

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 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 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.²

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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

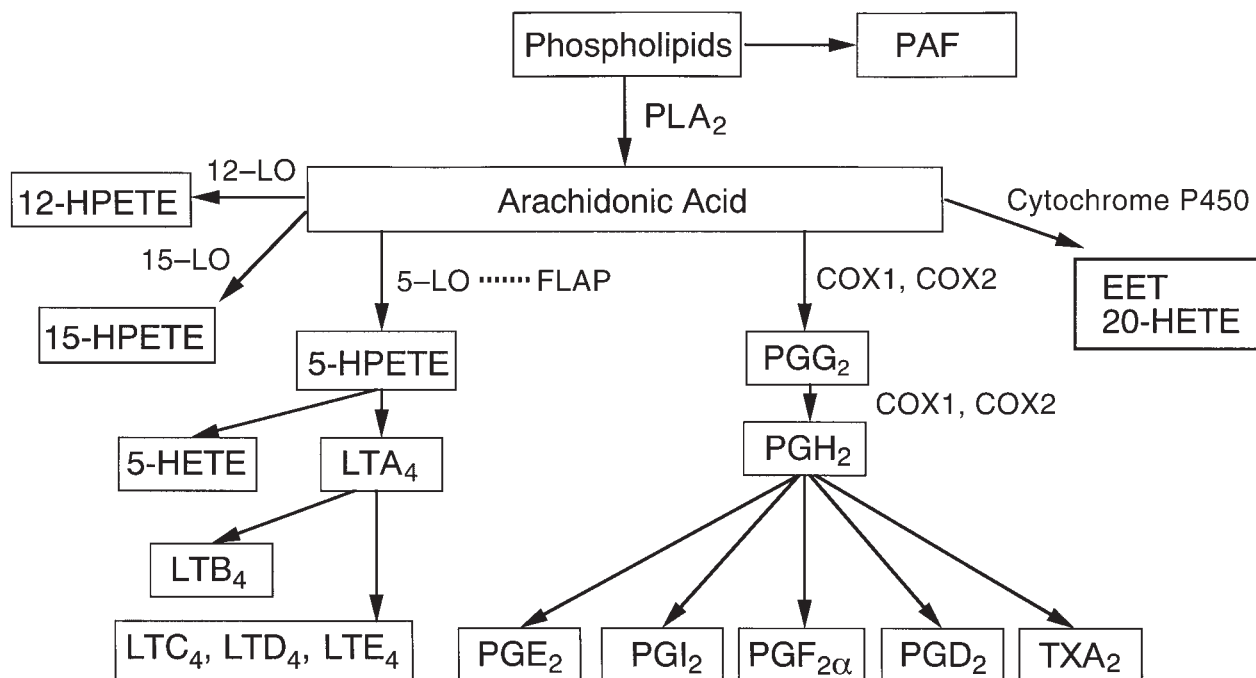


Fig. 1 Metabolic pathways of arachidonic acid. 5-LO, 5-lipoxygenase; COX, cyclo-oxygenase; EET, epoxyeicosatrienoic acid; FLAP, 5-lipoxygenase-activating protein; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid; LT, leukotriene; PAF, platelet-activating factor; PG, prostaglandin; TX, thromboxane; PLA₂, phospholipase A₂.

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.² For example, peptide LT and platelet-activating factor (PAF), TXA₂, PGF_{2α} and PGD₂ contribute to the contraction of bronchial smooth muscles and the peptide LT PGE₂, PGD₂ 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.^{2,3} In addition, active oxygen radicals are produced in these metabolic processes, which may also contribute to injury of the airway epithelium. However, PGE₂ 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 inhalation⁶ 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 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, LTB₄ and PAF. Mast cells produce PGD₂, PGF_{2α} and TXA₂,

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

Cell type	Prostanoid mediator				
	PGD ₂	PGF _{2α}	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 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 EP₄ receptors are related to the G_s-protein, cause elevations in intracellular cyclic AMP (cAMP) concentrations and are thought to mediate the activity of PGE₂ as a protective factor. The principal signal transduction pathway of the EP₃ 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 PGE₂ activity and, indeed, different concentrations of PGE₂ 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 subtypes¹⁸

