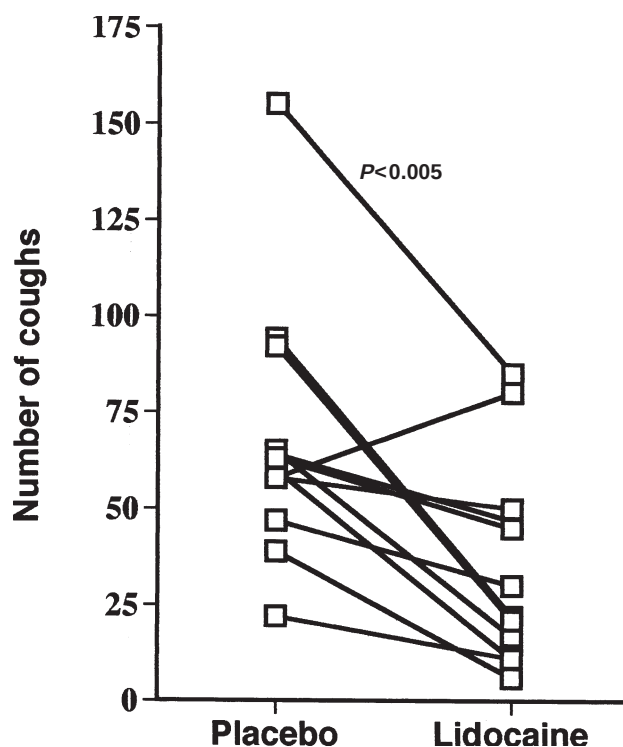


Figure 2. Inhalation of 1 ml of 10 μ M capsaicin after pretreatment with inhalation of lidocaine induced fewer coughs in 11 of 12 patients than did pretreatment with inhalations of placebo.

cell endings or to a remodulation of the nerve receptor, but the precise location of action remains unknown. Except for patients with asthma who did not cough more after capsaicin provocations than healthy controls (8), we do not know how patients with other causes of cough react to capsaicin provocation. Cough can depend also upon CNS function, voluntary and involuntary. Cough, which is induced by a reflex from the respiratory tract, is hard

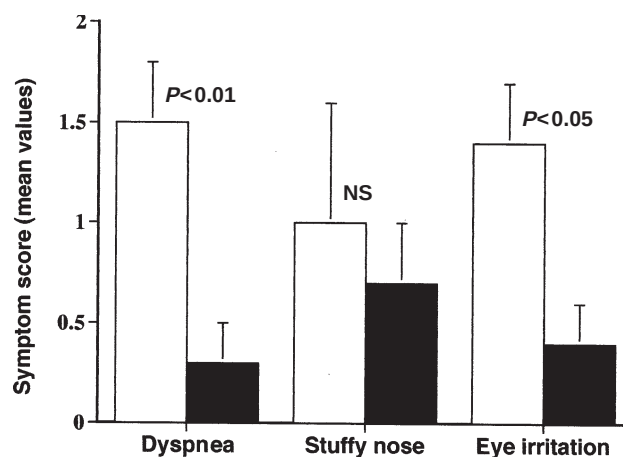


Figure 3. Mean scores of three symptoms – dyspnea, stuffy nose, and eye irritation – after inhalation of 1 ml of 10 μ M capsaicin, after pretreatment with inhalation of lidocaine (open columns) or of placebo (closed columns). Bars represent SEM.

to control, but it is possible to do so. However, in view of the dose-response effect of the capsaicin provocation and the blind randomization of the doses, it seems unlikely that patients with asthma-like symptoms could have influenced the number of coughs voluntarily. The patients do not have asthma, nor are the pathophysiologic mechanisms of asthma and asthma-like symptoms the same. The results also confirm a previous report in which capsaicin-induced cough in healthy subjects was dose-dependently inhibited by a preceding inhalation of lidocaine (12).

The common chemical sense that induces pain and irritation in the eyes and airways by chemical agents is known to depend on trigeminal innervation, and not on stimulation of the olfactory sense (14, 15). In patients with airway symptoms induced also by very low levels of chemical irritants, it seems likely that it is not the *smell* that causes problems but the *sensory hyperreactivity* of the common chemical sense. The capsaicin receptor, which has recently been identified, is known to transfer noxious stimuli via slow-acting afferent C-fibers (16). The precise site of action of inhaled capsaicin is not known, but, presumably, most of the aerosol is dispersed in the mouth, the larynx, and the proximal parts of the lower airways, which are also considered to be the most sensitive sites for cough provocation (17, 18). Stimulation of the afferent C-fibers in animals causes bronchoconstriction, but in man this effect of capsaicin provocation is uncertain. A minimal decrease in airway conductance has been found after capsaicin provocation, but with no difference between normal, smoking, or asthmatic subjects (10). This minor and short-lasting effect could probably not be detected by spirometry, an idea which is confirmed by this study and a previous one (8). Noxious stimuli cause pain and burning sensations, and more studies of the capsaicin receptor are in progress in the field of pain research. However, the symptoms in patients with airway *sensory hyperreactivity* are similar to symptoms in patients with chronic pain and may be just

another expression of the capsaicin receptor. A remodulation of this receptor could cause persistent pain as well as chronic asthma-like symptoms. In the rat brain, perfume modulates the neural transmission through ionotropic GABA receptors (19). Studies of neurogenic markers are needed to obtain more knowledge in this field.

It is uncertain whether the incidence of sensory hyperreactivity is increasing, because, until now, no diagnostic method has been available. The impression in our clinical practice is that an increasing number of patients suffer from air pollution and scents in the environment, and are referred to the Asthma and Allergy Center with suspected bronchial asthma.

The sensory hyperreactivity observed in our patients resembles multiple chemical sensitivity in some respects. In this condition, symptoms from various organs are induced by low concentrations of various chemical inhalants (20–23). The role of C-fiber neurons in chemical sensitivity is disputed, and several hypotheses have been proposed (24). Multiple chemical sensitivity has mostly been classified as a psychological disorder and is not regarded as an established organic disease (25). However, a few studies have tried to induce the symptoms in provocation models.

For patients with sensory hyperreactivity, it is first necessary to establish objective, diagnostic methods to avoid meaningless tests and medication. A diagnosis, even if there is no treatment, may be a relief for many such patients.

Acknowledgments

This study was supported by grants from the Vårdal Foundation, the Regional Health Care Authority of West Sweden, the Swedish National Association against Asthma and Allergy Diseases, and the Swedish Heart Lung Foundation. We are also grateful to Ewa Ternesten for help with the recordings.

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