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DIFFERENTIAL EFFECTS OF PROSTAGLANDINS ON CANINE INTRAPULMONARY ARTERIES AND VEINS

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1 The sensitivity and contractility of isolated canine intrapulmonary arteries and veins to a variety of primary prostaglandin compounds was studied.

2 Intrapulmonary arteries produced no measurable contractile responses to prostaglandin A_1 (PGA_1), PGA_2, PGB_1, PGD_2, PGE_1, PGE_2 or to $PGF_{1\alpha}$. However, high concentrations of both PGB_2 ($> 10^{-7}$ M) and $PGF_{2\alpha}$ ($> 10^{-6}$ M) elicited concentrated-related, but weak, contractile responses, measuring only 5–25% of KCl-induced maximum contractions.

3 Intrapulmonary arteries, partially contracted by 5-hydroxytryptamine (5-HT), exhibited concentration-related relaxations in response to PGE_1; PGE_2, PGA_1 or PGA_2 produced only weak superimposed contractions.

4 In contrast to intrapulmonary arteries, intrapulmonary veins contracted in a concentration-related fashion to all prostaglandins tested, where the contractile sensitivity was (based on EC_{50} s and threshold concentrations): $PGB_2 > PGB_1 > PGD_2 > PGF_{2\alpha} > PGA_2 \gg PGA_1 > PGF_{1\alpha} > PGE_2 > PGE_1$.

5 In terms of the ability to generate maximum contractile responses on intrapulmonary veins, the prostaglandins were also variable, with PGA_2 and PGB_2 being the most potent and PGD_2 the least potent.

6 Intrapulmonary veins, partially contracted by 5-HT, exhibited concentration-related relaxations to PGE_1 at low concentrations, followed by secondary contractile responses at higher concentrations.

7 Neither PGA_1 nor PGA_2 (3.4×10^{-8} to 3.4×10^{-5} M) inhibited or potentiated 5-HT responses of intrapulmonary arteries.

8 These data suggest that there are species, regional and major qualitative and quantitative, differences in the responsiveness of intrapulmonary arteries and veins to prostaglandin.

Introduction

Vasoactive lipids, including prostaglandins and a variety of like-acting substances, are known to be synthesized, released and metabolized in mammalian lungs during several pathophysiological conditions (Angaard & Samuelsson, 1965; Lindsey & Wyllie, 1970; Horton, Jones, Thompson & Poyser, 1971; Hamberg & Samuelsson, 1974; Said, Yoshida, Kitamura & Vreim, 1974; Dusting, Moncada & Vane, 1979). The precise role of prostaglandins in the regulation and maintenance of the pulmonary circulation is still poorly understood (Dusting *et al.* 1979).

Earlier, prostaglandins of the A and E series have been shown to induce relaxations of canine isolated intrapulmonary arteries (Joiner, Kadowitz, Hughes & Hyman, 1975; Kadowitz, Joiner & Hyman, 1975). Recently, in our laboratory, we were unable to demonstrate any relaxant effects of prostaglandins E_1, E_2, A_1 or A_2 on isolated pulmonary arteries of the rat (Chand & Altura, 1980a, b, c). These species-related major qualitative differences in the reactivity of rat and canine pulmonary arteries prompted us to study the effects of primary prostaglandins on isolated intrapulmonary arteries and veins of the dog.

Methods

Animals and vascular preparations

Thirty-five adult dogs of either sex, weighing between 16 to 20 kg, were anaesthetized by intravenous injection of pentobarbitone sodium (Nembutal, 30 mg/kg) and killed by thoracotomy. Lungs were immediately removed and placed in ice-cold oxygenated Krebs-Ringer bicarbonate solution (see composition below). A stainless steel probe of appropriate dia-

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meter was inserted into the lumen of the appropriate pulmonary blood vessels. Pulmonary arteries and veins of (2–3 mm o.d.) were then dissected out, and the adjacent lung parenchymal tissue was removed. The pulmonary vessels were cut into helical strips (2.5–3.0 mm in width by 30 mm in length) (Chand & Altura, 1980a–e) and set up isometrically, *in vitro*, under an optimal resting tension of 2 g (Chand & Altura, 1980a, b). The vascular strips were equilibrated for 2 h in 20 ml isolated tissue baths containing Krebs-Ringer bicarbonate (KRB) solution, the composition of which was (mmol/l): NaCl 118, KCl 4.7, $CaCl_2$ 2.5, KH_2PO_4 1.2, $MgSO_4.7H_2O$ 1.2, $NaHCO_3$ 25.0 and glucose 10.0, as described previously (Altura & Altura, 1970). The KRB solution was continuously oxygenated with a 95% O_2:5% CO_2 mixture and maintained at 37°C (pH 7.4 to 7.5). The loading tensions were maintained and adjusted periodically throughout the experiments. The incubation media were routinely changed every 10–15 min as a precaution against interfering metabolites (Altura & Altura, 1970).

Experimental protocol and statistics

After the 2 h incubation period, complete cumulative concentration-response curves to the prostaglandins were recorded at 30 to 60 min intervals with Grass FT.03C force-displacement strain gauges and a model 5 Grass Instrument four channel recorder (Altura & Altura, 1970). Dose-response curves to KCl were obtained in all experiments in order to assess reactivity of the prostaglandins.

