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*J Immunol* 2002; 169:3963-3969; doi: 10.4049/jimmunol.169.7.3963
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The Immunomodulatory Actions of Prostaglandin E₂ on Allergic Airway Responses in the Rat¹

James G. Martin,¹,²,* Masaru Suzuki,* Karim Maghni,* Rosa Pantano,* David Ramos-Barbón,* Daizo Ihaku,* François Nantel,† Danielle Denis,† Qutayba Hamid,* and William S. Powell*¹

PGE₂ has been reported to inhibit allergen-induced airway responses in sensitized human subjects. The aim of this study was to investigate the mechanism of anti-inflammatory actions of PGE₂ in an animal model of allergic asthma. BN rats were sensitized to OVA using Bordetella pertussis as an adjuvant. One week later, an aerosol of OVA was administered. After a further week, animals were anesthetized with urethan, intubated, and subjected to measurements of pulmonary resistance (R₉) for a period of 8 h after OVA challenge. PGE₂ (1 and 3 μg in 100 μl of saline) was administered by insufflation intratracheally 30 min before OVA challenge. The early response was inhibited by PGE₂ (3 μg). The late response was inhibited by both PGE₂ (1 and 3 μg). Bronchoalveolar lavage fluid from OVA-challenged rats showed eosinophilia and an increase in the number of cells expressing IL-4 and IL-5 mRNA. These responses were inhibited by PGE₂. Bronchoalveolar lavage fluid levels of cysteinyl-leukotrienes were elevated after OVA challenge and were reduced after PGE₂ to levels comparable with those of sham challenged animals. We conclude that PGE₂ is a potent anti-inflammatory agent that may act by reducing allergen-induced Th2 cell activation and cysteinyl-leukotriene synthesis in the rat. The Journal of Immunology, 2002, 169: 3963–3969.

¹Abbreviations used in this paper: AHR, airway hyperresponsiveness; LT, leukotriene; cys-LT, cysteinyl-LT; EAR, allergen-induced early response; MBP, major basic protein.

Received for publication December 7, 2001. Accepted for publication July 22, 2002.

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Materials and Methods

Animals and sensitization

Male BN rats between 7 and 9 wk of age were purchased from Harlan Sprague Dawley U.K. (Blackthorn, U.K.) and maintained in a conventional animal facility at McGill University (Montreal, Canada). All rats were actively sensitized with a s.c. injection of 1 mg of OVA (grade V; Sigma-Aldrich, St. Louis, MO) precipitated in 4.28 mg of aluminum hydroxide gel (Anachemia Chemicals, Montreal, Canada) in 1 ml of normal saline. Simultaneously, 0.5 ml of Bordetella pertussis vaccine containing 6 × 10⁶ heat-killed bacilli/ml (Institut Armand Frappier, Laval-Des-Rapides, Canada) was injected i.p. as an adjuvant. A booster sensitization was performed at 7 days. Animals were anesthetized with pentobarbital (35 mg/kg i.p.), intubated, and exposed to an aerosol of 5% OVA (w/v) for 5 min.
For the evaluation of the effects of PGE2 on the EAR, LAR, and airway inflammation, four groups of sensitized rats were studied. The first group was challenged with aerosolized OVA after administration of the vehicle saline (100 μl) intratracheally by insufflation. The second group was challenged with aerosolized OVA after an intratracheal insufflation of PGE2 (1 μg). The third group was challenged with aerosolized OVA after an intratracheal insufflation of PGE2 (3 μg), and the fourth group was challenged with aerosolized BSA after an intratracheal insufflation of saline (100 μl).

