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Prostaglandin I2 enhances cough reflex sensitivity to capsaicin in the asthmatic airway

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Abstract

Inflammatory mediators are involved in the pathogenesis of airway inflammation, but the role of prostaglandin I2 (PGI2) remains obscure. This study was designed to investigate the role of PGI2 in cough reflex sensitivity of the asthmatic airway, which is characterized by chronic eosinophilic airway inflammation. The effect of beraprost, a chemically and biologically stable analogue of PGI2, on cough response to inhaled capsaicin was examined in 21 patients with stable asthma in a randomized, placebo-controlled cross over study. Capsaicin cough threshold, defined as the lowest concentration of capsaicin eliciting five or more coughs, was measured as an index of airway cough reflex sensitivity. The cough threshold was significantly (p < 0.05) decreased after two weeks of treatment with beraprost [17.8 (GSEM 1.20) μM] compared with placebo [30.3 (GSEM 1.21) μM].

PGI2 increases cough reflex sensitivity of the asthmatic airway, suggesting that inhibition of PGI2 may be a novel therapeutic option for patients with asthma, especially cough predominant asthma.

Background

Chronic cough is one of the commonest respiratory symptoms. Cough has been considered to be a defense mechanism of the airway to remove irritant particles or excess mucus, whereas non-productive cough, which is not associated with the clearance of the tracheobronchial mucus, may occur via increased cough reflex sensitivity. Inflammatory mediators such as prostaglandins may adjust the cough reflex sensitivity. However, little is known about how cough reflex sensitivity is influenced by airway inflammatory processes. Although our previous study has clearly shown that arachidonate cyclooxygenase products can modulate airway cough reflex sensitivity to inhaled capsaicin [1], the effects of other mediators remains unknown.

It has been recognized that prostaglandin I2 (PGI2, prostacyclin) is the most abundant prostanoid generated on IgE-dependent challenge of human lung tissue in vitro [2,3]. Others reported that alveolar macrophages are able to synthesize large amount of PGI2 [4]. These findings indicate that PGI2 may play some role in the asthmatic airway and can affect airway cough reflex sensitivity. This study was conducted to elucidate this hypothesis. We investigated the effect of oral administration of beraprost, a chemically and biologically stable analog of PGI2
{sodium (±)-4[[(1R, 2R, 3aS, 8bS)-1, 2, 3a, 8b-tetrahydro-2-hydroxy-2[(3S, 4RS)-3-hydroxy-4-methyl-oct-6-yne-(E)-1-enyl]-5-cyclopenta [b] benzofuranyl] butyrate}, on cough reflex sensitivity to inhaled capsaicin in patients with stable asthma [5].

**Subjects and Methods**

**Subjects**

Twenty-one patients with bronchial asthma (12 males and 9 females) with a mean age of 73.2 ± 1.5 (± SEM) (range 54–83) yrs participated in this study. All patients were lifetime nonsmokers or ex-smokers with no history of viral infection for at least 4 weeks prior to the study. Characteristics of individual patients are shown in Table 1. Informed consent was obtained from all subjects. This study was approved by the Ethics Committee of our hospital.

Each asthmatic patient satisfied the American Thoracic Society 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 greater than 12 % and 200 ml increase in the forced expiratory volume in one second (FEV1) following a bronchodilator inhalation (Table 1). All patients had bronchial hyperresponsiveness as shown in Table 1. Classification of asthma severity was defined according to Global Strategy for Asthma Management and Prevention. Patients with atopy were recognized as having a hereditary tendency to produce IgE antibodies against common environmental allergens [7]. This study was carried out when symptoms were mild and stable, while patients were taking oral theophylline, oral (short-acting clenbuterol) and/or aerosol β2-agonists (short-acting procaterol), inhaled steroids (beclomethasone dipropionate), inhaled anti-cholinergic agents (oxitropium bromide) and/or mucolytic agents (carbocysteine) according to previous reports [8-10]. They had not received oral steroids for at least eight weeks.

