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Hiroshi Tanaka, Satoshi Kanako and Shosaku Abe

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A M E R I C A N C O L L E G E O F
 **C H E S T**
P H Y S I C I A N S

Prostaglandin E₂ Receptor Selective Agonists E-Prostanoid 2 and E-Prostanoid 4 May Have Therapeutic Effects on Ovalbumin-Induced Bronchoconstriction*

Hiroshi Tanaka, MD; Satoshi Kanako, MD; and Shosaku Abe, MD

Background: The pharmacologic actions of prostaglandin E₂ (PGE₂) are mediated through specific E-prostanoid (EP)-1, EP-2, EP-3, and EP-4 receptors. In this study, we determined which PGE₂ receptor subtype(s) contribute to the prevention of allergen-induced bronchoconstriction. **Methods:** We assessed the effects of these receptor agonists in ovalbumin (OA)-sensitized guinea pigs. The prostaglandin E receptor-subtype agonists tested were ONO-DI-004 (EP-1), ONO-AE1-259 (EP-2), ONO-AE-248 (EP-3), ONO-AE1-329 (EP-4), and sulprostone (EP-1 and EP-3) [Ono Pharmaceutical Company; Osaka, Japan]. We treated the animals with either PGE₂ or these agonists 15 min before OA challenge and measured respiratory resistance at 15 min, 1 h, and 3 h. **Results:** Allergen-induced bronchoconstriction was significantly ($p < 0.01$) suppressed at doses > 85 nmol/kg of PGE₂. The respiratory resistance elevations 15 min after OA challenge were significantly ($p < 0.01$) suppressed by preadministration of EP-2 and EP-4 agonists, but airway responsiveness to inhaled methacholine did not improve. EP-1, EP-3, or EP-1/EP-3 agonists had no effect on any parameter. **Conclusions:** These results suggest that inhibition of OA-induced bronchoconstriction by PGE₂ acts through EP-2 and EP-4 receptors. (CHEST 2005; 128:3717–3723)

Key words: animal model; asthma; prostaglandin E₂; receptor; smooth muscle

Abbreviations: AR = airway responsiveness; cAMP = cyclic adenosine monophosphate; DMSO = dimethylsulfoxide; EP = E-prostanoid; GTP = guanosine triphosphate; OA = ovalbumin; PGE₂ = prostaglandin E₂; sRaw = specific airway resistance

Prostaglandin E₂ (PGE₂) is a cyclooxygenase product of arachidonate metabolism that relaxes airway smooth muscle.^{1,2} PGE₂ acts through four different rhodopsin-type receptors (Table 1), designated as E-prostanoid (EP)-1, EP-2, EP-3, and EP-4, which are encoded by different genes and expressed differently in each tissue.^{3–5} PGE₂ counteracts exercise-induced,⁶ allergen-induced,^{7,8} and aspirin-induced bronchoconstriction.^{9,10} Inhaled PGE₂ prevents allergen-induced asthmatic responses when administered immediately before allergen challenge,¹¹ while having no effect on baseline FEV₁ or

on methacholine hyperreactivity.¹² However, PGE₂ can both relax and constrict airway smooth muscle *in vitro* and *ex vivo*.^{11,13} This paradox was explained when it was recognized that PGE₂ could simultaneously stimulate four different receptors, which are coupled to different intracellular signal transduction pathways. In vascular smooth muscle, PGE₂ is generally found to be a dilator through EP-2 or EP-4 receptors and a constrictor through EP-1 or EP-3 receptors.¹⁴ Both PGE₂-elicited contraction and the spontaneous tone of guinea pig tracheal smooth muscle were reported to be mediated through the activation of the EP-1 receptor.¹⁵ Tilley et al¹⁴ reported that the activation of EP-1/EP-3 receptors induced airway constriction, whereas PGE₂-induced bronchodilation resulted from activation of the EP-2 receptor in airway smooth muscle. In this study, we attempted to identify which EP receptor is involved in the protective effects of PGE₂ on ovalbumin (OA)-induced bronchoconstriction, using a specific agonist for each EP receptor in OA-sensitized guinea pigs.

*From the Third Department of Internal Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan. Manuscript received November 19, 2004; revision accepted May 24, 2005.

