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RENAL VASODILATOR ACTIVITY OF PROSTAGLANDIN E_2 IN THE RAT ANAESTHETIZED WITH PENTOBARBITONE

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1 The effect of intra-aortic administration (i.a.) of prostaglandin E_2 (PGE_2) on renal blood flow was studied in the rat anaesthetized with pentobarbitone. Renal blood flow was assessed in two ways, either by use of an electromagnetic flow probe or by measurement of the renal clearance of *p*-aminohippurate (PAH).

2 PGE_2 (0.1 μg/min, i.a.) increased renal blood flow measured by either method. However, PAH clearance overestimated the degree of vasodilatation compared to that obtained using the flow meter. The possibility that PGE_2 or a metabolite may increase PAH extraction by the kidney was considered.

3 The sensitivity of the rat to the renal vasodilator actions of PGE_2 was enhanced by using a flank retro-peritoneal approach from which to insert the flow probe, rather than a mid-line abdominal incision.

4 Dose-response curves demonstrate that under the conditions used, PGE_2 produced a biphasic change in renal vascular resistance, vasodilatation started at 0.01 μg/min and was maximal at about 3 μg/min, while at the highest dose used (20μg/min) PGE_2 induced renal vasoconstriction.

5 The results indicate that contrary to previous reports, the rat does not exhibit an important species difference in the response of its renal vasculature to PGE_2. Therefore, physiological and pathophysiological roles which have previously been attributed to vasoconstriction produced by PGE_2 synthesized in the kidney may now have to be considered.

Introduction

The renal vasodilator properties of prostaglandins of the E and A series have been described in the dog (Johnston, Herzog & Lauler, 1967; Fulgraff & Brandenbusch, 1974), in the rabbit (Fine & Trizna, 1977) and in man (Carr, 1970). It has been suggested that the rat exhibits an important species difference in its renal vascular response to prostaglandin E_2 (PGE_2) since renal vasoconstriction, not dilatation is produced in both the isolated perfused kidney (Malik & McGiff, 1975) and in the anaesthetized animal (Baer & McGiff, 1979; Gerber & Nies, 1979).

During experiments performed to determine the influence of PGE_2 on the cortico-medullary solute gradient in the rat kidney (Haylor & Lote, 1980b) the renal clearance of *p*-aminohippurate (PAH) increased in the presence of PGE_2, indicating renal vasodilatation. Other evidence also indicates that PGE_2 is not always associated with renal vasoconstriction in the rat. Inhibitors of cyclo-oxygenase do not increase renal blood flow in the rat as would be expected if PGE_2 synthesized in the kidney were helping to maintain vasoconstriction. In the rat, as in other species cyclo-oxygenase inhibition either has no effect on renal blood flow (Haylor & Lote, 1980a) or depending on the experimental conditions used, produces a moderate fall (Mimran, Casellas, Dupont & Barjon, 1975). On the other hand, in some of the early experiments on the renal properties of acidic lipids isolated from the kidney, vasodepressor lipid (which was later shown to contain PGE_2 by Daniels, Hinman, Leach & Muirhead, 1967) increased flow in the isolated perfused kidney of the rat (Hickler, Lauler, Saravis, Vagnucci, Steiner & Thorn, 1964).

In the present experiments we have attempted to substantiate our original findings (Haylor & Lote, 1980b) that PGE_2 can cause vasodilatation in the rat kidney. A preparation of the pentobarbitone-anaesthetized rat was used to compare the effects of PGE_2 on PAH clearance, with its effect on total renal blood flow measured with an electromagnetic flow meter. The sensitivity of the renal vasculature to the effects of PGE_2 was examined using two surgical approaches for insertion of the probe. Dose-response experiments to the effect of PGE_2 on renal vascular resistance were performed.

Contrary to previous reports, the results of these experiments demonstrate that in the rat, PGE_2 can increase renal blood flow to a similar degree to that originally described for PGE_1 in the dog (Johnston *et al.*, 1967).

