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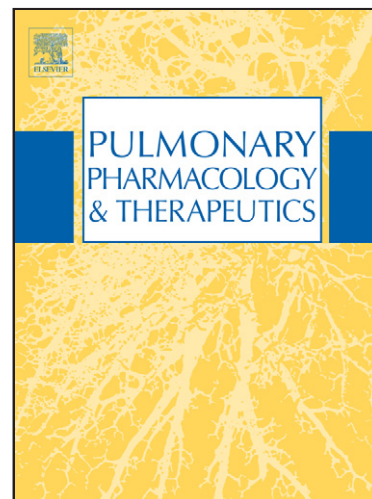
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**Inhaled ethanol potentiates the cough response to capsaicin in patients with  
airway sensory hyperreactivity**

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**Running title:** Inhaled ethanol potentiates the capsaicin cough response

**Keywords:** capsaicin, ethanol, chemical sensitivity, cough, human, sensory hyperreactivity

**Abbreviations:**

CI = Confidence interval

FEV<sub>1</sub> = Forced expiratory volume in one second

NS = Not significant

SHR = Sensory hyperreactivity

TRP channel = Transient receptor potential ion channel

TRPV1 = Transient receptor potential channel vanilloid subunit 1

TRPA1 = Transient receptor potential channel ankyrin subunit 1

**Abstract**

A suggested explanation for airway symptoms induced by chemicals and scents is sensory hyperreactivity (SHR) of airway mucosal nerves. Patients with SHR have increased cough sensitivity to inhaled capsaicin, mediated by transient receptor potential (TRP) ion channels.

In animal experiments, some TRP receptors are potentiated by ethanol, which is why in this study, the aim was to evaluate whether a pre-inhalation of ethanol could influence the capsaicin cough response in patients with SHR. Fifteen patients with SHR and 15 healthy controls were provoked on three occasions with two concentrations of inhaled capsaicin. Before each capsaicin provocation, a pre-inhalation of saline or one of two concentrations of ethanol was given in a double-blind, randomized fashion. The participants reacted in a dose-dependent way with cough on the capsaicin inhalations. Among the patients, but not in the control group, pre-inhalation of ethanol increased the cough response dose-dependently. The results suggest that the pathophysiology of SHR is related to airway mucosal TRP receptors in the sensory nerves. In scented products the combination of ethanol as a solvent and perfume may augment an airway reaction in sensitive individuals.

## 1. Introduction

Upper and lower airway symptoms induced by chemicals and scents are a common problem in society, and sometimes the experienced symptoms are excessive, leading individuals to seek health care [1,2]. A suggested explanation for this condition is a hyperreactivity of the sensory nerves of the entire airways. The condition is therefore called “sensory hyperreactivity (SHR)”, and it affects more than 6% of the adult population in Sweden [3]. Common symptoms are nasal blockage, rhinorrhea, eye irritation, heavy breathing, cough, hoarseness, and phlegm, as well as general symptoms, such as headache and nausea [4,5]. After capsaicin inhalation, changed levels of nerve growth factor in nasal secretions have been detected, indicating a neurochemical imbalance in the airways, which is related to SHR [6]. Cough sensitivity to capsaicin is a measure of airway sensory reactivity [7,8]. Patients with SHR react more strongly than healthy individuals to provocation with inhaled capsaicin, and the cutoff values for a positive reaction have been determined [4]. The capsaicin inhalation test in the diagnosis of SHR has good short-term and long-term reproducibility [5,9].

Capsaicin, the main, pungent ingredient in chili, stimulates the unmyelinated C-fibers of the sensory nervous system, giving a burning sensation by activating the ion channel of transient receptor potential vanilloid subunit 1 (TRPV1) [10]. This receptor is also activated by other stimuli, including noxious heat, lipids, and protons [11,12]. An increased expression of TRPV1 is found in several conditions characterized by general hypersensitivity, such as thermal hyperaesthesia, vulvodynia, rectal hypersensitivity, esophagitis, and chronic cough [13-18]. Recently, it has been found that ethanol potentiates the response of TRPV1 to capsaicin in different organs in rats

and guinea pigs [19-22]. If a corresponding effect could be achieved in humans, this would strongly indicate the role of the transient receptor potential (TRP) ion channels in the pathogenesis of SHR. In the future, the TRP ion channels may be an important key to understanding airway symptoms induced by chemicals and scents, our knowledge of which is so far limited. The aim of this study was therefore to evaluate whether pre-inhalation of ethanol could influence the capsaicin response in patients with SHR.

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## **2. Materials and Methods**

### **2.1. Subjects**

Fifteen non-smoking patients, 14 women and one man, 23–64 years old (mean age 53), with a history of at least 4 (mean 12) years of upper and lower airway symptoms induced by chemicals and scents, took part in the study. All had increased sensitivity to inhaled capsaicin and reached the cutoff for the diagnosis of SHR [4]. None of the patients demonstrated spirometric reversibility or variability in pulmonary function. Asthma was excluded by a negative methacholine test, in accordance with international guidelines [23]. All patients tested negative to the skin prick test with a standard panel of ten allergen sources common to Sweden.

