

Relationship of airway symptoms from chemicals to capsaicin cough sensitivity in atopic subjects

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Summary

Background It is well known that some patients with allergy complain of airway symptoms from chemicals (ASCs) and strong odours. However, the importance of such information for the treatment of allergic disease is not known. Such symptoms in non-allergic patients have previously been shown to be related to increased sensory nerve reactivity, which is expressed as increased cough sensitivity to inhaled capsaicin.

Objective The aim of this study was to examine ASC in atopic patients and relate it to cough reaction to capsaicin inhalation.

Materials and methods Fifty-seven consecutively chosen, skin prick-positive patients with symptoms of the upper and/or lower airways completed a questionnaire concerning ASC. The patients were then divided into two groups, those with and those without such symptoms. Both groups were provoked with inhaled capsaicin in three increments and compared with 73 healthy control subjects.

Results Out of 57 atopic patients, 34 reported ASC agents and 23 did not. The patients with ASC were older ($P < 0.01$) and coughed significantly more on capsaicin provocation ($P < 0.001$), but did not differ from them with respect to the allergic disease or its treatment or to smoking habits. Patients with atopy but without ASC did not differ from healthy controls with regard to sensitivity to capsaicin inhalation. The scored degree of ASC was directly related to the number of coughs during the capsaicin provocation.

Conclusion ASC in atopic patients are related to increased airway sensory nerve reactivity. There is still no explanation for this in certain patients with atopy, but age may be a confounding factor.

Keywords airway symptoms, asthma, atopy, capsaicin, chemicals, cough, neural responsiveness, sensory reactivity

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Introduction

Sensitivity to chemicals is a common problem frequently reported in population studies [1, 2]. Airway symptoms induced by inhaled chemicals have been described in different conditions such as multiple chemical sensitivity [3], sick building syndrome [4] and sensory hyper-reactivity [5], but there is a lack of objective findings, documented homogenous symptomatology and known pathophysiology [6]. Patients with asthma and allergy also frequently complain of airway symptoms induced by chemicals and strong odours such as perfume and flower scents, as recorded in standard questionnaires used in conjunction with interviewing patients during their first visit to an allergy centre. However, the pathogenesis behind airway symptoms induced by chemicals in allergic patients is not known.

Capsaicin (C₁₈H₂₇NO₃), the ingredient that produces the heat in hot peppers (*Capsicum*), is known to stimulate the non-myelinated slow C-fibres of the sensory nervous system. It has been used to induce cough in provocation models, and the degree of cough sensitivity induced reflects the reactivity of sensory C-fibres [7–9]. Patients with pronounced airway sensitivity to chemicals but without asthma or allergy have previously been shown to have an increased cough reactivity to capsaicin inhalation [5, 10]. Also, in one study an enhanced capsaicin cough sensitivity was reported in patients with asthma and chronic obstructive pulmonary disease [11], although other studies did not find such sensitivity in asthma [5, 12, 13]. No relation has been found between capsaicin cough sensitivity and methacholine sensitivity [11–14].

Inflammation in airway allergy is a frequently studied topic and is considered to be the key phenomenon behind airway hyper-reactivity [15]. Some studies indicate a change in neural responsiveness in connection with the allergic inflammation, especially in the nose [16–19], but how, and to what extent, a neurogenic inflammation plays a role in airway hyper-reactivity in the lower airways remains obscure [20, 21].

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The aim of the present study was to evaluate the importance of airway symptoms from chemical (ASC) in patients with verified atopy and symptoms from the upper and/or lower airways, and to relate these symptoms to capsaicin cough sensitivity.