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Methods

Male Wistar rats (370–430 g) were used, which had been allowed free access to water and had been maintained on a rat-cake diet, but had been deprived of food for 24 h before the experiment. Anaesthesia was induced by pentobarbitone sodium (60 mg/kg) injected intraperitoneally and maintained with pentobarbitone sodium (3 mg/kg) injected intravenously every 45–60 min. Body temperature was maintained at 37°C and a tracheostomy was performed. Cannulae were placed in the left carotid artery to record systemic blood pressure and to collect blood samples, and in the right jugular vein for the infusion of fluids. The left femoral artery was cannulated with tubing of external diameter 0.6 mm which was advanced up the aorta to a point just above the origin of the left renal artery but below the origin of either the right renal or superior mesenteric arteries. A slow infusion of heparin saline (10 μl/min: 50 units/ml) was maintained through this cannula. Renal blood flow was recorded electromagnetically using a 0.64 mm diameter flow probe attached to a flow meter (Carolina Model 501), two methods of approach being used:

Experiment A: from a mid-line abdominal approach together with PAH clearance

Following a mid-line abdominal incision, the alimentary canal was enclosed in a plastic bag to prevent fluid loss and the left adrenal vein (and sometimes the left adrenal artery) were ligated to allow the renal artery to be cleared, in order to receive the probe. The left ureter was cannulated. At time zero (which was regarded as the time at which the jugular vein had been cannulated) a loading dose of PAH (30 mg dissolved in 0.15 ml 1M NaOH and 0.35 ml 0.153 M NaCl) was injected into the jugular vein followed by a continuous infusion containing PAH (120 mg: 1.2 ml 1 M NaOH and 18.8 ml 0.153 M NaCl) delivered at 57 μl/min. After a 2 h equilibration period, blood and urine samples were collected in order to determine PAH clearance. The haematocrit was determined and plasma was obtained by centrifugation. Plasma proteins were precipitated by the method of Somogyi (1930) and both plasma and urine samples were assayed for PAH by a modification of the method of Smith, Finkelstein, Aliminosa & Graber (1945).

Experiment B: from a flank retro-peritoneal approach

NaCl (0.153 M) was infused into the jugular vein at 57 μl/min. A flank incision was made and the renal artery was cleared without disturbing the adrenal blood supply in order to receive the probe.

Whichever approach was used, care had to be taken when the probe was placed over the artery to ensure a good fit. The 3-dimensional position of the probe in relation to the artery was also important in order to prevent partial occlusion of the artery by the probe. Zero flow was established by occlusion of the artery at a point just distal to the probe, at intervals throughout each experiment. In a preliminary series of experiments stable recordings of renal blood flow with no drift of either its calibration or its zero could be obtained over a 3 h period provided a good position and fit had been obtained. Prostaglandin E_2 (Upjohn) was dissolved in heparin/saline (50 units/ml) and infused via the aortic cannula in a cumulative manner as used by Baer & McGiff (1979) in doses ranging from 0.01–20 μg/min. Each dose was infused for a 5 min period.

Results

Experiment A

The total renal blood flow measured over a 15 min period in 6 rats with the probe inserted from a mid-line abdominal approach was 6.9 ± 0.64 ml/min. Values for the effective renal blood flow calculated from PAH clearance and the haematocrit over the same period were 6.14 ± 0.51 ml/min, some 11% lower ($P < 0.05$) than the total renal blood flow. Such a difference would be expected since PAH is not completely extracted by the kidney although extraction studies were not performed. During a 15 min infusion of PGE_2 (0.1 μg/min), into the aorta, total renal blood flow increased ($P < 0.05$) while the calculated renal vascular resistance fell ($P < 0.02$) (see Table 1). There was no significant change in the systemic blood pressure. However, during the PGE_2 infusion the increase in effective renal plasma flow exceeded ($P < 0.05$) the increase in total renal blood flow by some 2.5 times (Figure 1). PAH clearance was not used therefore to assess the effects of PGE_2 on renal blood flow in any further experiments.

Using the probe again, inserted from a mid-line approach, dose-response experiments performed with 0.01–1.0 μg/min PGE_2 (i.a.) produced inconsistent changes in renal blood flow although vasodilatation was a prominent feature. The probe approach was therefore altered to a flank incision in a further experimental series to reduce surgical stress, temperature loss, fluid loss etc. with the hope of obtaining a more consistent response.

