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Original Article

Capsaicin provocation test as a diagnostic method for determining multiple chemical sensitivity

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Abstract

Background: Multiple chemical sensitivity (MCS) is characterized by chemically induced symptoms from multiple organs. These symptoms occur in response to demonstrable exposure to chemically unrelated compounds at doses far below those known to cause harmful effects in the general population. Although the mechanism of this action remains unclear and no acceptable and well-documented treatment for MCS has yet been established, regarding neurogenic inflammation, it has been hypothesized that an increased density of C-fiber neurons is found in symptomatic tissues.

Methods: Using capsaicin, we examined the sensitivity of the cough reflex in patients with MCS and chronic cough (CC) and compared the findings with those in control subjects. Fifteen patients (four males, 11 females; mean (± SD) age 38.3 ± 16.3 years) suffering from MCS and 29 patients (10 males, 19 females; mean age 46.4 ± 15.9 years) who had cough symptoms lasting 4 weeks or longer and normal chest radiograph findings (CC) were enrolled in the present study. Twenty-nine healthy subjects (14 males, 15 females; mean age 37.9 ± 9.5 years) who had no history of coughing during the previous 6 months and no chronic respiratory diseases were enrolled as controls. Subjects inhaled stepwise incremental concentrations of capsaicin (0.122–62.5 μmol/L) for 15 s. Inhalation was performed at 45 s intervals and the number of coughs per minute was counted. The provocation was terminated when the subject coughed five or more times. Ventilatory functions (forced vital capacity (FVC), forced expiratory volume in 1 s and the expiratory flow rate at 50 and 75% FVC (V_{50} and V_{25}, respectively)) were also measured.

Results: No significant differences were observed in ventilatory function test findings between the three groups. The log concentration of capsaicin causing five or more coughs (C5) was 0.150 ± 0.630, 0.611 ± 0.691 and 1.120 ± 0.612 μmol/L in MCS, CC and control subjects, respectively. The log C5 in MCS subjects was significantly lower than that in CC and control subjects.

Conclusions: Capsaicin is a cough-inducing agent in humans that possibly acts on non-myelinated C-fiber endings. The findings of the present study indicate that the mechanisms underlying MCS may originate in the sensory nervous system.

Key words: capsaicin provocation test, C-fiber, chronic cough, multiple chemical sensitivity, sensory hyperreactivity.

Introduction

Multiple chemical sensitivity (MCS) is a condition where previous exposure to hydrophobic organic solvents or pesticides appears to render people hypersensitive to a wide range of chemicals, including organic solvents.[1] It is also known as a 20th century disease and is called 'chemically acquired immunodeficiency syndrome', 'the total allergy syndrome' and 'idiopathic environmental intolerance'.[2,3]

In Japan, patients who demonstrate symptoms of headaches, dizziness, fatigue and eye irritation associated with their houses are diagnosed as having 'sick

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house syndrome' (SHS), a syndrome that was was named after 'sick building syndrome'.[4] These two diseases are very similar. Although the clinical features of MCS and SHS resemble those of asthma and allergy, the objective findings, including ventilatory function and bronchial methacholine tests, are normal, and skin prick tests or serum IgE and specific IgE show no evidence of allergy.

Although the pathophysiologic mechanisms underlying these conditions are not clear, some hypotheses have been proposed. One hypothesis is neurogenic inflammation; namely, an increased density of C-fiber neurons in symptomatic tissue.[5]

Capsaicin, the pungent ingredient in red pepper, is known to stimulate unmyelinated slow C-fibers of the sensory nervous system and it has been used to induce coughing in provocation models.[6,7]

The aim of the present study was to investigate the usefulness of a capsaicin provocation test as a diagnostic method for MCS. We hypothesized that the mechanism of MCS may be sensory hyperreactivity.

METHODS

The capsaicin provocation test was conducted according to the method reported previously.[8] Briefly, capsaicin (Sigma Chemical, St Louis, MO, USA) was dissolved in absolute ethanol to make a stock solution of 10^{-2} mol/L, which was further diluted with 0.9% saline to produce doubling concentrations from 0.122 to 62.5 μmol/L. Each dose was administered with a 1.40 kg force/cm^2 driving pressure from a PARI BOY with an LC PLUS jet nebulizer (PARI, Starnberg, Germany) filled with 5 mL solution. The output of this nebulizer is approximately 0.20 g/min and the mass median diameter of the aerosol droplets is 3.8 μm. Subjects wore nose clips and were instructed to breathe normally (tidal breathing through the mouthpiece). Subjects inhaled stepwise incremental concentrations of capsaicin for 15 s. Each inhalation was given at 45 s intervals and the number of coughs during that minute was counted. The provocation was terminated when the subject coughed five or more times per minute.

The log concentration of capsaicin causing five or more coughs (C5) was measured in each group.

