Review Article

Anti-inflammatory and bronchoprotective roles of endogenous prostaglandin E2

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ABSTRACT

Prostaglandin E2 (PGE2) is produced by resident cells in the airway, such as airway epithelial cells, airway smooth muscle cells and alveolar macrophages, and is always present in the airway. Various exogenous and endogenous stimuli cause immediate increases in PGE2 from several-fold to multiples of 10-fold. Prostaglandin E2 controls the function of cells that contribute to immune and inflammatory responses, such as lymphocytes, eosinophils, mast cells, macrophages and polymorphonuclear cells, and exhibits suppressor activity in the initial and advanced stages of allergic airway inflammation (establishment of sensitization, induction of early asthmatic response, chemotaxis of inflammatory cells and continuation of the late asthmatic response). Therefore, if the endogenous protective effects of PGE2 are weakened or absent, inflammation and hypersensitive responses readily occur in the airway. Although the effects of PGE2 remain to be clarified, the possibility of the involvement of decreased PGE2 activity in the pathogenesis of asthma exists. However, in aspirin-induced asthma the role of PGE2 as a protective factor, through an as yet undefined mechanism, is marked. It is thought that, in this type of asthma, symptoms may be induced by the elimination of the protective action of PGE2 by non-steroidal anti-inflammatory drugs (NSAID). It is possible that PGE2 agonists that produce little airway irritation and drugs that raise the endogenous PGE2 level have potential as new types of anti-inflammatory or anti-asthma drugs.

Key words: airway inflammation, arachidonic acid, aspirin-induced asthma, asthma, cyclo-oxygenase, prostaglandin E2.

INTRODUCTION

In the present review article, the role of prostaglandin (PG)E2 as an endogenous protective factor in the pathophysiology of allergic pulmonary diseases, especially bronchial asthma, will be discussed. The pathophysiology of bronchial asthma is complex and multifaceted and has been studied from many points of view. As to the mechanism of the development of allergic asthma, it has recently been hypothesized that eosinophils and mast cells interact with a cytokine network, with the lymphocyte at its center, and that the production of IgE antibodies, production and release of inflammatory mediators and impairment of airway epithelial cells result, causing the so-called 'eosinophilic inflammation' of the airway.1 In this process, various arachidonic acid metabolites contribute to the pathophysiology of asthma.2 Almost all arachidonic acid metabolites, such as leukotriene (LT)C4, thromboxane (TX)A2 and PGD2, cause airway inflammation and constriction and, thus, act to initiate or aggravate asthma, but there is evidence that PGE2 acts as a mediator that possesses endogenous anti-inflammatory and bronchoprotective effects.3

ARACHIDONIC ACID METABOLITES AND THE PATHOPHYSIOLOGY OF BRONCHIAL ASTHMA

Figure 1 shows the principal metabolic pathways of arachidonic acid. Arachidonic acid is bound to the
C2 position of the glycerol of phospholipids that form cell walls and is released by the enzyme action of phospholipase A2, whereupon it immediately acts as a substrate for cyclo-oxygenase (COX) and 5-lipoxygenase (5-LO). In this metabolic pathway, there are many mediators that can contribute to the pathophysiology of asthma. For example, peptide LT and platelet-activating factor (PAF), TXA2, PGF2α and PGD2 contribute to the contraction of bronchial smooth muscles and the peptide LT PG E2, PG D2 and PAF contribute to increased vascular permeability. Peptide LT and 5-hydroxyeicosatetraenoic acid (5-HETE) contribute to the secretion of mucus in the airway and LTB4, 5-HETE and PAF promote the chemotaxis of inflammatory cells into the airway. Furthermore, the peptide LT TXA2 and PAF are said to promote bronchial hyperresponsiveness. In addition, active oxygen radicals are produced in these metabolic processes, which may also contribute to injury of the airway epithelium. However, PG E2 has been found to have a number of protective actions: it dilates the human bronchial, inhibits early and late airway responses to antigen inhalation etc. Furthermore, these metabolites not only act directly on target cells as effectors but, as modulators, they also affect the production of cytokines, the activity of the autonomic nervous system (ANS) and the activation of mast cells. Conversely, the metabolic pathways of arachidonic acid are modulated at various stages by mediators of the ANS, glucocorticoids, cytokines and nitric oxide (NO).

