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PROTECTIVE ACTION OF PROSTAGLANDIN E_1 (PGE_1) AGAINST CONSTRICTOR MEDIATORS IN ISOLATED RAT HEART AND LUNG*

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Abstract—Prostaglandin (PG) E_1 (2.8 to 280 nmol/L) dose-dependently inhibited the platelet-activating factor (PAF)-induced increase in coronary perfusion pressure (CPP) in isolated constant flow perfused rat hearts. The PAF-induced release of immunoreactive leukotrienes (iLT) and thromboxane B_2 ($iTxB_2$) in isolated rat hearts was also attenuated. PAF induced a significant decrease in left ventricular cAMP content, which was antagonized by PGE_1. PGE_1 also decreased the production of iLT, but not of $iTxB_2$, in A23187-stimulated minced rat lung tissue. Furthermore, PGE_1 inhibited the increase in CPP induced by LTD_4 and arginine vasopressin (AVP) in the isolated perfused rat heart. The inhibitory effects of PGE_1 on coronary vasoconstrictor substances were not due to a nonspecific vasodilator effect since sodium nitroprusside neither inhibited the increase in CPP nor the release of eicosanoids induced by PAF. Moreover, PGE_1 did not inhibit the PAF-induced hypotension *in vivo*, indicating that PGE_1 is not a PAF receptor antagonist. These results suggest that PGE_1 may exert an important regulatory effect on coronary vascular homeostasis by stimulation of cyclic AMP and may be important in controlling eicosanoid metabolism in the rat heart. Furthermore, beneficial effects of PGE_1 in circulatory shock and myocardial ischemia may be related to this inhibitory effect of PGE_1.

Platelet activating factor (PAF; 1-*O*-alkyl-2-acetyl-*sn*-glyceryl-3-phosphorylcholine) is a new class of chemical mediator having diverse biological actions including stimulation of platelets and leukocytes, induction of hypotension, and enhancement of vascular permeability [1, 2]. In the isolated rat heart, PAF increases coronary perfusion pressure (CPP) related to the release of immunoreactive peptide leukotrienes (iLT) and thromboxane B_2 ($iTxB_2$) [3, 4]. Administration of a lipoxygenase inhibitor (e.g. propyl gallate) or a peptide leukotriene antagonist (e.g. LY-171,883) prevented the PAF-induced increase in CPP. However, a TxA_2 receptor and a thromboxane synthetase inhibitor were ineffective [4] in this regard. Thus, peptide leukotrienes appear to be intimately involved in the PAF-induced increase in coronary perfusion pressure in the rat [3, 4].

Prostaglandin E_1 (PGE_1) has several important biological actions including inhibition of platelet aggregation, vasodilation, and stabilization of lysosomal membranes [5]. PGE_1 also activates adenylate cyclase, and some of its biological actions (e.g. inhibition of platelet aggregation) are mediated by cyclic AMP [6]. In this connection, mobilization of intracellular Ca^{2+} interacts with cyclic AMP and stimulates the biosynthesis of a variety of vasoactive eicosanoids [7, 8].

The purpose of this investigation was to examine the effects of PGE_1 on changes in coronary vascular resistance and eicosanoid production induced by PAF in isolated perfused rat hearts and to investigate the mechanisms of these effects.

MATERIALS AND METHODS

Heart perfusion studies. Male Sprague–Dawley rats (250–300 g) were given 1000 I.U./kg of heparin intraperitoneally (i.p.) 15 min prior to the induction of anesthesia with sodium pentobarbital (40 mg/kg, i.p.). Following a midsternal thoracotomy, the hearts were rapidly excised and placed in ice-cold oxygenated (95% O_2 ± 5% CO_2) Krebs–Henseleit (K–H) solution according to the method of Roth *et al.* [9]. The K–H solution contained the following constituents (in mmol/L): NaCl, 118; KCl, 4.7; KH_2PO_4, 1.2; $MgSO_4 \cdot 7H_2O$, 1.2; $CaCl_2 \cdot 2H_2O$, 2.5; $NaHCO_3$, 12.5; and glucose, 11; at pH 7.3. Within 30 sec, the hearts were perfused retrogradely via the aorta with oxygenated K–H solution at pH 7.3 and 37° according to the Langendorff technique. The hearts were perfused at a constant pressure of 55 mm Hg for 10 min and then switched to constant flow perfusion at a perfusion pressure of 50 mm Hg according to previously described procedures [9]. CPP was measured in a side branch of the inflow line using a Statham P23AC pressure transducer and was recorded continuously on a Grass model 7 oscillographic recorder.