Relaxant responses to prostaglandin E_1 (PGE_1) and other prostaglandins were recorded from sustained contractions (25 to 50% of maximum response) induced by 5-HT (5–10 ng/ml on the arteries and 10–50 ng/ml on the veins).

The results of the experiments are expressed in mg of developed isometric tension to each prostaglandin and as a percentage of the maximal KCl-induced contractile response.

Cumulative dose-response curves to the prostaglandins were analysed in terms of 'contractility' i.e., intrinsic ability of the vascular smooth muscle strip to generate maximum isometric tensions and 'reactivity', i.e., the ability of each agonist to combine with its receptor as measured by threshold concentration and EC_{50} (effective concentration needed to develop 50% of its maximal response; Altura & Altura, 1970). The means (± s.e. mean) of the agonist responses were determined and, where appropriate, statistically analysed by means of Student's unpaired *t* test.

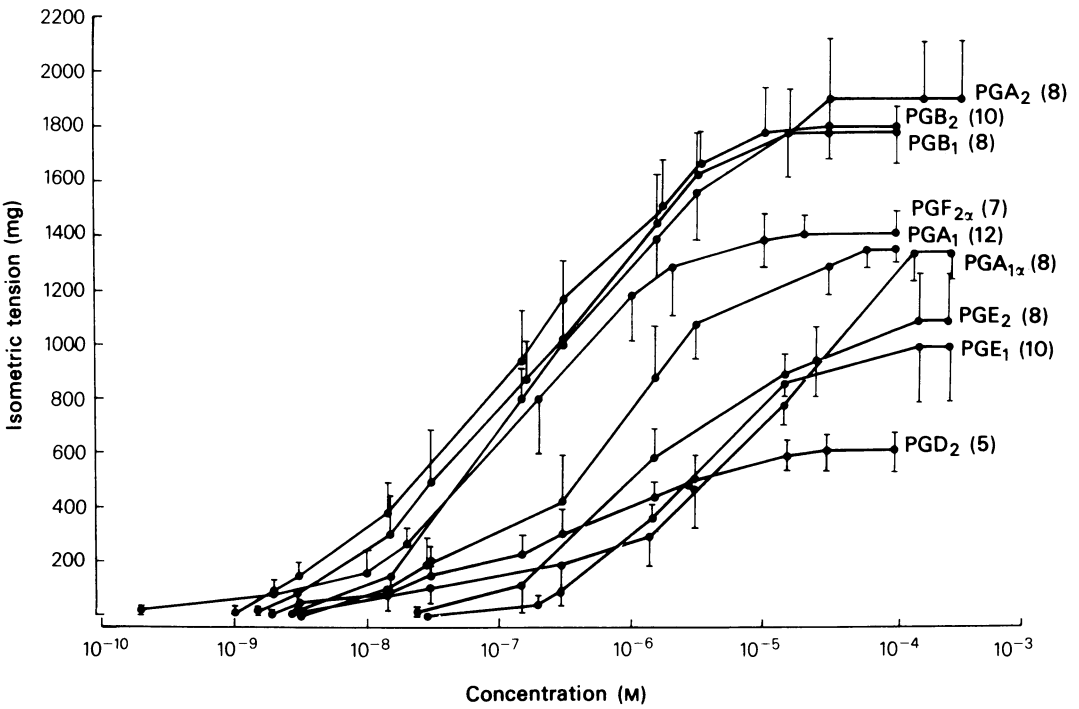

Figure 1 Comparative contractile concentration-effect curves for primary prostaglandins on canine isolated intrapulmonary veins. Each point indicates the mean and vertical lines show s.e. mean. Number in parentheses represents the number of different dogs examined.

Table 1 Comparative effects of prostaglandins on canine isolated intrapulmonary arteries

Prostaglandin	n	*Threshold conc.* (M)	EC_{50} (M)	*Maximum contractile tension* (mg)	*% maximum KCl response*
PGA_1	10	Inactive††	—	0	0
PGA_2	5	Inactive††	—	0	0
PGB_1	5	$3.2 \pm 0.8 \times 10^{-6}$	—†	75 ± 30	3 ± 1.2
PGB_2	5	$2.1 \pm 1.4 \times 10^{-7}$	$1.2 \pm 0.7 \times 10^{-5}$	600 ± 100	25 ± 7
PGD_2	4	Inactive††	—	0	0
PGE_1	5	$2.3 \pm 0.7 \times 10^{-7}$	—†	−50 ± −25**	—
PGE_2	5	$1.8 \pm 1.1 \times 10^{-6}$	—†	250 ± 110	11 ± 5
$PGF_{1\alpha}$	4	Inactive††	—	0	0
$PGF_{2\alpha}$	5	$0.8 \pm 0.7 \times 10^{-6}$	—†	150 ± 139	6 ± 4.5

Values are means ± s.e. means; † not calculable; ** minus sign signifies relaxation below 2 g baseline tension; †† no responses were observed up to 5×10^{-5} M.

Chemicals, prostaglandins and solvent

The chemicals used to make up the KRB solutions, as well as potassium chloride, were all A.C.S. certified reagent grade. PGA_1, A_2, B_1, B_2, D_2, E_1, E_2, $F_{1\alpha}$ and $F_{2\alpha}$ were generous gifts from The Upjohn Company.

All the vasoactive drugs were made up fresh in thrice distilled-deionized water as concentrated stock solutions so that the total volumes added to the 20 ml muscle baths never exceeded 0.65 ml. The prostaglandins were dissolved (< 1 mg/ml) in phosphate buffer (pH 7.4) rather than ethanol, as a precaution against solvent interactions (Altura & Edgarian, 1976).