The principal metabolic pathways are the COX and 5-LO pathways, but there are also pathways through 12-LO, 15-LO and cytochrome P450. Although not shown in Fig. 1, some non-enzymatic metabolites also have physiological activity. Furthermore, COX has two isozymes, CO X1 and CO X2, and conventional NSAID have almost no inhibitory activity on CO X2. Among these metabolites, the peptide LT and TXA2 are especially important as mediators that contribute directly to the genesis of asthma symptoms and it is well known that drugs that act as antagonists to them and those that inhibit their synthesis are now available as a new class of asthma drugs. Although all cells contain arachidonic acid (the substrate for COX and 5-LO) in their cell walls, not all the metabolic pathways described here are present in all cells.

Table 1 summarizes the production of prostanoids by resident cells in the lung and inflammatory cells. Alveolar macrophages produce almost all the prostanoids LTC4, LTD4 and PAF. Mast cells produce PG D2, PG F2α and TXA2,
as well as LTC₄ and PAF, and airway epithelial cells produce all the prostanoids mentioned here. The importance of airway epithelial cells as effector cells has been suggested and there are reports that PGE₂ and PGI₂ are even produced in airway smooth muscle cells.₁⁶,₁⁷ Furthermore, the prostanoids present in lung tissue and airways are derived from many cells. It has been shown that PGE₂ is produced by resident cells in the lung, such as alveolar macrophages, airway epithelial cells and airway smooth muscle cells, as well as by neutrophils and eosinophils.

**PROSTAGLANDIN E RECEPTORS**

The activity of PGE₂ is expressed through specific receptors (EP receptors), four subtypes, EP₁, EP₂, EP₃ and EP₄, which have been cloned and are closely related to the older pharmacological classification.₁⁸ Table 2 shows the order of affinities of the PGE₂ agonists to the various receptors.₁⁸ Table 3 shows the intracellular signal transduction systems that are related to the various EP receptors.₁⁸ The EP₂ and EP₃ receptors are related to the Gₛ-protein, cause elevations in intracellular cyclic AMP (cAMP) concentrations and are thought to mediate the activity of PG E₂ as a protective factor. The principal signal transduction pathway of the EP₁ receptor is the inhibition of adenylate cyclase by way of the Gₛ-protein; this receptor has four isoforms, A, B, C and D, and is thought to be linked with various different signal transduction systems.₁⁸

The multiplicity of EP receptors leads to the multiplicity and complexity of PGE₂ activity and, indeed, different concentrations of PGE₂ can cause completely opposite reactions in the same tissues and different reactions in different species.₁⁸

**ENDOGENOUS PROTECTIVE FACTORS RELATED TO THE PATHOGENESIS OF ASTHMA**

Among the endogenous protective factors against asthma symptoms, of primary consideration is the adreno-medullary sympathetic nervous system and epinephrine and norepinephrine, which act as mediators in this system. Additionally, the non-adrenergic, non-cholinergic inhibitory nervous system is protective and vasoactive intestinal peptide (VIP) and NO are considered to be the mediators of this system in humans. The glucocorticoids are also important protective factors. Among the eicosanoids, PGE₂ seems to be the only certain protective factor. When these protective factors fail to act normally, asthma

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**Table 1**  Resident and inflammatory cell sources of prostanoids in the lung²