Following the 10-min pre-equilibration period, a

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5-min control period was initiated during which constant flow perfusion was maintained at 15 ± 1 ml/min. This yielded a perfusion pressure of approximately 50 mm Hg. At the end of this period, PGE_1 or its vehicle [i.e. 5.4% bovine serum albumin (BSA) in 0.9% NaCl] was infused by a Harvard infusion pump (model 901) at 68 μl/min. This flow rate does not effect CPP [4]. One minute after the infusion of PGE_1 or its vehicle, coronary vasoactive agents were infused as follows: PAF at 1 ml/min for 2 min; arginine vasopressin (AVP) or LTD_4 at 0.2 ml/min for 30 sec. The effect of sodium nitroprusside on the PAF-induced increase in CPP and eicosanoid release was also examined. Sodium nitroprusside was dissolved in 0.9% NaCl, infused at a flow rate of 68 μl/min, and was also protected from light using aluminum foil wrapped tubing and glassware. Experiments involving sodium nitroprusside and PAF were conducted exactly comparable to those involving PGE_1 and PAF. Non-drug perfused hearts remained stable and showed no variation in CPP throughout the experimental period, up to 45 min.

Coronary effluent samples were collected at 0, 30 and 60 sec following introduction of PAF or AVP for analysis of peptide leukotriene and TxB_2 concentrations. Samples were obtained from the pulmonary artery and placed in ice-cold tubes and frozen at −78° for up to 48 hr until they were assayed.

Cyclic AMP measurement. Additional rat hearts were perfused as described above. These hearts were subjected to constant flow perfusion at a perfusion pressure of 50 mm Hg. PGE_1 or its vehicle was infused by a Harvard infusion pump (model 901) at 68 μl/min. One minute after the infusion of PGE_1 or its vehicle, PAF or its vehicle was infused at a rate of 1 ml/min for 2 min. The hearts were immediately removed, and a 100-mg tissue sample of the left ventricular free wall was excised and frozen in liquid nitrogen. Samples were then kept at −78° until they were assayed for cAMP, usually within 24 hr. Cyclic AMP was assayed by radioimmunoassay (Sigma, St. Louis, MO) with a detection limit of 500 pmol/ml.

Eicosanoid production in rat lung tissues. The experimental protocol for peptide leukotriene production from rat minced lungs was done as previously described [10]. Lobes of lung tissue were removed from pentobarbital anesthetized male Sprague–Dawley rats (250–300 g). The lung tissue was blotted free of blood and minced in ice-cold K–H buffer. Suspensions of minced lung tissue were prepared at a concentration of 10 mg/ml K–H buffer. The suspensions were incubated with A23187 (20 μmol/L) in the presence of its vehicle (i.e. ethanol), PGE_1 (56 and 840 nmol/L), ibuprofen (485 nmol/L) or propyl gallate (20 μmol/L) for 30 min at 37°. Aliquots (200 μl) of incubation buffer were removed at time 0 and 30 min of incubation for radioimmunoassay of peptide leukotrienes and TxB_2. Samples were placed in ice-cold tubes and frozen at −78° for up to 48 hr prior to radioimmunoassay.

Radioimmunoassay (RIA) for iLT and $iTxB_2$. The radioimmunoassay for peptide leukotrienes was carried out according to the method of Aharony *et al.* [11]. This antibody cross-reacts almost equally with LTC_4, LTD_4 and LTE_4 but not with prostaglandins, hydroperoxides, endoperoxides or thromboxanes. The limit of detection of this assay is 0.03 pmol/ml total peptide leukotrienes.

The samples were also subjected to RIA for TxB_2 using the method of Ingerman-Wojenski *et al.* [12]. The TxB_2 standard curve was constructed with a lower detection limit of 0.25 pmol/ml TxB_2.