Measurement of airway responses to Ag challenge

Two weeks after sensitization, animals were anesthetized with urethane (1.25 g/kg i.p.) for measurements of allergen-induced airway responses. Animals were intubated endotracheally with polyethylene tubing (PE240; Commercial Plastics, Montreal, Canada) and placed on a heating pad to maintain a rectal temperature of 36°C. Airflow was measured by placing the tip of the endotracheal tube inside a Plexiglas box (~250 ml). A pneumotachograph (Fleisch No. 0; Bioinetics, Montreal, Canada) coupled to a differential transducer (PX 170-14DV; Omega Engineering, Stamford, CN) was connected to the other end of the box to measure airflow. A water-filled catheter connected to a pressure transducer (Transpac II; Sorensen, Abbott, IL) was advanced into the lower esophagus to measure changes in transpulmonary pressure. Pulmonary resistance (Rt) was determined by multiple linear regression from transpulmonary pressure and airflow using commercial software (RHT Infodat, Montreal, Canada) (15). Animals were challenged for 5 min with an aerosol of either OVA or BSA (5% w/v). A disposable nebulizer (Hudson model 1400; Hudson, Temecula, CA) was used with an output of 0.15 ml/min. Rt was measured every 30 min for 30 min after challenge and subsequently at 15-min intervals for a total period of 8 h. The EAR was defined as the maximal value of Rt, expressed as percent baseline Rt1, in the first 30 min after challenge. The LAR was calculated as the area under the curve of Rt1 against time (cm H2O × ml × 1 min) from 3 to 8 h after challenge, after correction of Rd for the baseline value. Animals were then sacrificed for bronchoalveolar lavage (BAL).

Bronchoalveolar lavage

BAL was performed 8 h after challenge with five instillations of 5 ml of saline. The first 5-ml aliquot was spun, and the supernatant was used for analysis of cys-LTs. Approximately 22 ml of fluid were recovered with each BAL, and the volume did not differ significantly among treatment groups. The total cell count and cell viability were estimated using a hemacytometer and trypan blue stain. Slides were prepared using a Cytospin fi

Immunocytochemistry and in situ hybridization for eosinophils

Cytospin slides were prepared on poly-L-lysine-coated glass slides, fixed in 4% paraformaldehyde, and washed with PBS before processing. BAL cells were immunostained with an Ab, BMK13 mAb (kindly provided by Dr. R. Moqbel (University of Alberta, Edmonton, Canada), directed against major basic protein (MBP) using the alkaline phosphatase anti-alkaline phosphatase method. MBP-positive cells were counted by an investigator blinded to group status. A minimum of 500 BAL cells was counted, and the percent of cells expressing MBP immunoreactivity was evaluated.

In situ hybridization was performed as previously described (14) on cytopsin slides from rats in experimental groups 1, 3, and 4. Antisense and sense riboprobes were prepared from cDNAs coding for rat IL-4, IL-5, and IFN-γ mRNA. cDNAs were first inserted into a PGE2 vector and linearized with appropriate enzymes. In vitro transcription was conducted in the presence of [35S]-UTP and the T7 or SP6 RNA polymerases. After per- maeabilization and prehybridization steps, the preparations were incubated with antisense or sense probes (10^6 cpm/section). Posthybridization washing was performed in decreasing concentrations of standard saline citrate at 40°C. Unhybridized single-strand RNA was removed by RNase A (20 mg/ml). After dehyadrination, the slides were immersed in NBT2 emulsion and exposed for 10 days. The autoradiographs were developed in Kodak D-19, fixed, and counterstained with hematoxylin. Slides were coded, and positive cells were counted blindly. For negative controls, cytopsin slides were hybridized with sense probes or pretreated with RNase before the application of probes.

Statistical analysis

Comparisons among several means were performed by ANOVA, and post hoc testing was done with a Tukey test or a Fisher least significant difference test. Values of p < 0.05 were considered significant.

Results

Effects of PGE2 on early and late airway responses to OVA challenge

Sensitized rats undergoing challenge with OVA showed rapid al- beit minor increases in Rt1 (Fig. 1). The increase in Rt1 was sustained throughout most of the 8-h period of observation after challenge. There were further superimposed peaks in Rt1 ~200 and 350 min after challenge. Rats challenged with BSA had values of Rt1 that were slightly below the baseline, whereas rats challenged with OVA after PGE2 pretreatment (3 μg) had also markedly attenuated responses to OVA challenge (Fig. 1). A lower dose of PGE2, (1 μg) had a similar inhibitory effect (the data have been omitted from the figure for clarity). There was a significant EAR in the OVA-sensi- tized and OVA-challenged rats compared with the OVA-sensi- tized and BSA-challenged controls (p = 0.04). The EAR showed a dose-dependent reduction with PGE2 pretreatments of 1 and 3 μg intratracheally (Fig. 2). The inhibition reached significance after the 3 μg dose (p = 0.01). The LAR after OVA challenge was statistically significantly inhibited by PGE2, 1 μg (p = 0.02) and 3 μg (p = 0.002), and was different from the BSA-challenged controls (p = 0.004; Fig. 3).