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Correspondence to: Hiroshi Tanaka, MD, Third Departments of Internal Medicine, Sapporo Medical University School of Medicine, South-1, West-16, Chuo-ku, Sapporo, 060-8543, Japan; e-mail: tanakah@sapmed.ac.jp

Table 1—Receptors for PGE₂*

Subtypes	Selective Agonists	Transduction System	Distribution
EP-1	ONO-DI-004, sulprostone iloprost, 17-phenyl PGE ₂	Intracellular Ca ²⁺	Lung, kidney, GI tract
EP-2	ONO-AE1-259 butaprost, AH13025, misoprostol	cAMP via Gs	Lung, uterus, liver, ileum, stomach, thymus, spleen
EP-3	ONO-AE-248, sulprostone enprostil, GR63799, misoprostol	cAMP via Gi; PI turnover via Gq	Lung, kidney, stomach, uterus, liver
EP-4	ONO-AE1-329	cAMP via Gs?	Lung, heart, thymus, spleen, kidney, ileum, testis, uterus

*Gs = stimulatory GTP-binding protein; Gi = inhibitory GTP-binding protein; PI = inositol phospholipid; Gq = heteromeric GTP binding protein.

MATERIALS AND METHODS

Animals and Drugs

Male Hartley guinea pigs weighing 250 to 300 g (Nihon SLC; Shizuoka, Japan) were allowed bottled water and commercial chow *ad libitum*. PGE₂ was obtained from Sigma Chemical Company (St. Louis, MO). ONO-DI-004 (EP-1 agonist), ONO-AE1-259 (EP-2 agonist), ONO-AE-248 (EP-3 agonist), ONO-AE1-329 (EP-4 agonist), and sulprostone (EP-1 and EP-3 agonists)⁵ were gifts kindly provided by the Ono Pharmaceutical Company Ltd. (Osaka, Japan). The specificity of the respective EP agonists was analyzed by measuring the binding affinity of the agonists to the respective EPs expressed in Chinese hamster ovary cells.^{3,4}

Study Design

The guinea pigs were placed in polyacrylamide boxes (28 × 28 × 20 cm) and sensitized by using aerosolized 1% OA solution delivered via an ultrasonic nebulizer (NE-U10B; Omron; Tokyo, Japan). Sensitization was performed for 10 min once a week for 4 weeks. We have previously reported these procedures.^{16,17} An OA challenge test was then performed, and

OA-induced bronchoconstriction was observed in all animals. All experiments and procedures were approved by the Laboratory Animal Center of Sapporo Medical University.

Protocol of Experiment 1

As shown in Figure 1, we allocated the guinea pigs into two groups: a vehicle group (physiologic saline solution, 0.09 NaCl weight/volume in sterile water, subcutaneously) and a PGE₂ group (1, 3, 10, and 50 µg/kg, subcutaneously). Stock solution of PGE₂ was prepared at a concentration of 2 mg/mL by dissolving 10 mg of PGE₂ in 5.0 mL of 100% ethanol. This solution was stored at −70°C. Immediately before use, the PGE₂ was diluted with physiologic saline solution. Treatment was administered 15 min before OA challenge, and specific airway resistance (sRaw) was measured before and 15 min, 1 h, and 3 h after OA challenge. The vehicle control group consisted of 10 animals, and each treatment group consisted of seven animals.

Protocol of Experiment 2

OA-sensitized animals were classified into six groups as shown in Figure 2: the vehicle group (dimethylsulfoxide [DMSO], subcutaneously); the EP-1 receptor agonist group (ONO-DI-004