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Prostanoid mediator</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PG D₂</td>
</tr>
<tr>
<td><strong>Resident cells</strong></td>
<td></td>
</tr>
<tr>
<td>Alveolar macrophage</td>
<td>o</td>
</tr>
<tr>
<td>Mast cell</td>
<td>o</td>
</tr>
<tr>
<td>Airway epithelium</td>
<td>o</td>
</tr>
<tr>
<td>Airway smooth muscle</td>
<td>o</td>
</tr>
<tr>
<td>Vascular smooth muscle</td>
<td>o</td>
</tr>
<tr>
<td>Vascular endothelium</td>
<td>o</td>
</tr>
<tr>
<td><strong>Inflammatory cells</strong></td>
<td></td>
</tr>
<tr>
<td>Neutrophil</td>
<td>o</td>
</tr>
<tr>
<td>Eosinophil</td>
<td>o</td>
</tr>
<tr>
<td>Mononuclear</td>
<td>o</td>
</tr>
</tbody>
</table>

PG, prostaglandin; TX, thromboxane.

**Table 2**  Binding characteristics of prostaglandin E (EP) receptor subtypes¹⁸

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Kₐ (nmol/L)*</th>
<th>Rank order of binding affinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP₁</td>
<td>21</td>
<td>PG E₂ ≥ iloprost &gt; PG E₁ &gt; PG F₂α &gt; PG D₂ &gt; 17-phenyl-PGE₂ &gt; sulprostone</td>
</tr>
<tr>
<td>EP₂</td>
<td>40 (?)</td>
<td>PG E₂ = PG E₁ &gt;&gt; PG D₂, PG F₂α</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11-deoxy-PG E₁ = 16, 16-dimethyl-PG E₂, 16-deoxy-PG E₁ = butaprost &gt; AH13205, SC19220 = 0</td>
</tr>
<tr>
<td>EP₃</td>
<td>3</td>
<td>PG E₂ = PG E₁ &gt;&gt; iloprost &gt; PG D₂ &gt; PG F₂α</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M&amp;B-28767 &gt;&gt; butaprost, SC19220 = 0</td>
</tr>
<tr>
<td>EP₄</td>
<td>11</td>
<td>PG E₂ = PG E₁ &gt;&gt; PG D₂, PG F₂α, iloprost</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11-deoxy-PG E₁, misoprostol, SC19220 = AH23848 &gt;&gt; sulprostone, butaprost = 0</td>
</tr>
</tbody>
</table>

*| Ligand: [³H]-prostaglandin (PG)E₂.

**Table 3**  Second messengers associated with EP receptor subtypes¹⁸

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Isoform</th>
<th>G-protein</th>
<th>Second messenger</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP₁</td>
<td>G (?)</td>
<td>Ca²⁺ ↑</td>
<td></td>
</tr>
<tr>
<td>EP₂</td>
<td>Gₛ (?)</td>
<td>cAMP P ↑</td>
<td></td>
</tr>
<tr>
<td>EP₃</td>
<td>Gₛ</td>
<td>cAMP P ↑</td>
<td></td>
</tr>
<tr>
<td>EP₄</td>
<td>EP₃α</td>
<td>G₁</td>
<td>cAMP P ↓</td>
</tr>
<tr>
<td>EP₃β</td>
<td>Gₛ</td>
<td>cAMP P ↑</td>
<td></td>
</tr>
<tr>
<td>EP₃ε</td>
<td>Gₛ</td>
<td>cAMP P ↑</td>
<td></td>
</tr>
<tr>
<td>EP₃δ</td>
<td>Gₛ, G₅, G₇</td>
<td>cAMP P ↓, cAMP P ↑, Phosphatidylinositol response</td>
<td></td>
</tr>
</tbody>
</table>
attacks may be induced. A classic example is the induction of asthma by β-adrenergic antagonists. Furthermore, as will be discussed later, findings indicate that the induction of asthma by NSAID in patients with aspirin-induced asthma is due to the abolition of the activity of PG E as a protective factor. Asthma attacks induced by the failure of protective factors, such as those due to β-adrenergic antagonists and NSAID, are so violent that they may be fatal.