Effects of PGE2 on BALF cell counts

The total cell counts were significantly higher in the OVA-chal- lenged rats with or without PGE2 (3 μg) pretreatment compared with the BSA-challenged rats (p = 0.04; Fig. 4). The differential cell counts obtained using the May-Grünwald-Giemsa stain did not

Analysis of BAL in cys-LTs

The levels of cys-LTs in BALF were measured using an enzyme immunoassay following the manufacturer’s instructions (Cayman Chemical, Ann Arbor, MI). The antiserum is reported to have cross-reactivity for leukotrienes (LT) C4 (100%), D4 (100%), and E4 (67%). Methanol was added to each BALF sample (500 μl), and the precipitated protein was removed by centrifugation. A solid phase extraction cartridge (Cayman Chemical) was used to extract cys-LTs that were eluted with HPLC grade hexane. The samples were then dried by vacuum centrifugation and reconstituted in enzyme immunoassay buffer. Samples were placed in 96-well plates in duplicate and incubated for 18 h at room temperature with acetylcholinesterase tracer and cys-LT antiserum. Ellman’s reagent was then added and developed for 60–90 min. The plates were read at 405 nm. A standard curve was constructed using concentrations of LTD4 ranging from 7.8 to 1000 pg/ml. Results were not corrected for extraction efficiency.

Electropherogram in pulmonary tissues

We examined the distribution of EPR mRNA in the lungs of two sensitized and two naive rats. Fourteen days after sensitization, the lungs were re- moved, fixed, and sectioned in 4-μm-thin slices on silane-coated slides. Hybridization was performed using digoxigenin-labeled RNA probes. The probes were constructed using PCR amplification and cloning into the PCR-III vector (Invitrogen, San Diego, CA). The cRNA probe for the EP receptor mRNA was obtained from a 226-bp fragment from 715 to 941 of the EP2 coding sequence. For the EP1, receptor, we used a 192-bp cRNA probe hybridizing to a segment corresponding to positions 683–875. For the EP2, receptor, we used a 242-bp cRNA probe hybridizing to positions 765–1007. This particular probe hybridizes with all EP, splice variants. Finally, for the EP3 receptor, we used a 321-bp cRNA probe hybridizing to positions 1121–1133. The plasmids were linearized, and digoxigenin-la- beled cRNA sense and antisense probes were synthesized using the DIG- RNA labeling kit from Boehringer Mannheim (Laval, Canada). For in situ hybridization, a standard protocol was used as previously described (15). Detection of the digoxigenin-labeled cRNA probe was performed using HRP-linked Abs (Boehringer Mannheim) and diaminobenzidine substrate (Pierce, Rockford, IL). The tissues were counterstained with hematoxylin (Fisher, Nepean, Canada).
show any statistically significant differences. Although granulocyte numbers tended to be lower in the PGE$_2$-pretreated rats, these differences were not significant. No attempt was made to distinguish between neutrophils and eosinophils using May-Grunwald-Giemsa staining because of previous observations that this stain tends to lead to an underestimate of eosinophil numbers in OVA-challenged BN rats (16). For this reason, eosinophils were analyzed using immunochemical staining instead. There was a substantial eosinophilia after OVA challenge ($p < 0.001$). After 3 g PGE$_2$ pretreatment, there was a substantial reduction in eosinophil numbers to 2% of BAL cells ($p < 0.001$; Fig. 5). This latter value was not different from eosinophil numbers in the BALF of the BSA-challenged rats.