The control group consisted of 15 non-smoking individuals, 14 women and one man, 21–62 years of age (mean age 42). None had a history of airway symptoms in response to exercise, scents, chemicals, or allergies, and none was taking any medication for the airways.

Informed consent was obtained from all subjects at the start of the investigation. The study was approved by the Regional Ethical Review Board of Gothenburg, Sweden.

### **2.2. Study design**

Each participant visited the clinic on three occasions. A capsaicin inhalation test was performed at each visit. Before each test a pre-inhalation was given in a double-blind and randomized fashion, of either 1 mL saline, or 1 mL of 5% or 25% ethanol.



### ***2.3. Capsaicin inhalation test***

A compressor (Pariboy 36; Paulritzau Pari-werk KG, Starnberg-am-See, Germany) and a nebulizer (Pari Inhalerboy, No. 36.75; Paulritzau Pari-werk KG, Starnberg-am-See, Germany) were used for inhalation of aqueous dilutions of the odorless capsaicin solution. The test was initiated with a pre-inhalation of either 1 mL saline, or 1 mL ethanol (5% or 25%) for 6 minutes, followed by 4 minutes of rest, as previously described [3,5]. Thereafter, the subject was provoked in the same manner with two concentrations of capsaicin, namely, first 0.4 and then 2.0  $\mu\text{mol/L}$ , in a 1 mL solution. Each dose of 1 mL was inhaled through a mouthpiece without a nose clip by tidal volume breathing to completion, or for a maximum of 6 min, followed by 4 min of rest. The total number of evoked coughs was counted for 10 minutes from the onset of each inhalation. Forced expiratory volume in 1 second ( $\text{FEV}_1$ ) was measured using a spirometer (Vitalograph, Buckingham, UK) before and after each provocation for evaluation of any bronchial obstruction.

### ***2.5. Statistics***

The Mann-Whitney  $U$ -test was used for non-paired data, and the Wilcoxon's signed-rank test for paired data. Data are presented as means with 95% confidence intervals (CIs). Results were considered significant at  $p < 0.05$ . All data were analyzed using StatView 5.0.1.0 (SAS Institute, Inc., Cary, NC, USA).

### 3. Results

At each provocation, the patients and controls coughed dose-dependently as an effect of the capsaicin inhalations. The number of coughs after 0.4 and 2.0  $\mu\text{mol/L}$  capsaicin differed significantly (Figure 1), with a probability value of  $<0.001$  for patients and  $<0.05$  for controls. The basic mean  $\text{FEV}_1$  value was 101% of predicted value (95% CI 93–109) among the patients and 100% of predicted value (95% CI 94–105) among the controls and did not change significantly after any of the provocations (data not shown).

#### *3.1. The effect of ethanol on the capsaicin inhalation test*

Pre-inhalation of ethanol increased dose-dependently the effect of capsaicin (2.0  $\mu\text{mol/L}$ ) in the patients (Figure 2). After the use of saline as pre-inhalation, the mean number of cough on 2.0  $\mu\text{mol/L}$  capsaicin was 38 (95% CI, 26 to 50), after 5% ethanol 47 (95% CI, 31 to 63) and after 25% ethanol 62 (95% CI, 40 to 83). The increase induced by 5% and 25% ethanol was statistically significant,  $p<0.05$  and  $p<0.01$ , respectively. No such effect of ethanol was seen in the control group, where after pre-inhalation of saline, the mean number of cough on 2.0  $\mu\text{mol/L}$  capsaicin was 6 (95% CI, 2 to 10), after 5% ethanol 6 (95% CI, 3 to 9) and after 25% ethanol 7 (95% CI, 3 to 11) (Figure 2).

#### 4. Discussion

In this study, patients with SHR showed to be more cough sensitive to inhaled capsaicin when the provocation was preceded by an inhalation of ethanol. A pre-inhalation of 5% or 25% ethanol enhanced the cough reaction to capsaicin. A control group without airway symptoms did not have the corresponding reactions and coughed significantly less than the patients in accordance with earlier studies [3,5,24]. Since there were no changes of FEV<sub>1</sub> after any provocation the cough reactions can not be regarded as due to bronchoconstriction and asthma.