Ventilatory functions (forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and expiratory flow rate at 50 and 75% FVC (V_{50} and V_{25}, respectively)) were also measured using a hot-wire pneumotach (Autospiro AS-300; Minato, Osaka, Japan) just before and after the capsaicin provocation test.

Blood samples were taken to measure peripheral eosinophil counts, serum IgE and specific serum IgE (RAST, house dust, mite and cedar pollen).

Subjects

Fifteen patients (four males, 11 females; mean (± SD) age 38.3 ± 16.3 years) were enrolled as the MCS group. All patients satisfied Cullen's criteria[1] for MCS. They presented with the following symptoms: headaches, dizziness, fatigue and eye irritation. All these sumptoms were associated with the subjects' houses (diagnosed as SHS[4]). Subjects had never had a history of wheezing. The methacholine challenge tests using the Astograph method showed that these MCS patients had no bronchial hypersensitivity. Twenty-nine patients (10 males, 19 females; mean age 46.4 ± 15.9 years) who had cough symptoms lasting 4 weeks or longer and normal chest radiographs were also enrolled as a chronic cough (CC) group. As a control, 29 healthy subjects (14 males, 15 females; mean age, 38.9 ± 9.5 years), who had no history of coughing during the previous 6 months and no chronic respiratory diseases, were enrolled.

All subjects underwent a standard clinical assessment, which included a history and associated diseases, and physical examination, a medical questionnaire and a chest roentgenogram.

None of the subjects used any medication either 24 h before or during the study periods. Informed consent was obtained from all subjects and this study was approved by the Medical Ethics Committee at National Minami Fukuoka Chest Hospital.

Statistics and calculations

Ventilatory functions are expressed as the mean ± SD and logarithmic transformation was applied to the concentration of capsaicin (μmol/L) before performing the analysis. An analysis of variance on ranks was performed as a general test (Kruskal–Wallis test). If the results of this test were statistically significant, then a non-parametric test (Wilcoxon's two sample) was used for a pairwise post hoc comparison of the groups. Statistical significance was considered to exist at $P < 0.05$.

RESULTS

Table 1 shows the characteristics of the subjects. As indicated, there were no differences in ventilatory

function among the three groups. Total IgE and specific IgE were measured in the MCS and CC groups. There was no significant difference in total IgE between the two groups. The MCS subjects had higher cedar pollen IgE than CC subjects because more MCS subjects had pollinosis. The number of peripheral blood eosinophils was 137.2 ± 168.0, 144.2 ± 101.1 and 176.0 ± 141.9 /mm^3 in MCS, CC, and control subjects, respectively.

The log concentration of capsaicin causing five or more coughs (C5) was 0.150 ± 0.630, 0.611 ± 0.691 and 1.120 ± 0.612 μmol/L in MCS, CC, and control subjects, respectively. The log C5 in MCS subjects was significantly lower than that in CC and control subjects (Fig. 1).

Discussion

The present study confirmed that coughing was more easily induced by capsaicin in MCS patients than in either the chronic cough patients or healthy controls.

The sensitivity of the cough reflex may originate in the sensory nervous system and may be due to either an increase in sensory nerve cell endings or a remodulation of the nerve receptor so that it becomes sensitized. Capsaicin (*trans*-8-methyl-*N*-vanillyl-6-nonenamide), a pungent agent of red pepper, is a commonly used non-acid tussigenic agent. Capsaicin acts mainly on the afferent neurons of non-myelinated C-fibers by opening a non-selective cation channel of the vanilloid receptor, thus resulting in a flow of calcium and sodium ions down their concentration gradient.[9,10] This leads to depolarization and is associated with neurotransmitter release. Specifically, capsaicin is a cough-inducing agent in humans by possibly acting on non-myelinated C-fiber endings.[11]

The cough provocation test by capsaicin is a simple and reproducible laboratory method for assessing cough susceptibility in a wide range of diseases.[7]

In MCS conditions, the symptoms from various organs are induced by low concentrations of various chemical inhalants.[1] The role of C-fibers in MCS remains controversial and several hypotheses have been proposed.

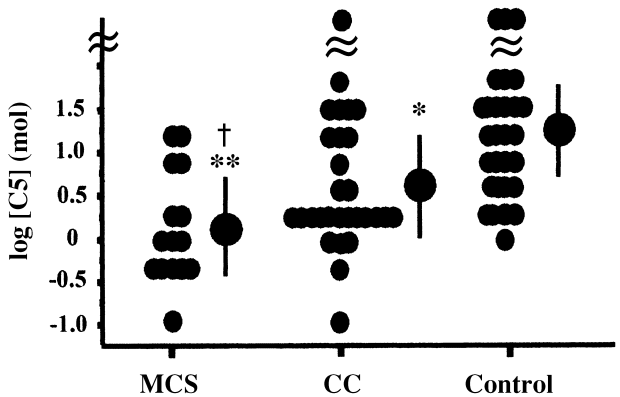

Fig. 1 Comparison of the capsaicin concentration values causing five or more coughs (C5) between the multiple chemical sensitivity (MCS), chronic cough (CC) and control groups. The log concentration of C5 was 0.150 ± 0.630, 0.611 ± 0.691 and 1.120 ± 0.612 μmol/L in the MCS, CC and control groups, respectively. *$P < 0.005$, **$P < 0.0001$ compared with control; †$P < 0.03$ compared with CC.