Effects of PGE$_2$ pretreatment on IL-4, IL-5, and IFN-γ mRNA-positive cells in BALF

Cytokine expression in BAL cells from OVA- or BSA-challenged and saline-pretreated rats was compared with OVA-challenged and PGE$_2$-pretreated animals. Only rats pretreated with PGE$_2$ 3 μg intratracheally were studied because this dose seemed to produce a maximal inhibitory effect on the LAR. Approximately 10% of BAL cells of OVA-challenged rats were positive for IL-5 mRNA by in situ hybridization (Fig. 6A). This number was reduced to 3% by PGE$_2$ ($p < 0.001$) which was comparable with the BSA-challenged rats (2%; $p = \text{NS}$). IL-4 mRNA-positive cells were 8% of the BAL cells in OVA-challenged rats (Fig. 6B), and there was a small but significant reduction in this number to 6% after PGE$_2$ pretreatment ($p = 0.012$). About 3% of BAL cells were IL-4 positive in the BSA-challenged group, which was significantly less than in the PGE$_2$-pretreated group ($p = 0.003$) and in the OVA-challenged group ($p < 0.001$). IFN-γ expression was very low in
saline-pretreated and OVA-challenged rats and was higher in BSA-challenged controls \( (p < 0.012; \text{Fig. 6C}) \). PGE\(_2\)-treated animals had intermediate numbers of IFN-\(\gamma\) cells that were not significantly different from either of the other groups.

Effects of PGE\(_2\) on cys-LT levels in BALF

There was a significant difference in BALF levels of cys-LT among the OVA-challenged/saline-pretreated, OVA-challenged/PGE\(_2\)-pretreated and BSA-challenged groups of rats \( (p = 0.02 \text{ by ANOVA}) \). The increase in cys-LTs in the BALF of OVA-challenged rats was significantly higher than in rats after BSA challenge \( (p = 0.047; \text{Fig. 7}) \). Animals treated with PGE\(_2\) before challenge had substantial and significant inhibition of cys-LTs \( (p = 0.007 \text{ compared with OVA-challenged and saline-pretreated rats}) \).

Pulmonary EP receptor distribution

The distribution of EP receptors was examined by in situ hybridization. There were no obvious differences between naive and sensitized animals. The most abundant receptor mRNA found was that of the EP\(_4\) subtype (Fig. 8). There was detectable expression on the alveolar epithelium, on vascular endothelial cells, and on inflammatory cells within the interstitium and air spaces. The expression of the EP\(_1\) and EP\(_2\) receptor subtypes was virtually undetectable. There was weak staining for the EP\(_3\) receptor on the alveolar epithelium. There was no detectable mRNA for any of the EP receptors on airway smooth muscle cells.

Discussion

The results of this study demonstrate the ability of PGE\(_2\) to modulate the magnitude of allergic bronchoconstriction and inflammation in an animal model. The reduction in Th2 cell cytokines that was observed suggests the possibility that an inhibitory effect on the CD4\(^+\) T cells was responsible for the reduction in airway inflammation. There was also a potent inhibition of cys-LT synthesis as evidenced by total inhibition of the allergen-induced increase in these mediators in BALF. The cys-LTs are of particular importance in mediating the LAR (17–19), and the reduction of their synthesis by PGE\(_2\) could account for the observed reduction of the LAR. The EAR was also significantly inhibited by PGE\(_2\). The predominant EP receptor expressed in the lungs was EP\(_4\). None of the EP receptors was detected by in situ hybridization on the airway smooth muscle.