Experiment B

Using the flank approach, the total renal blood flow was significantly higher at 8.14 ± 0.40 ml/min

Table 1 The effect of prostaglandin E_2 (PGE_2, 0.1 μg/min) on renal blood flow, renal vascular resistance and blood pressure in the anaesthetized rat

	Control	*PGE_2* (0.1 μg/min)	*Paired* t *test*
Blood pressure (mmHg)	132 ± 5.8	131 ± 5.7	NS
Renal blood flow (ml/min)	6.95 ± 0.64	7.48 ± 0.65	$P < 0.05$
Renal vascular resistance (mmHg ml min^{-1})	19.5 ± 1.93	18.1 ± 1.87	$P < 0.02$

Flow measurements were made using the flow probe inserted from a mid-line approach. Each value indicates mean ± s.e.mean ($n = 6$).

($P < 0.05$) during a 15 min control period, while PGE_2 (0.1 μg/min, i.a.) produced a significantly greater increase in renal blood flow and a reduction in renal vascular resistance of about 2.5 times that obtained using the mid-line approach (Figure 2). Systemic blood pressure still remained unchanged. A recording of the effect of intra-aortic administration of PGE_2 on renal blood flow and arterial blood pressure is shown in Figure 3.

In order to compare the results of the present experiments with those of Baer & McGiff (1979), cumulative dose-response curves were performed

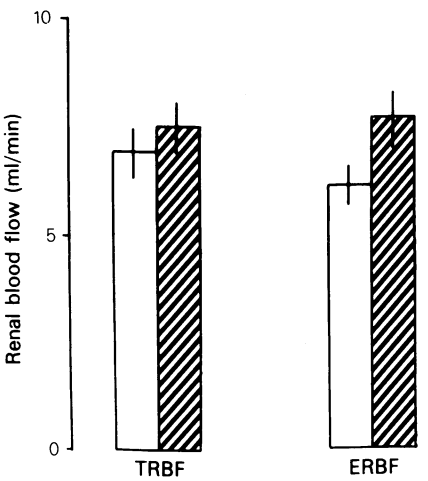

Figure 1 Effect of the method of renal blood flow measurement on prostaglandin E_2 (PGE_2)-induced renal vasodilatation in the rat. Renal blood flow was assessed simultaneously as either the total renal blood flow (TRBF), using the flow meter, or as the effective renal blood flow (ERBF) from the *p*-aminohippurate (PAH) clearance, both before (open columns) and during (hatched columns) a 15 min intra-aortic infusion of PGE_2 (0.1 μg/min), $n = 6$. Vertical bars represent the s.e.mean.

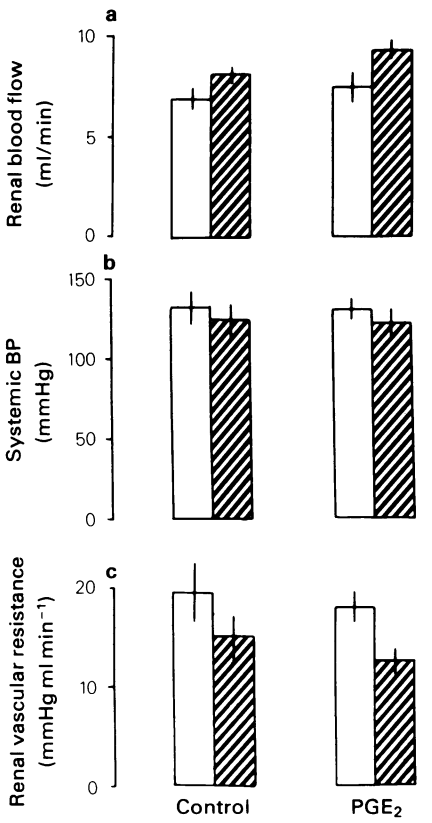

Figure 2 Effect of the extent of abdominal surgery on the sensitivity of the rat to prostaglandin E_2 (PGE_2)-induced renal vasodilatation. Renal blood flow (a) and systemic blood pressure (b) were measured with the flow probe inserted from either mid-line abdominal (open columns) or a flank (hatched columns) incision both before and during a 15 min intra-aortic infusion of PGE_2 (0.1 μg/min); $n = 6$ in both groups. Vertical bars represent the s.e.mean.

