Pulmonary Vascular Effects of Prostaglandin D₂, but Not Its Systemic Vascular or Airway Effects, Are Mediated Through Thromboxane Receptor Activation

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Prostaglandin D₂ (PGD₂) can cause pulmonary vasoconstriction or vasodilation depending on animal species and age. Because the constrictor effects of PGD₂ in some vascular beds may be mediated through thromboxane receptors, the purpose of this study was to determine whether the vascular or bronchial effects of PGD₂ are mediated through thromboxane/endoperoxide (TX/E) receptor activation. In chronically instrumented awake sheep, PGD₂ (5–25 μg/kg i.v.) produced a dose-dependent increase in pulmonary arterial pressure and in systemic arterial blood pressure. These changes were due to increases in resistance, because cardiac output remained unchanged. PGD₂ also decreased dynamic compliance at lower doses (0.1–5 μg/kg i.v.) than those required to produce pulmonary vasoconstriction, confirming that PGD₂ is a potent bronchoconstrictor. The airway and systemic vascular effects of PGD₂ were not altered by TX/E receptor antagonism. In contrast, PGD₂-induced pulmonary vasoconstriction was blocked by two TX/E receptor antagonists, SQ-29,548 and AH-23848, implying that this effect is mediated through activation of TX/E receptors. The pulmonary vasoconstrictor effects of PGD₂ could not be explained by thromboxane generation, because neither cyclooxygenase inhibition with ibuprofen nor thromboxane synthase inhibition with OKY-046 had any effect on PGD₂ actions. In contrast, a mild but consistent pulmonary vasodilatation produced by PGD₂ could be uncovered if the pulmonary vascular bed was preconstricted by hypoxia with simultaneous TX/E receptor blockade. These results indicate that TX/E receptor antagonists, although still useful pharmacological probes to determine the role of TX/E receptor activation in pathophysiological processes, should not be used to infer a role of endogenous thromboxane A₂. It is possible that PGD₂ participates in pulmonary processes previously ascribed uniquely to thromboxane A₂. (Circulation Research 1991;68:352–358)

Prostaglandin D₂ (PGD₂), a product of the cyclooxygenase pathway of arachidonic acid metabolism, is a major secretory product of activated mast cells¹ and also is released from lung

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Macrophages.² It is, therefore, potentially involved in a number of processes associated with activation of these cells, such as asthma,³ lung inflammation,⁴ and systemic mastocytosis.⁵ The mechanisms of vascular and airway effects of PGD₂ are not completely understood, partly because PGD₂ has vascular effects that vary with species, site, and age. PGD₂ produces pulmonary arterial dilation in fetal goats⁶ and lambs,⁷ whereas it produces pulmonary vasoconstriction in adult goats,⁶ dogs,⁸ and sheep.⁹ There is a transition from dilation to constriction after birth,⁶,¹⁰ but the mechanism for this effect is unknown. PGD₂ increases systemic arterial pressure in sheep but decreases blood pressure in humans¹¹ and dogs.⁸ Finally, PGD₂ administered by infusion or inhalation produces bronchoconstriction in humans¹² and dogs,¹³ as does its principal metabolite, 9α,11β-prostaglandin F₂¹⁴ This is of particular interest because
of the possible role mast cells are suspected to play in allergic asthma.

PGD₂ appears to activate several prostaglandin receptors, including a PGD₂ receptor (DP-receptor) and the thromboxane A₂/endoperoxide receptor (TX/E). The constrictor effects of PGD₂ in vascular smooth muscle in vitro are postulated to be mediated through the TX/E receptor, whereas the prostaglandin receptor by which PGD₂ induces bronchoconstriction is uncertain. In cats, SQ-29,548, a selective TX/E receptor antagonist, does not block PGD₂-induced bronchoconstriction.

In this study, we examined the effect of PGD₂ on respiratory mechanics and on the pulmonary and systemic vasculature in adult sheep. Our aim was to determine if the effects of PGD₂ were mediated through activation of TX/E receptors. Our results indicate that PGD₂ produces pulmonary vasoconstriction through activation of TX/E receptors. On the other hand, PGD₂ produces systemic vasoconstriction and bronchoconstriction independent of TX/E receptor activation. Finally, in the preconstricted pulmonary circulation, PGD₂ causes vasodilation when TX/E receptors are blocked.

