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Prostanoids and cough response to capsaicin in asthma and chronic bronchitis

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Prostanoids and cough response to capsaicin in asthma and chronic bronchitis. M. Fujimura, Y. Kamio, K. Kasahara, T. Bando, T. Hashimoto, T. Matsuda. ©ERS Journals Ltd 1995.

ABSTRACT: Cyclooxygenase products are released by chronic airway inflammation. Our working hypothesis for the present study was that prostanoids augment airway cough sensitivity.

The effects of a cyclooxygenase inhibitor, indomethacin (100 mg·day^{-1} for 4 days), and a thromboxane synthesis inhibitor, OKY-046 (400 mg·day^{-1} for 4 days), on cough response to inhaled capsaicin were examined in eight patients with asthma, 10 patients with chronic bronchitis, and 10 normal subjects. Capsaicin cough threshold, the lowest concentration of capsaicin eliciting five or more coughs, was measured as an index of airway cough sensitivity.

In asthmatics, the cough thresholds with indomethacin treatment (15.7 (GSEM 1.38) μM) and OKY-046 (10.2 (GSEM 1.20) μM) were significantly greater than the value with placebo (6.05 (GSEM 1.25) μM). In patients with chronic bronchitis, the cough threshold was significantly greater with indomethacin (5.94 (GSEM 1.50) μM) than with placebo (3.41 (GSEM 1.33) μM and OKY-046 2.97 (GSEM 1.43) μM). In normal subjects, the capsaicin cough threshold was not altered by indomethacin or OKY-046 treatment.

These results support our hypothesis and suggest that thromboxane A_2 may be one of the cyclooxygenase products augmenting airway cough sensitivity in asthma, but not in chronic bronchitis.

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Cough is a major manifestation of respiratory disease. Cough reflex testing has been used to study the pathophysiology of the cough reflex and the antitussive effects of various drugs. Capsaicin, which is the active ingredient of red pepper, is a commonly used cough receptor stimulant, and has been presumed to produce cough mainly by stimulating C-fibre endings [1–3]. We have previously reported that airway cough sensitivity to inhaled tartaric acid was heightened in patients with chronic bronchitis but not bronchial asthma, compared with normal subjects [4]. As bronchial asthma consists of chronic airway inflammation with eosinophils and lymphocytes [5], and since neutrophil and lymphocyte infiltration into the airway wall is seen in chronic bronchitis [6], these two airway diseases involve chronic airway inflammation.

We have also shown that bronchial responsiveness to methacholine is reduced by indomethacin in patients with chronic bronchitis, and by a thromboxane synthetase inhibitor OKY-046 in asthmatic patients [7]. In addition, it has been shown that prostaglandin E_2 and $F_{2\alpha}$ augment cough induced by capsaicin in normal subjects [8, 9]. From these findings, we hypothesized that cyclooxygenase products, including thromboxane A_2 (TxA_2), as inflammatory mediators may modulate airway cough sensitivity. Indeed, our preliminary study [10] showed that cough sensitivity to inhaled capsaicin was reduced by indomethacin in patients with chronic bronchitis. This study was designed to clarify the hypothesis. Therefore, the effects of a cyclooxygenase inhibitor, indomethacin, and a selective thromboxane synthetase inhibitor, OKY-046 [11], on cough induced by inhaled capsaicin were examined in patients with asthma and chronic bronchitis and in normal subjects.

OKY-046 is a selective thromboxane synthetase inhibitor [11]. It is named as ozagrel hydrochloride (Domenan® Kissei Pharmaceuical Co., Ltd., Matsumoto, Japan, Bega®, Ono Pharmaceutical Co., Ltd., Osaka, Japan), and has been prescribed as an anti-asthma drug since June 1992 in Japan. The dose of 400 mg·day^{-1} tested in this study is the usual dose recommended to treat asthma. It has been proved by Phase II and III study for treatment of asthma.