Results

Sensitivity, expressed in terms of minimum effective concentrations and EC_{50}s as well as contractility (i.e., ability of intrapulmonary arteries and veins to generate maximum contractile tensions), are summarized in Tables 1 and 2, and Figure 1.

It is evident from Table 1, that, in general, intrapulmonary arterial strips are relatively insensitive to prostaglandins of the A, B, E and F series. High concentrations of PGB_2 (i.e., > 10^{-7} M) and $PGF_{2\alpha}$ (i.e., > 10^{-6} M) induced weak contractile responses, measuring only up to 5 to 25% of KCl-induced maximum responses. Low concentrations of $PGF_{2\alpha}$ (i.e.,

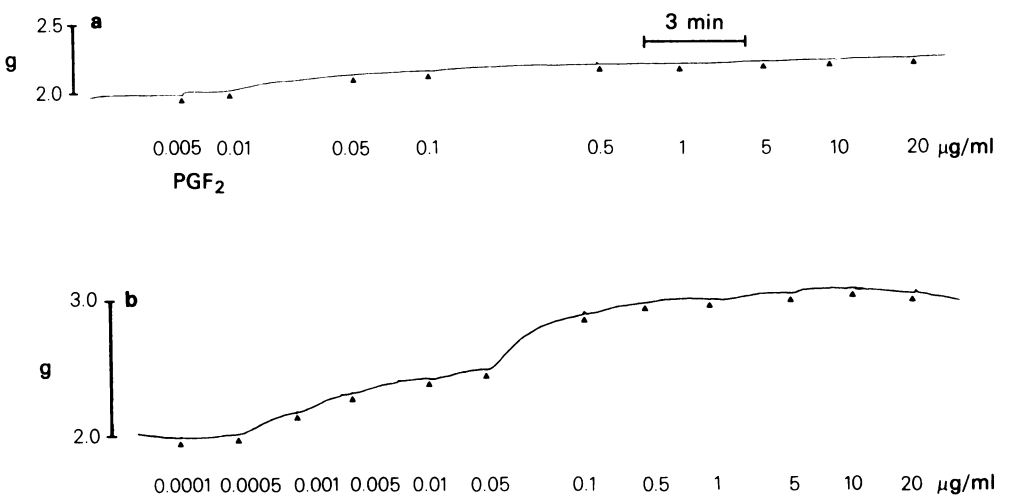

Figure 2 Comparative contractile actions of the cumulative addition of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) (µg/ml, added at triangles) on intrapulmonary artery (a) and intrapulmonary vein (b). Bars on left represent induced tension (above 2.0 g baseline) in g. Similar above baseline tension designations are also (except for Figure 4) indicated in the other figures.

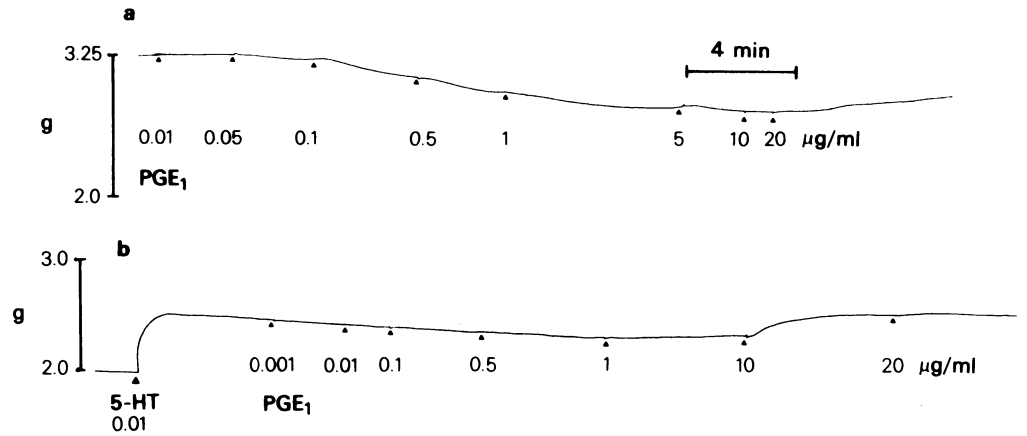

Figure 3 Prostaglandin E_1 (PGE_1 μg/ml, added at small triangles) induced concentration-dependent relaxations on intrapulmonary artery (a) and intrapulmonary vein (b) partially contracted with 5-hydroxytryptamine (5-HT 0.01 μg/ml). Note PGE_1-induced contractions at concentrations > 5 μg/ml. Bars on left represent tension in g.

10^{-8} to 10^{-7} M) usually were inactive on pulmonary arteries. However, in one intrapulmonary artery (e.g., Figure 2), such low concentrations of $PGF_{2\alpha}$ did elicit threshold contractile responses.

Pulmonary arterial strips partially contracted with 5-HT reacted with concentration-dependent (10^{-7} to 10^{-5} M) relaxations to only PGE_1 (Table 3, Figures 3 an 4); PGA_1, A_2 and E_2 (10^{-10} to 10^{-6} M) were usually inactive, and high concentrations (5×10^{-6} to 5×10^{-5} M) induced weak, superimposed contractile responses (Figure 5). In some strips (5/15), PGE_2 (10^{-8} to 10^{-6} M) induced weak relaxation (10 to 50 mg lowering of tension) on 5-HT-contracted arterial strips. PGE_1 failed to evoke any consistent (measurable) relaxations on arterial strips under resting (loading) tensions.

