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Review Article

Anti-inflammatory and bronchoprotective roles of endogenous prostaglandin E_2

Hiroki Sakakibara

Division of Respirology and Allergology, Department of Internal Medicine, Fujita Health University, School of Medicine, Toyoake, Aichi, Japan

Abstract

Prostaglandin E_2 (PGE_2) 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 PGE_2 from several-fold to multiples of 10-fold. Prostaglandin E_2 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 PGE_2 are weakened or absent, inflammation and hypersensitive responses readily occur in the airway. Although the effects of PGE_2 remain to be clarified, the possibility of the involvement of decreased PGE_2 activity in the pathogenesis of asthma exists. However, in aspirin-induced asthma the role of PGE_2 as a protective factor, through an as yet undetermined mechanism, is marked. It is thought that, in this type of asthma, symptoms may be induced by the elimination of the protective action of PGE_2 by non-steroidal anti-inflammatory drugs (NSAID). It is possible that PGE_2 agonists that produce little airway irritation and drugs that raise the endogenous PGE_2 level have potential as new types of anti-inflammatory or anti-asthma drugs.

Correspondence: Dr Hiroki Sakakibara, Division of Respirology and Allergology, Department of Internal Medicine, Fujita Health University, School of Medicine, 1-98 Dengakugakubo, Kutsukake-Cho, Toyoake, Aichi 470-11, Japan.
Email: <hsaka@na.rim.or.jp>
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Introduction

In the present review article, the role of prostaglandin (PG)E_2 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)C_4, thromboxane (TX)A_2 and PGD_2, cause airway inflammation and constriction and, thus, act to initiate or aggravate asthma, but there is evidence that PGE_2 acts as a mediator that possesses endogenous anti-inflammatory and bronchoprotective effects.[2]