Subjects and methods

Subjects

Eight patients with asthma (6 males and two females), with a mean age of 62 (range 52–72) yrs, 10 patients with chronic bronchitis (6 males and 4 females), with a

Table 1. – Characteristics of patients with asthma or chronic bronchitis

Patient No.	Age yrs	Sex	Height cm	Weight kg	Smoking	Sinus radiograph*	Sputum bacteria	Treatment
Asthma								
1	72	M	162	57	Never	++	-	Theo, Clen, Carbo
2	64	F	156	70	Never	NT	-	Theo, Carbo, Pro
3	60	M	161	54	Never	+	-	Carbo, Pro
4	59	M	170	51	Never	-	-	Carbo, Pro
5	63	M	166	65	Ex (1)	-	-	Theo, Carbo, Pro
6	62	F	147	60	Never	-	-	Theo, Clen, Carbo, Pro
7	61	M	164	58	Ex (3)	-	-	Theo, Carbo, Pro
8	52	M	158	74	Ex (1)	+	-	Theo, Clen, Carbo
Chronic bronchitis								
9	65	M	160	58	Never	+++	St, H	Carbo, EM
10	79	M	154	52	Ex (17)	+++	St	Carbo, Amb, EM
11	72	F	148	53	Never	++	H	Carbo
12	75	F	151	41	Never	+++	H	Carbo, EM
13	71	M	170	65	Never	++	H	Carbo
14	71	M	168	74	Ex (7)	+++	K	Carbo, EM
15	63	M	177	75	Never	+++	B	Carbo
16	48	M	150	52	Ex (5)	++	H	Carbo
17	33	F	162	48	Never	++	H	Carbo
18	60	F	147	50	Never	+++	H	Carbo, EM
Difference	NS	NS	NS	NS	NS	$p<0.001$		

Never: lifetime nonsmoker; Ex: ex-smoker (years after cessation in parenthesis). *: +++ = severe; ++ = moderate; + = mild; - = negative regarding abnormal findings on sinus radiograph. H: *Haemophilus influenzae*; St: *Streptococcus pneumoniae*; B: *Branhamella catarrhalis*; K: *Klebsiella pneumonia* cultured from sputum. Theo: theophylline; Pro: inhaled procaterol on demand; Clen: clenbuterol; Carbo: carbocisteine; Amb: ambroxol; EM: long-term, low dose erythromycin (300–600 mg·day^{-1}).

mean age of 64 (range 33–79) yrs, and 10 normal subjects (5 males and 5 females), with a mean age of 56 (range 43–74) yrs, participated in this study. All subjects were lifetime nonsmokers or ex-smokers with no history of viral infection for at least 4 weeks prior to the study. Baseline pulmonary function data in patients with asthma and chronic bronchitis and in normal subjects are shown in table 1. Informed consent was obtained from all subjects. This study was approved by the Ethics Committee of our university hospital.

Each asthmatic patient satisfied the American Thoracic Society (ATS) definition of asthma, with symptoms of episodic wheezing, cough, and shortness of breath responding to bronchodilators, and reversible airflow obstruction documented on at least one previous pulmonary function study [6]. Reversibility was defined as a greater than 15% increase in the forced expiratory volume in one second (FEV_1) following a bronchodilator inhalation [12]. The mean value (±SEM) of % increase in FEV_1 by inhalation of salbutamol (300 µg) was 29 (±8) % in the eight patients. All patients had intrinsic asthma with no familial history of allergic diseases, no increased levels of specific immunoglobulin E (IgE) antibodies, and no positive skin test to 10 common allergens.

Although all patients with chronic bronchitis satisfied the definition recommended by the ATS [6], they were diagnosed as sinobronchial syndrome. Sinobronchial syndrome is a common bronchial disorder in Japan, which is not related to smoking. We provide some details, as it is not recognized as a diagnostic category by the ATS. Sinobronchial syndrome is defined as a coexisting chronic sinusitis and nonspecific chronic inflammatory lesion of the lower airways presenting with expectoration (*e.g.* chronic bronchitis, diffuse bronchiectasis, and diffuse panbronchiolitis [13]). SUZAKI *et al.* [14] reported that the sinobronchial syndrome was found in 10% of 309 patients with chronic sinusitis and in 55% of 74 patients with chronic lower respiratory infectious diseases. They suggested that there is a gene controlling the susceptibility to sinobronchial syndrome, especially diffuse panbronchiolitis, which was significantly associated with human leucocyte antigen (HLA)-Bw54; this was found specifically in Japanese and not in Caucasians. The obstructive form of sinobronchial syndrome is known as "diffuse panbronchiolitis" [13].

Recognition of the sinobronchial syndrome is very important in Japan because long-term, low dose erythromycin therapy is specifically effective [15], as inhaled steroid therapy is for bronchial asthma. In our patients, diagnosis of the sinobronchial syndrome was based on the following criteria: 1) recurrent productive cough for at least 3 months over two consecutive years; 2) chronic sinusitis; 3) lack of a history of wheezing or asthma; 4) lack of significant emphysema documented on chest computed tomographic scan. A diagnosis of chronic sinusitis was based on symptoms (postnasal drip, nasal discharge, and nasal obstruction), physical examination, and radiography.

