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INHIBITION OF THE PULMONARY INACTIVATION OF PROSTAGLANDINS *in vivo* BY DI-4-PHLORETIN PHOSPHATE

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1 Inactivation of prostaglandin E_2 in the pulmonary circulation of rabbits *in vivo* was measured by comparing the hypotensive effects of doses given intravenously and intra-arterially.

2 Di-4-phloretin phosphate (DPP) 25-100 $\mu g\ kg^{-1}\ min^{-1}$ inhibited the inactivation of prostaglandin E_2 in the pulmonary circulation.

3 These doses of DPP caused a marked shift to the left of the dose-response curve to prostaglandin E_2 given intravenously but did not affect the dose-response curve to prostaglandin E_2 given intra-arterially.

4 Inhibition of pulmonary inactivation of prostaglandins E_2 and $F_{2\alpha}$ caused marked potentiation of their gastrointestinal effects.

5 At these doses antagonism of the hypotensive action of prostaglandin E_2 by DPP was seldom seen but the gastrointestinal effect of prostaglandin $F_{2\alpha}$ was sometimes antagonized.

6 After treatment with DPP 100 $\mu g\ kg^{-1}\ min^{-1}$, high doses of prostaglandin were sometimes lethal.

Introduction

Prostaglandins of the E and F series are almost completely inactivated (90-98%) in one passage through the pulmonary circulation of cat, dog and rabbit *in vivo* (Ferreira & Vane, 1967a) and of guinea-pig isolated lungs *in vitro* (Piper, Vane & Wyllie, 1970). We have previously shown that inactivation of prostaglandins E_2 and $F_{2\alpha}$ *in vitro* can be inhibited by low concentrations of di-4-phloretin phosphate (DPP) and polyphloretin phosphate (Crutchley & Piper, 1974). At higher concentrations, polyphloretin phosphate selectively antagonizes certain prostaglandin actions *in vitro* and *in vivo* (Eakins, Karim & Miller, 1970; Villanueva, Hinds, Katz & Eakins, 1972).

The present study investigates whether DPP inhibits the pulmonary inactivation of prostaglandins *in vivo*. Impairment of this inactivation would allow relatively more of an intravenous dose of prostaglandin to survive passage through the pulmonary circulation and so appear in increased amounts in the systemic circulation. Thus, the systemic actions of prostaglandins would be expected to be potentiated. We have examined the effects of DPP on two actions of prostaglandins E_2 and $F_{2\alpha}$; these were changes in blood pressure and intestinal motility.

A preliminary report of this work was given to a meeting of the British Pharmacological Society (Crutchley & Piper, 1975).

Methods

Pulmonary inactivation of prostaglandin E_2

Male Dutch rabbits 1.8-2.5 kg were anaesthetized with pentobarbitone sodium 40 mg/kg intravenously. A polyethylene cannula for intra-arterial infusions (after the lungs) was introduced retrogradely into the aortic arch via a common carotid artery. A similar cannula for intravenous infusions (before the lungs) was introduced into the superior vena cava via a jugular vein. Blood pressure was recorded from the remaining carotid artery or a femoral artery. Falls in blood pressure to prostaglandin E_2 were obtained by giving random 1.5 min infusions either intra-arterially or intravenously. Since the resting blood pressures ranged between 80-110 mmHg, to allow for differences between individual animals, percentage falls in blood pressure were measured and dose-response curves were plotted. Control

measurements were made in the presence of a continuous infusion of 0.9% w/v NaCl solution (saline) (0.05 ml/min) into the remaining jugular vein. Test measurements were then made during an infusion of DPP in solution in saline (0.05 ml/minute).

Since bradykinin and noradrenaline are inactivated in a single passage through the pulmonary circulation (Ferreira & Vane, 1967b; Vane, 1969; Alabaster & Bakhle, 1972), we also investigated the action of DPP on the pulmonary inactivation of these compounds in rabbits *in vivo*. The method used estimated the inactivation by comparing the blood pressure responses to injections or infusions of bradykinin (depressor) or noradrenaline (pressor) by the intravenous and intra-aortic route.