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

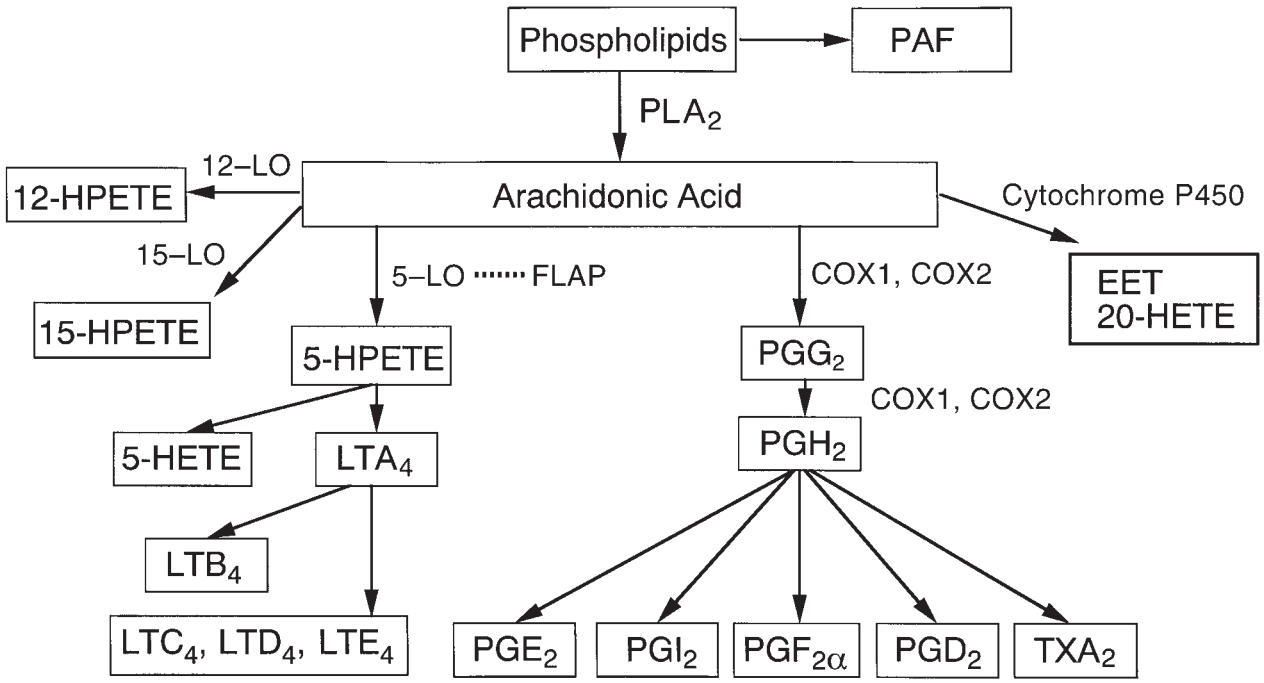

Fig. 1 Metabolic pathways of arachidonic acid. 5-LO, 5-lipoxygenase; COX, cyclo-oxygenase; EET, epoxyeicosatrienoic acid; FLAP, 5-lipoxygenase-activating protein; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid; LT, leukotriene; PAF, platelet-activating factor; PG, prostaglandin; TX, thromboxane; PLA_2, phospholipase A_2.

C2 position of the glycerol of phospholipids that form cell walls and is released by the enzyme action of phospholipase A_2, 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.[2] For example, peptide LT and platelet-activating factor (PAF), TXA_2, $PGF_{2\alpha}$ and PGD_2 contribute to the contraction of bronchial smooth muscles and the peptide LT PGE_2, PGD_2 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 LTB_4, 5-HETE and PAF promote the chemotaxis of inflammatory cells into the airway. Furthermore, the peptide LT TXA_2 and PAF are said to promote bronchial hyperresponsiveness.[2,3] In addition, active oxygen radicals are produced in these metabolic processes, which may also contribute to injury of the airway epithelium. However, PGE_2 has been found to have a number of protective actions: it dilates the human bronchi,[4,5] inhibits early and late airway responses to antigen inhalation[6] etc. Furthermore, these metabolites not only act directly on target cells as effectors but, as modulators, they also affect the production of cytokines,[7] the activity of the autonomic nervous system (ANS)[8] and the activation of mast cells.[9] Conversely, the metabolic pathways of arachidonic acid are modulated at various stages by mediators of the ANS, glucocorticoids,[10] cytokines[11,12] and nitric oxide (NO).[13]

The principal metabolic pathways are the COX and 5-LO pathways, but there are also pathways through 12-LO, 15-LO and cytochrome P450.[14] Although not shown in Fig. 1, some non-enzymatic metabolites also have physiological activity. Furthermore, COX has two isozymes, COX1 and COX2, and conventional NSAID have almost no inhibitory activity on COX2.[15] Among these metabolites, the peptide LT and TXA_2 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 LTC_4, LTB_4 and PAF. Mast cells produce PGD_2, $PGF_{2\alpha}$ and TXA_2,

Table 1 Resident and inflammatory cell sources of prostanoids in the lung[2]

Cell type	Prostanoid mediator				
	PGD_2	$PGF_{2\alpha}$	TXA_2	PGE_2	PGI_2
Resident cells					
Alveolar macrophage	○	○	○	○	
Mast cell	○	○	○		
Airway epithelium	○	○	○	○	○
Airway smooth muscle				○	○
Vascular smooth muscle					○
Vascular endothelium		○			○
Inflammatory cells					
Neutrophil			○	○	
Eosinophil		○	○	○	
Mononuclear			○		

PG, prostaglandin; TX, thromboxane.

as well as LTC_4 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 PGE_2 and PGI_2 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 PGE_2 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 PGE_2 is expressed through specific receptors (EP receptors), four subtypes, EP_1, EP_2, EP_3 and EP_4, which have been cloned and are closely related to the older pharmacological classification.[18] Table 2 shows the order of affinities of the PGE_2 agonists to the various receptors.[18] Table 3 shows the intracellular signal transduction systems that are related to the various EP receptors.[18] The EP_2 and EP_4 receptors are related to the G_s-protein, cause elevations in intracellular cyclic AMP (cAMP) concentrations and are thought to mediate the activity of PGE_2 as a protective factor. The principal signal transduction pathway of the EP_3 receptor is the inhibition of adenylate cyclase by way of the G_i-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 PGE_2 activity and, indeed, different concentrations of PGE_2 can cause completely opposite reactions in the same tissues and different reactions in different species.[18]

Table 2 Binding characteristics of prostaglandin E (EP) receptor subtypes[18]