Clinical characteristics of our patients are shown in table 1. None had perennial or vasomotor rhinitis. They

were taking oral mucolytic agents, such as carbocisteine and ambroxol, but not theophylline, β_2-adrenoceptor stimulants, or steroids. The mean value (±SEM) of % increase in FEV1 by inhalation of salbutamol (300 µg) was 3.3 (±1.2) % in the 10 patients.

Normal subjects were chosen when they had no respiratory symptom, such as cough, sputum, wheeze, dyspnoea attack, nasal obstruction, nasal discharge or postnasal drip, on the questionnaire.

This study was carried out when symptoms were mild and stable, while patients were taking oral theophylline (Theo-Dur®, Nikken Chemical Co., Ltd., Tokyo, Japan), oral (short-acting clenbuterol) and/or aerosol β_2-agonists (short-acting procaterol) and/or mucolytic agents (carbocisteine) (table 1). They had not received inhaled or oral steroid therapy for at least 8 weeks.

Assessment of cough receptor sensitivity to inhaled capsaicin

Cough receptor sensitivity was measured by capsaicin provocation test [16]. Capsaicin (30.5 mg) was dissolved in Tween 80 (1 mL) and ethanol (1 mL) and then dissolved in physiological saline (8 mL) to make a stock solution of 1×10^{-2} M, which was stored at -20°C. This solution was diluted with physiological saline to make solutions starting at a concentration of 0.49 µM and increasing by doubling concentrations up to 1000 µM. Each subject inhaled a control solution of physiological saline followed by progressively increasing concentrations of the capsaicin solution. Solutions were inhaled for 15 s every 60 s, by tidal mouth-breathing wearing a noseclip from a Bennett Twin nebulizer (3012-60cc, Puritan-Bennett Co., Carlsbad, California, USA). Increasing concentrations were inhaled until five or more coughs were elicited. The nebulizer output was 0.21 $mL\cdot min^{-1}$. Capsaicin-induced cough number was counted by a blinded medical technician in our pulmonary function laboratory. Cough threshold was defined as the lowest concentration of capsaicin that elicited five or more coughs.

Study protocol

In patients with asthma and chronic bronchitis, the medication was stopped at 9.00 p.m. on the previous day to allow a washout time of 12 h or more before the measurements of cough threshold to inhaled capsaicin at 10.00 a.m. on each test day.

Each subject attended on 3 days, separated by 14 days, at the same time of day. Treatment with indomethacin, OKY-046, and placebo was performed in a double-blind, randomized, cross-over fashion. Indomethacin capsule (25 mg) was given orally four times a day for 3 days, and at 8.00 a.m. on the 4th day (test day). OKY-046 tablet (200 mg) was taken orally twice a day for 3 days, and at 8.00 a.m. on the test day. FEV1 was measured on a dry wedge spirometer (Transfer Test, P.K. Morgan Ltd, UK) before capsaicin challenge to assess bronchoactive effect of the treatment regimens.

Data analysis

Capsaicin cough threshold values were expressed as geometric means with the geometric standard error of the mean (GSEM). FEV1 was shown as arithmetic mean value±SEM. The cough threshold values and the FEV1 values were compared between the three treatment regimens by the Wilcoxon's signed rank test. To assess the difference in the cough threshold between any pair of patients with asthma, patients with chronic bronchitis, and normal subjects, the Mann-Whitney U-test was employed. To compare the changes in cough threshold induced by indomethacin or OKY-046 as compared to the value with placebo between patients with asthma and chronic bronchitis and normal subjects, the ratio of the cough threshold with indomethacin or OKY-046 to the cough threshold with placebo was compared by analysis of variance (ANOVA) followed by Fisher's Protected Least Significant Difference (PLSD). In assessing the correlations of cough threshold to age, height, weight, forced vital capacity (FVC), FEV1 and FEV1/FVC ratio, Spearman rank correlation analysis was employed. A p-value of 0.05 or less was taken as significant.

Results

Geometric mean value of the cough threshold to inhaled capsaicin after treatment with placebo was 6.05 (GSEM 1.25), 3.41 (GSEM 1.33) and 20.6 (GSEM 1.46) µM in patients with asthma and chronic bronchitis and normal subjects, respectively. The value was significantly lower in patients with asthma ($p<0.02$) and bronchitis ($p<0.01$) than in normal subjects. There was no significant difference in the cough threshold between asthmatic and bronchitic patients.