PAF-induced hypotension in anesthetized rats. Male Sprague–Dawley rats (250–300 g) were anesthetized prior to surgery with sodium pentobarbital (40 mg/kg, i.p.). The trachea was cannulated to maintain a patent airway, and polyethylene catheters filled with heparinized saline (10 units/ml in 0.9% NaCl) were introduced into the left carotid artery and right jugular vein for the measurement of mean arterial blood pressure (MABP) and injection of compounds respectively. MABP was recorded continuously on a Grass model 7 oscillographic recorder using a Statham P23AC pressure transducer. In a group of rats, vehicle (i.e. 0.9% NaCl), CV-6209 (1.6 nmol/kg) or PGE_1 (2.8 nmol/kg) was given 1–2 min after PAF (2.0 nmol/kg). Another group of rats received vehicle, CV-6209 (1.6 nmol/kg) or PGE_1 (2.8 nmol/kg) 2 min prior to PAF (570 pmol/kg) induced hypotension.

Materials. The following compounds were used during the course of this study: arginine vasopressin from Sigma, St. Louis, MO, U.S.A.; leukotriene D_4 (LTD_4) from Stuart Pharmaceuticals, Wilmington, DE, U.S.A.; sodium ibuprofen and prostaglandin E_1 (aloprostadil) from The Upjohn Co., Kalamazoo, MI, U.S.A.; 1-*O*-alkyl-2-acetyl-*sn*-glyceryl-3-phosphorylcholine (PAF) from Avanti Polar-lipids, Inc., Birmingham, AL, U.S.A.; the calcium ionophore A23187 from Calbiochem-Boehringer, La Jolla, CA, U.S.A.; and the PAF receptor antagonist CV-6209, 2-[*N*-acetyl-*N*-(2-methoxy-3-octadecylcarbamoyloxy-propoxycarbonyl) aminomethyl]-1-ethylpyridinium chloride, from the Takeda Chemical Co., Osaka, Japan [13]. All drug solutions were prepared fresh daily.

Statistical analysis. Student's *t*-test was used for intergroup comparisons with $P < 0.05$ considered significant. Significance was confirmed using analysis of variance (ANOVA). All values are expressed as means ± SEM.

RESULTS

Figure 1 demonstrates the effect of PGE_1 (2.8 to 280 nmol/L) on the PAF-induced increase in coronary perfusion pressure (CPP) in isolated perfused rat hearts. Two minutes after the infusion of PAF (25 nmol/L), CPP increased to a peak of 16 ± 2 mm Hg. PGE_1 inhibited the increase in CPP in a dose-dependent manner. Thus, PGE_1 can inhibit the PAF-induced increase in CPP in the isolated perfused rat heart indicative of a modulation of the vasoconstrictor effect of PAF by PGE_1.

Table 1 illustrates the effect of PAF on the release of immunoreactive peptide leukotrienes (iLT) in the coronary effluent of the isolated perfused rat heart in the presence and absence of PGE_1. A marked release of iLT was observed at 30 and 60 sec following the introduction of PAF into the perfusate. PGE_1 (2.8 and 28 nmol/L) significantly reduced the release of iLT at both concentrations of the prostaglandin.

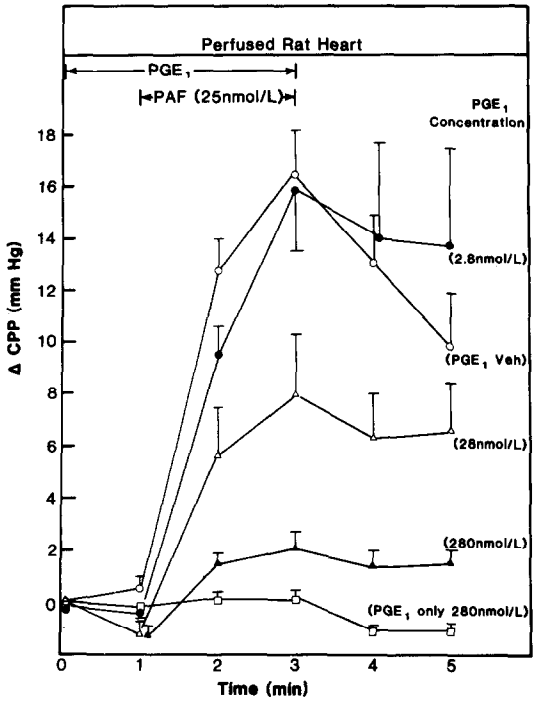

Fig. 1. Effect of PGE_1 (2.8 to 280 nmol/L) in the isolated perfused PAF (25 nmol/L) stimulated rat heart. Control coronary perfusion pressure (CPP) was maintained at 50 ± 1 mm Hg. Each group represents the mean of six to eight hearts. PGE_1 infusion began 1 min prior to PAF infusion and terminated with the finish of the PAF infusion (i.e. at 3 min). All points are means; brackets indicate SEM.