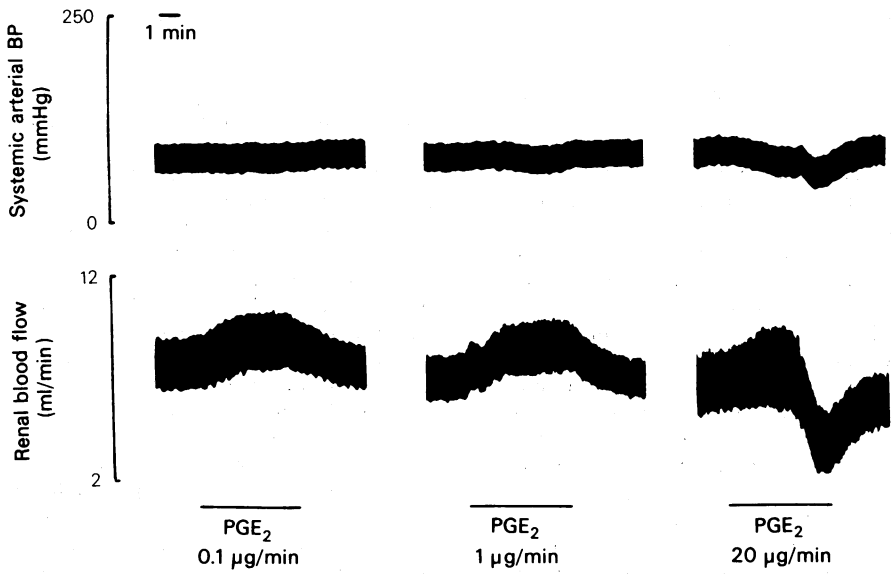

Figure 3 A recording of the dose-dependent response of intra-aortic prostaglandin E_2 (PGE_2) on renal blood flow and systemic blood pressure in the rat anaesthetized with pentobarbitone. Each dose was infused for a 5 min period.

using doses of PGE_2 of 0.01–20 μg/min; the results are presented in Figure 4. A maximal increase in renal blood flow was seen at 0.3 μg/min above which PGE_2 started to decrease sytemic blood pressure. A maximal decrease in renal vascular resistance was produced at about 3 μg/min while at 20 μg/min renal blood flow fell and renal vascular resistance increased.

Discussion

The small size of the rat presents some additional problems in assessing the effects of prostaglandins on renal blood flow compared to larger species such as the dog or rabbit, where PGE_2-induced renal vasodilatation has been consistently demonstrated (Nasjletti, Malik & Kauker, 1978). In particular, both the

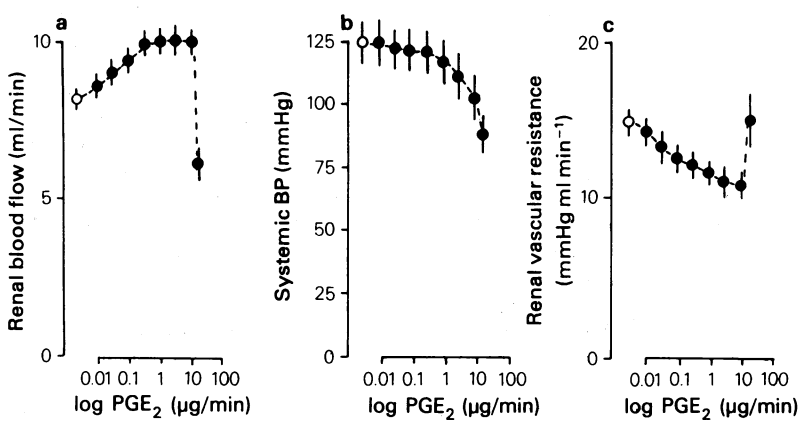

Figure 4 Cumulative dose-response curves of the effect of intra-aortic prostaglandin E_2 (PGE_2, ●) on renal blood flow (a), blood pressure (b) and calculated renal vascular resistance (c) in the rat. $n = 6$. Control values (○) were taken in the 15 min period before PGE_2 administration. Vertical bars are the s.e.mean.

continuous measurement of renal blood flow and drug delivery to the kidney by close renal arterial injection are difficult to achieve, which is why the isolated perfused preparation represents an attractive alternative.