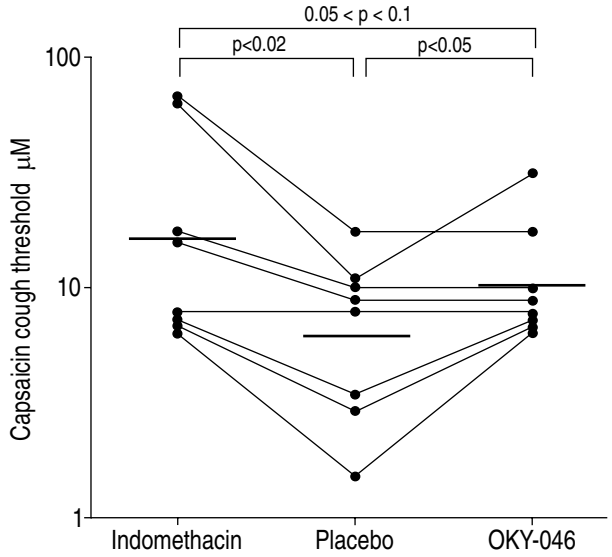

Fig. 1. – Effect of indomethacin and OKY-046 on the capsaicin cough threshold in eight patients with asthma. Capsaicin cough threshold was defined as the lowest concentration of capsaicin solution eliciting five or more coughs. Each horizontal bar represents geometric mean value. Differences in the cough threshold among treatments with indomethacin, OKY-046 and placebo were analysed by Wilcoxon signed rank test.

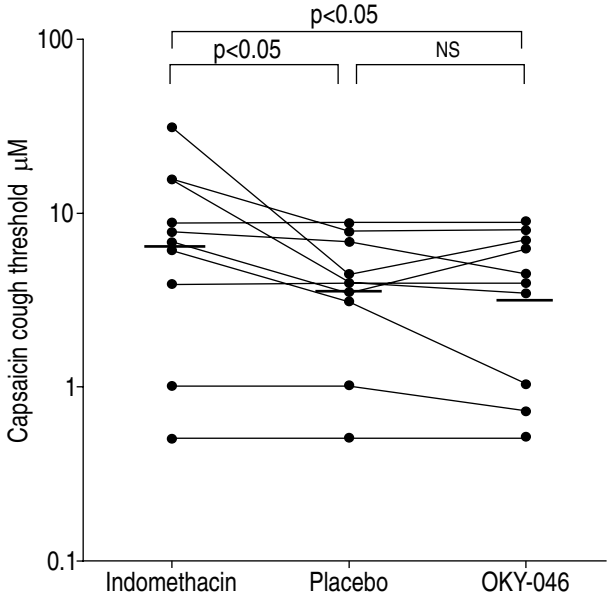

Fig. 2. – Effect of indomethacin and OKY-046 on the capsaicin cough threshold in 10 patients with chronic bronchitis. Capsaicin cough threshold was defined as the lowest concentration of capsaicin solution eliciting five or more coughs. Each horizontal bar represents geometric mean value. Differences in the cough threshold among treatments with indomethacin, OKY-046 and placebo were analysed by Wilcoxon signed rank test. NS: not significant.

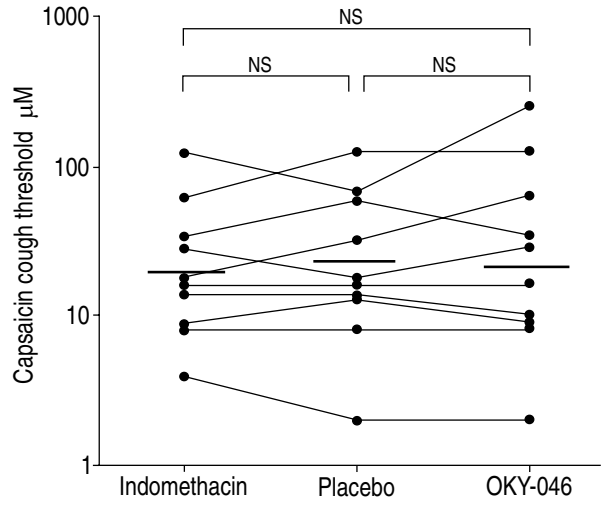

Fig. 3. – Effect of indomethacin and OKY-046 on the capsaicin cough threshold in 10 normal subjects. Capsaicin cough threshold was defined as the lowest concentration of capsaicin solution eliciting five or more coughs. Each horizontal bar represents geometric mean value. NS: not significant.