Materials and Methods

Animal Preparation

Adult sheep (25–35 kg) were instrumented for measurement of vascular pressures and lung mechanics as previously described. A total of 17 sheep were studied. After induction with 300–500 mg i.v. thiamylal sodium, sheep were intubated and mechanically ventilated with a mixture of oxygen and halothane. Silastic envelopes (0.01-inch thickness) were placed in the right pleural space through a right thoracotomy for measurement of pleural pressure. Silastic catheters (0.062-in. i.d., 0.125-in. o.d.) were placed in the pulmonary artery and left atrium through a left thoracotomy for pressure measurements. A 16-mm Transonic flow probe (TI01 Ultrasonic Bloodflow Meter, Transonic Systems, Inc., Ithaca, N.Y.) was placed around the main trunk of the pulmonary artery. Through a neck incision, a Silastic catheter was passed into the carotid artery for measurement of systemic pressure and sampling of blood for gas tensions and pH. An 8F Cordis introducer (Cordis Corp., Miami) was inserted into the external jugular vein for later placement of a 7F Swan-Ganz thermodilution catheter. On a different occasion, a tracheostomy was performed. Animals then were allowed to recover for at least four days before experimentation. Sheep were kept in metabolic cages with free access to food and water at all times.

Hemodynamics

Pulmonary arterial (P₂A), left atrial (P₂A), and systemic arterial (P₂A) pressures were measured continuously during the experiments (MP-15D transducers, Micron Instruments, Los Angeles; 7754B system strip-chart recorder, Hewlett-Packard Co., Palo Alto, Calif.). The level of the left atrium was used as the reference for transducer placement. Cardiac output (CO) was measured continuously with the Transonic flow probe and recorded on the strip-chart recorder. CO measurements by flow probe were calibrated to thermodilution CO values (model 9520A cardiac output computer, Edwards Laboratories, Santa Ana, Calif.) by linear regression analysis, using isoprotenerol infusion to produce stepwise increases in CO. Pulmonary vascular resistance (PVR) was calculated as (mean P₂A−mean P₂A)/CO. Mean arterial blood pressure (MABP) was calculated as ½ systolic+½ diastolic pressure. Total systemic resistance was calculated as MABP/CO. Heart rate was determined from the systemic arterial pressure tracing.

Lung Mechanics

During experiments, a number 10 cuffed Shiley tracheal tube was inserted into the tracheostomy. Airway opening pressure was measured through a multiple-sidehole catheter positioned 0.5 cm beyond the end of the tracheal tube. Pleural pressure was measured directly from the Silastic envelope placed in the pleural space. Transpulmonary pressure was calculated as the difference between airway opening pressure and pleural pressure. All pressure signals were measured using Validyne differential pressure transducers and amplifiers (Validyne Engineering Corp., Northridge, Calif.). Airflow was measured with a Fleisch No. 1 pneumotachograph connected to the tracheal tube. Signals were electronically integrated with a pulmonary mechanics computer (Buxco Electronics, Sharon, Conn.). Dynamic compliance was calculated as tidal volume divided by transpulmonary pressure at points of zero flow and expressed in milliliters per centimeter of water. Airflow, tidal volume, transpulmonary pressure, and dynamic compliance were recorded breath-by-breath (recorder 8818, Gould, Cleveland, Ohio) throughout the experiment. Before each set of measurements of lung mechanics, the animals’ lungs were inflated to 40 cm H₂O airway opening pressure using a tube in water connected to the expiratory port.