These results suggest that the inhibition of the PAF-induced increase in CPP by PGE_1 may be partially mediated via decreased peptide leukotriene release. The vasoconstrictor, arginine vasopressin (AVP), had no significant effect on the release of iLT, indicating that not all vasoconstrictors release leukotrienes in the rat heart.

Table 2 summarizes the effect of PAF on the release of immunoreactive thromboxane B_2 ($iTxB_2$) in the coronary effluent of the isolated perfused rat heart in the presence and absence of PGE_1. A marked release of $iTxB_2$ was observed at 30 and 60 sec following the infusion of PAF. However, PGE_1 (2.8 and 28 nmol/L) significantly decreased the release of $iTxB_2$ from the isolated perfused heart at both concentrations. Thus, PGE_1 can also inhibit PAF-induced release of $iTxB_2$ in the isolated perfused rat heart.

To investigate the possibility that PGE_1 may functionally block PAF receptors, we tested the interaction between PGE_1 and PAF in the intact anesthetized rat. Typical recordings of the PAF-induced hypotension are shown in Fig. 2. PAF, at concentrations of 570 pmol and 2.0 nmol/kg, markedly decreased MABP by 66 ± 4 and 71 ± 4 mm Hg respectively. CV-6209, a PAF receptor antagonist, reversed the PAF-induced hypotension (upper panel). However, rats receiving PGE_1 (2.8 nmol/kg) failed to show a reversal of the PAF-induced hypotension. Furthermore, pretreatment with CV-6209 (1.6 nmol/kg) antagonized the PAF-induced (570 pmol/kg) decrease in MABP (lower panel). In contrast, PGE_1 failed to inhibit this hypotensive phase. In response to CV-6209 and PAF, MABP decreased by only 5 ± 4 mm Hg, but decreased by 61 ± 5 mm Hg in response to PGE_1 and PAF. These data suggest that PGE_1 does not act as a PAF receptor antagonist.

To determine the specificity of PGE_1 as a blocker of the PAF-induced coronary vasoconstriction, we tested the effect of PGE_1 against other known coronary constrictors. PGE_1 also blocked the increase in CPP initiated by other coronary constrictors as shown in Table 3. PGE_1 (280 nmol/L) significantly attenuated the increase in CPP by 88, 90, and 95% for PAF, AVP and LTD_4 respectively. AVP (1.7 I.U./L) did not release any detectable iLT (see Table 1). Therefore, blockade of the vascular actions of LTD_4 may not be the only mechanism of PGE_1 inhibition of the PAF-induced coronary constriction. Moreover, PGE_1 can block coronary constriction by three chemically different agents, a

Table 1. Effects of PAF and AVP on the release of immunoreactive leukotrienes ($iLTC_4$ and LTD_4) by the perfused rat heart in the presence or absence of PGE_1

		Concentration of $iLTC_4$ and LTD_4 (pmol/ml)	
		Time after administration of PAF	
Group	N	30 sec	60 sec
PAF (25 nmol/L)	8	0.12 ± 0.03	0.24 ± 0.05
PAF (25 nmol/L) + PGE_1 (2.8 nmol/L)	6	0.03 ± 0.03*	0.06 ± 0.03*
PAF (25 nmol/L) + PGE_1 (28 nmol/L)	6	ND	ND
AVP (1.7 I.U./L)	6	ND	ND

The detection limit of this RIA was 0.03 pmol/ml LTD_4. All values are means ± SEM. N represents the number of samples assayed in each group. Abbreviations: PAF, platelet activating factor; AVP, arginine vasopressin; and ND, not detectable. Control hearts (i.e. perfused without any drugs) had non-detectable iLT concentrations.

* $P < 0.05$, compared to PAF (25 nmol/L) perfused hearts.

