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RENAL FUNCTION AND RENAL VENOUS PROSTAGLANDIN CONCENTRATIONS DURING DIFFERENT STAGES OF EXPERIMENTAL RENAL HYPERTENSION IN THE RAT

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1 Renal hypertension was produced in rats and the changes in renal function, renal venous prostaglandin E_2 and $F_{2\alpha}$ concentrations and secretion rates were studied at various times.

2 Renal plasma flow transiently fell in the ischaemic kidney 2 weeks after clamping, whilst that of the other kidney did not change. Glomerular filtration rate remained constant in both kidneys throughout the entire study.

3 Prostaglandins E_2 and $F_{2\alpha}$ concentrations rose in the venous plasma from the ischaemic kidney, but did not change in the other kidney and appeared to be inversely related to renal plasma flow.

4 Calculated secretion rate of both prostaglandins fell in the ischaemic kidney and did not change in the other kidney.

5 Clamping the second kidney, two weeks after the first, caused a further elevation in blood pressure, a fall in renal plasma flow and a fall in prostaglandin secretion rate in both kidneys.

6 The implications of these prostaglandin changes are discussed.

Introduction

Acute renal ischaemia increases the concentration of prostaglandin E-like material in renal venous blood of the dog and this has been interpreted as a rise in output of renal prostaglandins (McGiff, Crowshaw, Terragno, Lonigro, Strand, Williamson, Lee & Ng, 1970). Such a mechanism may protect the kidney from the antinatriuretic/vasoconstrictor influence of the renin and sympathetic systems (Lonigro, Terragno, Malik & McGiff, 1973).

The contralateral renal prostaglandins have also been assigned a role. The contralateral kidney of the Goldblatt hypertensive dog has an antihypertensive function, independent of excretion (Grollman, Muirhead & Vanatta, 1949). Such a system is also present in the rat kidney, when perfused at hypertensive pressures (Tobian, Schonning & Seefeldt, 1964). Lee (1973) believes that the renal prostaglandins may play a role.

No study has yet examined renal venous prostaglandin concentrations in chronic renal ischaemia of experimental origin nor attempted to evaluate the rate of output of renal prostaglandins.

In this study we examined renal function and renal venous prostaglandin E_2 and $F_{2\alpha}$ concentrations of both kidneys of rats at various stages after clamping the left renal artery and also after clamping both renal arteries.

Methods

One hundred and thirty six male and female Wistar rats, of approximately similar size and fed on a standard laboratory diet, with water *ad lib.*, were divided into seven experimental groups, 30 rats serving as controls. Renal hypertension was induced by clipping the left renal artery with a small silver clip (first operation) and in some rats, clipping the right renal artery (second operation) two weeks later. The rats were killed at various stages after clipping as follows: group 1, 20 rats killed 1 week after the first operation; group 2, 20 rats killed 2 weeks after the first operation; group 3, 20 rats killed 3 weeks after the first operation; group 4, 20 rats killed 4 weeks after the first operation; group 5, 20 rats killed 1 week after the second operation; group 6, 20 rats killed 2 weeks after the second operation and group 7, 16 rats killed 10

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weeks after the second operation (the chronic hypertensive group).

The rats were weighed weekly and arterial blood pressure was measured by the indirect tail-cuff method using a Rat Blood Pressure Monitor (Huntingdon Instruments, England).

From each group, 6 to 8 rats were used for the estimation of bilateral renal function, namely renal plasma flow (RPF) and glomerular filtration rate (GFR) and the remaining rats were used for the estimation of renal venous prostaglandin concentrations.

RPF and GFR were estimated by means of the clearances of para-aminohippurate (PAH) and of inulin respectively. The rats were anaesthetized with pentobarbitone (40 mg/kg i.p.) and tracheotomized. The left subclavian vein was catheterized for the infusion of the clearance solution at a rate of 0.05 ml/min by means of a motor driven syringe (Braun). The clearance solution was composed of 1% inulin, 1% PAH and 2% Na_2SO_4 dissolved in 0.9% w/v NaCl solution and buffered to pH 7.4 with bicarbonate.