Subtype	K _d (nmol/L)*	Rank order of binding affinity
EP ₁	21	PGE ₂ ≥ iloprost > PGE ₁ > PGF _{2α} > PGD ₂ 17-phenyl-PGE ₂ > sulprostone >> AH6809, butaprost
EP ₂	40 (?)	PGE ₂ = PGE ₁ >> PGD ₂ , PGF _{2α} 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 _{2α} M&B-28767 >>> butaprost, SC19220 = 0
EP ₄	11	PGE ₂ = PGE ₁ >> PGD ₂ , PGF _{2α} , iloprost 11-deoxy-PGE ₁ > misoprostol, M&B-28767 > AH23848 >> sulprostone, butaprost = 0

*Ligand: [³H]-prostaglandin (PG)E₂.

Table 3 Second messengers associated with EP receptor subtypes¹⁸

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 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

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 PGE₂ 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 E₂ has been widely recognized as a cytoprotective PG in the stomach mucosa²⁰ and PGE derivatives are used as therapy for stomach ulcers. A large quantity of PGE₂ 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 E₂-PRODUCING CELLS IN THE AIRWAY

Prostaglandin E₂ is present in human bronchoalveolar lavage fluid (BALF),²³ sputum²⁴ and airway secretions.²⁵ Large quantities of PGE₂, as well as PGF_{2 α} 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.²⁴ Concentrations of PGE₂, PGF_{2 α} , 6-keto-PGF_{1 α} 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 PGE₂ are as high as 100-fold the plasma concentration.²⁵ A basal level of release of the peptide LT, TXB₂ and PGE₂ 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 PGE₂ and TXB₂ are produced from inflamed bronchial epithelium.²⁶ Cultured epithelial cells from the bovine trachea produce large amounts of PGE₂ in a dose-dependent manner when exposed to ozone.²² However, PGF_{2 α} and inflammatory and bronchospastic eicosanoids, such as TXB₂ and LTB₄, are also produced at the same time.²² Cultured human tracheal epithelial cells produce large quantities of PGE₂ 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 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 PGE₂ 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 PGE₂ ON VARIOUS INFLAMMATORY CELL FUNCTIONS

Prostaglandin E₂ inhibits the production and release of mediators from various kinds of inflammatory cells. For example, PGE₂ 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 survival⁷ and the production of LTB₄ and 5-HETE from human polymorphonuclear leukocytes.²⁹ In addition, PGE₂ 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 cells³³ and are thought to be mediated by EP₂ and EP₄ receptors. Thus, PGE₂ 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 PGE₂ ON AIRWAY SMOOTH MUSCLES AND THE CHOLINERGIC NERVOUS SYSTEM IN THE AIRWAY

That inhaled PGE₂ dilates the human airway has been known for more than 20 years.^{4,5} However, because PGE₂ stimulates afferent C fibers of the airway, it induces coughing³⁴ and, therefore, its clinical use as a bronchodilator has been restricted. Experiments using canine

and human airways have shown that endogenous PGE₂, 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 E₂ 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 E₂ markedly increases plasma extravasation due to histamines, LTC₄ and LTB₄,^{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 PGE₂.³⁷ Thus, PGE₂ 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 PGE₂.

INHIBITORY EFFECTS OF EXOGENOUS PGE₂ IN HYPERSENSITIVITY RESPONSES

Exogenous PGE₂ inhibits various hypersensitivity responses. The inhalation of PGE₁ or PGE₂ inhibits histamine-induced anaphylaxis in guinea-pigs, with an effect greater than that of isoproterenol.³⁸ The PGE₁ 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 PGE₂ 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 PGE₂ suppresses exercise-induced asthma in humans, but does not affect the methacholine inhalation threshold value.³⁹ Thus, the activity of PGE₂ 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 PGE₂, 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 PGE₂, also contributes to this effect.^{40,42,43} Furthermore, the inhalation of furosemide suppresses antigen-induced airway responses,⁴⁴ exercise-induced asthma⁴⁵ 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 rats⁴⁸ and it is possible that the inhibitory activity of furosemide in the airway is also mediated by the production of endogenous PGE₂.