Depressor and intestinal stimulant actions of prostaglandins E_2 and $F_{2\alpha}$

In these experiments the aortic cannula for intra-arterial infusion was not inserted. A midline incision was made in the abdomen, and the ileum exposed. An enterotomy was performed and a small airfilled latex balloon was inserted. The balloon was inflated to a pressure of 30 mmHg, and ileal motility was measured by recording the intraluminal pressure via a S.E. Laboratory (SE4-82) pressure transducer. The pressure in the balloon always declined throughout the experiment irrespective of treatment. Blood pressure was recorded simultaneously from a carotid artery.

Prostaglandins were administered intravenously either by 1.5 min infusion or by injection. In the latter case, 0.1-0.25 ml prostaglandin solution was washed in with 0.3 ml saline. Dose-response curves to prostaglandins on intra-ileal and blood pressures were obtained during intravenous infusions of saline (control) and then DPP in saline (test).

Materials

All drugs were dissolved in saline before use. The following compounds were used: bradykinin (Sandoz); carbachol (Sigma); di-4-phloretin phosphate (Leo, A.B. and Nelson Research & Development Co.); (−)-noradrenaline bitartrate (Sigma); prostaglandins E_2 and $F_{2\alpha}$ (Dr J.E. Pike, Upjohn Co., Kalamazoo, Mich.). In the cases where salts were used, doses of drugs are expressed in terms of free base.

Results

Effect of DPP on pulmonary inactivation of prostaglandin E_2

The depressor effects of prostaglandin E_2 were much less when it was given intravenously (before the lungs) compared with those when given intra-arterially (after the lungs). The difference gives a measure of the pulmonary inactivation of the prostaglandin (Figure 1). In the majority of experiments, the dose-response curve for intravenously administered prostaglandin was steeper than that obtained when it was given intra-arterially. This has been noticed by Bedwani & Marley (1975) and may be due to a variety of reasons. The most probable is that large intravenous doses of prostaglandin swamp the inactivating enzymes and so relatively more prostaglandin enters the systemic circulation as the dose is increased. Due to this non-parallelism at high doses, we calculated the inactivation of prostaglandins from falls in blood pressure not exceeding 15%. The mean control percentage removal was found to be 94.0 ± 0.6 (n = 23).

DPP administered by intravenous injection (5-20 mg/kg) either had no observed effects, or produced a transient potentiation of the depressor effects of intravenously administered prosta-

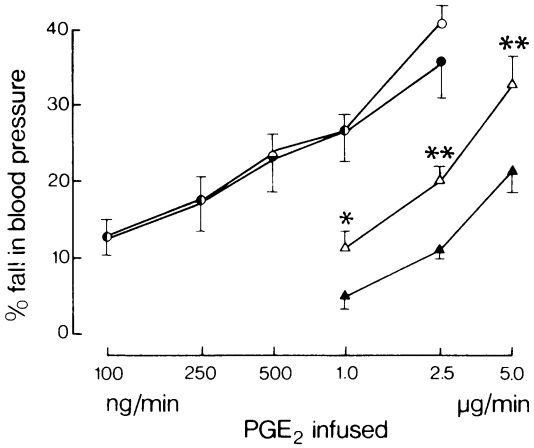

Figure 1 Inhibition of the pulmonary inactivation of prostaglandin E_2 (PGE_2) by di-4-phloretin phosphate (DPP). Random 1.5 min infusions of prostaglandin E_2 were given and the resulting falls in blood pressure noted. (●) Prostaglandin E_2 infused intra-arterially, during an intravenous infusion of saline (control).; (▲) prostaglandin E_2 infused intravenously (control); (○) prostaglandin E_2 infused intra-arterially, during an intravenous infusion of DPP 50 $\mu g\ kg^{-1}\ min^{-1}$ (test); (△) prostaglandin E_2 infused intravenously (test). Each point is the mean of up to eight experiments. Vertical bars show s.e. mean. Test and control were done in the same animals. Significance levels were obtained by the paired t test. * $P < 0.01$; ** $P < 0.001$.