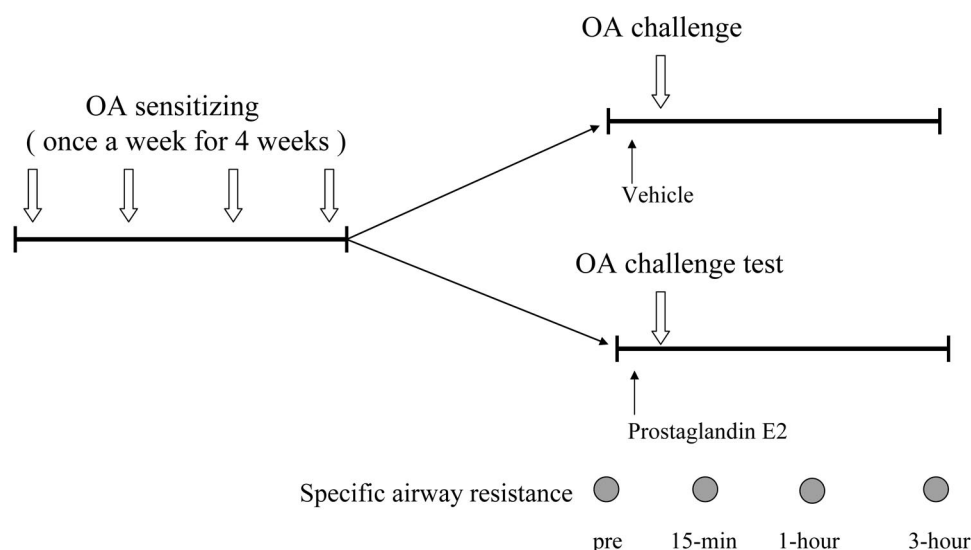


FIGURE 1. Protocol of experiment 1.

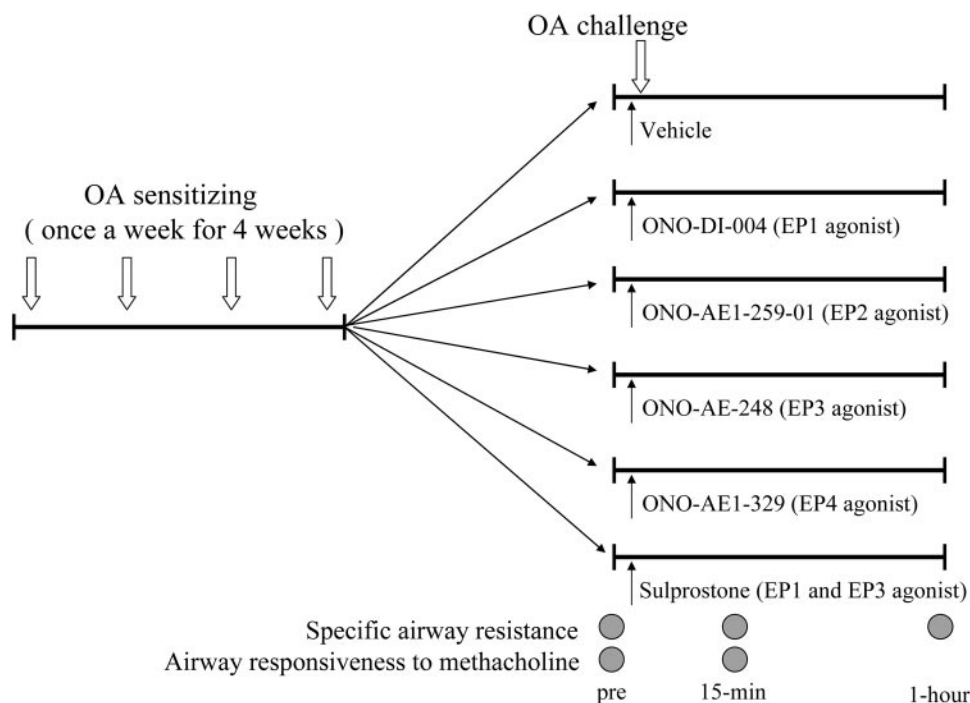


FIGURE 2. Protocol of experiment 2.

dissolved in methyl cellulose at doses of 20 nmol/kg and 200 nmol/kg body weight, po); the EP-2 receptor agonist group (ONO-AE1-259 dissolved in DMSO at doses of 20 nmol/kg and 200 nmol/kg body weight, subcutaneously); the EP-3 receptor agonist group (ONO-AE1-248 dissolved in DMSO at doses of 20 nmol/kg and 200 nmol/kg body weight, subcutaneously); the EP-4 receptor agonist group (ONO-AE1-329 dissolved in DMSO at doses of 2 nmol/kg and 20 nmol/kg of body weight, subcutaneously); and the EP-1 and EP-3 receptor agonist group (sulprostone dissolved in DMSO at doses of 20 nmol/kg and 200 nmol/kg body weight, subcutaneously). Drugs were administered 15 min before OA challenge, and sRaw was measured before and 15 min and 1 h after OA challenge. OA-induced bronchoconstriction in OA-sensitized guinea pigs was not affected by the oral low dose of methyl cellulose (data not shown). The vehicle control group consisted of 10 animals, and each treatment group consisted of 7 animals.