In our experiments, the measurement of renal blood flow presented two major problems. Firstly the PAH clearance technique appeared to overestimate the renal dilator response to PGE_2 (Haylor & Lote, 1980b) when compared to flow probe measurements (Haylor & Towers, 1981). Although extraction studies have yet to be performed, it would seem possible that PGE_2 or a metabolite could alter the renal secretion of PAH. However, PAH clearance has proved extremely useful as an *in vivo* method of checking the calibration of the flow probe. Secondly, only a single size of probe (0.64 mm diameter) was found to be suitable for blood flow measurements in the rat renal artery. Both the fit and position of the probe were critical to prevent partial occlusion and zero drift. In an attempt to standardize the diameter of the arteries both the body weight and the degree of volume expansion of each rat were closely controlled.

PGE_2 was not delivered to the kidney by close arterial injection in the present experiments. The 'local' delivery of PGE_2 was obtained by the use of an aortic cannula, the tip of which was below the bifurcation with the superior mesenteric or coeliac arteries. The cannula tip was placed in this position to avoid local vasodilatation of the gastrointestinal tract and possible reduction in renal perfusion pressure leading to the stimulation of renin release. The concentrations of PGE_2 infused were estimated to include those which would produce renal arterial concentrations similar to those which have been shown to vasodilate the kidney in the dog (Fulgraff & Brandenbusch, 1974). For example, for the lowest dose at which we were able to demonstrate vasodilatation (10 ng/min), renal arterial concentrations were estimated to be approximately 300 pg/ml. An additional practical point was that ethanol, a common storage solvent for prostaglandins was excluded from these experiments since it has been shown to interfere with PGE-induced vascular responses at low concentrations *in vitro* (Altura & Edgarian, 1976).

The condition of the anaesthetized rat also appeared to influence the renal vascular changes produced by PGE_2. The use of a flank retro-peritoneal approach from which to position the probe avoided major abdominal surgery and the handling of the gastro-intestinal tract, with its concomitant loss of both heat and fluid. Generally, compared to the mid-line abdominal approach, such animals had a lower systemic blood pressure, a lower haematocrit, a lower renal vascular resistance and an increased ability to excrete an isotonic saline infusion. The use of the flank approach produced a marked increase in the sensitivity of the kidney to the renal vasodilator action of PGE_2.

The suggestion that the vasoconstrictor activity of PGE_2 in the rat kidney may represent an important species difference in the renal vascular response to prostaglandins was first put forward by Malik & McGiff (1975). Their hypothesis was based on comparative experiments in rat and rabbit isolated kidneys perfused at constant flow with Tyrode solution. In the rabbit isolated kidney, PGE_2 decreased the perfusion pressure (vasodilatation) as expected but in the rat isolated kidney, PGE_2 increased the perfusion pressure (vasoconstriction). Support for such a species difference in the rat has also been obtained *in vivo* by Gerber & Nies (1979) and Baer & McGiff (1979) who showed that PGE_2 could induce renal vasoconstriction in a variety of anaesthetized rat preparations. However, not all experiments concerned with the effects of prostaglandins on renal vascular resistance in the rat indicate that the E-series are vasoconstrictors. Support for the vasodilator activity of PGE_2 in the rat kidney was provided by Needleman, Marshall & Johnson (1974) who demonstrated that a mixture of PGE_1/E_2 could prevent the potentiation of vasoconstriction due to electrical stimulation by indomethacin. Baylis, Deen, Myers & Brenner (1976) have shown that PGE_1 can increase single nephron plasma flow to surface glomeruli in the Munich Wistar rat, while Dunham (1976) in a meetings abstract also suggested that PGE_2 can vasodilate the rat kidney. Following the clear demonstration in the present experiments of PGE_2-induced renal vasodilatation in the rat, the hypothesis put forward by Malik & McGiff (1975) needs to be reconsidered and other factors investigated which might explain the vasoconstriction produced by PGE_2 in the rat kidney.