Table 2. Effect of PGE_1 on the PAF (25 nmol/L)-induced release of immunoreactive TxB_2

Group	N	Concentration of $iTxB_2$ (pmol/ml)	
		Time after administration of PAF	
		30 sec	60 sec
PAF + vehicle	8	4.2 ± 0.5	3.8 ± 0.8
PAF + PGE_1 (2.8 nmol/L)	6	1.8 ± 0.7*	1.5 ± 0.6*
PAF + PGE_1 (2.8 nmol/L)	6	0.3 ± 0.1†	0.3 ± 0.1†

The detection limit of this RIA was 0.25 pmol/L. All values represent means ± SEM. N represents the number of samples studied in each group. Control hearts (i.e. perfused without any drugs) had non-detectable $iTxB_2$ concentration.

* $P < 0.05$, compared to hearts receiving vehicle.

† $P < 0.01$, compared to hearts receiving vehicle.

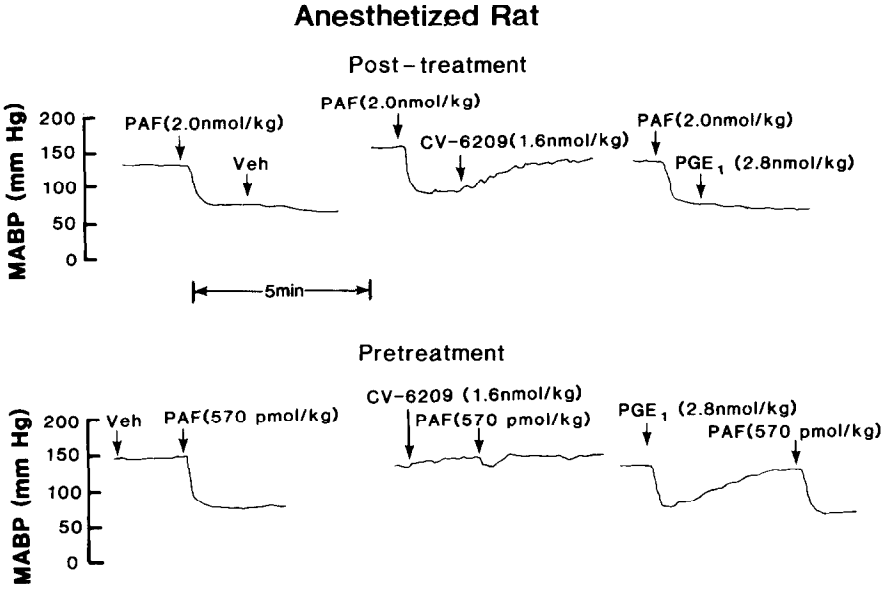

Fig. 2. Typical recordings in anesthetized rats of the PAF-induced decrease in mean arterial blood pressure (MABP) observed in the presence of CV-6209 or PGE_1. The upper panel illustrates the post-treatment effects of CV-6209 and PGE_1 on PAF-induced hypotension. Pretreatment effects of CV-6209 and PGE_1 are shown in the lower panel.

phospholipid (e.g. PAF), a peptide (e.g. AVP) and an eicosanoid (e.g. LTD_4).

Figure 3 summarizes the effect of PGE_1 on iLT formation by the rat minced lung preparation. The calcium ionophore A23187 (20 μmol/L) released iLT (62 ± 12 pmol/ml) after 30 min of incubation. The lipoxygenase inhibitor propyl gallate (20 μmol/L) significantly ($P < 0.001$) attenuated the release of iLT (6 ± 4 pmol/ml). Moreover, PGE_1 at concentrations of 56 and 840 nmol/L inhibited iLT formation. These data show that PGE_1 can also inhibit leukotriene formation in a second tissue (i.e. lung),

Table 3. Effects of PGE_1 on agonist-induced increases in coronary perfusion pressure (CPP)

Agonist	Increase in CPP (mm Hg)		
	Vehicle	PGE_1	% Inhibition
PAF (25 nmol/L)	17 ± 2	2 ± 1	88
AVP (1.7 I.U./L)	29 ± 5	3 ± 1	90
LTD_4 (25 nmol/L)	39 ± 3	2 ± 1	95

The concentration of PGE_1 was 280 nmol/L. All values represent means ± SEM; the number of hearts studied in each group was six to eight. AVP = arginine vasopressin; LTD_4 = leukotriene D_4. The vehicle for LTD_4 and AVP was 0.9% NaCl and 0.2% BSA for PAF.