Subtype	K_d (nmol/L)*	Rank order of binding affinity
EP_1	21	$PGE_2 \geq$ iloprost > PGE_1 > $PGF_{2\alpha}$ > PGD_2 17-phenyl-PGE_2 > sulprostone >> AH6809, butaprost
EP_2	40 (?)	PGE_2 = PGE_1 >> PGD_2, $PGF_{2\alpha}$ 11-deoxy-PGE_1 = 16, 16-dimethyl-PGE_2 > butaprost > AH13205, 19(R)-OH-PGE_2 > 1-OH-PGE_1, M&B-28767 >> sulprostone = 0
EP_3	3	PGE_2 = PGE_1 >> iloprost > PGD_2 > $PGF_{2\alpha}$ M&B-28767 >>> butaprost, SC19220 = 0
EP_4	11	PGE_2 = PGE_1 >> PGD_2, $PGF_{2\alpha}$, iloprost 11-deoxy-PGE_1 > misoprostol, M&B-28767 > AH23848 >> sulprostone, butaprost = 0

*Ligand: [^{3}H]-prostaglandin (PG)E_2.

Table 3 Second messengers associated with EP receptor subtypes[18]

Subtype	Isoform	G-protein	Second messenger
EP_1		G (?)	Ca^{2+} ↑
EP_2		G_s (?)	cAMP ↑
EP_4		G_s	cAMP ↑
EP_3	EP_{3A}	G_i	cAMP ↓
	EP_{3B}	G_s	cAMP ↑
	EP_{3C}	G_s	cAMP ↑
	EP_{3D}	G_i, G_s, G_q	cAMP ↓, cAMP ↑, Phosphatidylinositol response

cAMP, cyclic AMP; EP, prostaglandin E receptor subtypes.

Endogenous protective factors related to the pathogenesis of asthma

Among the endogenous protective factors against asthma symptoms, of primary consideration is the adrenomedullary 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, PGE_2 seems to be the only certain protective factor. When these protective factors fail to act normally, asthma

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 PGE_2 as a protective factor.[19] 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 E_2 has been widely recognized as a cytoprotective PG in the stomach mucosa[20] and PGE derivatives are used as therapy for stomach ulcers. A large quantity of PGE_2 is also produced from the airway epithelium, as with the stomach mucosa,[21,22] but there have been few studies of the role that it may play.

Prostaglandin E_2-producing cells in the airway

Prostaglandin E_2 is present in human bronchoalveolar lavage fluid (BALF),[23] sputum[24] and airway secretions.[25] Large quantities of PGE_2, as well as $PGF_{2\alpha}$ and TXB_2, 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.[24] Concentrations of PGE_2, $PGF_{2\alpha}$, 6-keto-$PGF_{1\alpha}$ and TXB_2 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 PGE_2 are as high as 100-fold the plasma concentration.[25] A basal level of release of the peptide LT, TXB_2 and PGE_2 from human bronchial biopsy specimens has been observed and, with the addition of arachidonic acid, such quantities increase several fold.[26] In particular, large quantities of PGE_2 and TXB_2 are produced from inflamed bronchial epithelium.[26] Cultured epithelial cells from the bovine trachea produce large amounts of PGE_2 in a dose-dependent manner when exposed to ozone.[22] However, $PGF_{2\alpha}$ and inflammatory and broncospastic eicosanoids, such as TXB_2 and LTB_4, are also produced at the same time.[22] Cultured human tracheal epithelial cells produce large quantities of PGE_2 when stimulated with endogenous stimulants, such as bradykinin and calcium ionophore A23187, if serum is present.[21] Furthermore, cultured human tracheal smooth muscle cells produce PGE in a dose-dependent manner when stimulated with bradykinin.[16] Prostaglandin E_2 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 PGE_2 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.[27]

Inhibitory effects of PGE_2 on various inflammatory cell functions

Prostaglandin E_2 inhibits the production and release of mediators from various kinds of inflammatory cells. For example, PGE_2 or the PGE analog misoprostol inhibit the generation of superoxide anions from inflammatory cells, including alveolar macrophages and eosinophils,[28] and they inhibit eosinophil chemotaxis induced by C5a and PAF,[7] IL-5- and IL-3-induced prolongation of eosinophil survival[7] and the production of LTB_4 and 5-HETE from human polymorphonuclear leukocytes.[29] In addition, PGE_2 and misoprostol inhibit granulocyte–macrophage colony stimulating factor (GM-CSF)[7] and IL-4-induced IgE production by peripheral blood lymphocytes,[30] as well as anti-IgE-induced histamine release from chopped human lung and dispersed human lung mast cells.[9] 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.[31,32] These inhibitory effects are accompanied by increased cAMP in the cells[33] and are thought to be mediated by EP_2 and EP_4 receptors. Thus, PGE_2 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 PGE_2 on airway smooth muscles and the cholinergic nervous system in the airway

That inhaled PGE_2 dilates the human airway has been known for more than 20 years.[4,5] However, because PGE_2 stimulates afferent C fibers of the airway, it induces coughing[34] and, therefore, its clinical use as a bronchodilator has been restricted. Experiments using canine

and human airways have shown that endogenous PGE_2, at low concentrations, inhibits the release of acetylcholine from the nerve ends of the cholinergic nervous system and inhibits neurotransmission through the vagus.[35]

Activity of vasodilation and increasing blood flow: Advantageous or not?