Pulmonary veins strips elicited contractile responses to all of the primary prostaglandins tested in a concentration-dependent fashion (Table 2 and Figures 2, 6). The relative order of potency, based on EC_{50} s, was: $PGB_2 > PGB_1 > PGD_2 \cong PGF_{2\alpha} \cong PGA_2 > PGA_1 > PGE_2 \cong PGF_{1\alpha} > PGE_1$, whereas in terms of contractility it was: $PGA_2 > PGB_2 \cong PGB_1 > PGF_{2\alpha} \cong PGA_1 \cong PGF_1 > PGE_2 > PGE_1 \gg PGD_2$. Although PGF_2 and PGD_2 were approximately equi-active, at the EC_{50} level, $PGF_{2\alpha}$ elicited threshold contractile responses at much lower concentrations and produced greater maximal tensions. It is clear from Figure 6 and Table 3 that PGE_1 (10^{-8} to 10^{-6} M) initially induced weak relaxations (50 to 300 mg lowering of tensions) on 5-HT-contracted veins, but evoked contractile responses at higher concentrations (5×10^{-6} to 10^{-4} M).

Since it has been suggested that PGA_1 and PGA_2 (in non-contractile concentrations) may be able to alter vasoactive agonist-induced contractions

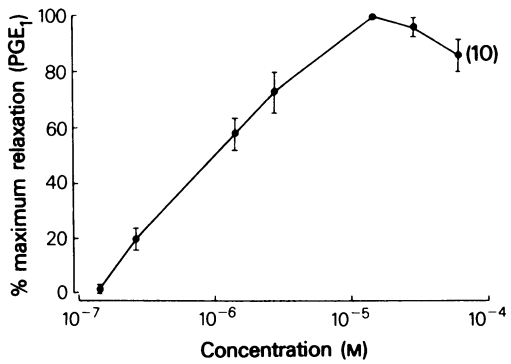

Figure 4 Relaxant concentration-effect curve for canine isolated intrapulmonary arteries. Number in parentheses represents different number of animals examined. Values are given as mean % relaxation; vertical lines show s.e. mean.

(Kadowitz *et al.*, 1975) we performed experiments on vessels from either different dogs to examine such a possibility. Despite the use of a wide concentration range (i.e., 3.4×10^{-8} to 3.4×10^{-5} M) of PGA_1 and PGA_2, we could not detect any potentiation or inhibition of 5-HT contractions on isolated intrapulmonary arteries (e.g., see Figure 7).

Discussion

The data, presented in this study, demonstrate marked, qualitative and quantitative differences in the reactivity of canine intrapulmonary veins and arteries to the vasoactive lipid prostaglandins.

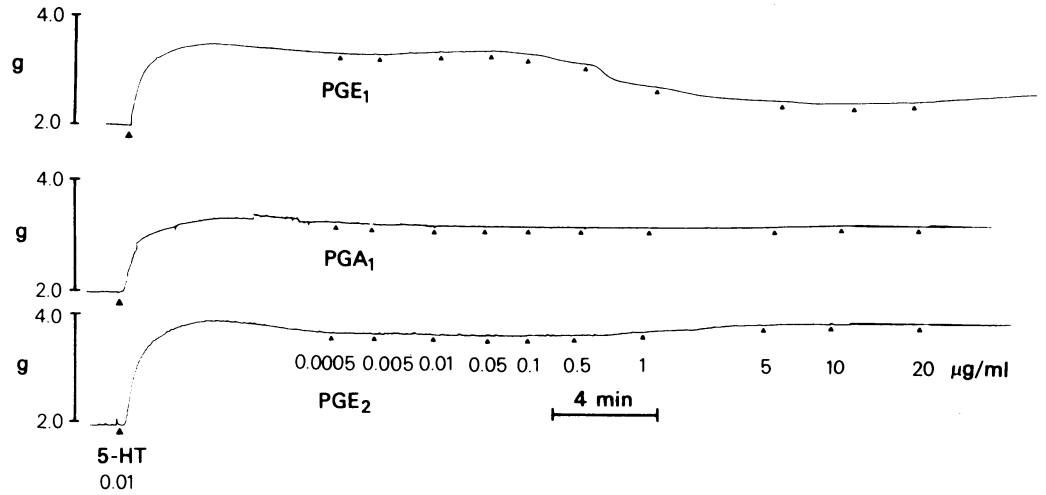

Figure 5 Comparative actions of the cumulative addition of prostaglandin E_1 (PGE_1), PGA_1, and PGE_2 upon intrapulmonary arteries that were partially contracted to 5-hydroxytryptamine (5-HT, 0.01 μg/ml). Prostaglandins added at small triangles. Note concentration-dependent relaxation upon addition of PGE_1 and failure of either PGA_1 or PGE_2 to induce any relaxation.

Qualitatively, some of our data are consistent with some previous studies in a number of mammalian species, whereas other findings in this paper represent a departure and extension of other work on the canine pulmonary vasculature.