Table 1 Characteristics of subjects

Group	MCS	CC	Control	*P*
No. subjects (male/female)	15 (4/11)	29 (10/19)	29 (14/15)	
Age (years)	38.3 ± 16.3	46.4 ± 15.9	37.9 ± 9.5	NS
log IgE (IU/mL)	1.827 ± 0.961	1.736 ± 0.586		NS
RAST HD ≥ 2 (%)	12.5	29.2		NS
RAST Mite ≥ 2 (%)	33.3	34.6		NS
RAST Cedar pollen ≥ 2 (%)	66.7	19.2		< 0.01
Peripheral Eo (/mm^3)	137.2 ± 168.0	144.2 ± 101.1	176.0 ± 141.9	NS
%FVC	96.2 ± 12.5	95.8 ± 11.1	98.2 ± 11.1	NS
$FEV_{1.0}$/FVC%	88.0 ± 6.8	87.9 ± 7.5	86.6 ± 5.6	NS
$\%V_{50}$	84.2 ± 26.5	80.6 ± 19.2	81.5 ± 18.4	NS
$\%V_{25}$	76.4 ± 35.9	71.8 ± 23.0	61.8 ± 15.0	NS
No. polinosis (%)	7 (46.7)	3 (10.3)	0 (0)	
No. atopic dermatitis (%)	2 (13.3)	0 (0)	0 (0)	
No. rheumatoid arthritis (%)	0 (0)	2 (6.9)	0 (0)	

Where appropriate, data are the mean ± SD.

Eo, eosinophils; FVC, forced vital capacity; $FEV_{1.0}$, forced expiratory volume in 1 s; MCS, multiple chemical sensitivity; CC, chronic cough; V_{50}, V_{25}, expiratory flow rate at 50 and 75% FVC, respectively.

One hypothesis suggests that MCS patients produce greater quantities of neuropeptides and prostanoids than non-sensitive subjects in response to exposure to low levels of capsaicin or irritant chemicals. As a result, MCS patients are considered to have an increased density of C-fiber neurons in symptomatic organs.[5] Although we had no direct evidence, our results could support this hypothesis.

Multiple chemical sensitivity has been classified as a psychologic disorder disease and has been rejected as an established organ disease because it has not been possible to provoke the symptoms.[12] Our results showed that the mechanisms underlying the symptoms demonstrated by patients with MCS may originate in the sensory nervous system, namely, MCS may be a condition of sensory hyperreactivity. Millqvist *et al*.[13,14] reported that MCS patients coughed more than control subjects after the inhalation of capsaicin. They concluded that airway sensory reactivity increased in patients with MCS, a finding that suggests neurogenic factors may play an important role in this phenomenon. In the present study, we compared the cough sensitivity of MCS subjects with that of CC and control subjects. Consequently, the cough sensitivity of MCS subjects was found to be still lower than that of CC subjects.

Chronic cough can be caused by many diseases, such as post-nasal drip syndrome (PNSD), gastroesophageal reflux (GERD), bronchial asthma, including cough variant asthma (CVA), chronic bronchitis due to smoking and eosinophilic bronchitis.[15] Postinfectious coughing is also an important cause of chronic cough, such as in post-viral infections. The sensitivity of the cough reflex in these chronic cough patients depends on the basic disease of each patient. For example, the sensitivity of the cough reflex in CVA patients is normal, whereas sensitivity is high in eosinophilic bronchitis patients.[16] In the present study, the values of log C5 varied greatly from low to high. The average log C5 in CC subjects was significantly higher than that in MCS subjects and significantly lower than that in control subjects.

Although almost all MCS patients had no cough, the log C5 in MCS was significantly lower than that for CC subjects and this was a surprising result.

The pathophysiologic mechanisms of MCS remain to be elucidated and there is still no useful method for diagnosing MCS, except for the noxious gas provocation test, such as the formalin provocation test. The noxious gas provocation test is very complex and costly. In addition, this test needs a special room for the provocation. Moreover, because there are many different types of noxious gas, the causative substance is often unproven. However, the capsaicin provocation test is both easier and cheaper to perform. If the patient has a high sensitivity for capsaicin (i.e. C5 is low) and symptoms of headaches, dizziness, fatigue and eye irritation, the diagnosis of MCS may be suggested. Therefore, capsaicin provocation may be a potentially useful modality for diagnosing patients with MCS.

Further studies are called for to clarify the precise mechanism of MCS.

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