**Assessment of cough reflex sensitivity to inhaled capsaicin**

Cough reflex sensitivity was assessed by capsaicin provocation test [11]. 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

| Patient number | Age (yr) | Sex | Height (cm) | Type | Severity | Total IgE in serum (IU/ml) | Specific IgE in serum | Complication of allergic disease | PC20-FEV1 (mg/ml)* | Bronchodilator response (%)** | Treatment |
|----------------|---------|-----|-------------|------|----------|--------------------------|----------------------|--------------------------|----------------|-----------------------------|-----------|
| 1              | 54      | M   | 161         | Int  | Moderate | 420                      | -                    | -                        | 2.5             | 15.2                        | BDP 800   |
| 2              | 72      | F   | 147         | Ext  | Moderate | 642                      | Mite, HD AR          | 0.31                    | 31.5            | 800                         | Theophylline |
| 3              | 70      | M   | 161         | Ext  | Mild     | 312                      | Mite, HD, Cedar      | 0.08                    | 20.2            | 600                         | Clenbuterol |
| 4              | 71      | F   | 140         | Int  | Mild     | 17                       | -                    | 1.25                    | 17.6            | 800                         | Carbocysteine |
| 5              | 83      | M   | 154         | Ext  | Mild     | 345                      | Mite, HD, Cedar      | 5                       | 17.1            | 800                         | Bronchodilator |
| 6              | 71      | M   | 165         | Ext  | Moderate | 146                      | Mite, HD AR          | 1.25                    | 15.6            | 0                           | Treatment |
| 7              | 77      | F   | 144         | Int  | Mild     | 51                       | -                    | 0.31                    | 17.9            | 0                           | Treatment |
| 8              | 71      | M   | 155         | Int  | Mild     | 42                       | -                    | 2.5                     | 29.4            | 800                         | Treatment |
| 9              | 80      | M   | 152         | Ext  | Moderate | 66                       | -                    | 1.25                    | 39              | 800                         | Treatment |
| 10             | 75      | M   | 162         | Ext  | Mild     | 143                      | Candids              | 2.5                     | 14.1            | 800                         | Treatment |
| 11             | 80      | F   | 145         | Ext  | Mild     | 3                        | HD, Cedar            | 0.08                    | 37.1            | 800                         | Treatment |
| 12             | 63      | F   | 154         | Ext  | Moderate | 77                       | Cedar AR             | 1.25                    | 14.7            | 800                         | Treatment |
| 13             | 77      | F   | 142         | Int  | Mild     | 105                      | -                    | 5                       | 17              | 0                           | Treatment |
| 14             | 70      | M   | 155         | Int  | Moderate | 82                       | -                    | 0.31                    | 15.4            | 800                         | Treatment |
| 15             | 70      | F   | 151         | Ext  | Mild     | 467                      | Mite, HD             | 2.5                     | 20.4            | 800                         | Treatment |
| 16             | 72      | F   | 150         | Int  | Mild     | 57                       | -                    | 5                       | 22.3            | 600                         | Treatment |
| 17             | 81      | M   | 163         | Ext  | Moderate | 64                       | -                    | 0.31                    | 33.4            | 800                         | Treatment |
| 18             | 71      | M   | 150         | Int  | Mild     | 107                      | -                    | 5                       | 16.4            | 800                         | Treatment |
| 19             | 80      | M   | 160         | Int  | Mild     | 87                       | -                    | 2.5                     | 29.5            | 0                           | Treatment |
| 20             | 68      | M   | 167         | Ext  | Mild     | 264                      | Cedar               | 5                       | 27              | 0                           | Treatment |
| 21             | 80      | F   | 152         | Ext  | Mild     | 54                       | -                    | 2.5                     | 17.3            | 0                           | Treatment |

Ext, extrinsic; Int, Intrinsic; HD, house dust; AR, allergic rhinitis; UR, urticaria; BDP, beclomethasone dipropionate inhalation.

* PC20-FEV1 shows concentration of inhaled methacholine causing a 20% fall in FEV1.

** Bronchodilator response means percent increase in forced expiratory volume in 1s (FEV1) from the baseline value after inhalation of 300 μg of salbutamol sulfate.

All patients used inhaled β2-agonists (salbutamol or procaterol) on demand.
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 it 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 (3012-60 cc, Puritan-Bennett Co., Carlsbad, California, USA). Increasing concentrations were inhaled until five or more coughs were elicited. The nebulizer output was 0.21 mL/min. The number of capsaicin-induced coughs was counted by a blinded medical technician in our pulmonary function laboratory. The cough threshold was defined as the lowest concentration of capsaicin that elicited five or more coughs.