In the rat, as in other species, PGE_2 can directly stimulate renin release (Suzuki, Franco-Saenz, Tan & Mulrow, 1981). PGE_2-induced renal vasoconstriction in the rat could therefore be mediated by angiotensin II. Schor, Ichikawa, Troy & Brenner (1979) were able to uncover the dilator activity of intra-aortic prostacyclin in the rat kidney using saralasin, the angiotensin II antagonist.

In the present experiments the response to PGE_2 was in fact biphasic, vasoconstriction being seen at the highest dose used. However, in the two major papers published on PGE_2-induced renal vasoconstriction *in vivo* by Baer & McGiff (1979) and Gerber & Nies (1979), the rats used were much more sensitive to this effect. Compared to our own experiments, the animals used by both groups had a 40% higher basal renal vascular resistance when calculated per g wet wt. of renal tissue at a similar level of blood pressure. Under such conditions a high output of endogenous prostaglandin may have obscured the

response to exogenously added PGE_2. Other differences included the use of higher doses of PGE_2 delivered less locally to the kidney either by bolus injection into the heart (Gerber & Nies, 1979) or by infusion into the aorta at a point above the origin of the superior mesenteric artery (Baer & McGiff, 1979).

Ex vivo, in the isolated preparation, PGE_2 is a much more potent vasoconstrictor than *in vivo*, and the response to other vasoconstrictor stimuli is also potentiated (Malik & McGiff, 1975). Stimulation of renin release is unlikely to explain PGE_2-induced vasoconstriction in the isolated perfused kidney of the rat due to a lack of substrate for angiotensin II. However, the rat isolated kidney perfused at constant flow with a physiological solution represents a poor model of a functioning kidney. The glomerular filtration rate is low and only approximately 50% of the filtered load is reabsorbed. This is mainly due to the lack of plasma protein in the perfusate which normally provides the oncotic force for sodium and water reabsorption in the peritubular capillaries (Rose, 1977). Another result of the lack of plasma protein is oedema which is a major factor contributing to the stable basal perfusion pressure of such preparations (Little & Cohen, 1974). Preliminary experiments in our own laboratory using the rat isolated perfused kidney indicate that PGE_2-induced vasoconstriction may well develop *ex vivo* (Haylor & Pegg, unpublished observations). It is of interest to note that in the superior mesenteric vascular bed from the rat, PGE also produces vasoconstriction in the isolated perfused preparation *ex vivo* (Horrobin, Manku, Karmali, Nassar & Davies, 1974), while vasodilatation is seen *in vivo* (Weiner & Kaley, 1969).

If in the rat, PGE_2-induced renal vasoconstriction is not the result of an important species difference, then the conclusions drawn from experiments based on such a hypothesis may now have to be reconsidered. For example, Armstrong, Blackwell, Flower, McGiff, Mullane & Vane (1976) suggested that the renal synthesis of PGE_2 may be involved in the development of high blood pressure in the New Zealand strain of hypertensive rat. The evidence put forward to support this suggestion was that such rats had (i) a reduced ability to metabolize PGE_2 elevating its concentration, (ii) an increased sensitivity to the renal vasoconstrictor effect of PGE_2, (iii) an increased ability to potentiate vasoconstriction due to other agents; Gerber & Nies (1979) have also suggested that the reduction in renal blood flow produced in the rat by inhibitors of cyclo-oxygenase, must be due to a reduction in vasodilator prostacyclin, since it could not be mediated by a decrease in vasoconstrictor PGE_2. Finally several groups i.e. Greiner, Kemper, Osswald & Schmidtz (1977) have linked the ability of PGE_2 to constrict the kidney to a reduction in sodium excretion and thereby to the effects of anti-inflammatory acids on urine composition in the rat. However, under the conditions in which we could demonstrate PGE_2-induced renal vasodilatation, PGE_2 increases sodium excretion and urine flow, while urine osmolality is reduced (Haylor & Lote, 1980b). PGE_1 also has diuretic properties in the rat (Benscath, Kottra & Csaszar, 1979). Thus, together with its ability to decrease renal vascular resistance, the effects of PGE_2 on urine composition indicate that in the rat, the renal properties of PGE_2 are similar to those described in both the dog (Fulgraff & Brandenbusch, 1974) and in the rabbit (Fine & Trizna, 1977).

An account of part of the information in this paper has been presented to the Physiological Society (Haylor & Towers, 1981).

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