Prostaglandin E2 has been widely recognized as a cytoprotective PG in the stomach mucosa and PG E derivatives are used as therapy for stomach ulcers. A large quantity of PG E2 is also produced from the airway epithelium, as with the stomach mucosa, but there have been few studies of the role that it may play.

**PROSTAGLANDIN E2-PRODUCING CELLS IN THE AIRWAY**

Prostaglandin E2 is present in human bronchoalveolar lavage fluid (BALF), sputum and airway secretions. Large quantities of PG E2, as well as PG F2α and TXB2, are present in the sputum of subjects with chronic inflammatory airway diseases, such as chronic bronchitis and chronic bronchiolitis; quantities of these prostanoids can be decreased by the inhalation of indomethacin. Concentrations of PG E2, PG F2α, 6-keto-PGF1α and TXB2 in the epithelial lining fluid in the lower respiratory tract are more than 10-fold higher than in plasma and it has been reported that such concentrations of PG E2 are as high as 100-fold the plasma concentration. A basal level of release of the peptide LT, TXB2 and PG E2 from human bronchial biopsy specimens has been observed and, with the addition of arachidonic acid, such quantities increase several fold. In particular, large quantities of PG E2 and TXB2 are produced from inflamed bronchial epithelium. Cultured epithelial cells from the bovine trachea produce large amounts of PG E2 in a dose-dependent manner when exposed to ozone. However, PG F2α and inflammatory and broncospastic eicosanoids, such as TXB2 and LTB4, are also produced at the same time. Cultured human tracheal epithelial cells produce large quantities of PG E2 in a dose-dependent manner when stimulated with endogenous stimuli, such as bradykinin and calcium ionophore A23187, if serum is present. Furthermore, cultured human tracheal smooth muscle cells produce PG E in a dose-dependent manner when stimulated with bradykinin. Prostaglandin E2 is constantly present in the airway, as mentioned earlier, and is mainly produced by resident cells, such as airway epithelial and smooth muscle cells. Moreover, the quantity of PG E2 produced is immediately increased several fold, or even by multiples of 10-fold, by endogenous or exogenous stimuli to reach levels at which it exhibits physiological activity.

**INHIBITORY EFFECTS OF PG E2 ON VARIOUS INFLAMMATORY CELL FUNCTIONS**

Prostaglandin E2 inhibits the production and release of mediators from various kinds of inflammatory cells. For example, PG E2 or the PG E analog misoprostol inhibit the generation of superoxide anions from inflammatory cells, including alveolar macrophages and eosinophils, and they inhibit eosinophil chemotaxis induced by C5a and PAF, IL-5- and IL-3-induced prolongation of eosinophil survival and the production of LTB4 and 5-HETE from human polymorphonuclear leukocytes. In addition, PG E2 and misoprostol inhibit granulocyte-macrophage colony stimulating factor (GM-CSF) and IL-4-induced IgE production by peripheral blood lymphocytes, as well as anti-IgE-induced histamine release from chopped human lung and dispersed human lung mast cells. Prostaglandin E has a strong inhibitory effect on the function of T cells and it inhibits proliferation responses induced by mitogen stimulants, such as concanavalin A and phytohemagglutinin, as well as the production of lymphokines, such as macrophage-stimulating factor and IL-2, and the induction of cytotoxic T cells. These inhibitory effects are accompanied by increased cAMP in the cells and are thought to be mediated by EP3 and EP4 receptors. Thus, PG E2 exhibits various inhibitory activities at various stages (establishment of sensitization, induction of immediate responses, chemotaxis of inflammatory cells and continuation of delayed responses) in the establishment and progression of allergic airway inflammation. There are a large variety of target cells, including lymphocytes, mast cells, eosinophils, alveolar macrophages and polymorphonuclear leukocytes.