Protocol of Experiment 3

To measure the concentration of airway PGE₂, we performed BAL. OA-sensitized animals were classified into five groups similar to that shown in Figure 2: the vehicle group (DMSO, subcutaneously), the EP-1 receptor agonist group (ONO-DI-004, 200 nmol/kg po), the EP-2 receptor agonist group (ONO-AE1-259, 200 nmol/kg subcutaneously), the EP-3 receptor agonist group (ONO-AE1-248, 200 nmol/kg subcutaneously), and the EP-4 receptor agonist group (ONO-AE1-329, 20 nmol/kg subcutaneously) groups. BAL was performed 15 min after OA challenge.

Measurement of Airway Function

sRaw was measured using respective sensors of air flow equipped at the front and rear chambers according to the method

described by Pennock et al.¹⁷ and by us.^{16,17} Briefly, an awake guinea pig was positioned with its neck extending through the partition of a two-chamber, whole-body plethysmograph. Each chamber was fitted with identical wire screen pneumotachographs and identical differential pressure transducers (model DP-45; Validyne Engineering Corporation; Northridge, CA). These transducers were connected to a respiratory analyzer (Pulmos-I; M.I.P.S.; Osaka, Japan), and a personal computer was used for the on-line breath-to-breath measurement of sRaw.

Airway Responsiveness to Methacholine

Airway responsiveness (AR) was evaluated by the airway response to methacholine as previously described by us.^{15,16} Methacholine aerosols were generated by an ultrasonic nebulizer (model T-10; Sineo Industries; Saitama, Japan), with a flow rate of 0.8 L/min delivered into the chamber. Methacholine solutions were prepared in concentrations of 0.0078, 0.0156, 0.0312, 0.0625, 0.125, 0.25, 0.5, and 0.1 mg/mL. After each inhalation for 1 min, sRaw was measured for 1 min. Inhalation was repeated with aerosols of increasing concentrations until sRaw increased to more than twice baseline. AR was evaluated by the concentration of methacholine required to increase sRaw to twice the baseline level.

BAL

After the animal received a lethal dose of pentobarbital sodium (100 mg/kg intraperitoneally), the chest was opened and both lungs were lavaged by instillation and withdrawal of four aliquots of 1 mL of sterile pathogen-free saline solution. BAL fluid was placed on ice and centrifuged at 400g for 5 min at 4°C. Supernatants were decanted and frozen at -80°C for subsequent use. Levels of PGE₂ were determined by radioimmunoas-

say (Prostaglandin E₂ [¹²⁵I] RIA Kit; PerkinElmer Life Sciences; Boston MA). The kit was able to detect concentrations of PGE₂ as low as 0.1 pg/mL.

Statistical Analysis

Results are expressed as mean and SEM, or median and 10th to 90th percentiles. Statistical analysis was performed using a two-factor, repeated-measures analysis of variance. When differences were significant, the Fisher least significant difference test for multiple comparison was applied. Values were considered significantly different at $p < 0.05$.

RESULTS

Effect of PGE₂ on OA-Induced Bronchoconstriction

The results of sRaw measured before and 15 min, 1 h, and 3 h after OA challenge are shown in Figure 3. PGE₂ significantly reduced the sRaw at 15 min in the group receiving $> 3 \mu\text{g/kg}$ of PGE₂ compared with sham control animals, and sRaw 1 h after OA challenge was significantly decreased only in the group receiving $50 \mu\text{g/kg}$ of PGE₂. There was no significant difference between the values obtained from different treatment doses at 3 h after OA challenge among the groups.

Effect of Different EP Receptor Antagonist

The baseline data of sRaw before OA challenge were from 1.6 to 2.4 cm H₂O/mL/s, and there were no significant differences among the treatment