Materials

PGD₂ (Cayman Chemical Co. Inc., Ann Arbor, Mich.) was initially dissolved to a concentration of 10 mg/ml in 100% ethanol and stored at −20°C. PGD₂ then was diluted in normal saline the day of the study and kept on ice until use. The TX/E receptor antagonist SQ-29,548, a generous gift of E.R. Squibb and Sons, Princeton, N.J., was dissolved in 100% ethanol with Trizma Base; approximately 90% of the ethanol was evaporated under nitrogen gas before dilution in normal saline to a concentration of 1 mg/ml. SQ-29,548 was prepared fresh for each experiment. In vitro studies have shown that SQ-29,548 is a selective TX/E receptor antagonist. In particular, SQ-29,548 has no effect on platelet PGD₂ receptors even at concentrations 100-fold higher than those required to block TX/E receptors. In vivo, higher doses than
the ones used in the present study had no effect on PGD₂-induced bronchoconstriction in cats. The TX/E receptor antagonist AH-23848, a gift of Clinical Supplies Unit, Glaxo Group Research, Ware, Herts, UK, was dissolved in 100% ethanol and 10% sodium carbonate and then diluted in normal saline before administration. OKY-046, an inhibitor of thromboxane synthase, a gift of Kissie Pharmaceutical Co., Matsumoto, Japan, was dissolved in normal saline and stored at −20°C. Ibuprofen, a cyclooxygenase inhibitor, was a gift of Upjohn Co., Kalamazoo, Mich. The thromboxane mimetic U46619, a gift from the Upjohn Co., was dissolved to 10 mg/ml in 100% ethanol and stored at −20°C and was diluted to a concentration of 25 μg/ml in normal saline before use.

Protocols

Hemodynamic and airway functions were stable for a 45–60-minute baseline period before experiments. PGD₂, 0.1–25 μg/kg, was infused as a slow bolus injection over 2 minutes in random order into the superior vena cava through the proximal port of a Swan-Ganz catheter or into the left atrium. Infusions were made at 20–30-minute intervals, allowing time for hemodynamic values to return to baseline. After the initial set of infusions, sheep received one of the following drugs intravenously: SQ-29,548, 0.2 mg/kg loading dose followed by a 0.2 mg/kg/hr infusion; AH-23848, 1 mg/kg given over 10 minutes; OKY-046, 10 mg/kg given over 10 minutes; and ibuprofen, 10 mg/kg given over 5 minutes. PGD₂ doses then were repeated approximately 15 minutes after each inhibitor was infused. Only one drug was tested each experimental day. In ancillary studies we showed that the hemodynamic responses to PGD₂ were reproducible over time.

The doses of receptor blockers and cyclooxygenase inhibitors used here were chosen because they have been shown previously to be effective in this animal model. In particular, we have shown that the dose of ibuprofen used effectively inhibits formation of cyclooxygenase products in sheep. Kubo and Kobayashi have shown that OKY-046 at the doses we used inhibits thromboxane formation under identical experimental conditions. Likewise, the dose of SQ-29,548 we used produces a 10-fold shift to the right of the dose–response curve of the thromboxane mimetic U46619 on pulmonary vasoconstriction in unanesthetized sheep.

To determine if the effects of PGF₂α were mediated through TX/E receptor activation, this eicosanoid was infused into the superior vena cava at 25–75 μg/kg before and during TX/E receptor blockade with SQ-29,548. Hemodynamic measurements were done as described above.

To determine the effects of PGD₂ on the preconstricted pulmonary vascular bed, hypoxic vasoconstriction was induced by connecting the tracheostomy tube to a humidified blended gas reservoir that delivered a gas mixture containing 12% O₂–88% N₂ until P₁ decreased to a stable value, usually after 7–10 minutes. An arterial blood gas was drawn to confirm a Pao₂ of less than 50 mm Hg. PGD₂ (10–25 μg/kg, n = 8) then was infused into the superior vena cava. Sheep were returned to breathing room air after the maximal effect of PGD₂ had been observed. This protocol then was repeated while the sheep received SQ-29,548.

Statistics

The effects of PGD₂ were evaluated by one-way analysis of variance. Two-way analysis of variance was used to determine the effects of the different interventions on PGD₂ actions. Analysis was done using the NCSS statistical software (NCSS, Kaysville, Utah). A value of p < 0.05 was significant. Results are reported as mean ± SEM.

Results

Effects of Prostaglandin D₂

Infusion of PGD₂ into the superior vena cava (n = 6) resulted in a dose-dependent increase in P₁, PVR, MABP, and heart rate. P₁ and CO did not change significantly from baseline (Figure 1).

Infusion of PGD₂ into the left atrium (n = 6) also increased P₁, but this increase was of considerably less magnitude than that seen after infusion into the superior vena cava. Furthermore, PVR did not change significantly with left atrium infusions of PGD₂. P₁ increased after infusion of PGD₂ into the left atrium. This increase was similar to that seen after superior vena cava administration (Table 1).