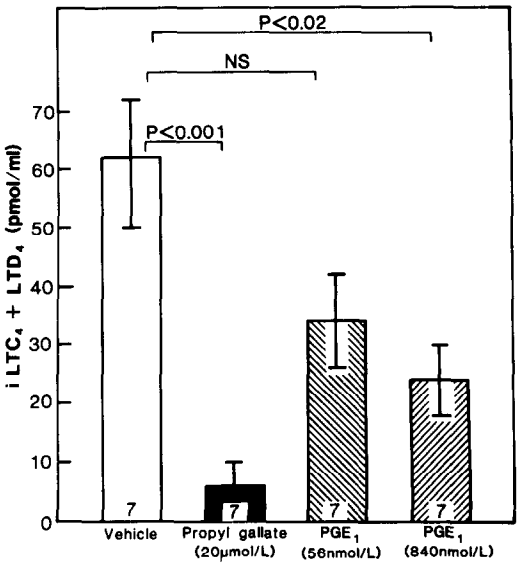

Fig. 3. Production of immunoreactive LTC_4 and LTD_4 ($iLTC_4$ and LTD_4) in A23187 (20 μmol/L) stimulated minced rat lung. Bar heights indicate means; brackets indicate ±SEM; and numbers at the bottom of the bars represent the number of experiments performed.

suggesting that PGE_1 may exert a fundamental biochemical action resulting in inhibition of leukotriene synthesis or release. This effect is clearly not dependent on the reduced tension in vascular smooth muscle cells as a direct result of PGE_1-induced vasodilation.

While PGE_1 inhibited the formation of iLT in the rat lung, it did not attenuate the synthesis of pulmonary $iTxB_2$ as shown in Fig. 4. Suspensions of minced lung receiving vehicle and stimulated with A23187 produced significant amounts of $iTxB_2$ (21 ± 5 pmol/ml). The cyclooxygenase inhibitor, ibuprofen (485 nmol/L), significantly ($P < 0.001$) inhibited the formation of $iTxB_2$. However, PGE_1 (56 and 840 nmol/L) added to lung suspensions did not alter significantly $iTxB_2$ formation. Thus, PGE_1 does not directly inhibit TxB_2 formation in the A23187-stimulated rat lung, indicating that PGE_1 is not a phospholipase A_2 or a cyclooxygenase inhibitor *per se*.

To rule out the possibility that PGE_1 inhibits the PAF-induced increase in CPP by a nonspecific vasodilating effect, we tested sodium nitroprusside in this system. Sodium nitroprusside (2.8 μmol/L) has been shown previously to increase significantly cyclic GMP levels in the rat heart [14]. Figure 5 indicates that sodium nitroprusside (2.8 μmol/L) failed to antagonize the increase in CPP caused by PAF (25 nmol/L). Furthermore, iLT (0.11 ± 0.02 pmol/ml) and $iTxB_2$ (2.7 ± 0.5 pmol/ml) concentrations were not significantly different at 30 sec following PAF infusion in the presence of nitroprusside compared to those hearts receiving PAF alone (Tables 1 and 2). Thus, the use of a cyclic GMP stimulating vasodilator does not antagonize the coronary vasoactivity of PAF in the isolated perfused rat heart.

Figure 6 summarizes the cyclic AMP content of the left ventricle of those hearts subjected to PAF, its vehicle, or to PAF + PGE_1 given together. PAF (25 nmol/L) infusion resulted in a significant decrease in cAMP values. PGE_1 (280 nmol/L) significantly antagonized the PAF-induced decrease in