In asthmatic patients, the cough thresholds after the indomethacin treatment (15.7 (GSEM 1.38) μM) and OKY-046 treatment (10.2 (GSEM 1.20) μM) were significantly greater than the value after the placebo (6.05 (GSEM 1.25) μM) ($p<0.02$ and $p<0.05$, respectively). The value with the indomethacin treatment was not significantly ($0.05 < p < 0.1$) different from that with the OKY-046 treatment (fig. 1). FEV_1 value was 1.71±0.16, 1.66±0.20 and 1.65±0.16 L after treatment with indomethacin, OKY-046 and placebo, respectively. There were no significant differences between any pair of these values.

In patients with chronic bronchitis, the cough threshold after the indomethacin treatment (5.94 (GSEM 1.50) μM) was significantly ($p<0.05$ and $p<0.05$) greater than the values after the placebo and OKY-046 treatments (2.97 (GSEM 1.43) μM). These values were not different between the placebo and OKY-046 treatments (fig. 2). FEV_1 value was 2.12±0.19, 2.14±0.19 and 2.11±0.17 L after treatment with indomethacin, OKY-046 and placebo, respectively. There were no significant differences between any pair of these values.

In normal subjects, the capsaicin cough threshold was 19.3 (GSEM 1.39), 19.3 (GSEM 1.49) and 20.6 (GSEM 1.46) μM after the treatment with indomethacin, OKY-046 and placebo, respectively. There were no significant differences between these values (fig. 3). FEV_1 values were 2.68±0.26, 2.70±0.25, and 2.67±0.25 L with indomethacin, OKY-046, and placebo, respectively, and these values did not differ from each other.

Changes in the cough threshold by treatment with indomethacin or OKY-046 in relation to the value with placebo in the three groups are summarized in table 2. The change with the indomethacin treatment was significantly (ANOVA, $p<0.01$) different between the three groups: the value being significantly greater in asthmatic patients ($p<0.01$) and in bronchitic patients ($p<0.05$) as compared with normal subjects. Although there was no significant difference ($0.05 < p < 0.1$) in the change in cough threshold with OKY-046 between the three groups using ANOVA, the value was greater in patients with asthma than in patients with chronic bronchitis ($p<0.05$) and normal subjects ($0.05 < p < 0.1$).

Table 3 summarizes differences in age, height and pulmonary function between any pair of three groups and results of simple regression analysis between the cough threshold and these parameters. Logarithmic value of capsaicin cough threshold significantly correlated to FVC but not to the other parameters when analysed in all subjects.

Table 2. – Changes† in capsaicin cough threshold with indomethacin and OKY-046 treatments in relation to placebo treatment in patients with asthma and chronic bronchitis and normal subjects

Treatment	Asthma	Chronic bronchitis	Normal control	p-value
Indomethacin	2.60 (1.25)**	1.74 (1.25)*	0.93 (1.21)	$p<0.01$
OKY-046	1.68 (1.24)+	0.93 (1.21)	1.00 (1.20)	$0.05 < p < 1.0$

†: Data are presented as geometric mean value (geometric standard error of the mean) for the ratio of cough threshold with indomethacin or OKY-046 to cough threshold with placebo. Differences among three groups were analyzed by analysis of variance (ANOVA). **: $p<0.001$ and *: $p<0.04$, compared with control group; +: $p<0.05$ compared with bronchitis group and $0.05 < p < 0.1$ compared with control group by Fisher's Protected Least Significant Difference (PLSD) following ANOVA.

Table 3. – Pulmonary function of studied subjects

	Asthma	Chronic bronchitis	Normal control	Correlation to cough threshold##
Age yrs	62±2.0	64±4.4	56±3.4	r=-0.341, NS
Sex M/F#	6/2	6/4	5/5	NT
Height cm	160.5±2.5	158.7±3.3	159.3±3.1	r=0.284, NS
FVC L	2.79±0.28	2.97±0.28	3.36±0.27	r=0.434, p<0.05
FVC % pred	87±7	99±5	103±5	r=0.143, NS
FEV_1 L	1.65±0.16*	2.11±0.17	2.68±0.25	r=0.391, NS
FEV_1 % pred	63±7**	85±5*	103±6	r=0.220, NS
FEV_1/FVC ratio %	61±4**	72.7±2.8	81.2±2.9	r=0.056, NS
Airway reversibility %$	29.2±2.9++	3.3±1.2	NT	r=0.228, NS
Airway responsiveness† $mg \cdot mL^{-1}$	0.26 (1.63)++	14.2 (1.46)	NT	r=0.450, NS