Materials and methods

Patients

Seventy-five atopic patients consecutively referred to an allergy centre in Skövde, Sweden, for suspected allergy were asked to take part in the study. Of these, 57 (76%) performed a capsaicin inhalation provocation. The reasons for declining to participate were mainly lack of time or communication difficulties (long travelling time). Of the 57 patients included in the study 26 were women and 31 were men, aged between 18 and 73 years (average age 33 years). The patients visited the centre during the winter season, following the system of the clinic to test patients with suspected allergy mainly during the winter period to avoid a possible influence of pollen. All patients had a positive skin prick test (SPT) to at least one agent from a standard panel of 12 allergen sources common to Sweden: birch, timothy grass, mugwort, cat, horse and dog, as well as two species of house dust mite (*Dermatophagoides farinae* and *D. pteronyssinus*) and three of mould (*Aspergillum*, *Penicillium*, *Cladosporium* and *Alternaria*). Histamine and blank tests were used as controls. A weal-and-flare response of a mean diameter of 3 mm or more was regarded as a positive SPT reaction. In accordance with the international consensus report of the diagnosis and management of asthma [22], the term 'asthma' is used to describe the condition of patients with a history of recurrent episodes of wheezing and breathlessness, and an increase of at least 15% in forced expiratory volume in 1 s after inhalation of a β_2 -agonist.

There were higher proportions of women patients with cough and patients taking inhaled corticosteroids (ICSs) among the patients with ASC, although the differences were not statistically significant. Nor were there any statistical differences regarding asthma or perennial or seasonal allergy symptoms; however, the chemical-sensitive patients were significantly older (Table 1).

Controls subjects

The 73 control subjects (42 women and 31 men, 17–72 years of age, average age 42 years), a control material included in a previous study [23], were recruited among the hospital personnel and screened by simple questions concerning allergy, airway symptoms and symptoms from chemicals. Exclusion criteria were the presence or a past medical history of any of these conditions. The control subjects did not perform any further medical exams, tests or questionnaires.

Questionnaire

The patients were classified as having ASC or not based on their response to the simple question, 'Do you get ASC agents and odours such as perfumes and solvents?' They were also asked to score airway symptoms from (a) the eyes; and (b) the

Table 1. Demographic data, symptoms, results of the SPT and treatment in 57 atopic patients, 34 with and 23 without ASC

	ASC	Non-ASC	P-value
Number (%)	34 (60)	23 (40)	–
Women/men (% women)	18/16 (53)	8/15 (35)	NS
Mean age, years (range)	36 (28–73)	29 (18–68)	<0.01
Smokers (%)	3 (9)	4 (17)	NS
Asthma (%)	13 (38)	10 (43)	NS
Rhinitis (%)	31 (91)	23 (100)	NS
History of cough (%)	12 (35)	4 (17)	NS
Persistent (perennial)/intermittent (seasonal) positive SPT (%)	6/13 (18/38)	3/7 (13/30)	NS
Persistent (perennial) and intermittent (seasonal) positive SPT (%)	15 (44)	13 (57)	NS
Inhaled corticosteroids (%)	9 (26)	3 (13)	NS

SPT, skin prick test; ASC, airway symptoms from chemical; NS, non-significant.

upper; and (c) the lower airways in relation to chemical agents and odours on a scale of 0–3 (0 = no symptoms; and 1 = mild; 2 = moderate; and 3 = severe symptoms). The maximum possible total symptom score was 9 points. This was a local questionnaire that had been used in clinical practice and regarded as giving satisfying information, but which had not been scientifically validated.

Capsaicin inhalation provocation

To induce coughing with a nebulizer (Pariboy 36, type 37.0130; Paulritzu Pari-Werk KG, Starnberg-am-See, Germany) patients inhaled 1 mL of saline through a mouthpiece by tidal volume breathing to completion or during a maximum of 6 min, followed by a 4-min rest, as previously reported [5]. The number of coughs from the onset of provocations was counted for 10 min and tape-recorded. Thereafter, provocations were carried out in the same way by using increasing concentrations of capsaicin (0.4, 2 and 10 μ mol/L in a 1 mL solution). If over 70 coughs resulted from one dose of capsaicin, provocation was terminated. The order of the capsaicin doses was not blinded to either the nurse or the participants in the study. However, the nurse did not know whether the patients had been classified as having ASC or not by the doctor at their first visit. Peak expiratory flow (PEF) (L/min) was measured before and directly after the provocation, and the highest of three values was recorded. During the study, the patients continued their normal treatment except for antihistamines, which were withheld for at least 5 days because of the SPT that was performed on the same occasion. Among the control subjects, the provocation procedure was the same except for the saline inhalation and the PEF measurements that were excluded.