Because PGE\(_2\) has been shown to induce bronchodilation in mice through interaction with EP\(_2\) receptors (20), it is possible that a direct effect on airway smooth muscle cells could have contributed to the inhibitory response to this PG. However, the paucity of
expression of EP receptors on airway smooth muscle cells in the
BN rat would suggest that the allergic airway responses may not
have been mediated primarily by a direct effect of PGE2 on airway
smooth muscle. However, such an effect is not excluded by the
current study because the inhibition of the EAR that was observed
may have been the result of either inhibition of airway smooth
muscle contraction or inhibition of mast cell degranulation. The
extent to which direct actions of PGE2 on airway smooth muscle
account for any of its salutary effects on allergic airway responses
in the current study or in any of the published studies is unclear.
There are several studies of the effects of PGE2 on the mast cell.
It has been reported to both enhance IgE-dependent mast cell de-
granulation (histamine release) in vitro (7, 8) and inhibit Ag-in-
duced histamine release (21). Although PGE2 has been shown to
reduce the early response in human subjects, it appears to do so
predominantly through an effect on PGD2 synthesis (3). In this
latter study, the effect of PGE2 on cys-LTs was not significant,
suggesting a differential effect on the inhibition of these two ar-
chidonate-derived mediators synthesized by the mast cell. The
inhibition of the late response in the current study can also be ac-
counted for by inhibition of mediator release.

In vitro experiments have provided substantial evidence of the
potential for PGE2 to have anti-inflammatory and immunomodu-
latory actions. PGE2 has been shown to alter mast cell cytokine
synthesis; it induces IL-6 (7, 8) and GM-CSF (8), whereas it sup-
presses TNF-α synthesis (7). Several other targets of the actions
of PGE2 warrant mention, in particular B and T lymphocytes. Our
data using in situ hybridization indicate that T cell cytokine ex-
pression was reduced by PGE2, indicating an effect on T cell func-
tion. Because T cell activation is presumably caused by presenta-
tion of Ag to T cells in the airway wall, then PGE2 could exert
effects on the T cell through actions either on the T cell itself or on
APCs. Mitogen-stimulated CD4+ T cells have been shown to un-
dergo a change in phenotype in vitro on exposure to PGE2 with a
reduction in IFN-γ and an increase in IL-5 expression (10). Dif-
fferences in the salutary effects on allergic airway responses
in the current study or in any of the published studies is unclear.

PGE2 has effects that are of interest in the consideration of this
substance as a therapeutic agent for allergic asthma. It inhibits
IL-4-induced production of IgE by human B cells (9). There is
contrary evidence indicating that PGE2 may also affect T cell help
for Ab synthesis so as to favor IgE synthesis and allergic type
inflammation. PGE2 has been shown to suppress the Th1 type cy-
tokines IL-2 and IFN-γ cells and to stimulate Th2 cells (10, 22).
A similar role in Th2 biasing of T cell responses has been shown in
BALB/c mice through inhibition of IFN-γ (11). Our results indicate that the net result of the
complex actions of PGE2 in vivo is a selective inhibition of Th2
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tory effect on eosinophil infiltration as PGD 2 has been shown to be
the application of this molecule as a therapeutic agent. 

findings support the notion that PGE 2 could be a useful anti-
by effects of PGE2 on the eosinophil itself. Interestingly, cyclooxy-
reduction in eosinophils. Eosinophilia perhaps could be reduced also
a potent chemoattractant for these cells (29). Cys-LTs were also
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known. Although unproven, eosinophils are considered to be a
probable source of cys-LTs in human asthmatic subjects. In ro-
ents, however, eosinophils do not synthesize significant amounts of
cys-LTs (36, 37). Mast cells or macrophages are alternative
sources (37), but to date their implication in cys-LT synthesis in
vivo in rats has not been confirmed. Inhibition by PGE2 of the
synthesis of LTB4, another product of 5-lipoxygenase, by poly-
morphonuclear leukocytes has also been reported (38). If this oc-
curred in the current experiment, it may have contributed to the
reduction in BAL eosinophilia, that has been shown to inhibited by
antagonists of LTB4 in this animal model (39).

In conclusion, PGE2 is a potent inhibitor of allergic airway
responses in the BN rat model of allergic asthma. The effects are
likely exerted at several sites, but the current study clearly shows effects
on T cell cytokine expression and on the control of eosin-
ophilia. The synthesis of cys-LTs is also inhibited by PGE2. These
findings support the notion that PGE2 could be a useful anti-
flammatory treatment for asthma. However PGE2 has complex
immunomodulatory properties in vitro so that elucidation of the
pertinence of these effects in vivo would be important preceding
the application of this molecule as a therapeutic agent.

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