Data are presented as mean±standard error of the mean (SEM). Differences were analysed by Mann-Whitney U-test and # by Chi-squared test. *: $p<0.05$ and **: $p<0.01$ compared with normal control; ++: $p<0.01$ compared with bronchitis patients. $: percentage increase in FEV_1 by inhalation of 300 µg of salbutamol; †: provocative concentration ($mg \cdot mL^{-1}$) of methacholine causing 20% or more fall in FEV_1 and shown as geometric mean value (geometric standard error of the mean). NT: not tested. NS: not significant; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; % pred: percentage of predicted; M: male; F: female. ##: results of simple regression analysis between the cough threshold and each parameter studied in all subjects, except for airway reversibility and airway responsiveness, which were analysed in patients with asthma and chronic bronchitis only.

Discussion

This study has shown that the cyclooxygenase inhibitor indomethacin increases the cough threshold to inhaled capsaicin in patients with asthma or chronic bronchitis, but not in normal subjects. A thromboxane synthesis inhibitor provided protection only in patients with asthma. These findings suggest that cyclooxygenase products lower the cough sensitivity in inflammatory airway diseases.

Cough usually results from the stimulation of sensory nerves in the airway [17]. The larynx has two types of cough receptors: myelinated irregularly firing irritant receptors [18], and nonmyelinated C fibre endings [19]. The tracheobronchial tree has also two types of cough receptors: myelinated rapidly adapting receptors (or "irritant receptors") [20], and nonmyelinated bronchial C fibre endings [21]. It has been postulated that capsaicin, the active ingredient of red pepper, produces cough mainly by stimulating C fibre endings [1–3], but as capsaicin also stimulates some rapidly adapting receptors with myelinated fibres, this view has been questioned [17]. Inhaled capsaicin probably acts mainly on the larynx, trachea and major bronchi, which are areas of the greatest sensitivity for provocation of cough [22, 23]. Although the larynx may be the initial site of cough stimulation, the sublaryngeal airways may also contribute to the response, as we have found that laryngectomised patients cough when they inhale capsaicin through their tracheotomy tubes.

Cough reflex testing using capsaicin has been commonly used for studies on the pathophysiology of cough reflex and antitussive effects of drugs. In normal subjects, the reproducibility of the dose-response curve for capsaicin-induced cough has been well established when the challenge is repeated at an interval of more than 15 min [24]. Recently, MIDGREN *et al.* [25] have confirmed the reproducibility of sensitivity as well as of the dose-response curve for capsaicin-induced cough.

In this study, the cough threshold after placebo treatment was significantly lower in patients with asthma and chronic bronchitis than in normal subjects. Although it agrees with our previous report [4] that the cough threshold to inhaled tartaric acid was significantly lower in patients with chronic bronchitis as compared to normal subjects, the lower cough threshold in asthma is seemingly in contrast with previous reports that the cough reflex is not hypersensitive in asthmatics as compared with normal subjects [4, 24, 26]. Although it is known that cough sensitivity is greater in women than in men [27], the number of females was less in the asthmatics as compared with the normal subjects in this study. The capsaicin cough threshold was significantly correlated to FVC but not to other pulmonary functions, height or ageing. FVC was smaller in asthmatics than in normals, whilst the difference was not significant. The smaller FVC seems to be responsible for the lower cough threshold in asthmatics, but we do not know the exact reason for the lowered cough threshold in asthma in this study.

The present study showed that treatment with indomethacin significantly reduced the cough sensitivity to inhaled capsaicin in patients with asthma and chronic bronchitis, and the change in cough threshold with indomethacin from the value with placebo was significantly greater in both groups as compared to that in normals. The OKY-046 treatment reduced the cough sensitivity only in asthmatic patients. As neither indomethacin nor OKY-046 treatment changed the cough response in normal subjects, it is thought that these two treatments have no nonspecific or direct effect on the cough reflex. Our earlier studies [7, 28, 29] showing that the thromboxane synthetase inhibitor, OKY-046, and a thromboxane A_2 receptor antagonist, AA-2414, but not the cyclooxygenase inhibitor, indomethacin, reduced bronchial responsiveness to methacholine in patients with asthma indicate that thromboxane A_2 is continuously released by asthmatic chronic airway inflammation.