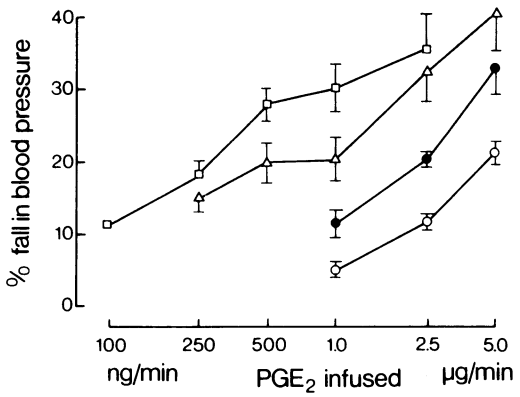

Figure 2 Dose-related effects of di-4-phloretin phosphate (DPP) on the pulmonary inactivation of prostaglandin E_2 (PGE_2). The percentage falls in blood pressure after random 1.5 min infusions of prostaglandin E_2 are shown. (•) Prostaglandin E_2 infused intravenously, during DPP 50 $\mu g\,kg^{-1}\,min^{-1}$ intravenously (eight experiments); (△) prostaglandin E_2 infused intravenously during DPP 100 $\mu g\,kg^{-1}\,min^{-1}$ (up to ten experiments); (○) prostaglandin E_2 infused intravenously during saline (control); (□) prostaglandin E_2 infused intra-arterially (control). These control measurements were obtained by combining the individual controls for DPP 50 or 100 $\mu g\,kg^{-1}\,min^{-1}$ (up to 18 experiments). Vertical bars are s.e. mean.

glandin E_2. Continuous intravenous infusion of DPP 25 $\mu g\,kg^{-1}\,min^{-1}$ had no effects on either blood pressure or the depressor response to prostaglandin given intra-arterially. However, a small potentiation of the responses to intravenously administered prostaglandin occurred, as shown by a shift to the left of the dose-response curve (five experiments). However, only at a dose of 5 μg/min prostaglandin was the shift significant ($P < 0.02$). This shift in the absence of any effect on the responses to intra-arterially administered prostaglandin, suggests that DPP is acting to impair the pulmonary inactivation of the prostaglandin. At this concentration of DPP, the amount of prostaglandin surviving pasage through the pulmonary circulation increased 1.3 fold.

Continuous intravenous infusion of DPP 50 $\mu g\,kg^{-1}\,min^{-1}$ again had no effect on either blood pressure or the responses to prostaglandin given intra-arterially but significantly potentiated the response to intravenous prostaglandin, as shown by a larger shift to the left of the dose-response curve (eight experiments) (Figure 1). The amount of prostaglandin surviving passage through the lungs increased 2.5 fold. No increase of the effect of DPP with time was seen at these low doses (25 and 50 $\mu g\,kg^{-1}\,min^{-1}$) despite continuous infusion for up to 3 hours.

Continuous intravenous infusion of DPP 100 $\mu g\,kg^{-1}\,min^{-1}$ had no effect on blood pressure before infusion of prostaglandin, but once this started, there was often a progressive fall in blood pressure as the experiment continued. This was particularly noticeable after high doses of prostaglandin, which may have been recirculating due to seriously impaired lung inactivation. Often this progressive decline in blood pressure after high doses of prostaglandin was fatal.

At this concentration DPP again had no effect on the blood pressure responses to prostaglandin given intra-arterially but caused a considerable potentiation of the responses to prostaglandin given intravenously (ten experiments). The amount of prostaglandin surviving passage through the lungs increased 16.4 fold (Figure 2). The animals often had diarrhoea after prostaglandin administration, presumably as a result of this increase. It was observed that the blood had an increased tendency to coagulate during intravenous infusion of DPP 100 $\mu g\,kg^{-1}\,min^{-1}$. This occurred even after administration of heparin, 1000 iu/kg intravenously.

Thus, DPP itself had no effect on blood pressure, except at 100 $\mu g\,kg^{-1}\,min^{-1}$ in the presence of prostaglandin. It had no significant effect on blood pressure responses to prostaglandin when given intra-arterially and hence had no noticeable prostaglandin inhibitory action at these doses. It did cause a potentiation of the responses to prostaglandin administered intravenously, an effect which was dose-related. From this we conclude that DPP inhibits the pulmonary inactivation of prostaglandin E_2.

Reports from Leo AB indicate that DPP is 99.9% bound to plasma protein, so presumably the effective (unbound) concentration is a small fraction of the doses used.