Prostaglandin E_2 promotes vasodilation of the small arteries and increases in local blood flow.[36,37] This activity, in the case of hypersensitivity responses, may promote local blood vessel permeability, with the unfavorable consequence of edema. Prostaglandin E_2 markedly increases plasma extravasation due to histamines, LTC_4 and LTB_4,[36,37] but does not cause plasma leakage by itself.[37] Indomethacin increases local plasma extravasation due to an immediate allergic response and this activity is nullified by the pre-administration of PGE_2.[37] Thus, PGE_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 PGE_2.

Inhibitory effects of exogenous PGE_2 in hypersensitivity responses

Exogenous PGE_2 inhibits various hypersensitivity responses. The inhalation of PGE_1 or PGE_2 inhibits histamine-induced anaphylaxis in guinea-pigs, with an effect greater than that of isoproterenol.[38] The PGE_1 analog misoprostol inhibits human Arthus-type skin reactions induced by mite antigens.[7] This effect is due to inhibition of the infiltration of inflammatory cells into the locality.[7] The inhalation of PGE_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.[6] The inhalation of PGE_2 suppresses exercise-induced asthma in humans, but does not affect the methacholine inhalation threshold value.[39] Thus, the activity of PGE_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 PGE: Induction of refractoriness and effects of furosemide inhalation

The results discussed so far concern investigations of the effects of exogenous PGE_2, but there are also several reports suggesting the possibility that endogenous PGE suppresses airway responses. The weakening or disappearance of airway responses is seen after the inhalation of distilled water,[40] after exercise-induced asthma attacks[41,42] and after the inhalation of sodium metabisulfite.[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 PGE_2, also contributes to this effect.[40,42,43] Furthermore, the inhalation of furosemide suppresses antigen-induced airway responses,[44] exercise-induced asthma[45] and aspirin-induced asthma.[46] The inhalation of furosemide is also sometimes effective against natural asthma symptoms.[47] It has been shown that furosemide increases PGE production in a dose-dependent manner in the renal medulla of rats[48] and it is possible that the inhibitory activity of furosemide in the airway is also mediated by the production of endogenous PGE_2.

The importance of PGE_2 as an endogenous protective factor in aspirin-induced asthma

As mentioned previously, there is a strong possibility that PGE 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 PGE_2 production is not very important in most patients with asthma. However, PGE play an important role as endogenous protective factors against aspirin-induced asthma, and several studies have shown that aspirin-induced asthma can lead to PGE-addicted or -dependent states.[19,23,49] In aspirin-induced asthma, the PGE_2 level in BALF is high and PGE_2 levels are reduced, together with levels of other PG, by the inhalation of lysine–aspirin, thereby inducing asthma attacks in patients.[23] However, if such patients are pretreated with inhaled PGE_2, the airway response to the inhalation of lysine–aspirin is inhibited, as is the elevation of urinary

LTE_4.[19] Also, if a minute quantity of PGE_1 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.[49] Furthermore, airway dilation in response to inhaled PGE_1 is reduced in cases of aspirin-induced asthma[50] and tachyphylaxis due to increased endogenous PGE is possible.

Concluding remarks

Prostaglandin E_2 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 E_2 is produced locally due to various stimuli, but $PGF_{2\alpha}$, TXA_2 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 PGE_2 as an endogenous protective factor are carefully observed, we are not aware of its presence. However, PGE_2 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 PGE_2 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 PGE_2 bronchoprotective activity may contribute to the pathogenesis of asthma. In contrast, in aspirin-induced asthma, the role of PGE_2 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 PGE_2 by NSAID. Agonists of PGE_2, which produce little airway irritation, and drugs that raise the endogenous PGE_2 level may become new types of anti-inflammatory or anti-asthma drugs.

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