The present studies clearly confirm that primary prostaglandins of the A, B, D and F series contract canine intrapulmonary veins, whereas PGE_1 can relax these venous vessels as well as intrapulmonary arteries (Joiner *et al.*, 1975; Kadowitz *et al.*, 1975; Gruetter, McNamara, Hyman & Kadowitz, 1978; Kadowitz, Spannhake, Levin & Hyman, 1980). Our findings, in contrast to others (Joiner *et al.*, 1975; Kadowitz *et al.*, 1975), indicate that, depending upon concentration, PGE_1 can induce either relaxation or contraction of canine intrapulmonary veins. Others have reported that: (1) PGA_1 and PGA_2 can induce potent relaxation of canine intrapulmonary arteries (Kadowitz *et al.*, 1980), (2) PGE_2 can induce relaxation of canine intrapulmonary arteries (Kadowitz *et al.*, 1975), (3) PGB_2 and $PGF_{2\alpha}$ exert no effects on these arteries (Kadowitz *et al.*, 1975), and (4) $PGF_{1\alpha}$ can induce contraction of canine intrapulmonary arteries (Kadowitz *et al.*, 1975). Our results do not support these findings; i.e., the present data on canine intrapulmonary arteries: (1) fail to demonstrate a relaxant effect for PGA_1 or PGA_2, (2) indicate that PGB_2 and $PGF_{2\alpha}$ can induce contraction,(3) showed no relaxation with PGE_2 and (4) no contraction to $PGF_{1\alpha}$. Moreover, the present results demonstrate that, in terms of ability to evoke a maximal contractile response on canine intrapulmonary veins, PGA_2 is more potent than either PGB_2 or PGB_1 (Table 2), just the reverse of what has been suggested by others (Kadowitz *et al.*, 1975).

We believe several factors could be responsible for these divergent findings: (a) Other investigators (Joiner *et al.*, 1975; Kadowitz *et al.*, 1975; 1980;

Table 2 Comparative sensitivity and contractility of canine isolated intrapulmonary veins to prostaglandins

Prostaglandin	n	*Threshold conc.* (M)	EC_{50} (M)	*Maximum contractile tension* (mg)	*% maximum KCl response*
PGA_1	12	$9.1 \pm 0.4 \times 10^{-9}$	$9.9 \pm 2.8 \times 10^{-7}$	1375 ± 75	163 ± 11
PGA_2	8	$3.0 \pm 0.1 \times 10^{-9}$	$4.4 \pm 0.4 \times 10^{-7}$	1925 ± 225	209 ± 24
PGB_1	8	$2.6 \pm 0.4 \times 10^{-9}$	$2.2 \pm 0.1 \times 10^{-7}$	1805 ± 120	201 ± 9
PGB_2	10	$2.2 \pm 0.8 \times 10^{-9}$	$1.5 \pm 0.6 \times 10^{-7}$	1825 ± 150	205 ± 17
PGD_2	5	$2.5 \pm 0.2 \times 10^{-9}$	$2.7 \pm 0.5 \times 10^{-7}$	625 ± 75	56 ± 9
PGE_1	10	$9.4 \pm 0.5 \times 10^{-8}$	$3.5 \pm 0.4 \times 10^{-6}$	1025 ± 225	89 ± 22
PGE_2	8	$2.2 \pm 0.7 \times 10^{-7}$	$1.6 \pm 0.2 \times 10^{-6}$	1150 ± 175	101 ± 15
$PGF_{1\alpha}$	8	$3.1 \pm 0.5 \times 10^{-9}$	$2.1 \pm 0.6 \times 10^{-6}$	1375 ± 125	159 ± 16
$PGF_{2\alpha}$	7	$2.4 \pm 0.3 \times 10^{-10}$	$3.1 \pm 0.6 \times 10^{-7}$	1425 ± 75	171 ± 9

Values are means ± s.e. means.

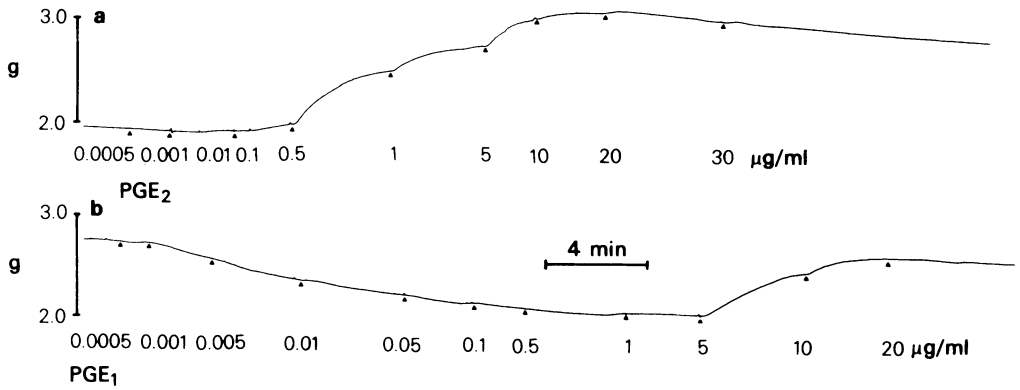

Figure 6 Differential effects of prostaglandin E_1 (PGE_1) and PGE_2 on canine isolated intrapulmonary veins. PGE_2 (a) was added to relaxed vein (i.e., at baseline tension) whereas PGE_1 (b) was added to a vein that was partially contracted to 5-hydroxytryptamine (0.01 μg/ml).