Both ureters were catheterized after the method of Mercer (1971) and a 10 min urine sample was collected from each ureter 50 min after the infusion had begun. After heparinization (1000 u/kg), blood samples (0.5 ml) were removed from a carotid artery catheter 50 and 60 min after the start of the infusion, for the calculation of mean plasma PAH and inulin concentrations, which we tried to hold at about 7 and 30 mg% respectively.

The blood was centrifuged in Eppendorf tubes and 0.2 ml of plasma removed and subjected to plasma protein precipitation with Somogyi reagent. The urine was carefully transferred to a volumetric flask and diluted to 100 ml. Diluted urine and protein-free plasma were analysed for inulin and PAH using a resorcinol method for the former and *N* (1-napthyl)-ethylene diamine as a coupling reagent for the latter and both were compared with standard solutions in a spectrophotometer (Bausch and Lomb, SP 20, U.S.A.).

The clearances of PAH and inulin were calculated and expressed in terms of body weight. The extraction ratio for PAH was not taken into account. Girndt & Ochwadt (1969) have shown that 4 weeks after clamping a renal artery, PAH extraction was unaltered in both the clamped and the contralateral kidneys (0.84 approx.).

Blood samples for the estimation of prostaglandins were drawn from the renal veins of anaesthetized rats after a midline laparotomy and catheterization of the inferior vena cava. Within each group, the left and right renal venous blood samples were pooled separately (final volume about 10 ml). A known amount of deuterium isotope, 1 μg d_4 prostaglandin E_2 and 500 ng d_4 prostaglandin $F_{2\alpha}$ was added to each plasma sample and the prostaglandins were extracted and subjected to silicic acid column chromatography (Poyser, 1972). Methyl ester/methoxime/trimethylsilyl and methyl ester/trimethylsilyl derivatives were made of the extracted prostaglandins E_2 and $F_{2\alpha}$ respectively (Thompson, Los & Horton, 1970; Blatchley, Donovan, Horton & Poyser, 1972). Using multiple ion detection (Finnigan 3000D mass

Table 1 Changes in blood pressure (mmHg) and prostaglandin (PG) level (ng/ml) in renal venous blood of control and renal hypertensive rats

Group	(n)	Blood pressure		PGE_2		$PGF_{2\alpha}$	
		Systolic	Diastolic	Left renal vein	Right renal vein	Left renal vein	Right renal vein
Controls	(30)	126 ± 2.73	100 ± 2.55	4.0	3.8	2.7	2.2
1	(20)	139 ± 5.17	111 ± 4.69	4.4	2.7	3.7	2.1
		$P<0.05$	$P<0.05$				
2	(20)	142 ± 4.71	112 ± 3.91	5.6	3.6	4.3	2.7
		$P<0.01$	$P<0.02$				
3	(20)	148 ± 5.13	123 ± 4.26	4.6	2.6	3.2	2.0
		$P<0.001$	$P<0.001$				
4	(20)	148 ± 5.62	118 ± 4.14	3.2	5.0	1.2	2.9
		$P<0.001$	$P<0.001$				
5	(20)	152 ± 4.57	121 ± 3.87	3.0	4.5	1.6	4.4
		$P<0.001$	$P<0.001$				
6	(20)	193 ± 7.61	153 ± 7.84	4.7	6.2	2.7	3.1
		$P<0.001$	$P<0.001$				
7	(16)	183 ± 5.55	150 ± 5.14	2.9	4.5	1.9	3.3
		$P<0.001$	$P<0.001$				

n is the number of rats in each group. Values are mean ± s.e. Groups 1 to 4 had clipped left kidneys. Groups 5 to 7 had both kidneys clipped.

spectrometer), the ratio of proton to deuterium peaks of the prostaglandin derivatives was obtained and compared with a standard calibration curve over the range of 1 to 1000 ng of protium. (Hensby & Naylor, 1974.)

Statistical analysis of the results was performed by Student's two-tailed t test, except for the renal function results, where a one-tailed t test was used (Dixon & Massay, 1969). Values are expressed as mean ± s.e. and only probabilities less than 0.05 were accepted as being statistically significant.