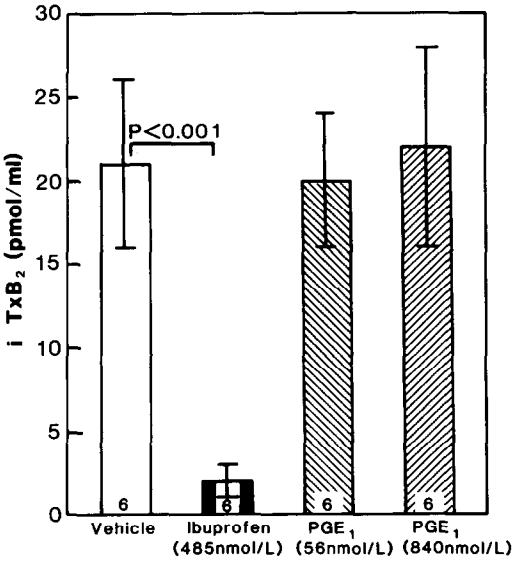

Fig. 4. Production of immunoreactive TxB_2 ($iTxB_2$) in the A23187-stimulated minced rat lung. Bar heights indicate means; brackets indicate ± SEM; and the numbers at the bottom of the bars represent the number of experiments performed.

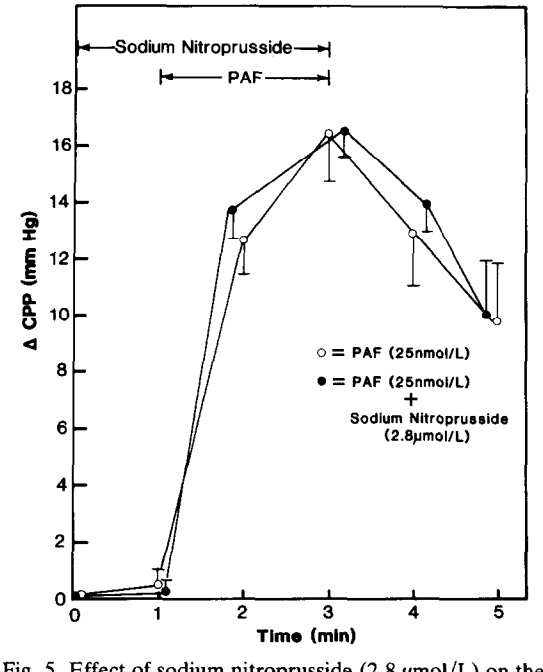

Fig. 5. Effect of sodium nitroprusside (2.8 μmol/L) on the PAF (25 nmol/L) induced increase in coronary perfusion pressure (CPP) in the isolated perfused rat heart. Sodium nitroprusside infusion began 1 min prior to PAF infusion and continued during PAF infusion. Each group represents the mean of six to eight hearts.

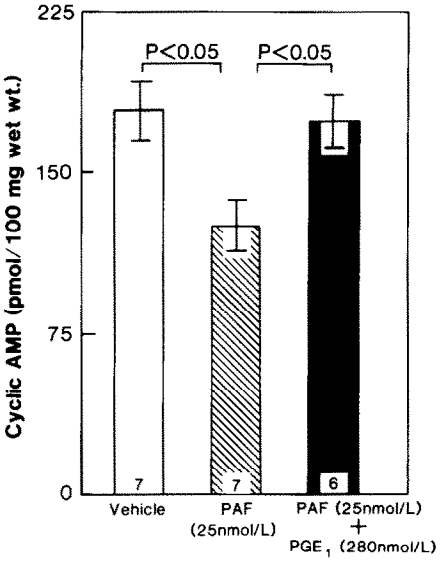

Fig. 6. Effects of PGE_1 and PAF on myocardial cAMP. Bar heights indicate means; brackets indicate ±SEM, and numbers at the bottom of the bars represent the number of hearts studied.

myocardial cAMP ($P < 0.05$). This concentration of PGE_1 significantly blocked the vasoactive action of PAF as illustrated in Fig. 1. Therefore, these data provide support for the concept that PGE_1 inhibits the PAF-induced increase in coronary perfusion pressure by blocking the PAF-induced decrease in myocardial cAMP.