During the last years there has been an increasing interest for the family of transient receptor (TRP) ion channels. They are important by means for multiple organ systems to interact with their environment [25,26]. They are able to sense temperature, stretch, osmolarity and pain, among others and may be involved in different diseases by an increased level of channel expression [26,27]. The TRPV1, belonging to one of the six subfamilies of TRP ion channels, is not only activated by capsaicin but also by noxious stimuli and heat, and potentiated by extracellular acidic pH, and interacts with vanilloid-like compounds [28-30]. Patients with chronic cough have shown a five-folded increase of TRPV1-staining nerve profiles and, furthermore, a significant correlation between capsaicin response and the number of TRPV1-positive nerves [18]. Hopefully, specific TRPV1 antagonists could be useful in treating disorders such as pain, chronic cough, and irritable bowel syndrome [31]. Also the ion channel TRPA1 (Transient receptor potential channel ankyrin subunit 1) is activated by a variety of noxious stimuli, including cold temperatures, pungent natural compounds, and environmental irritants [32]. Many "sensory compounds" presumed to be specific have a promiscuous relationship with different TRP channels [33].

The present outcome also agrees with earlier findings in animals. In biopsies from rat spinal cord, oesophagus and skin, ethanol potentiated the response of TRPV1 to capsaicin and protons and lowered the threshold for heat activation of TRPV1 [19,20]. In guinea pig airways, in vitro, ethanol stimulated peptidergic primary sensory neurons and caused TRPV1-dependant inflammation which was interpreted as a possible proof of the role of the TRPV1 in asthma [19]. Although it has been proven in many studies that inhaled capsaicin causes powerful bronchoconstriction in guinea pigs [34,35] this connection is not that evident in humans [36-39]. However, there seems to be a similar pattern in different organ systems and in different species that ethanol enhances stimuli with a potential to be irritating but to our knowledge this has not earlier been shown in human. In scented products the combination of ethanol as a solvent and perfume may augment an airway reaction in sensitive individuals. The results of the present study indicate an ethanol-mediated modulation of the TRPV1 or TRPA1 function. Still it is unclear whether this effect is specific like that in animal studies or nonspecific, as the fact that the patients coughed even after saline inhalations indicate.

The tidal breathing method of capsaicin challenge, used in the present study, was developed for SHR and has been modified with time and has shown good reproducibility [5,9,24,40]. The testing of cough sensitivity with capsaicin inhalation is otherwise often performed with a "single-breath" technique using increasing concentrations of capsaicin until the individual coughs, for example, two or five times (C2 or C5), which has shown a good reproducibility [41,42]. Others, who used both techniques, found that the tidal breathing method with a fixed time and concentration

showed good reproducibility and dose-response relationship in the short term, as well as in the long term [8,43]. The single-breath technique was more dependent on a standardized inhalation technique compared to the fixed time and concentration technique [44]. One potential problem with using the “single-breath” technique is that patients with SHR have an easily evoked cough reflex, and even inhalation of saline can induce coughing [9,40]. The occurrence of a tachyphylaxis problem after performing the test with the single-breath technique speaks in favour of the tidal breathing technique used in this study, which has also been discussed by other authors [45].

In conclusion, our present results suggest that the pathophysiology behind SHR is related to TRP receptors of the sensory nerves in the airway mucosa and that patients with SHR differ from healthy controls in that respect.

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**Legends**

## Figure 1

Mean number of coughs ( $\pm$  95% confidence intervals, CIs) after inhalation of saline and capsaicin in 15 patients with sensory hyperreactivity (SHR) (squares) and 15 control subjects (circles) on provocation with 0.4 and 2.0  $\mu\text{mol/L}$  capsaicin.

## Figure 2

Mean number of coughs ( $\pm$  95% confidence intervals, CIs) after inhalation of capsaicin in 15 patients with sensory hyperreactivity (SHR) (dark bars) and 15 control subjects (light bars) on provocation with 2.0  $\mu\text{mol/L}$  capsaicin after pre-inhalation of either saline, or 5% or 25% ethanol.

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Figure 1

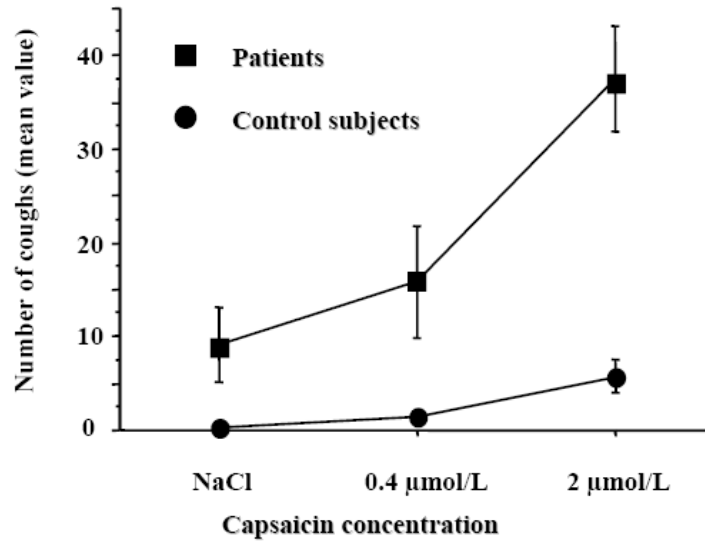


Figure 2