Results

Development of hypertension

One week after the production of renal ischaemia (groups 1 to 4), there was a significant rise in blood pressure, which reached a peak by the third week (group 3). Systolic blood pressure rose from 126 ± 2.73 mmHg to 148 ± 5.13 mmHg ($P < 0.001$) and diastolic pressure increased from 100 ± 2.55 mmHg to 123 ± 4.26 mmHg ($P < 0.001$) three weeks after clamping (group 3) (Table 1).

Cardiac hypertrophy also occurred over this period as seen by the rise in the heart/body weight ratio (Table 2). The left kidney/body weight ratio rose in group 1 rats but fell in group 2 and was not significantly different from control in later groups. The right kidney hypertrophied in each of the unilaterally clamped groups, except for group 2 (Table 2).

An inverse relationship between renal mass and the level of systemic hypertension was noted in almost all cases.

During ischaemia of the right kidney, as well as of the left, (groups 5, 6 and 7), systolic and diastolic pressures rose further, within the range 126/100 to 183/150 mmHg 10 weeks after the second operation (the chronic hypertensive group).

The left, earlier ischaemic kidney, was now firm and shrunken, especially in the chronic group (group 7). The right kidney, which had previously been hypertrophied before the second operation, was now not significantly different from control. Cardiac hypertrophy was very marked in these bilaterally ischaemic rats.

Renal function changes

After unilateral renal ischaemia, RPF of the clamped kidney fell significantly 2 weeks after clamping (group 2), from 8.23 ± 1.28 ml min^{-1} kg^{-1} to 4.28 ± 1.55 ml min^{-1} kg^{-1} ($P < 0.05$) and subsequently rose again to control values (Table 3). The contralateral kidney showed no significant change in RPF at this time. Due to the well maintained GFR, the filtration fraction (FF) rose significantly only in the ischaemic kidneys of group 2 rats.

On clamping the right kidney, RPF fell 2 weeks later in group 6 from 9.12 ± 1.31 ml min^{-1} kg^{-1} to 3.43 ± 0.25 ml min^{-1} kg^{-1} ($P < 0.025$) (Table 3). Left RPF also fell, from 8.23 ± 1.29 ml min^{-1} kg^{-1} to 4.44 ± 0.44 ml min^{-1} kg^{-1} ($P < 0.025$). This fall was also significant ($P < 0.0005$) when compared with group 4, which had undergone exactly the same procedures and time course, except for the second

Table 2 Average organ/body weights in control and experimental rats.

Group	(n)	*Body weight (g)*	*Heart/body weight*	*Left kidney/ body weight*	*Right kidney/ body weight*
Controls	(30)	257 ± 12	32.4 ± 0.6	35.2 ± 0.5	35.9 ± 0.6
1	(20)	226 ± 8	36.7 ± 1.2	39.8 ± 1.8	42.7 ± 2.0
			$P < 0.01$	$P < 0.02$	$P < 0.001$
2	(20)	228 ± 15	35.4 ± 0.7	32.6 ± 1.2	35.5 ± 1.4
			$P < 0.01$	$P < 0.05$	$P > 0.5$
3	(20)	248 ± 8	34.2 ± 0.5	35.3 ± 1.8	40.4 ± 1.2
			$P < 0.05$	$P > 0.5$	$P < 0.01$
4	(20)	212 ± 11	38.5 ± 1.2	34.8 ± 1.3	41.3 ± 1.3
			$P < 0.001$	$P > 0.5$	$P < 0.001$
5	(20)	292 ± 15	33.4 ± 1.4	31.3 ± 1.1	35.5 ± 1.2
			$P > 0.5$	$P < 0.01$	$P > 0.5$
6	(20)	188 ± 13	41.5 ± 1.4	31.6 ± 1.9	40.1 ± 2.3
			$P < 0.001$	$P < 0.05$	$P > 0.05$
7	(16)	187 ± 16	41.4 ± 2.1	30.2 ± 2.1	39.8 ± 2.7
			$P < 0.001$	$P < 0.02$	$P > 0.1$

Body weights are expressed in grams. Organ/body weights are expressed $\times 10^{-4}$. n is the number of rats in each group. Values are mean ± s.e. Groups 1 to 4 had clipped left kidneys. Groups 5 to 7 had both kidneys clipped.

operation. As GFR was so well maintained, FF rose in the left kidneys of group 6. In group 7, the chronic hypertensive group, no difference was detected between either kidney and control.