Statistics

The Mann–Whitney's *U*-test for non-paired data and Wilcoxon's signed-rank test for paired data were used to analyse differences between subjects in the group of patients with ASC and between atopic patients with ASC, patients without ASC and healthy control subjects. Data are

presented as means and 95% confidence intervals (within brackets). Linear regression was used in the analyses between the symptom score and the capsaicin provocation. In analysing the proportions of different subgroups of patients, χ^2 tests were used.

Results

Thirty-four (60%) of the atopic patients answered 'yes' to the screening question of whether they had ASC agents and odours such as solvents and perfumes. In this group, the mean symptom score was 3.7 [2.8–4.6]. The mean duration of the ASC was 11 years [8–14]. Even in the non-sensitive group, some patients scored symptoms; the mean symptom score for this group was 0.5 [0.04–1.0]. Seven of the patients thought their symptoms were due to earlier contact with chemicals (lasting several years) and two claimed that their problems had started after smoking cessation. Twenty-five patients had upper airway symptoms (nasal congestion and/or rhinorrhoea) from chemicals and 13 had lower airway symptoms. Eighteen reacted with an eye irritation.

Patients as well as controls coughed dose-dependently during the capsaicin provocations (Fig. 1). The mean number of coughs in the patient group with ASC was 0.5 [0.2–2.2] with the initial saline inhalation, 15 [4.8–26.1] with 0.4 $\mu\text{mol/L}$ capsaicin, 34 [20.7–46.6] with 2 $\mu\text{mol/L}$ capsaicin and 55 [43.2–67.7] with 10 $\mu\text{mol/L}$ capsaicin. The corresponding values among the non-sensitive patients were 0, 0.2 [0.8–2.7], 7 [4.2–9.2] and 22 [13.3–30.5]. The mean cough values for the healthy control subjects were 1 [0.6–1.9], 6 [3.8–7.5] and 21 [17.7–24.6] with the three capsaicin doses 0.4, 2 and 10 $\mu\text{mol/L}$. With each dose of capsaicin, the patients with ASC coughed significantly more than did the non-sensitive patients ($P < 0.01$ for 0.4 $\mu\text{mol/L}$ capsaicin, $P < 0.005$ for 2 $\mu\text{mol/L}$ and $P < 0.001$ for 10 $\mu\text{mol/L}$) (Fig. 1). The patients with ASC also differed significantly from the control subjects ($P < 0.0001$ for each dose of capsaicin). Between the non-sensitive patients and the control subjects, there were no statistical differences.

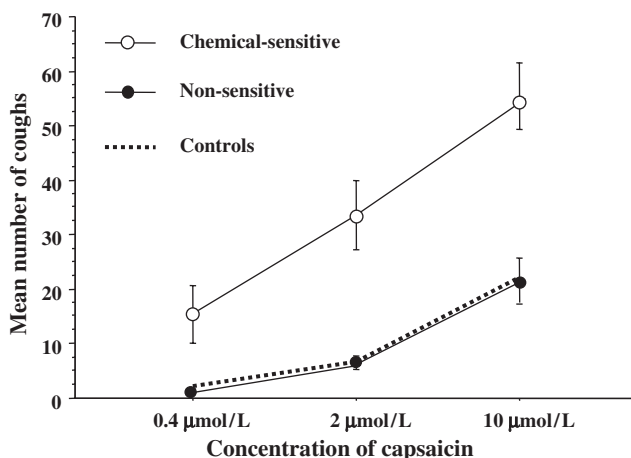


Fig. 1. Mean number of coughs ($\pm$ standard error of the mean (SEM)) after capsaicin inhalation provocation in atopic patients with ($n = 34$) and without ($n = 23$) airway symptoms from chemical and in healthy controls ($n = 73$).