Gruetter *et al.*, 1978) used 23.8 mM tris (hydroxymethyl) aminomethane (Tris) as a buffer in their bathing media instead of bicarbonate and phosphate. It has been shown recently that substitution of Tris for the latter natural buffers results in attenuation and inhibition of effects of contractile substances, including prostaglandins on vascular (and pulmonary) smooth muscle (Turlapaty, Altura & Altura, 1978; Altura, Altura, Carella & Turlapaty, 1980; Altura, Carella & Altura, 1980). (b) Our bathing medium contained magnesium ions whereas the previous studies (Joiner *et al.*, 1975; Kadowitz *et al.*, 1975; 1980; Gruetter *et al.*, 1978) used bathing media lacking Mg^{2+}. Removal of Mg^{2+} from the medium is known to result in loss of contractile activity to some prostaglandins in many vascular (including pulmonary) smooth muscles (Altura & Altura, 1976). (c) We solubilized our prostaglandins in phosphate buffer, whereas other investigators (Joiner *et al.*, 1975; Kadowitz *et al.*, 1975; 1980; Gruetter *et al.*, 1978) used ethanol as a solvent. It has been shown that the low doses of ethanol which are commonly present in the vasoactive concentrations of the prostaglandins used here, and elsewhere (Joiner *et al.*, 1975; Kadowitz *et al.*, 1975; Gruetter *et al.*, 1978) interact with prostaglandins either to inhibit or potentiate the actions of the vasoactive lipids on vascular muscles depending upon the prostaglandin and ethanol dose (Altura & Altura, 1976; Altura & Edgarian, 1976). The use by others (Joiner *et al.*, 1975; Kadowitz *et al.*, 1975; 1980; Gruetter *et al.*, 1978) or artificial buffers and ethanol, together with the failure to include Mg^{2+} in the medium, also may account for the lower sensitivity and contractility of previous investigators' preparations (Kadowitz *et al.*, 1975; Gruetter *et al.*, 1978) to the primary prostaglandins.

In view of the higher sensitivity of canine intrapulmonary veins and rat pulmonary arteries (Chand & Altura, 1980a) to prostaglandins of the B series rather than to any other primary prostaglandin, one should consider that isomerization of the PGAs to PGBs (Jones, Cammock & Horton, 1972) in the pulmonary vasculature may serve as an important *in vivo* humoral regulatory system.

Table 3 Comparison of the sensitivity of canine isolated intrapulmonary arteries and veins, that were partially contracted to 5-hydroxytryptamine, to the relaxant action of prostaglandins

Prostaglandin	n	*Threshold conc.* (M)	EC_{50} (M)	*Maximum tension* (mg)†
Arteries				
PGA_1	10	$1.1 \pm 1.3 \times 10^{-6}$	—**	250 ± 60††
PGA_2	5	$1.6 \pm 1.1 \times 10^{-6}$	—**	190 ± 50††
PGE_1	10	$2.7 \pm 0.5 \times 10^{-7}$	$1.3 \pm 0.3 \times 10^{-6}$	−625 ± −175
PGE_2	4	$0.5 \pm 0.6 \times 10^{-7}$	—**	−50 ± −25
Veins				
PGE_1	5	$1.4 \pm 0.7 \times 10^{-9}$	—**	−150 ± −25

Values are means ± s.e. means; †minus sign signifies relaxation; **not calculable; ††superimposed contractile responses.

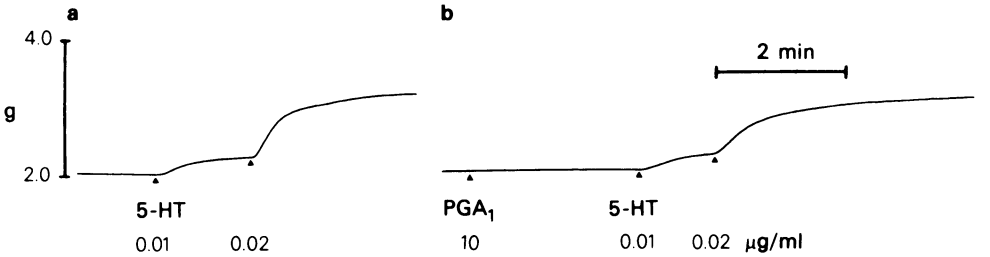

Figure 7 Failure of prostaglandin A_1 (PGA_1) to modify 5-hydroxytryptamine (5-HT)-induced contractile responses of canine isolated intrapulmonary artery. (a) Control contractile responses to 5-HT, 0.01 and 0.02 μg/ml. (b) Shows that a 3 min preincubation with PGA_1 10 μg/ml fails to alter the control contractile response to 5-HT.

Prostaglandins of the D series are the predominant products of arachidonic acid metabolism in homogenates of rat lungs (Nugteren & Hazelhof, 1973). Originally PGD_2 was reported to be biologically inactive (Nugteren & Hazelhof, 1973) but recently, it has been shown to contract bovine isolated pulmonary artery and veins (Gruetter *et al.*, 1978). PGD_2 is virtually inactive on canine intrapulmonary arteries (Gruetter *et al.*, 1978; this study) but as demonstrated here, it induces potent contractions of intrapulmonary veins. The latter effect may be responsible for the increase in pulmonary vascular resistance in intact dogs (Kadowitz *et al.*, 1975; Wassermann, Ducharme, Griffin, DeGraaf & Robinson, 1977; Dusting *et al.*, 1979).