groups. Both ONO-AE1-259-01 and ONO-AE1-329 suppressed OA-induced bronchoconstriction, and the extent of the inhibition was similar to that achieved by PGE₂ (Fig 4). In contrast, ONO-DI-004, ONO-AE-248, and sulprostone did not inhibit the bronchoconstriction caused by OA challenge. The changes in AR to methacholine (Δ of log concentration of methacholine required to increase sRaw to twice the baseline level) on treatment with vehicle and different EP receptor antagonists were as follows: vehicle (0.09 ± 0.24); ONO-DI-004 (20 nmol, 0.11 ± 0.16 ; 200 nmol, 0.45 ± 0.18); ONO-AE1-259 (20 nmol, 0.09 ± 0.14 ; 200 nmol, 0.06 ± 0.17); ONO-AE-248 (20 nmol, 0.12 ± 0.15 ; 200 nmol, 0.07 ± 0.17); ONO-AE1-329 (2 nmol, 0.08 ± 0.10 ; 20 nmol, 0.11 ± 0.14); and sulprostone (20 nmol, 0.06 ± 0.25 ; 200 nmol, 0.11 ± 0.22). There were no significant differences among these groups. As shown in Figure 5, there were no significant differences in PGE₂ levels in BAL fluid among the five treatment groups: vehicle, ONO-DI-004, ONO-AE1-259, ONO-AE-248, and ONO-AE1-329.

DISCUSSION

This study demonstrated that inhibition of OA-induced bronchoconstriction by PGE₂ occurs through EP-2 and EP-4 receptors in a sensitized guinea pig model. Our results also demonstrated for the first time that both EP-2- and EP-4-selective

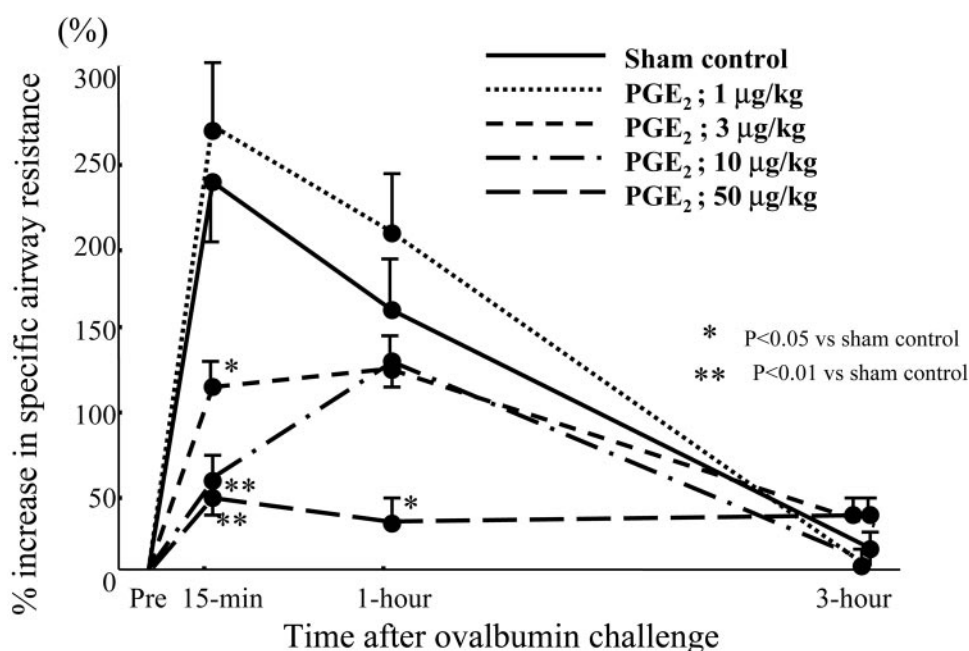


FIGURE 3. Effect of PGE₂ on OA-induced bronchoconstriction. PGE₂ significantly reduced sRaw 15 min after OA challenge in a dose-dependent manner.