PGD₂ produced a dose-dependent decrease in dynamic compliance (n = 5); the duration of the response appeared to be dose-dependent as well. Airways were considerably more responsive to PGD₂ than the pulmonary vasculature. The effects of PGD₂ on dynamic compliance were already maximal at 5 μg/kg, a dose that had no significant effect on P₁ (Figure 2B).

Effect of Thromboxane A₂/Endoperoxide Receptor Antagonists and Enzyme Inhibitors

To determine if the hemodynamic actions of PGD₂ were due to activation of TX/E receptors, two unrelated and selective thromboxane A₂ receptor antagonists were used. Both SQ-29,548 (n = 6) and AH-23848 (n = 5) produced significant blockade of the increase in P₁ (Figure 3) but had no effect on the systemic vasoconstriction (Figure 2A) or on the tachycardia produced by PGD₂ (changes in heart rate produced by 25 μg/kg PGD₂ were 62±15 and 51±17 beats/min before and after SQ-29,548, respectively; p > 0.05). Likewise, PGD₂-induced dynamic compliance was not blocked by SQ-29,548 (n = 5, Figure 2B). In contrast, thromboxane receptor antagonism with SQ-29,548 blocked the fall in dynamic compliance (−16±8% versus −61±4%) as well as the increase in P₁ (5±1 versus 40±7 cm H₂O) produced by the thromboxane analogue U46619 (n = 4).

To rule out the possibility that PGD₂ would cause vasoconstriction through a secondary generation of
thromboxane in the lungs, the effects of PGD$_2$ were compared before and after cyclooxygenase inhibition or thromboxane synthase inhibition. Neither ibuprofen ($n=4$) nor OXY-046 ($n=3$) blocked PGD$_2$-induced pulmonary hypertension (Figure 3). They also had no effect on systemic pressure or heart rate changes produced by PGD$_2$.

**Effect of Prostaglandin D$_2$ in the Preconstricted Pulmonary Vascular Bed**

To determine if a vasodilatory effect of PGD$_2$ could be uncovered, the effects of PGD$_2$ on the pulmonary vasculature were determined in eight sheep during normoxia, during preconstriction of the pulmonary vasculature with hypoxia, and during combined hypoxia and thromboxane receptor blockade with SQ-29,548. During normoxia, PGD$_2$ increased P$_{PA}$ by +19.5±4 cm H$_2$O. Sheep then were made to breathe 12% O$_2$-88% N$_2$. Hypoxia increased P$_{PA}$ from 17±1 to 29±2 cm H$_2$O. From this higher baseline, PGD$_2$ produced a further increase in P$_{PA}$ when the group was averaged (mean, +8±5 cm H$_2$O). However, PGD$_2$ decreased P$_{PA}$ in three of these eight sheep. After a return to baseline on room air, the TX/E receptor antagonist SQ-29,548 was given, and sheep then were made hypoxic again. Pretreatment with SQ-29,548 did not prevent hypoxic vasoconstriction (16±2 to 28±2 cm H$_2$O). During combined hypoxia and TX/E blockade, PGD$_2$ decreased P$_{PA}$ in all sheep (mean, −9±2 cm H$_2$O, Figure 4).

**Effect of Thromboxane A$_2$/Endoperoxide Receptor Antagonisms on the Actions of Prostaglandin F$_{2\alpha}$**

In three sheep, PGF$_{2\alpha}$ produced a dose-dependent increase in P$_{PA}$ and also increased MABP (Table 2). TX/E receptor antagonist with SQ-29,548 antagonized the effect of PGF$_{2\alpha}$ on the pulmonary vasculature, while having no effect on its systemic actions (Table 2).

**Discussion**

In agreement with previous studies, PGD$_2$ produced pulmonary vasoconstriction in adult sheep. This effect, however, was blocked by two structurally unrelated and selective TX/E receptor antagonists,
SQ-29,548 and AH-23848, indicating that PGD₂-induced pulmonary vasoconstriction is not mediated through activation of DP-receptors but rather through TX/E receptor activation. It could be argued that the TX/E antagonists used also may block DP-receptors. However, the selectivity of these antagonists for TX/E receptors and their lack of effect on DP-receptors is well established. Furthermore, these TX/E antagonists blocked only PGD₂-induced pulmonary vasoconstriction, while having no effect on the other actions of PGD₂. It seems unlikely, therefore, that the results could be explained by blockade of DP-receptors.