THE IMPORTANCE OF PGE₂ 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 PGE₂ 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 PGE₂ level in BALF is high and PGE₂ 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 PGE₂, the airway response to the inhalation of lysine-aspirin is inhibited, as is the elevation of urinary

LTE₄.¹⁹ Also, if a minute quantity of PGE₁ 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 PGE₁ is reduced in cases of aspirin-induced asthma⁵⁰ and tachyphylaxis due to increased endogenous PGE 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 PGF_{2α}, 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 PGE₂ as an endogenous protective factor are carefully observed, we are not aware of its presence. However, PGE₂ 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 PGE₂ 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 PGE₂ bronchoprotective activity may contribute to the pathogenesis of asthma. In contrast, in aspirin-induced asthma, the role of PGE₂ 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 PGE₂ by NSAID. Agonists of PGE₂, which produce little airway irritation, and drugs that raise the endogenous PGE₂ level may become new types of anti-inflammatory or anti-asthma drugs.

REFERENCES

1 National Heart, Lung, and Blood Institute, National Institute of Health, USA. Global initiative for asthma: Global strategy

- for asthma management and prevention NHLBI/WHO workshop. NIH Publication Number 95-3659, 1995.
- 2 Kleeberger SR, Freed AN. Prostanoids. In: Busse WW, Holgate ST (eds). *Asthma and Rhinitis*. Boston: Blackwell Science, 1995; 825–37.
 - 3 Kaye MG, Smith LJ. Effects of inhaled leukotriene D₄ and platelet-activating factor on airway reactivity in normal subjects. *Am. Rev. Respir. Dis.* 1990; **141**: 993–7.
 - 4 Kawakami Y, Uchiyama K, Irei T, Murao M. Evaluation of aerosol of prostaglandins E₁ and E₂ as bronchodilators. *Eur. J. Clin. Pharmacol.* 1973; **6**: 127–32.
 - 5 Mathe AA, Hedqvist P. Effect of prostaglandins F_{2α} and E₂ on airway conductance in healthy subjects and asthmatic patients. *Am. Rev. Respir. Dis.* 1975; **111**: 313–20.
 - 6 Pavord ID, Wong CS, Williams J, Tattersfield AE. Effect of inhaled prostaglandin E₂ on allergen-induced asthma. *Am. Rev. Respir. Dis.* 1993; **148**: 87–90.
 - 7 Alam R, Dejarnatt A, Stafford S, Forsythe PA, Kumar D, Grant JA. Selective inhibition of the cutaneous late but not immediate allergic response to antigens by misoprostol, a PGE analog: Results of double-blind, placebo-controlled randomized study. *Am. Rev. Respir. Dis.* 1993; **148**: 1066–70.
 - 8 Ito I, Suzuki H, Aizawa H, Hirose T, Hakoda H. Prejunctional inhibitory action of prostaglandin E₂ on excitatory neuro-effector transmission in the human bronchus. *Prostaglandins* 1990; **39**: 639–55.
 - 9 Peters SP, Schulman ES, Schleimer RP, Macglasman Jr DW, Newball HH, Lichtenstein LM. Dispersed human lung mast cells: Pharmacologic aspects and comparison with human lung tissue fragments. *Am. Rev. Respir. Dis.* 1982; **126**: 1034–9.
 - 10 Masferrer JL, Reddy ST, Zwifel BS *et al.* *In vitro* glucocorticoids regulate cyclooxygenase-2 but not cyclooxygenase-1 in peritoneal macrophages. *J. Pharmacol. Exp. Ther.* 1994; **270**: 1340–4.
 - 11 Rossi V, Breviario F, Ghezzi P. Prostacyclin synthesis induced in vascular cells by interleukin-1. *Science* 1985; **229**: 174–6.
 - 12 Kawakami M, Ishibashi S, Ogawa H. Cachectin/TNF as well as interleukin-1 induces prostacyclin synthesis in cultured vascular endothelial cells. *Biochem. Biophys. Res. Commun.* 1986; **141**: 482–7.
 - 13 Salvemini D, Seibert K, Masferrer JL, Misko TP, Currie MG, Needleman P. Endogenous nitric oxide enhances prostaglandin production in a model of renal inflammation. *J. Clin. Invest.* 1994; **93**: 1940–7.
 - 14 Fitzpatrick FA, Murphy RC. Cytochrome P-450 metabolism of arachidonic acid: Formation and biological actions of 'epoxygenase'-derived eicosanoids. *Pharmacol. Rev.* 1989; **40**: 229–41.
 - 15 Mitchell JA, Akarasereenont P, Thiemermann C, Flower RJ, Vane JR. Selectivity of nonsteroidal antiinflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase. *Proc. Natl Acad. Sci. USA* 1994; **90**: 11 693–7.
 - 16 Delamere F, Holland E, Patel S, Bennett J, Pavord I, Knox A. Production of PGE₂ by bovine cultured airway smooth muscle cells and its inhibition by cyclo-oxygenase inhibitors. *Br. J. Pharmacol.* 1994; **111**: 983–8.