Prostaglandins E_2 and $F_{2\alpha}$ renal venous concentrations

After the first operation, left renal venous prostaglandin E_2 and $F_{2\alpha}$ concentrations were higher than control, whereas the concentrations in the right renal venous plasma were similar or slightly lower than control, except for group 4 (see Table 1, groups 1 to 4).

After the second operation, prostaglandins E_2 and $F_{2\alpha}$ concentrations rose in the right renal venous plasma 1 week later (group 5). By the second week (group 6), prostaglandin E_2 had risen even more in the right renal venous plasma but prostaglandin $F_{2\alpha}$ had fallen, although still above control. Both prostaglandins rose transiently in the left renal venous plasma. In the chronic hypertensive rats (group 7), right renal venous prostaglandin E_2 and $F_{2\alpha}$ concentrations were higher than control, in contrast to the left renal venous concentrations, which were lower than control.

Prostaglandin secretion rates

Secretion rate of each prostaglandin may be calculated from the product of the total mean RPF and the prostaglandin concentration for each group since prostaglandins appear to be released on synthesis (Ånggård, Bohman, Griffin, Larsson & Maunsbach, 1972). This assumes that all the arterial prostaglandins presented to the kidney are cleared in one passage because of the high activity of the metabolizing enzyme, 15 hydroxy prostaglandin dehydrogenase, in the renal cortex (Ånggård, Larsson & Samuelsson, 1971). The clamped kidney showed a fall in secretion rate of prostaglandin E_2 from 8.68 ng/min to 6.24, 5.57, 8.51 and 4.84 ng/min in groups 1, 2, 3 and 4 respectively. Prostaglandin $F_{2\alpha}$ secretion rate also fell, from 5.86 ng/min to 5.25, 4.28, 5.92 and 1.81 ng/min in each of the above respective groups (see Table 4). The contralateral kidney of these groups showed no change in secretion rate of either prostaglandin. After ischaemia of the right kidney, secretion rate of both prostaglandins began to fall in the right kidney and continued falling in the left kidney (groups 5, and 6). A subnormal secretion rate of both prostaglandins existed in the two kidneys of the chronic hypertensive group (group 7).

Discussion

Four weeks after clamping a renal artery, the resultant hypertension was associated with normal PAH and inulin clearances in both the clamped and contralateral kidneys of rats (Girndt & Ochwadt, 1969). However, medullary blood flow was elevated in the contralateral kidney as determined by the ^{86}Rubidium method. Our results are essentially in agreement with these findings. However, at variance with this, Kramer & Ochwadt (1974) reported that rat kidneys clamped 6 to 10 weeks previously, had lower PAH and inulin clearances in comparison with the contralateral kidney.

Table 3 Glomerular filtration rate and renal plasma flow

Group	(n)	*Glomerular filtration rate*		*Renal plasma flow*		*Filtration fraction*	
		Left kidney	*Right kidney*	*Left kidney*	*Right kidney*	*Left kidney*	*Right kidney*
Controls	(10)	1.80±0.25	2.20±0.28	8.23±1.29	9.12±1.31	0.24±0.03	0.27±0.05
1	(8)	1.50±0.26	2.66±0.28	6.34±1.32	10.14±1.25	0.28±0.03	0.30±0.04
		$P>0.2$	$P>0.05$	$P>0.05$	$P>0.2$	$P>0.2$	$P>0.2$
2	(8)	1.57±0.39	2.41±0.59	4.28±1.55	8.56±2.92	0.41±0.07	0.38±0.05
		$P>0.2$	$P>0.2$	$P<0.05$	$P>0.2$	$P>0.05$	$P>0.1$
3	(8)	—	—	7.46±1.12	9.00±1.39	—	—
				$P>0.2$	$P>0.2$		
4	(8)	1.88±0.18	2.09±0.33	7.59±0.35	10.95±2.25	0.21±0.02	0.28±0.06
		$P>0.02$	$P>0.2$	$P>0.2$	$P>0.2$	$P>0.5$	$P>0.5$
5	(8)	1.62±0.15	2.09±0.23	5.85±0.95	7.14±0.89	0.30±0.02	0.31±0.01
		$P>0.2$	$P>0.2$	$P>0.05$	$P>0.05$	$P>0.05$	$P>0.2$
6	(7)	1.84±0.27	1.45±0.35	4.44±0.44	3.43±0.25	0.42±0.09	0.45±0.14
		$P>0.2$	$P>0.05$	$P<0.025$	$P<0.025$	$P\geqslant0.05$	$P>0.2$
7	(6)	1.50±0.16	1.68±0.19	5.49±0.79	6.30±0.75	0.34±0.06	0.37±0.08
		$P>0.2$	$P>0.05$	$P>0.05$	$P>0.05$	$P>0.1$	$P>0.1$