In some experiments, the intravenous infusion of DPP was stopped and the time-course of recovery noted. This was quite rapid; pulmonary inactivation of prostaglandin often started to recover after 20-30 minutes.

Control percentage inactivations of bradykinin were 92.7 ± 1.5 and of noradrenaline 19.2 ± 4.6 (three experiments each). During a continuous infusion of DPP 100 $\mu g\,kg^{-1}\,min^{-1}$ intravenously which would seriously impair the lung inactivation of prostaglandin E_2, the percentage inactivation of bradykinin was found to be 93.8 ± 2.3 and that of noradrenaline 15.8 ± 4.6. This shows that DPP has no significant effect on the pulmonary inactivation of bradykinin or noradrenaline.

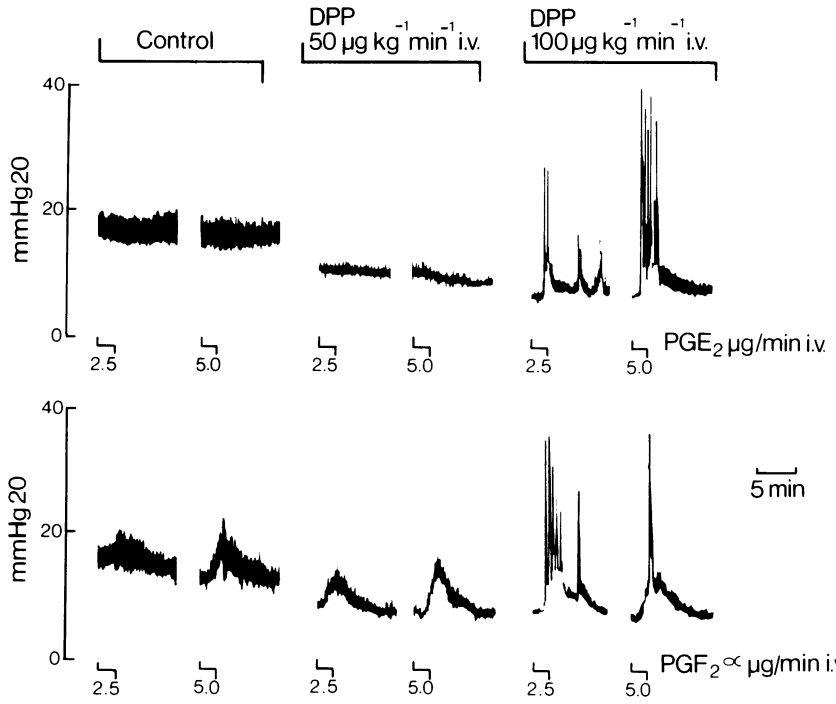

Figure 3 Potentiation by di-4-phloretin phosphate (DPP) of the effects of intravenous prostaglandins E_2 (PGE_2) and $F_{2\alpha}$ ($PGF_{2\alpha}$) on ileal motility. The effects of 1.5 min intravenous infusions of prostaglandin E_2 (upper trace) and $F_{2\alpha}$ (lower trace) on intra-ileal pressure are shown. Control measurements were made during a continuous intravenous infusion of saline. About 20 min after the start of a continuous intravenous infusion of DPP 50 $\mu g\ kg^{-1}\ min^{-1}$, slight potentiation of the responses to prostaglandin $F_{2\alpha}$ were seen. During a continuous intravenous infusion of DPP 100 $\mu g\ kg^{-1}\ min^{-1}$ potentiation of the effects of both prostaglandins occurred.

Effects of DPP on the depressor and intestinal stimulant actions of prostaglandins E_2 and $F_{2\alpha}$

Prostaglandin E_2 was administered by intravenous injection (1.0-10.0 μg, three experiments) or infusion (1.0-5.0 μg/min, one experiment). It caused dose-dependent falls in blood pressure and small increases in intra-ileal pressure. DPP 50 and 100 $\mu g\ kg^{-1}\ min^{-1}$ had no effect on blood pressure or intra-ileal pressure but potentiated the falls in blood pressure and increased the rises in intra-ileal pressure caused by prostaglandin given intravenously (Figure 3). This effect of DPP was dose-related. DPP at these concentrations had no effect on the responses of the ileum to prostaglandin given intra-arterially (three experiments).