The vascular effects of prostaglandins of the E series are highly variable, depending upon the concentration, species, region, blood vessels, media and spasmogen used to induce tone (Lewis & Eyre, 1972; Burka & Eyre, 1974; Joiner *et al.*, 1975; Kadowitz *et al.*, 1975; 1980; Altura & Altura, 1976; Altura & Edgarian, 1976; Kitamura, Suzuki & Kuriyama, 1976; Chand & Eyre, 1977; Altura *et al.*, 1980b; Chand & Altura, 1980a, c). In this study, PGE_1 but not PGE_2, clearly induced concentration-dependent relaxations on precontracted intrapulmonary arteries of dogs. However, fairly high concentrations of PGE_1 (e.g. $> 10^{-7}$ M) are needed in order to demonstrate these concentration-dependent relaxations. In contrast, neither PGE_1 nor PGE_2 can induce relaxation of rat pulmonary arteries but induce only contractions at relatively higher concentrations (Chand & Altura, 1980a, c). Higher concentrations of PGE_1 induced pulmonary venoconstrictions under resting tensions, following initial, but weak, relaxations on partially 5-HT-contracted veins. In view of the high concentrations required for PGE_1-induced pulmonary relaxation, the inconsistency from species to species (Kadowitz *et al.*, 1975; Su & Bevan, 1976; Dusting *et al.*, 1979), and variability from segment to segment of the individual (Somlyo & Somlyo, 1970; Chand & Altura, 1980a; 1980c), together with the rapid pulmonary metabolism of PGE_1 and PGE_2 (Dusting *et al.*, 1979), it is doubtful whether either of these primary prostaglandins plays an important role in regulating the pulmonary vasculature in either the dog or rat.

As indicated above, our findings with prostaglandins of the F series were not unexpected. $PGF_{2\alpha}$ induced only weak contractile responses of canine intrapulmonary arteries, even at extremely high concentrations. These findings are in contrast to the potent pulmonary arterial constrictions demonstrated for the prostaglandins in other mammals (Lewis & Eyre, 1972; Burka & Eyre, 1974; Kadowitz *et al.*, 1975; Altura & Altura, 1976; Chand & Eyre, 1977; Chand & Altura, 1980a, c). However, both $PGF_{1\alpha}$ and $PGF_{2\alpha}$ did produce concentration-related, and potent, contractions of canine intrapulmonary veins, thus extending findings on pulmonary veins of several other mammalian species, noted by others for $PGF_{2\alpha}$ (Lewis & Eyre, 1972; Burka & Eyre, 1974; Joiner *et al.*, 1975; Kadowitz, *et al.*, 1975; 1980; Ketamura *et al.*, 1976; Chand & Eyre, 1977; Gruetter *et al.*, 1978; Dusting *et al.*, 1979). Whether or not such findings are suggestive of a role for PGF's in the pathophysiology of the pulmonary vasculature remains unclear, especially in view of the rapid metabolism of these primary prostaglandins by the lungs (Dusting *et al.*, 1979).

From our results, it seems reasonable to conclude that, as opposed to rat pulmonary arteries (Chand & Altura, 1980a, b, d), canine pulmonary arteries appear to have a paucity of receptors which subserve contraction for primary prostaglandins and prostaglandin endoperoxides. In contrast, rat pulmonary arteries lack receptors for prostaglandins which subserve relaxation (Chand & Altura, 1980a, c). Interestingly, canine pulmonary veins behave similar to rat pulmonary arteries, as far as their contractile responses to prostaglandins are concerned. The species and regional differences in the responsiveness of pulmonary blood vessels to prostaglandins suggest that extrapolation of data from one species to another, or from one segment, or region, to another is extremely difficult, if not impossible.

We are tempted to conclude, from the results of the present study, that there are remarkable qualitative

and quantitative differences in the reactivity of pulmonary veins and arteries to prostaglandins within a single species. Such differential reactivity may be a reflection of their differential role(s) in the pathogenesis of pulmonary vascular diseases (e.g. hypoxic pulmonary vasoconstriction, pulmonary hypertension and oedema), as has recently been suggested by others (Dusting *et al.*, 1979).

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References

ALTURA, B.M. & ALTURA, B.T. (1970). Differential effects of substrate depletion on drug-induced contractions of rabbit aorta. *Am. J. Physiol.*, **219**, 1698–1705.

ALTURA, B.M. & ALTURA B.T. (1976). Vascular smooth muscle prostaglandins. *Fedn Proc.* **35**, 2360–2366.

ALTURA, B.M., ALTURA, B.T., CARELLA, A. & TURLAPATY, P.D.M.V. (1980a). Adverse effects of artificial buffers on contractile responses of arterial and venous smooth muscle. *Br. J. Pharmac.*, **69**, 207–214.

ALTURA, B.M., CARELLA, A. & ALTURA, B.T. (1980b). Adverse effects of Tris. HEPES and MOPS buffers on contractile responses of arterial and venous smooth muscle induced by prostaglandins. *Prostaglandins and Med.*, **5**, 123–130.

ALTURA, B.M. & EDGARIAN, H. (1976). Ethanol–prostaglandin interactions in contraction of vascular smooth muscle. *Proc. Soc. Exp. Biol. Med.*, **152**, 334–337.

ANGGARD, E. & SAMUELSSON, B. (1965). Biosynthesis of prostaglandins from archidonic acid in guinea pig lungs. *J. biol. Chem.*, **240**, 3518–3521.