**EFFECTS OF PG E2 ON AIRWAY SMOOTH MUSCLES AND THE CHOLINERGIC NERVOUS SYSTEM IN THE AIRWAY**

That inhaled PG E2 dilates the human airway has been known for more than 20 years. However, because PG E2 stimulates afferent C fibers of the airway, it induces coughing and, therefore, its clinical use as a bronchodilator has been restricted. Experiments using canine
and human airways have shown that endogenous PG\textsubscript{E\textsubscript{2}}, at low concentrations, inhibits the release of acetylcholine from the nerve ends of the cholinergic nervous system and inhibits neurotransmission through the vagus.\textsuperscript{35}

**Activity of Vasodilation and Increasing Blood Flow: Advantageous or Not?**

Prostaglandin E\textsubscript{2} promotes vasodilation of the small arteries and increases in local blood flow.\textsuperscript{36,37} This activity, in the case of hypersensitivity responses, may promote local blood vessel permeability, with the unfavorable consequence of edema. Prostaglandin E\textsubscript{2} markedly increases plasma extravasation due to histamines, LTC\textsubscript{4} and LTB\textsubscript{4},\textsuperscript{36,37} but does not cause plasma leakage by itself.\textsuperscript{37} Indomethacin increases local plasma extravasation due to an immediate allergic response and this activity is nullified by the pre-administration of PG\textsubscript{E\textsubscript{2}}.\textsuperscript{37} Thus, PG\textsubscript{E\textsubscript{2}} increases the activity of the released mediators of plasma extravasation by vasodilation and increased blood flow, but its net effect during the hypersensitivity response is probably to inhibit plasma leakage by inhibiting the endogenous production and release of vasoactive mediators. Increases in local blood flow promote local clearance of harmful substances and could, conceivably, be one of the protective activities of PG\textsubscript{E\textsubscript{2}}.

**Inhibitory Effects of Exogenous PG\textsubscript{E\textsubscript{2}} in Hypersensitivity Responses**

Exogenous PG\textsubscript{E\textsubscript{2}} inhibits various hypersensitivity responses. The inhalation of PG\textsubscript{E\textsubscript{1}} or PG\textsubscript{E\textsubscript{2}} inhibits histamine-induced anaphylaxis in guinea-pigs, with an effect greater than that of isoproterenol.\textsuperscript{38} The PG\textsubscript{E\textsubscript{1}} analog misoprostol inhibits human Arthus-type skin reactions induced by mite antigens.\textsuperscript{7} This effect is due to inhibition of the infiltration of inflammatory cells into the locality.\textsuperscript{7} The inhalation of PG\textsubscript{E\textsubscript{2}} not only inhibits human immediate and late asthma responses induced by the inhalation of allergens, but also suppresses the accompanying phenomenon of the promotion of airway hypersensitivity.\textsuperscript{6} The inhalation of PG\textsubscript{E\textsubscript{2}} suppresses exercise-induced asthma in humans, but does not affect the methacholine inhalation threshold value.\textsuperscript{39} Thus, the activity of PG\textsubscript{E\textsubscript{2}} is not due to direct action on the smooth muscles, such as bronchodilator activity in the airway, but probably due to an inhibition of the release of inflammatory and bronchoconstrictor mediators.

**Inhibition of Airway Responses Due to Induction of Endogenous PG\textsubscript{E\textsubscript{2}}: Induction of Refractoriness and Effects of Furosemide Inhalation**

The results discussed so far concern investigations of the effects of exogenous PG\textsubscript{E\textsubscript{2}}, but there are also several reports suggesting the possibility that endogenous PG\textsubscript{E} suppresses airway responses. The weakening or disappearance of airway responses is seen after the inhalation of distilled water,\textsuperscript{40} after exercise-induced asthma attacks\textsuperscript{41,42} and after the inhalation of sodium metabisulfite.\textsuperscript{41,43} However, this phenomenon of ‘refractoriness’ disappears when NSAID, such as indomethacin, are administered before an event that may produce an airway response and it is said that the production of PG, including PG\textsubscript{E\textsubscript{2}}, also contributes to this effect.\textsuperscript{40,42,43} Furthermore, the inhalation of furosemide suppresses antigen-induced airway responses,\textsuperscript{44} exercise-induced asthma\textsuperscript{45} and aspirin-induced asthma.\textsuperscript{46} The inhalation of furosemide is also sometimes effective against natural asthma symptoms.\textsuperscript{47} It has been shown that furosemide increases PG\textsubscript{E} production in a dose-dependent manner in the renal medulla of rats\textsuperscript{48} and it is possible that the inhibitory activity of furosemide in the airway is also mediated by the production of endogenous PG\textsubscript{E\textsubscript{2}}.