**Study protocol (Figure 1)**

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 measurement of cough threshold to inhaled capsaicin at 10.00 a.m. on each test day to reduce the diurnal variability of the cough response.

Each patient attended 4 times separated by 2 weeks, at the same time each day. Control measurement of capsaicin cough threshold was carried out 2 weeks before initiation of the first treatment (run-in). Two weeks treatment with beraprost sodium or placebo was performed separated by a two-week washout period in a randomized, cross-over fashion. Two beraprost sodium tablets (40 μg) and their placebo were taken orally three times a day for 14 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 the bronchoactive effect of the treatment regimens. Serum total IgE levels and the number of peripheral eosinophils were measured to assess anti-allergic effect of the test drugs.

**Data analysis**

Capsaicin cough threshold values were expressed as geometric mean with geometric standard error of the mean (GSEM). Forced vital capacity (FVC), FEV1 and maximal mid expiratory flow (MMF) were shown as arithmetic mean values ± SEM. The FVC values, the FEV1 values and the MMF values were compared between each pair of the four groups (run-in, washout, beraprost sodium and placebo) by the Wilcoxon signed-ranks test. A p-value of 0.05 or less was taken as significant.

**Results**

Cough threshold to inhaled capsaicin before each treatment (run-in, washout) and after treatment with beraprost and placebo are shown in Figure 2. Geometric mean values for the cough threshold were 29.5 (GSEM 1.17) μM in the run-in period, 26.5 (GSEM 1.18) μM in the washout period, 17.8 (GSEM 1.20) μM after beraprost treatment and 30.3 (GSEM 1.21) μM after placebo treatment.
The cough threshold after the beraprost treatment was significantly (p < 0.05) lower than the value after the placebo treatment. FVC, FEV1 or MMF value was not significantly different between run-in period, washout period, beraprost treatment and placebo treatment as shown in Table 2.

Table 2: Pulmonary function on beraprost and placebo treatments in patients with bronchial asthma

|                  | Run-in     | Placebo    | Washout    | Beraprost  |
|------------------|------------|------------|------------|------------|
| FVC as % pred. (%) | 96.8 ± 5.7 | 103.4 ± 3.3 | 104.4 ± 3.1 | 103.4 ± 3.4 |
| FEV1 as% pred. (%) | 90.9 ± 5.7 | 94.1 ± 5.5  | 93.0 ± 5.6  | 93.2 ± 5.6  |
| MMF as% pred. (%)  | 50.7 ± 6.7 | 52.0 ± 6.0  | 50.1 ± 6.4  | 51.5 ± 6.4  |

Data are shown as standard error of the mean for FVC, FEV1 and MMF.
* p < 0.05 compared with each control value (Wilcoxon signed-ranks test).
Figure 2
Individual data of capsaicin cough threshold at run-in period, at washout period and on treatment with beraprost and placebo in patients with stable bronchial asthma. Each horizontal bar represents geometric mean value. Closed circles and open circles represent patients undergoing steroid inhalation therapy and patients without steroid inhalation therapy, respectively. P values: Wilcoxon signed-ranks test using logarithmically transformed values.

Figure 3
Individual data of serum IgE at run-in period, at washout period and on treatment with beraprost and placebo in patients with stable bronchial asthma. Each horizontal bar represents geometric mean value. Closed circles and open circles represent patients undergoing steroid inhalation therapy and patients without steroid inhalation therapy, respectively. P values: Wilcoxon signed-ranks test using logarithmically transformed values.
bronchodilation and it may explain the role of PGI2 in the asthmatic airway which has been unknown so far.

Overall, our data support the conclusion that inhibition of PGI2 formation or action may be a novel treatment for chronic non-productive cough in asthmatic airway, especially in cough variant asthma or cough predominant asthma with normal baseline pulmonary function. This is the first report demonstrating the role of PGI2 in cough reflex sensitivity in the asthmatic airway. Further studies may be required to elucidate the role of PGI2 in other eosinophilic bronchial disorders presenting with non-productive cough with normal baseline pulmonary functions [29-31].

Abbreviations
cLT = cysteinyl leukotriene; CVA = cough variant asthma; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; GSEM = geometric standard error of the mean; PGE2 = prostaglandin E2; PGF2α = prostaglandin F2α; PGI2 = prostaglandin I2; MMF = maximal mid expiratory flow; TxA2 = thromboxane A2.

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