BURKA, J.F. & EYRE, P. (1974). Studies of prostaglandins and prostaglandin antagonists on bovine pulmonary vein in vitro. *Prostaglandins*, **6**, 333–343.

CHAND, N. & ALTURA, B.M. (1980a). Reactivity of isolated rat and canine pulmonary arteries to prostaglandins. *Prostaglandins and Med.*, **5**, 59–67.

CHAND, N. & ALTURA, B.M. (1980b). Occurrence of inhibitory histamine H_2-receptors in isolated pulmonary blood vessels of dogs and rats. *Experientia*, **36**, 1186–1187.

CHAND, N. & ALTURA, B.M. (1980c). Reactivity and contractility of rat pulmonary arteries to vasoactive agents. *J. appl. Physiol.*, **49**, 1016–1022.

CHAND, N. & ALTURA, B.M. (1980d). Reactivity of isolated rat and canine pulmonary blood vessels to synthetic endoperoxide (PGH_2) analogs. *Prostaglandins and Med.* **5**, 469–476.

CHAND, B. & ALTURA, B.M. (1980e). Serotonin receptors subserve only contraction in canine and rat pulmonary arteries and veins. *Artery*, **7**, 232–2245.

CHAND, N. & EYRE, P. (1977). Autacoid and anaphylactic reactivity of pulmonary and hepatic smooth musculature of the cat. *Eur. J. Pharmac.*, **45**, 213–220.

DUSTING, G.J., MONCADA, S. & VANE, J.R. (1979). Prostaglandins, their intermediates and precursors: Cardiovascular actions and regulatory roles in normal and abnormal circulatory systems. *Progr. Cardiovascular Dis.*, **21**, 405–430.

GRUETTER, C.A., McNAMARA, D.B., HYMAN, A.L. & KADOWITZ, P.J. (1978). Contractile effects of a PGH_2 analog and PGD_2 on intrapulmonary vessels. *Am. J. Physiol.*, **234**, H139–H145.

HAMBERG, M. & SAMUELSSON, B. (1974). Prostaglandin endoperoxides. VII. Novel transformations of arachidonic acids in guinea pig lung. *Biochem. biophys. Res. Comm.*, **61**, 942–949.

HORTON, E., JONES, R., THOMPSON, C. & POYSER, N. (1971). Release of prostaglandins. *Ann. N.Y. Acad. Sci.*, **180**, 351–362.

JOINER, P.D., KADOWITZ, P.J., HUGHES, J.P. & HYMAN, A.L. (1975). Actions of prostaglandins E_1 and $F_{2\alpha}$ on isolated intrapulmonary vascular smooth muscle. *Proc. Soc. exp. Biol. Med.*, **150**, 414–421.

JONES, R.L., CAMMOCK, S. & HORTON, E.W. (1972). Partial purification and properties of cat plasma prostaglandin A isomerase. *Biochim. biophys. Acta*, **280**, 588–601.

KADOWITZ, P.J., JOINER, P.D. & HYMAN, A.L. (1975). Physiological and pharmacological roles of prostaglandins. *A. Rev. Pharmac.*, **15**, 285–306.

KADOWITZ, P.J., SPANNHAKE, E.W., LEVIN, J.L. & HYMAN, A.L. (1980). Differential actions of the prostaglandins on the pulmonary vascular bed. In *Advances in Prostaglandin and Thromboxane Research*, Vol. 7, ed Samuelsson, B, Ramwell, P.W. & Paoletti, E., pp. 731–744, New York: Raven Press.

KITAMURA, H., SUZUKI, H. & KURIYAMA, H. (1976). Prostaglandin action on the main pulmonary artery and portal vein of the rabbit. *Jap. J. Physiol.*, **26**, 681–692.

LEWIS, A.J. & EYRE, P. (1974). Some cardiovascular and respiratory effects of prostaglandins E_1, E_2 and $F_{2\alpha}$ in the calf. *Prostaglandins*, **2**, 55–64.

LINDSEY, H.E. & WYLLIE, J.H. (1970). Release of prostaglandins from embolized lungs. *Br. J. Surg.*, **57**, 738–741.

NUGTEREN, D.H. & NAZELHOF, E. (1973). Isolation and properties of intermediates in prostaglandin biosynthesis. *Biochim. biophys. Acta*, **326**, 448–461.

SAID, S.I., YOSHIDA, T., KITAMURA, S. & VREIM, C. (1974). Pulmonary alveolar hypoxia: Release of prostaglandins and other humoral mediators. *Science*, **185**, 1181–1183.

SOMLYO, A.P. & SOMLYO, A.V. (1970). Vascular smooth muscle II. Pharmacology of normal and hypertensive vessels. *Pharmac. Rev.*, **22**, 249–353.

SU, C. & BEVAN, J.A. (1976). Pharmacology of pulmonary blood vessels. *Pharmac. Ther. B.*, **2**, 275–288.

TURLAPATY, P.D.M.V., ALTURA, B.T. & ALTURA, B.M. (1978). Influence of Tris on contractile responses of isolated rat aorta and portal vein. *Am. J. Physiol.*, **235**, H208–H213.

WASSERMAN, M.A., DUCHARME, D.W., GRIFFIN, R.L., DeGRAAF & ROBINSON, F.G. (1977). Bronchiopulmonary and cardiovascular effects of prostaglandin D_2 in the dog. *Prostaglandins*, **13**, 255–269.

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