**The Importance of PG\textsubscript{E\textsubscript{2}} as an Endogenous Protective Factor in Aspirin-Induced Asthma**

As mentioned previously, there is a strong possibility that PG\textsubscript{E} may act as an endogenous protective factor in hypersensitivity responses of various types in the airway. However, because the administration of NSAID does not worsen asthma, except in those patients with aspirin-induced asthma, it appears that the bronchoprotective role of basal PG\textsubscript{E\textsubscript{2}} production is not very important in most patients with asthma. However, PG\textsubscript{E} play an important role as endogenous protective factors against aspirin-induced asthma, and several studies have shown that aspirin-induced asthma can lead to PG\textsubscript{E}-addicted or -dependent states.\textsuperscript{19,23,49} In aspirin-induced asthma, the PG\textsubscript{E\textsubscript{2}} level in BALF is high and PG\textsubscript{E\textsubscript{2}} levels are reduced, together with levels of other PG, by the inhalation of lysine–aspirin, thereby inducing asthma attacks in patients.\textsuperscript{23} However, if such patients are pretreated with inhaled PG\textsubscript{E\textsubscript{2}}, the airway response to the inhalation of lysine–aspirin is inhibited, as is the elevation of urinary
LTE₄. Also, if a minute quantity of PG E₁ sufficient for the maintenance of physiological concentrations is continuously drip infused into subjects with aspirin-induced asthma who also have mite hypersensitivity, airway responses to the inhalation of mite antigens is not inhibited, but the hypersensitive response to intravenous injections of lysine–aspirin is completely inhibited. Furthermore, airway dilation in response to inhaled PG E₁ is reduced in cases of aspirin-induced asthma⁵⁰ and tachyphylaxis due to increased endogenous PG E is possible.

**CONCLUDING REMARKS**

Prostaglandin E₂ is produced by airway resident cells, such as airway epithelial cells and smooth muscle cells, and alveolar macrophages and is always present in the airway. It is increased immediately after exogenous or endogenous stimuli from several-fold to multiples of 10-fold. Furthermore, it controls the function of lymphocytes, eosinophils, mast cells, macrophages and neutrophils, which contribute to the formation of immune and inflammatory responses.

Prostaglandin E₂ is produced locally due to various stimuli, but PG F₂α, TXA₂ and peptide LT are also produced at the same time and we can only observe the net effects of the interactions of these eicosanoids and other mediators. Therefore, unless the effects of PG E₂ as an endogenous protective factor are carefully observed, we are not aware of its presence. However, PG E₂ has strong inhibitory activity, especially against T lymphocytes, and it is also possible that it strongly inhibits the formation and progression of allergic inflammation over the long term. If the endogenous protective activity of PG E₂ is weakened or lacking, inflammatory and hypersensitive responses in the airway occur more readily. One cannot deny the possibility that an insufficiency of this kind of PG E₂ bronchoprotective activity may contribute to the pathogenesis of asthma. In contrast, in aspirin-induced asthma, the role of PG E₂ as a protective factor seems to be important and it is thought that asthma symptoms may be induced by the cancellation of the protective activity of PG E₂ by NSAID. Agonists of PG E₂, which produce little airway irritation, and drugs that raise the endogenous PG E₂ level may become new types of anti-inflammatory or anti-asthma drugs.

**REFERENCES**