Prostaglandin $F_{2\alpha}$ was similarly administered by intravenous injection (three experiments) or infusion (four experiments). It was more potent than prostaglandin E_2 in increasing ileal motility. DPP 50 and 100 $\mu g\ kg^{-1}\ min^{-1}$ potentiated the effects of prostaglandin $F_{2\alpha}$ given by infusion (one experiment) see Figure 3. In a further three experiments, DPP had no effect. DPP also potentiated the ileal response to prostaglandin $F_{2\alpha}$ administered by intravenous injection (one experiment). In a further two experiments, the responses to prostaglandin $F_{2\alpha}$ were depressed. This variable reaction of the ileum to prostaglandin $F_{2\alpha}$ in the presence of DPP may be due to direct antagonism by DPP of smooth muscle actions of the prostaglandin.

Prostaglandin $F_{2\alpha}$ had little or no effect on blood pressure except at high rates of infusion (25.0 μg/min) when it was depressor. During DPP 50 and 100 $\mu g\ kg^{-1}\ min^{-1}$, the highest doses of prostaglandin $F_{2\alpha}$ were strongly depressor. This may be due to impairment of the pulmonary inactivation of the prostaglandin allowing a higher effective concentration in the systemic circulation.

From these results we conclude that DPP potentiates the actions of intravenously adminis-

tered prostaglandin E_2 on blood pressure and intra-ileal pressure. It possibly potentiates the actions of prostaglandin $F_{2\alpha}$ on blood pressure and has a variable effect on the responses of the ileum to this prostaglandin.

The potentiation of responses to prostaglandin was probably not a non-specific cardiovascular change as DPP 100 $\mu g\,kg^{-1}\,min^{-1}$ had no effect on either the depressor or intestinal stimulant actions of carbachol 1.0-3.0 μg intravenously (three experiments).

Discussion

The method used to determine the pulmonary inactivation of prostaglandin E_2 is a modification of that of Horton & Jones (1969) and has been used by other workers (Ueda, Hatanaka, Ito, Kokubu & Hamamura, 1973; Bedwani & Marley, 1974). It assumes that the depressor effects of prostaglandin E_2 are due solely to peripheral vasodilatation. Prostaglandins of the E series are potent vasodilators in a wide variety of vascular beds in a number of species, an effect which probably accounts for their systemic depressor actions (Horton, 1969).

The effects of the F-type prostaglandins on the circulation are complex. Prostaglandins $F_{1\alpha}$ and $F_{2\alpha}$ exert mild to moderate depressor actions in the cat and rabbit (Änggård & Bergström, 1963; Horton & Main, 1963) but are pressor in rat and dog, probably due to venoconstriction (Du Charme, Weeks & Montgomery, 1968). In cats, an increased pulmonary resistance, indicated by an increase in right ventricular pressure, may contribute to the depressor action (Änggård & Bergström, 1963). Hence, the pulmonary inactivation of prostaglandin $F_{2\alpha}$ was not determined by this method.

We have previously shown that DPP selectively inhibits the pulmonary inactivation of prostaglandins E_2 and $F_{2\alpha}$ by guinea-pig *in vitro* (Crutchley & Piper, 1974). The present studies show that DPP, when given by intravenous infusion, also inhibits the inactivation of prostaglandin E_2, and possibly $F_{2\alpha}$ by rabbit lungs *in vivo*. The inactivation of bradykinin in the pulmonary circulation is enzymatic (Ryan, Roblero & Stewart, 1968) whereas that of noradrenaline is apparently due to an uptake mechanism (Vane, 1969). Since at the doses used DPP inhibits the inactivation of prostaglandins but not of bradykinin and noradrenaline it does not appear to be a general inhibitor of the inactivating functions of the lung.

Since the lungs are a major factor in the inactivation of circulating E and F prostaglandins, inhibition of this inactivation would be expected to potentiate the systemic effects of intravenously administered prostaglandin. We have shown that DPP does potentiate the depressor and intestinal stimulant actions of prostaglandins E_2 and $F_{2\alpha}$, although some direct antagonism of the actions of prostaglandin $F_{2\alpha}$ were seen. At 100 $\mu g\,kg^{-1}\,min^{-1}$ DPP greatly inhibited the lung inactivation of prostaglandins, and the depressor effects of prostaglandin E_2 given intravenoulsy were potentiated to such an extent that they often proved fatal.