In the patient group, a significant correlation was found between the total symptom score (0–9 points) and the number of coughs with each dose of capsaicin ($r = 0.4, 0.6$ and 0.5 for 0.4, 2 and 10 $\mu\text{mol/L}$ capsaicin, respectively; $P < 0.001$). Analysis of the three different symptoms (eye symptoms, and the upper and the lower airway symptoms, with a possible score of 0–3 for each symptom) included in the total score showed significant correlations between lower airway symptoms and the number of coughs with each dose of capsaicin ($r = 0.5, 0.7$ and 0.5 for 0.4, 2 and 10 $\mu\text{mol/L}$ capsaicin, respectively; $P < 0.001$). With regard to the upper airway symptoms, a correlation was found after the middle and highest concentration of capsaicin ($r = 0.3$ and 0.4 for 2 and 10 $\mu\text{mol/L}$; $P < 0.02$ and $P < 0.001$). With respect to the eye symptoms, a correlation was found after the highest concentration of capsaicin ($r = 0.3$; $P < 0.05$). Women coughed more than men ($P < 0.05$ for 0.4 and 10 $\mu\text{mol/L}$ capsaicin in the patient group and $P < 0.05$ for 0.4 $\mu\text{mol/L}$ and $P < 0.001$ for 2 and 10 $\mu\text{mol/L}$ capsaicin among the healthy control subjects).

There was a small but significant fall in PEF ($P < 0.001$) among the patients after the capsaicin provocation. The mean fall in PEF was 13 [7.8–19] L/min. No differences were found in this respect between patients with or without ASC.

Discussion

This study, which can be regarded as a pilot study because of its small size, confirms the clinical impression that atopic patients often complain of ASCs and strong odours. Their symptoms induced by chemicals were found in the airways, at the same localization as their allergic disease, and should not be mixed up with the more generalized symptoms described in the wider concept of self-reported environmental intolerances [24]. The majority (60%) of patients in the present study with a positive SPT claimed ASC. One explanation for the high ratings of ASC may be that when the regular allergy medication does not have the desired effect, the general practitioner often refers the patient to an allergy clinic even if the main inducing factors are chemicals. However, before drawing any major conclusions there is a need for larger studies with validated questionnaires that have now been developed [25].

In the present study, there was a clear difference between patients who reported ASC and patients who did not, regarding the objective parameter of cough sensitivity to capsaicin. In accordance with previous studies in non-allergic patients, this supports the theory that a history of ASC is important with regard to an enhanced sensitivity of the C-fibres of the sensory nervous system [5, 10]. The large number of atopic patients complaining of such symptoms indicates that there is a connection between the allergic disease and sensory nervous mechanisms. On the other hand, the finding that non-sensitive, atopic patients coughed in just the same way as did the healthy control subjects may point to two parallel mechanisms. Other studies report conflicting findings with regard to capsaicin cough sensitivity in asthmatic patients compared with healthy control subjects; however, in these studies no consideration was given to whether airway

symptoms were induced by chemicals or not [5, 11, 26, 27]. The findings of a positive correlation between the capsaicin cough reaction and the symptom score confirm the value of using inhaled capsaicin to estimate the degree of sensory reactivity to chemicals. The strongest correlation was found between the symptom score from the lower airways and the capsaicin cough sensitivity, which is natural in view of the provocation target.

In the present study, there was an evident difference between patients having ASC or not with regard to age, indicating that increased age in atopic patients may be a confounding factor of developing an enhanced sensitivity of the airway sensory nerves. There was also a tendency of more women, as well as patients with cough and patients taking ICSs being among those with ASC, although the differences were not statistically significant, probably owing to the small size of the study.

The noxious, odourless substance capsaicin stimulates the non-myelinated slow C-fibres of the sensory nervous system via the genetically identified vanilloid receptor one (VR1) [28]. Other noxious stimuli-like chemicals with or without a smell may also evoke sensory nerve potentials via the 'VR family' on the C-fibres. C-fibre receptors can be found in all parts of the upper and lower airways and the alveoli. In the upper airways they originate mainly from the trigeminal nerve and in the lower airways, from the vagal nerve. Most C-fibres contain neuropeptides such as substance P, neurokinin A and neuropeptide K (all tachykinins), as well as calcitonin gene-related peptide (CGRP). Both in the upper and in the lower airways neuropeptides from afferent fibres can cause neurogenic inflammation with vasodilatation, plasma extravasation and mucus secretion, which may cause cough [29]. An increased sensitivity of the VR1 (shown with capsaicin cough reaction) may be related to a raised sensitivity to other noxious chemicals and hence contribute to what is perceived as 'chemical sensitivity' or 'sensitivity to strong scents' (since most chemicals also have a smell). The relation between the allergic inflammation and the increased sensory neural reactivity seems evident in this study, although further research is needed to clarify the mechanisms and the clinical implications of this connection.

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