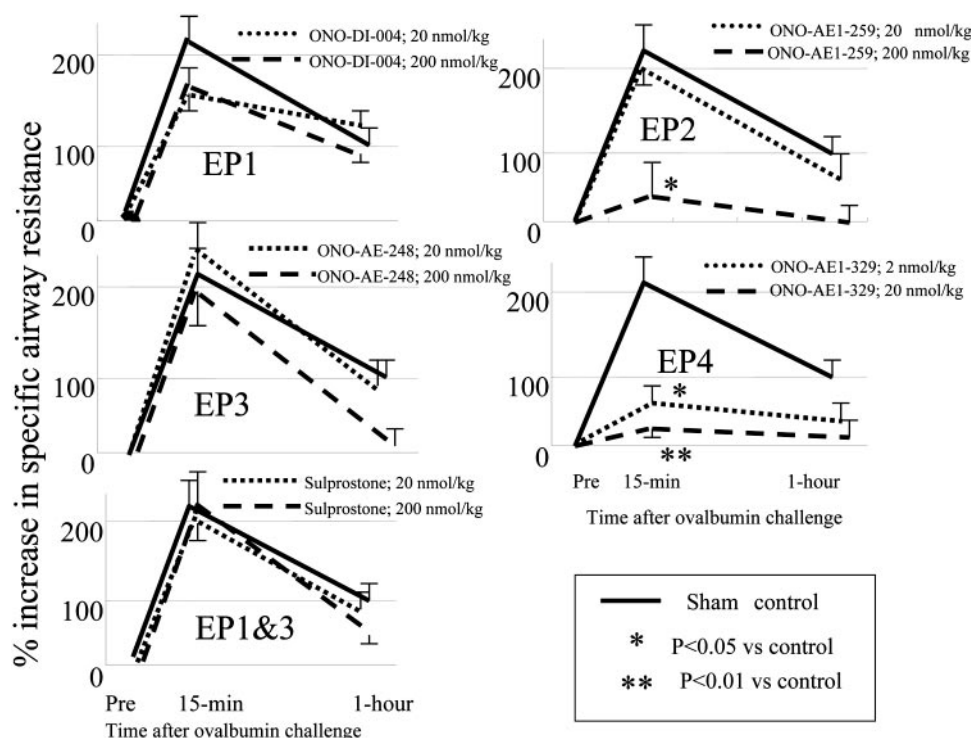


FIGURE 4. Effect of each EP receptor antagonist on OA-induced bronchoconstriction. Both ONO-AE1-259-01 (EP-2 agonist) and ONO-AE1-329 (EP-4 agonist) significantly suppress (analysis of variance) the OA-induced bronchoconstriction as compared with sham control animals. ONO-DI-004 (EP-1 agonist), ONO-AE-248 (EP-3 agonist), and sulprostone (an EP-1 and EP-3 agonist) produce no suppression.

agonists inhibited the OA-induced bronchoconstriction when administered immediately before OA challenge, but these treatments did not affect AR. Fortner et al,¹⁸ using mice homozygous for a gene targeted deletion of the EP-2 receptor, reported that EP-2 receptors were of primary importance in the airway relaxation to PGE₂ and that relaxation to adenosine triphosphate was mediated through PGE₂ acting on EP-2 receptors. Using a knockout mouse model, Tilley et al¹⁴ found that PGE₂-induced bronchodilation resulted from activation of the EP-2 receptor on airway smooth muscle, whereas activation of EP-1/EP-3 receptors induced airway constriction. Our results are consistent with these previous reports. Activation of EP-1 receptors increases intracellular Ca²⁺, and EP-3 couples to inhibitory guanosine triphosphate (GTP)-binding protein with a decrease in cyclic adenosine monophosphate (cAMP). However, EP-2 and EP-4 are coupled to stimulatory GTP-binding protein, activating adenylyl cyclase and increasing cAMP, a signal known to relax airway smooth muscle. In total, these findings indicate that the bronchoprotective effects of PGE₂ may occur through stimulation of EP-2 and EP-4 receptors but not through EP-1 and EP-3 receptors.

The effects of PGE₂-induced smooth-muscle re-

laxation *in vitro* are sometimes inconsistent,^{11,13} probably due to simultaneous stimulation of different prostaglandin-like receptors with inhibitory and stimulatory activity on intrinsic tone. We suppose that PGE₂ inhibition of the bronchoconstriction may occur at levels consistent with an interaction of the PGE₂ receptors. The strong bronchoprotective effects of PGE₂ have not been exploited for asthma therapy partly because of its adverse effects of cough and retrosternal burning.²⁰ Additionally, PGE₂ can stimulate intrapulmonary C fibers and to a lesser extent rapidly adapting irritant receptors.²¹ Our results suggest that EP-2 or EP-4 receptor agonists might have better therapeutic potential rather than PGE₂, provided EP-2 or EP-4 receptor agonists do not have adverse effects.