Values are mean ± s.e. Clearances are expressed in ml min^{-1} kg^{-1} body weight. *n* is the number of rats in each group. Groups 1 to 4 had clipped left kidneys. Groups 5 to 7 had both kidneys clipped.

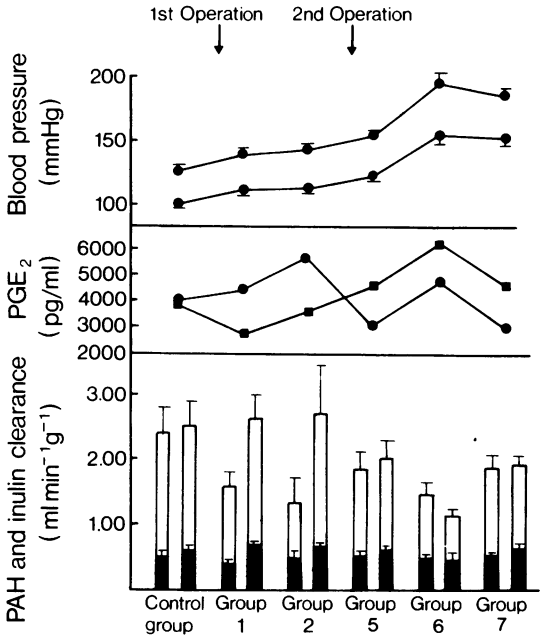

Figure 1 Systolic and diastolic blood pressures (mmHg), renal venous prostaglandin E_2 concentrations of the left (●) and right (■) kidneys and RPF (white bars) and GFR (black bars) of the left and right kidneys respectively in each pair, at different stages of hypertension. Values are mean ± s.e.

McGiff *et al.* (1970) propose that the kidney releases prostaglandin-like material in response to reduced renal blood flow caused by constricting the renal artery. Herbaczynska-Cedro & Vane (1973) obtained a rise in renal venous prostaglandin E-like material on reducing perfusion pressure and renal blood flow, in the pump perfused canine kidney and suggested that increased secretion of prostaglandin E mediated autoregulation of blood flow since indomethacin abolished autoregulation and the prostaglandin release. However, this concept may be no longer tenable in the intact, naturally perfused kidney (Owen, Ehrhart, Weidner, Haddy & Scott, 1974; Venuto, O'Dorisio, Ferris & Stein, 1975; Anderson, Taher, Cronin, McDonald & Schrier, 1975). Using essentially the same approach as Herbaczynska-Cedro & Vane, autoregulation was found to be resistant to meclofenamate (10 mg/kg, i.v.) although absolute flow fell (Dighe, Hall, Smith & Ungar, unpublished results). It remains to be seen whether rat kidney behaves in a similar manner.

Renal prostaglandins may have a natriuretic role and protect the kidney against the vasoconstrictor/antidiuretic influence of the renin and sympathetic systems (McGiff & Nasjletti, 1973; Lonigro, *et al.*, 1973). However, in the isolated kidney of the rat, unlike other species, prostaglandin E_2 potentiates renal sympathetic nerve stimulation and at higher doses causes vasoconstriction similar to that induced by prostaglandin $F_{2\alpha}$ (Malik & McGiff, 1975).