The increased coagulability of the blood observed during prostaglandin E_2 treatment in the presence of DPP may also have been due to recirculating prostaglandin. Prostaglandin E_2 may play a physiological role in haemostasis and blood clotting. Although circulating blood normally contains little or no prostaglandin E_2 large amounts may be formed by platelets in response to thrombin generated by haemostasis or thrombosis (Silver, Smith, Ingerman & Kocsis, 1972). Prostaglandin E_2 also enhances the adenosine 5′-pyrophosphate-induced aggregation of platelets *in vitro* in a variety of species (Kloeze, 1967).

Both DPP and polyphloretin phosphate (PPP) are known to be specific antagonists of many of the smooth muscle actions of prostaglandins E_2 and $F_{2\alpha}$ *in vitro* (Eakins *et al.*, 1970; Mathé, Strandberg & Åström, 1971; Eakins, Fex, Fredholm, Högberg & Veige, 1973). PPP also antagonizes some of the smooth muscle actions of prostaglandins E_2 and $F_{2\alpha}$ *in vivo* (Villanueva *et al.*, 1972). In these experiments, however, PPP was administered by injection. In our experiments, injected DPP (5-20 mg/kg i.v.) had little effect on the lung inactivation of prostaglandin E_2. It appears that DPP exhibits marked prostaglandin-inactivation inhibitory properties only if infused continuously. We have observed that prostaglandin inactivation recovers fairly rapidly after cessation of the DPP infusion; recovery starts after about 20 minutes. Similarly, DPP washes out quickly from guinea-pig isolated perfused lungs (Crutchley & Piper, 1974). Villanueva *et al.* (1972) observed that certain of the actions of prostaglandins were potentiated shortly after the injection of PPP. This may have been due to transient inhibition of the inactivating enzymes of the lungs.

Since the effects of low doses of DPP do not increase despite continuous infusion for up to 3 h, it would appear that the effective concentration of DPP in the blood remains essentially constant. This may be due to binding to plasma protein, or metabolism in the liver. However, high doses (100 $\mu g\,kg^{-1}\,min^{-1}$) do appear to recirculate and cumulative effects were observed as the infusion of DPP continued.

Villanueva *et al.* (1972) reported that PPP appears to be more potent as an antagonist of prostaglandin $F_{2\alpha}$ than of prostaglandin E_2 *in vivo*. Only certain of the effects of prostaglandin E_2 were antagonized by PPP. Our studies confirm this as at the doses used, direct antagonism by DPP occurred only to prostaglandin $F_{2\alpha}$.

The dual properties of DPP are interesting. On the one hand, inhibition of pulmonary prostaglandin inactivation would tend to potentiate the systemic effects of intravenously administered prostaglandins. On the other hand, antagonism of prostaglandin action would tend to reduce their effects. It appears that PPP inhibits some of the *in vivo* effects of prostaglandin E_2 more readily than others (Villanueva *et al.*, 1972). This raises the possibility of the development of an analogue, which would both increase prostaglandin survival on passage through the lung, and selectively antagonize unwanted prostaglandin actions. If this were possible, not only would the effective dose of intravenous prostaglandin be reduced, but the desirable effect would be preferentially potentiated, and thus the therapeutic ratio increased.

Our results emphasize the importance of the lungs in removing prostaglandins from the circulation. However, other sites especially the liver are capable of inactivating circulating prostaglandins (Vane, 1969). Prostaglandin dehydrogenase, the enzyme playing a key role in the biological inactivation of prostaglandins, has been found in lung, spleen, kidney, stomach, testicle and small intestine of the swine (Samuelsson, Granström, Gréen & Hamberg, 1971). As yet we have no information on the ability of DPP to inhibit the dehydrogenase in these tissues. However, since DPP did not potentiate the responses of the ileum to prostaglandins given intra-arterially either the dehydrogenase present in the ileum is relatively unimportant in the inactivation of circulating prostaglandins, or it is not inhibited by DPP, possibly due to the enzyme's location. Although the lungs are probably the most important site of prostaglandin inactivation, once this is impaired, other sites of inactivation may become relatively more important.

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