- 17 Holtzman MJ. Arachidonic acid metabolism in airway epithelial cells. *Annu. Rev. Physiol.* 1992; **54**: 303–29.
- 18 Ushikubi F, Hirata M, Hirata T *et al.* Prostaglandin receptors. *Gendai Iryo* 1995; **27**: 1873–86 (in Japanese).
- 19 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**: 572–5.
- 20 Robert A, Nezamis JE, Lancaster C, Hanchar AJ. Cytoprotection by prostaglandins in rats. Prevention of gastric necrosis produced by alcohol, HCL, NaOH, hypertonic NaCl, and thermal injury. *Gastroenterology* 1979; **77**: 433–43.
- 21 Churchill L, Chilton FH, Resau JH, Bascom R, Hubbard WC, Proud D. Cyclooxygenase metabolism of endogenous arachidonic acid by cultured human tracheal epithelial cells. *Am. Rev. Respir. Dis.* 1986; **140**: 449–59.
- 22 Leikauf GD, Driscoll KE, Wey HE. Ozone-induced augmentation of eicosanoid metabolism in epithelial cells from bovine trachea. *Am. Rev. Respir. Dis.* 1988; **137**: 435–42.
- 23 Sladek K, Dworski R, Soja J *et al.* Eicosanoids in bronchoalveolar lavage fluid of aspirin-intolerant patients with asthma after aspirin challenge. *Am. J. Respir. Crit. Care Med.* 1994; **149**: 940–6.
- 24 Tamaoki J, Chiyotani A, Kobayashi K, Sakai N, Kanemura T, Takizawa T. Effect of indomethacin on bronchorrhea in patients with chronic bronchitis, diffuse panbronchiolitis, or bronchiectasis. *Am. Rev. Respir. Dis.* 1992; **145**: 548–52.
- 25 Ozaki T, Rennard SI, Crystal RG. Cyclooxygenase metabolites are compartmentalized in the human lower respiratory tract. *J. Appl. Physiol.* 1987; **62**: 219–22.
- 26 Schafer D, Lindenthal U, Wagner M, Bolcskei PL, Baenkler HW. Effect of prostaglandin E₂ on eicosanoid release by human bronchial biopsy specimens from normal and inflamed mucosa. *Thorax* 1996; **51**: 919–23.
- 27 Pavord ID, Tattersfield AE. Bronchoprotective role for endogenous prostaglandin E₂. *Lancet* 1994; **344**: 436–8.
- 28 Sakakibara H, Takamatsu J, Said SI. Vasoactive intestinal polypeptide (VIP) inhibits superoxide anion release from rat alveolar macrophages. *Am. Rev. Respir. Dis.* 1990; **141**: A645.
- 29 Ham EA, Soderman DD, Zanetti ME, Dougherty HW, McCauley E, Kuehl Jr FA. Inhibition by prostaglandins of leukotriene B₄ release from activated neutrophils. *Proc. Natl Acad. Sci. USA* 1983; **80**: 4349–53.
- 30 Pene J, Rousset F, Briere F *et al.* IgE production by normal human lymphocytes is induced by interleukin 4 and suppressed by interferons γ and α and prostaglandin E₂. *Proc. Natl Acad. Sci. USA* 1988; **85**: 6880–4.
- 31 Baker PE, Fahey JV, Munck A. Prostaglandin inhibition of T-cell proliferation is mediated at two levels. *Cell. Immunol.* 1981; **61**: 52–61.
- 32 Leung KH, Mihich E. Prostaglandin modulation of development of cell-mediated immunity in culture. *Nature* 1980; **288**: 597–600.
- 33 Lim LK, Hunt NH, Evans T *et al.* Rapid changes in the activities of the enzymes of cyclic AMP metabolism after addition of A23187 to macrophages. *Biochem. Biophys. Res. Commun.* 1981; **103**: 745–50.