We have shown that prostaglandin E_2 and $F_{2\alpha}$ concentrations rise in the plasma from ischaemic kidneys, whereas the contralateral renal venous concentrations remain unaltered or may perhaps fall slightly. As Figure 1 shows, there is an inverse relationship between prostaglandin E_2 concentration and RPF for both kidneys. This may either be a result or a cause of the blood flow changes. Thus an increase in prostaglandin E_2 or $F_{2\alpha}$ concentrations may reduce RPF by the mechanism described by Malik & McGiff (1975) and conversely a fall in RPF may be due to a fall in prostaglandin concentration.

Alternatively, the concentration changes may be a consequence of flow changes. This is supported by the findings of Beckman & Zehr (1975) in the dog. On halving renal blood flow, renal venous prostaglandin

Table 4 Estimated prostaglandin (PG) secretion rates (ng/min) in kidneys from control and experimental rats

	PGE_2		$PGF_{2\alpha}$	
Group	*Left kidney*	*Right kidney*	*Left kidney*	*Right kidney*
Control	8.68	8.71	5.86	5.04
1	6.24	6.82	5.25	5.31
2	5.57*	8.06	4.28*	6.05
3	8.51	6.65	5.93	5.11
4	4.84	11.41	1.81	6.62
5	5.62	9.25	2.64	9.04
6	4.13*	5.51*	2.37*	2.75*
7	3.08	6.67	2.02	4.81

Values were obtained from the product of total mean RPF of each group and the respective prostaglandin concentration and are expressed in nanograms per minute. Groups 1 to 4 had left kidneys clipped. Groups 5 to 7 had both kidneys clipped.

* Signifies secretion rates where a statistically significant fall in RPF was observed.

E_2, as detected by radioimmunoassay, rose, but calculated secretion rate fell. We have also obtained similar results in the pump perfused canine kidney (Dighe, Hall, Smith and Ungar, unpublished observations). This is in contrast to what is generally believed and demonstrates the possible fallacy of equating concentration changes with secretion changes especially when concentration and flow change in an inverse manner as they do in the clamped kidney.

Our results also suggest that secretion rates of prostaglandin E_2 and $F_{2\alpha}$ fall in the chronically ischaemic rat kidney, with little change in the contralateral kidney. It must be borne in mind that our secretion figures were obtained from two groups of rats, namely those used for prostaglandin estimations and those for renal function tests, but there is no reason why these rats should not have been representative.

A reduced release of prostaglandin E-like material by the isolated kidney of one kidney Goldblatt rats, perfused at constant flow and challenged with pressor doses of noradrenaline, has been reported (Leary, Ledingham & Vane, 1974). Reduced synthetic capacity of prostaglandins was also found in the kidneys of renal and spontaneously hypertensive rats (Sirvios & Gagnon, 1974).

In contrast, using radioimmunoassay, Jaffe, Parker, Marshall & Needleman (1972) observed a rise in prostaglandin E in both the clamped and contralateral kidneys of chronic hypertensive rats. Arterial levels were also raised, suggesting a genuine increase in synthesis, but not necessarily from the kidney.

In earlier investigations (Somova, 1971; 1973) an increase in prostaglandin E-like material was seen in the ischaemic kidney of the rat during the acute phase of hypertension, with a decrease in the chronic stages.

The contralateral kidney has an endocrine antihypertensive role, distinct from excretion as demonstrated by Grollman *et al.* (1949) and Kolff (1958) in the dog. Similar findings have been reported in the rat kidney, when introduced into the circulation of the hypertensive rat (Tobian *et al.*, 1964). Muirhead, Germain, Brooks & Stephenson (1973) have attributed this property to the renal medulla and probably to the renal interstitial cells, which have been shown to synthesize prostaglandins. Rabbit renomedullary lipid is antihypertensive in rat (Muirhead, Leach, Daniels & Hinman, 1968) and rat renal medulla, especially that from hypertensive rats, is antihypertensive when implanted into hypertensive rats (Tobian & Azar, 1971). However, the antihypertensive principle may not be the renal prostaglandins but the neutral lipid (ANRL), which the renal interstitial cells also elaborate (Muirhead, Leach, Germain, Byers & Armstrong, 1974).

Certainly our results do not agree with the concept that the antihypertensive function of the kidney is due to an enhanced release of prostaglandin E_2 since secretion rate in the contralateral kidney does not change.

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