This protective action of PGE₂ might not only result from a direct effect on airway smooth-muscle relaxation but also by inhibition of many inflammatory processes, including mast-cell degranulation, leukotriene B₄ production by alveolar macrophages, and eosinophil activation.^{7,8,22,23} PGE₂ inhalation suppresses mast-cell release of prostaglandin metabolites, resulting in significantly lower concentrations of prostaglandin D₂ after antigen stimulation.²³ However, in the preliminary studies, the EP-2 and

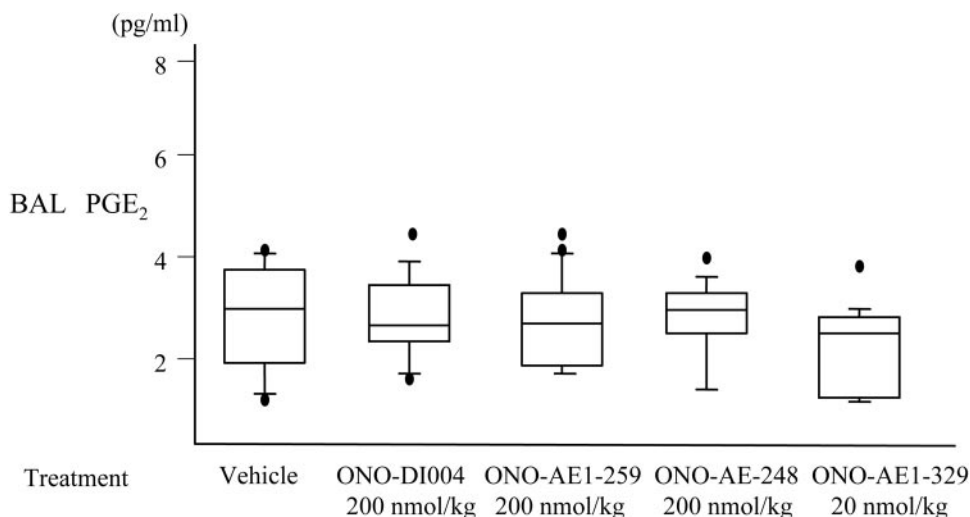


FIGURE 5. BAL fluid PGE₂ levels in each treatment group. Each group consists of seven guinea pigs. No significant differences exist among vehicle, ONO-DI-004 (EP-1 agonist), ONO-AE1-259 (EP-2 agonist), ONO-AE-248 (EP-3 agonist), and ONO-AE1-329 (EP-4 agonist). The rectangle includes the range from the 25th to 75th percentiles, the horizontal line indicates the median, and the vertical line indicates the range from the 10th to 90th percentiles.

EP-4 agonists used in our experiments did not suppress the release of prostaglandin D₂ from mast cells, and these agonists had no effect on methacholine-induced airway responsiveness. PGE₂ levels in BAL fluid did not differ among the treatment groups, suggesting that none of the EP agonists act to release PGE₂ from any of the possible cell types. Mechanisms of the bronchoprotective actions of EP-2 and EP-4 require further examination.

In conclusion, the inhibition of airway smooth-muscle contraction by PGE₂ acts through EP-2 and EP-4 receptors in OA-sensitized guinea pigs. Although PGE₂ might be of therapeutic benefit, PGE₂ itself has the potential to cause the adverse effects of cough and retrosternal burning when inhaled by humans. Moreover, PGE₂ also stimulates other prostaglandin-like receptors having inhibitory and stimulatory activity on the intrinsic tone of the airway smooth muscle. Thus, it is feasible to suggest that EP-2 or EP-4 receptor agonists, if free of adverse effects on human airways, may have therapeutic benefit instead of inhaled PGE₂.