- 34 Coleridge HM, Coleridge JCG, Ginzel KH, Baker DG, Banzett RB, Morrison MA. Stimulation of 'irritant' receptors and afferent C-fibres in the lungs by prostaglandins. *Nature* 1976; **264**: 451–3.
- 35 Ito Y, Tajima K. Actions of indomethacin and prostaglandins on neuro-effector transmission in the dog trachea. *J. Physiol.* 1981; **319**: 379–92.
- 36 Williams TJ, Peck MJ. Role of prostaglandin mediated vasodilatation in inflammation. *Nature* 1977; **270**: 530–2.
- 37 Raud J, Dahlen SE, Sydbom A, Lindbom L, Hedqvist P. Enhancement of acute allergic inflammation by indomethacin is reversed by prostaglandin E₂: Apparent correlation with *in vivo* modulation of mediator release. *Proc. Natl Acad. Sci. USA* 1988; **85**: 2315–19.
- 38 Wasserman M, Griffin RL, Marsalisi FB. Inhibition of bronchoconstriction by aerosols of prostaglandins E₁ and E₂. *J. Pharmacol. Exp. Ther.* 1980; **214**: 68–73.
- 39 Melillo E, Woolley KL, Manning PJ, Watson RM, O'Byrne PM. Effect of inhaled PGE₂ on exercise-induced bronchoconstriction in asthmatic subjects. *Am. J. Respir. Crit. Care Med.* 1994; **149**: 1138–41.
- 40 Mattoli S, Foresi A, Corbo GM, Valente S, Ciappi G. The effect of indomethacin on the refractory period occurring after the inhalation of ultrasonically nebulized distilled water. *J. Allergy Clin. Immunol.* 1987; **79**: 678–83.
- 41 Pavord I, Lazarowicz H, Inchley D, Baldwin D, Knox A, Tattersfield A. Cross refractoriness between sodium metabisulphite and exercise induced asthma. *Thorax* 1994; **49**: 245–9.
- 42 O'Byrne PM, Jones G. The effect of indomethacin on exercise-induced bronchoconstriction and refractoriness after exercise. *Am. Rev. Respir. Dis.* 1986; **134**: 69–72.
- 43 Pavord I, Wisniewski A, Tattersfield A. Refractoriness to sodium metabisulphite-induced bronchoconstriction in subjects with mild asthma. *Eur. Respir. J.* 1994; **7**: 50–4.
- 44 Bianco S, Pieroni MG, Refini RM, Rottoli L, Sestini P. Protective effect of inhaled furosemide on allergen-induced early and late asthmatic reactions. *N. Engl. J. Med.* 1989; **321**: 1069–73.
- 45 Bianco S, Vaghi A, Robuschi M *et al.* Prevention of exercise-induced bronchoconstriction by inhaled frusemide. *Lancet* 1988; **ii**: 252–5.
- 46 Vargas FS, Croce M, Teixeira LR *et al.* Effect of inhaled frusemide on the bronchial response to lysine–aspirin inhalation in asthmatic subjects. *Chest* 1992; **102**: 408–11.
- 47 Nannini LJ, Pendino JC, Molfino NA *et al.* Inhaled furosemide and salbutamol in acute asthma. *Am. Rev. Respir. Dis.* 1992; **145**: A422.
- 48 Craven PA, DeRubertis FR. Calcium-dependent stimulation of renal medullary prostaglandin synthesis by furosemide. *J. Pharmacol. Exp. Ther.* 1982; **222**: 306–14.
- 49 Taniguchi M, Sakakibara H, Suetsugu S *et al.* Subbioactive dose of prostaglandin E specifically inhibits aspirin-induced attacks in patients with aspirin-sensitive asthma. *Am. J. Respir. Crit. Care Med.* 1997; **155**: A975.

- 50 Szczeklik A, Mastalerz L, Nizankowska E, Cmiel A. Protective and bronchodilator effects of prostaglandin E and salbutamol in aspirin-induced asthma. *Am. J. Respir. Crit. Care Med.* 1996; **153**: 567-71.