Neither cyclooxygenase inhibition with ibuprofen nor inhibition of thromboxane synthase with OKY-046 prevented the pulmonary vasoconstriction produced by PGD₂. Therefore, the possibility that the pulmonary effects of PGD₂ could be secondary to

**Figure 2.** Effects of prostaglandin D₂ (PGD₂) after pretreatment with vehicle (solid circles) or the thromboxane receptor antagonist SQ-29,548 (open circles) on pulmonary and systemic hemodynamics (panel A) and pulmonary dynamic compliance (panel B). PGD₂ was infused as bolus injections into the superior vena cava in five adult sheep. The p value denotes significant differences between groups from two-factor analysis of variance. Ppa, pulmonary arterial pressure; MABP, mean arterial blood pressure.

**Figure 3.** Effects of bolus injection of prostaglandin D₂ (PGD₂) (25 μg/kg i.v.) on pulmonary arterial pressure (Ppa) before (filled bars) and after (hatched bars) thromboxane receptor antagonism with SQ-29,548 (0.2 mg/kg followed by 0.2 mg/kg/hr, n=6) or AH-23848 (1 mg/kg, n=2); cyclooxygenase inhibition with ibuprofen (10 mg/kg, n=4); and thromboxane synthase inhibition with OKY-046 (10 mg/kg, n=3).
vasodilation by PGD2. Whether this represents actual loss of PGD2 receptors as a function of age remains to be determined. A similar age-related change has been shown for histamine H1 and H2 receptors in dogs.27

PGD2 caused systemic hypertension when infused into the left atrium or into the superior vena cava. The systemic response to PGD2 was not blocked by TX/E receptor antagonists or by cyclooxygenase or thromboxane synthase inhibitors. In the absence of specific DP-receptor antagonists, we can only speculate on the nature of the receptor that mediates this vasoconstrictive action. Because PGD2 produces vasodilation in most other animal species,15 it is unclear if the vasoconstrictive actions observed in the present study are mediated through DP-receptors. It also is possible that the systemic vasoconstriction was due to conversion of PGD2 into its vasoconstrictive metabolite 9α,11β-PGF2.28 It must be noted that 9α,11β-PGF2 is the principal in vivo metabolite of PGD2 in humans, and its production increases markedly after systemic mast cell activation.5,29

PGD2 produced a dose-dependent decrease in dynamic compliance, in agreement with previous reports indicating PGD2-induced bronchoconstriction.12,13 The mechanism of this action is not yet fully understood, because the putative DP-receptor is considered to mediate relaxation of smooth muscle.15 In the present study, the TX/E receptor antagonist SQ-29,548 had no effect on the PGD2-induced fall in dynamic compliance, while effectively blocking the airways response of U46619, a thromboxane mimetic used as a positive control. This suggests that PGD2 acts on different receptors in the airways than on the pulmonary vasculature. Of interest is the observation that the airways were considerably more sensitive to PGD2-induced constriction than the pulmonary vasculature. This, coupled with the differential effects of TX/E receptor antagonism on the actions of PGD2 on these two types of smooth muscle, further suggests that the receptor that mediates pulmonary vasoconstriction is different from the one that produces bronchoconstriction.

In summary, we have found that PGD2 acts on at least two types of receptors in awake adult sheep. PGD2 produces pulmonary vasoconstriction by activating thromboxane receptors. On the other hand, PGD2 causes potent bronchoconstriction and systemic vasoconstriction through a different prostaglandin receptor, the identification of which will require the development of specific antagonists.30,31 Finally, our results offer further evidence that the vasoconstrictive TX/E receptor is not “specific” for thromboxane, as it can be activated by PGD2 and PGF2α. This implies that TX/E receptor antagonists, although still useful pharmacological probes to determine the role of TX/E receptor activation in pathophysiological processes, should not be used to infer a unique role of endogenous thromboxane A2, as has been previously suggested.22 By the same token, it is possible that PGD2 participates in pulmo-

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Values are mean±SEM. Ppa, pulmonary arterial pressure; MABP, mean arterial blood pressure; p values are those of two-factor analysis of variance between groups (vehicle vs. SQ-29,548).
nary processes previously ascribed solely to thrombox-
ane A₂ on the basis of studies with receptor antagonists.

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