Bronchoprotective prostanoids, such as prostaglandin I_2 and E_2, are also produced in the airway of asthma. We also reported that indomethacin reduced bronchial responsiveness to methacholine in patients with chronic bronchitis, but not in normal subjects [7]. This indicates that cyclooxygenase products are continuously released by chronic airway inflammation of chronic bronchitis, resulting in potentiation of bronchial responsiveness. Taken together, these findings support our hypothesis that, both in asthma and chronic bronchitis, cyclooxygenase products released in the inflamed airways sensitize the cough receptors to capsaicin. Indeed, it has been demonstrated that prostaglandin E_2 and $F_{2\alpha}$, which are cyclooxygenase metabolites, potentiate cough induced by capsaicin in normal subjects [8, 9].

In asthmatic patients, the attenuating effect of indomethacin on the capsaicin-induced cough tended to be stronger than that of OKY-046, and the cough threshold with the indomethacin treatment increased nearly to the level of normal subjects. It is well-known that thromboxane synthetase inhibitors, such as OKY-046, not only inhibit thromboxane synthesis but also augment the production of other prostanoids, such as prostaglandin E_2 and $F_{2\alpha}$ [11]. This may be responsible for our result showing that indomethacin was superior to OKY-046 in attenuating cough sensitivity to capsaicin in asthmatic patients. Accordingly, it is likely that endogenous thromboxane A_2 is a modulator of cough sensitivity in asthma. Further studies are needed to clarify this issue, by using specific thromboxane receptor antagonists. On the other hand, the increase in cough threshold to capsaicin with the OKY-046 treatment was seen in only half of our asthmatics (fig. 1). It is possible that the involvement of thromboxane A_2 in cough threshold in asthma is significant in some patients but not in others, as we have reported that thromboxane inhibitors clearly improve bronchial hyperresponsiveness in only 30–50% of patients with asthma [7, 28, 29].

Although the improvement of cough response to inhaled capsaicin with indomethacin was statistically significant in patients with chronic bronchitis, the improved cough threshold was still lower than that of normal subjects, and the improvement was seen in only five individuals but not in the other five patients (fig. 2). This indicates that prostaglandins may not be involved in all patients with chronic bronchitis, and other factors may contribute to the heightened cough reflex in those patients.

Involvement of cyclooxygenase products in the cough reflex to inhaled capsaicin has also been shown in patients with cough produced by inhibitors of angiotensin converting enzyme but not in patients with idiopathic dry, unproductive cough [30]. Thus, it remains unclear whether the same mechanism operates in other chronic inflammatory airway diseases, such as eosinophilic bronchitis without asthma.

In conclusion, this study indicates that cyclooxygenase products augment airway cough sensitivity in both bronchial asthma and chronic bronchitis, and that thromboxane A_2 may be one of these products in asthma but not in chronic bronchitis.

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References

1. Coleridge HM, Coleridge JCG. Impulse activity in afferent vagal C-fibers with endings in the intrapulmonary airways of dogs. *Respir Physiol* 1977; 29: 125–142.
2. Fuller RW, Jackson DM. Physiology and treatment of cough. *Thorax* 1990; 45: 425–430.
3. Lundberg JM, Saria A. Capsaicin-induced desensitization of airway mucosa to cigarette smoke, mechanical and chemical irritants. *Nature* 1983; 302: 251–253.
4. Fujimara M, Sakamoto S, Kamio Y, *et al*. Cough threshold to inhaled tartaric acid and bronchial responsiveness to methacholine in patients with asthma and sinobronchial syndrome. *Intern Med* 1992; 31: 17–21.
5. Barnes PJ. Mechanisms: Inflammation. *In*: Weiss EB, Stein M, eds. Bronchial Asthma, Mechanisms and Therapeutics. 3rd edn. Boston, Toronto, London, Little, Brown and Co., 1993; pp. 80–94.
6. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis* 1987; 136: 225–244.
7. Fujimura M, Sakamoto S, Matsuda T. Attenuating effect of a thromboxane synthetase inhibitor (OKY-046) on bronchial responsiveness to methacholine is specific to asthma. *Chest* 1990; 98: 656–660.
8. Choudry NB, Fuller RW, Pride NB. Sensitivity of the human cough reflex: effect of inflammatory mediators prostaglandin E_2, bradykinin, and histamine. *Am Rev Respir Dis* 1989; 140: 137–141.
9. Nichol G, Nix A, Barnes PJ, Chung KF. Prostaglandin $F_{2\alpha}$ enhancement of capsaicin-induced cough in man: modulation by $beta_2$-adrenergic and anticholinergic drugs. *Thorax* 1990; 45: 694–698.
10. Fujimura M, Kamio Y, Sakamoto S, Bando T, Myou S, Matsuda T. Tachyphylaxis to capsaicin-induced cough and its reversal by indomethacin, in patients with the sinobronchial syndrome. *Clin Autonomic Res* 1992; 2: 397–401.
11. Naito J, Komatsu H, Ujiie A, Hamano A, Kubota T, Tsuboshima M. Effects of thromboxane synthetase inhibitors on aggregation of rabbit platelets. *Eur J Pharmacol* 1983; 91: 41–48.
12. Light RW, Conrad SA, George RB. The one best test for evaluating the effects of bronchodilator therapy. *Chest* 1977; 72: 512–516.
13. Homma H, Yamanaka A, Tanimoto S, *et al*. Diffuse panbronchiolitis, a disease of the transitional zone of the lung. *Chest* 1983; 83: 63–69.
14. Suzaki H, Ichimura K, Kudoh S, Sugiyama Y, Maeda H. Symposium II. Sinobronchial syndrome and its related subjects: clinical observation in sinobronchial syndrome from a viewpoint of otorhinolaryngology. *J Jpn Bronchoesophagol Soc* 1987; 38: 181–186.
15. Kudoh S, Uetake K, Hirayama M, Kyo E, Kimura H, Sugiyama Y. Clinical effect of low-dose long-term erythromycin chemotherapy on diffuse panbronchiolitis (in Japanese with English abstract). *Jap J Thorac Dis* 1987; 25: 632–642.
16. Fujimura M, Sakamoto S, Kamio Y, Matsuda T. Effects of methacholine-induced bronchoconstriction and