DISCUSSION

We have shown that PGE_1 inhibited the increase in coronary vascular resistance produced by PAF in the isolated perfused rat heart in a dose-dependent manner. Furthermore, PGE_1 attenuated the release of immunoreactive peptide leukotrienes and TxB_2 associated with the PAF-induced increases in CPP. Previous experiments have shown that PAF receptor antagonists attenuate the increase in CPP and inhibit the release of iLT and $iTxB_2$ in this preparation [4]. On the basis of these results, one might speculate that PGE_1 is a PAF receptor antagonist. However, both pre-treatment and post-treatment with PGE_1 failed to antagonize the decrease in MABP induced by PAF in the intact anesthetized rat. Moreover, in six isolated perfused guinea pig hearts, PAF (50 pmol/L) increased CPP by 13 ± 3 mm Hg. In guinea pig hearts, where PAF induces direct effects on the coronary vasculature [15], PGE_1 (280 nmol/L) failed to inhibit this PAF-induced increase in CPP (17 ± 5 mm Hg), suggesting that the blockade of PAF-induced coronary constriction is not a direct effect on PAF receptors. In addition, PGE_1 significantly antagonized the increase in CPP induced by LTD_4 and AVP. These results suggest that PGE_1 exerts a broader based blockade of coronary constrictors. Furthermore, the inhibition of the PAF-induced increase in CPP in the isolated perfused heart appears to be species specific.

The mechanism of the anti-PAF action of PGE_1 appears to be due to its preservation of cAMP levels in the myocardium rather than to some nonspecific vasodilator effect of PGE_1. In this regard, nitroprusside failed to antagonize PAF in this system. This is also consistent with the known effect of PGE_1 to activate adenylate cyclase which catalyzes the biosynthesis of cyclic AMP (cAMP) in a variety of tissues, including cardiac and vascular smooth muscle [6, 16]. Cyclic AMP increases the Ca^{2+} uptake by the sarcoplasmic reticulum and regulates the mobilization of cytosolic Ca^{2+} [7]. The vasoconstrictor actions of many agonists (e.g. PAF and LTD_4) are thought to be mediated by the increase of cytosolic Ca^{2+} through the activation of receptors coupled to Ca^{2+} channels possibly related to phosphoinositide turnover [17–19]. Thus, PGE_1 appears to inhibit the vasoactive actions of PAF, LTD_4 and AVP through the suppression of Ca^{2+} mobilization via a cAMP-dependent mechanism.

The mechanism by which PGE_1 inhibits eicosanoid release is unknown at present but may also involve cAMP. Ham *et al.* [20] have shown that PGE_1 inhibits the release of LTB_4 from polymorphonuclear leukocytes via a cAMP-dependent mechanism. Prostacyclin, which also increases cAMP, decreases LTC_4 release in the calcium-stimulated perfused rat hearts [21]. Thus, in our study, PGE_1 may increase cAMP and thereby inhibit the synthesis of peptide leukotrienes in the rat heart and lung.

The ability of PGE_1 to inhibit the PAF-induced release of leukotrienes and TxB_2 in the isolated perfused rat heart is particularly interesting since PGE_1 attenuated the biosynthesis of iLT but not of $iTxB_2$ in the A23187-stimulated rat lung. Several possibilities exist which could explain these findings. First, eicosanoids are known to stimulate the synthesis and release of other eicosanoids [22]. In this connection, the peptide leukotrienes may induce the release of TxB_2 in the isolated PAF-stimulated rat heart. A decrease in leukotriene synthesis may therefore result in decreased TxB_2 production. In the rat lung, this mechanism may not exist. Second, the cellular composition and stimulus used for each tissue are different. PAF is known to decrease cAMP, inhibit adenylate cyclase, and promote arachidonate release in human and rabbit leukocytes [23]. Thus, the thromboxane A_2 synthesized in the rat lung may come from a cellular source which does not exist in the rat heart but is stimulated by the calcium ionophore in the lung.

In summary, we have shown that PGE_1 can inhibit the increase in coronary perfusion pressure induced by PAF, LTD_4 and AVP. PGE_1 attenuated the PAF-induced decrease in myocardial cAMP. The iLT and $iTxB_2$ released in the PAF-stimulated perfused rat heart were also attenuated by PGE_1. However, in the A23187-stimulated minced rat lung, iLT but not $iTxB_2$ release was inhibited by PGE_1. The mechanism of action of PGE_1 is not due to a nonspecific vasodilator effect since a vasodilator concentration of sodium nitroprusside did not antagonize the PAF-induced increase in CPP. PGE_1 is unlikely to be a PAF receptor antagonist. However, PGE_1 may block PAF via a mechanism related to its adenylate cyclase stimulatory action. These effects of PGE_1 plus its

ability to vasodilate, inhibit platelet aggregation, and stabilize lysosomal membranes [5], may be of benefit in myocardial ischemia, circulatory shock and other ischemic and inflammatory diseases.

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