REFERENCES

- 1 Main IHM. The inhibitory actions of prostaglandins on respiratory smooth muscle. *Br J Pharmacol* 1964; 22:511-519
- 2 Kleeberg SR, Freed AN. Prostanoids. In: Busse WW, Holgate ST, eds. *Asthma and rhinitis*. Boston, MA: Blackwell Scientific Publications, 1995; 825-837
- 3 Kiriya M, Ushikubi F, Kobayashi T, et al. Ligand binding specificities of the eight types and subtypes of the mouse prostanoid receptors expressed in Chinese hamster ovary cells. *Br J Pharmacol* 1997; 122:217-224
- 4 Yamamoto H, Maruyama T, Sakata K, et al. Novel four selective agonists for prostaglandin E receptor subtypes. The Sixth International Eicosanoid Conference, The Westin. Boston MA: 1999; 152
- 5 Suzawa T, Miyaura C, Inada M, et al. The role of prostaglandin E receptor subtype (EP1, EP2, EP3, and EP4) in bone resorption: an analysis using specific agonists for the respective EPs. *Endocrinology* 2000; 141:1554-1559
- 6 Melillo E, Wooley KL, Manning PJ, et al. Effect of inhaled PGE₂ on exercise-induced bronchoconstriction in asthmatic subjects. *Am J Respir Crit Care Med* 1994; 149:1138-1141
- 7 Pavord ID, Wong CS, Williams J, et al. Effect of inhaled prostaglandin E₂ on allergen-induced asthma. *Am Rev Respir Dis* 1993; 148:87-90
- 8 Pasargiklian M, Bianco S, Allegra L. Clinical, functional and pathogenetic aspects of bronchial reactivity to prostaglandins F₂α, E₁, and E₂. *Adv Prost Throm Res* 1976; 1:461-475
- 9 Delamere F, Holland E, Patel S, et al. Production of PGE₂ by cultured airway smooth muscle cells and its inhibition by prostaglandin synthetase inhibitor. *Br J Pharmacol* 1994; 111:983-988
- 10 Sestini P, Armetti L, Gambaro G, et al. Inhaled PGE₂ prevents aspirin-induced bronchoconstriction and urinary LTE₄ excretion in aspirin-sensitive asthma. *Am J Respir Crit Care Med* 1996; 153:572-575
- 11 Gauvreau GM, Watson RM, O'byrne PM. Protective effects of inhaled PGE₂ on allergen-induced airway responses and airway inflammation. *Am J Respir Crit Care Med* 1999; 159:31-36
- 12 Pavord ID, Wisniewski R, Mathur I, et al. Effect of inhaled prostaglandin E₂ on bronchial reactivity to sodium metabisulphite and methacholine in subjects with asthma. *Thorax* 1991; 46:633-637
- 13 Qian YM, Jones RL, Chan KM, et al. Potent contractile actions of prostanoid EP3-receptor agonist on human isolated pulmonary artery. *Br J Pharmacol* 1994; 113:369-374
- 14 Tilley SL, Hartney JM, Erikson CJ, et al. Receptors and

- pathways mediating the effects of prostaglandin E_2 on airway tone. *Am J Physiol Lung Cell Mol Physiol* 2003; 284:L599–L606
- 15 Teramoto S, Tanaka H, Kaneko S, et al. Short-time inhalation of sulfuric acid aerosol enhanced airway hyperresponsiveness to methacholine in sensitized guinea pigs; effects of neurokinin-1 and 2 receptor antagonist. *Int Arch Allergy Immunol* 2000; 121:53–56
 - 16 Teramoto S, Tanaka H, Kaneko S, et al. Neurokinin-1 and 2 antagonism inhibits long-term acid fog-induced airway hyperresponsiveness. *Chest* 2003; 123:524–529
 - 17 Pennock BE, Cox CP, Rogers RM, et al. A noninvasive technique for measurement of changes in specific airway resistance. *J Appl Physiol* 1979; 46:399–406
 - 18 Fortner CN, Breyer RM, Paul RJ. EP_2 receptors mediate airway relaxation to substance P, ATP, and PGE_2 . *Am J Physiol Lung Cell Mol Physiol* 2001; 280:L469–L474
 - 19 Mathe AA, Hedqvist P. Effects of prostaglandin $F_{2\alpha}$ and E_2 on airway conductance in healthy subjects and asthmatic patients. *Am Rev Respir Dis* 1975; 111:313–320
 - 20 Coleridge HM, Coleridge JC, Ginzel KH, et al. Stimulation of 'irritant' receptors and afferent C-fibers in the lungs by prostaglandins. *Nature* 1976; 264:451–453
 - 21 Peters SP, Schulman ES, Schleimer RP, et al. Dispersed human lung mast cells: pharmacologic aspects and comparison with human lung fragments. *Am Rev Respir Dis* 1982; 126:1034–1039
 - 22 Kita H, Abu-Ghazaleh RI, Gleich GJ, et al. Regulation of Ig-induced eosinophil degranulation by adenosine 3',5'-cyclic monophosphate. *J Immunol* 1991; 146:2712–2718
 - 23 Hartert TV, Dworski RT, Mellen BG, et al. Prostaglandin E_2 decreases allergen-stimulated release of prostaglandin D_2 in airways of subjects with asthma. *Am J Respir Crit Care Med* 2000; 162:637–640

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