procaterol-induced bronchodilation on cough receptor sensitivity to inhaled capsaicin and tartaric acid. *Thorax* 1992; 47: 441–445.
17. Karlsson JA, Sant'Ambrogio G, Widdicombe J. Afferent neural pathways in cough and reflex bronchoconstriction. *J Appl Physiol* 1988; 65: 1007–1023.
18. Boushey HA, Richardson PS, Widdicombe JG, Wise JCM. The response of laryngeal afferent fibres to mechanical and chemical stimuli. *J Physiol* 1974; 240: 153–175.
19. Boushey HA, Richardson PS, Widdicombe JG. Reflex effects of laryngeal irritation of the pattern of breathing and total lung resistance. *J Physiol* 1972; 224: 501–513.
20. Bartlett D Jr, Jeffery P, Sant'Ambrogio G, Wise JCM. Location of stretch receptors in the trachea and bronchi of the dog. *J Physiol* 1976; 258: 409–420.
21. Jammes Y, Fornaris E, Mei N, Barrat E. Afferent or efferent components of the bronchial vagal branches in cats. *J Autonom Nerv Syst* 1982; 5: 165–176.
22. Sant'Ambrogio G. Information arising from the tracheobronchial tree of mammals. *Physiol Rev* 1982; 62: 531–569.
23. Widdicombe JG. Receptors in the trachea and bronchi of the cat. *J Physiol* 1954; 123: 71–104.
24. Collier JG, Fuller RW. Capsaicin inhalation in man and the effects of sodium cromoglycate. *Br J Pharmacol* 1984; 81: 113–117.
25. Midgren B, Hansson L, Karlsson J, Simonsson BG, Persson GA. Capsaicin-induced cough in humans. *Am Rev Respir Dis* 1992; 146: 347–351.
26. Fujimura M, Sakamoto S, Kamio Y, Bando T, Kurashima K, Matsuda T. Effect of inhaled procaterol on cough receptor sensitivity to capsaicin in patients with asthma, chronic bronchitis and normal subjects. *Thorax* 1993; 48: 615–618.
27. Fujimura M, Sakamoto S, Kamio Y, Matsuda T. Sex difference in the inhaled tartaric acid cough threshold in nonatopic healthy subjects. *Thorax* 1990; 45: 633–634.
28. Fujimura M, Sakamoto S, Saito M, Miyake Y, Matsuda T. Effect of a thromboxane A_2 receptor antagonist (AA-2414) on bronchial hyperresponsiveness to methacholine in asthmatic subjects. *J Allergy Clin Immunol* 1991; 87: 23–27.
29. Fujimura M, Sasaki F, Nakasumi Y, *et al*. Effect of a thromboxane synthetase inhibitor (OKY-046) and a lipoxygenase inhibitor (AA-861) on bronchial responsiveness to acetylcholine in asthmatic subjects. *Thorax* 1986; 41: 955–959.
30. McEwan JR, Choudry NB, Fuller RW. The effect of sulindac on the abnormal cough reflex associated with dry cough. *J Pharmacol Exp Ther* 1990; 255: 161–164.