Enhanced Renal Prostaglandin Production in the Dog
II. EFFECTS ON INTRARENAL HEMODYNAMICS
By Lucas C. T. Chang, Jacek A. Splawinski, John A. Oates, and Alan S. Nies

ABSTRACT
The effects of enhanced endogenous production of prostaglandins by the kidney on the distribution of blood flow in the renal cortex were assessed by infusing sodium arachidonate, the precursor of the renal prostaglandins, into one renal artery of the dog. The changes produced with arachidonate (3 x 10^{-6} g/kg min^{-1} and 10^{-5} g/kg min^{-1}) were compared with those produced by infusions of prostaglandin (PG) E_2 (10^{-7} g/kg min^{-1}) and PGF_{2a} (3 x 10^{-7} g/kg min^{-1}) into one renal artery. Distribution of renal blood flow was measured by the radioactive microsphere technique. Sodium arachidonate caused an increase in blood flow to the inner cortical zones with no change in flow to the nephrons in the outermost quarter of the cortex. PGE_2 increased flow to all cortical zones, and PGF_{2a} produced no change in flow. Since arterial blood pressure did not change, changes in vascular resistance were reciprocal to changes in flow. Thus, vascular resistance fell in the inner cortical regions but not in the outer regions, with arachidonate infusions and in all regions of the cortex with PGE_2 infusions; no changes were seen with PGF_{2a} infusions. These data indicate that prostaglandin formed endogenously in the kidney affects the vascular resistance of only the inner cortical nephrons; the data thus support the hypothesis that renal prostaglandins are one mediator of renal autoregulation of blood flow.

KEY WORDS arachidonic acid microspheres renal autoregulation regional renal vascular resistance juxtamedullary nephrons renal blood flow

The functional significance of the renal prostaglandins is still uncertain. It has been postulated that these unsaturated fatty acids are important in renal function, renal blood flow, or both (1, 2). Most of the data have been derived from experiments in which prostaglandins are infused into the renal arteries or the production of prostaglandins is reduced by inhibitors of prostaglandin synthetase. We have shown that another approach to defining possible physiological roles for renal prostaglandins is to increase endogenous prostaglandin production occurring at the sites of prostaglandin synthetase by infusing the fatty acid precursor, arachidonic acid, into the renal artery of the dog (3). When the availability of the substrate for prostaglandin synthetase is increased, prostaglandins are produced by the kidney itself. Such increased endogenous prostaglandin production occurring at the sites of prostaglandin synthetase results in an increased urinary sodium and potassium excretion and small changes in renal blood flow; in contrast, exogenous PGE_2, which produces similar increases in electrolyte excretion, induces much larger increases in renal blood flow and exogenous PGF_{2a} causes no changes in total renal blood flow or electrolyte excretion.

One postulated role for prostaglandins is renal autoregulation (4). When renal perfusion is decreased, renal blood flow is maintained by a decrease in the vascular resistance. This autoregulation does not occur uniformly in the cortex: there is a preferential decrease in resistance in the inner cortical nephrons (5, 6). Associated with the autoregulation is an increase in the prostaglandin content of renal venous blood, and if prostaglandin synthesis is blocked renal autoregulation is impaired (4).

If prostaglandins are involved in autoregulation, then the change in renal resistance with endogenous prostaglandin production should be in the inner cortical nephrons. Thus, we wanted to determine whether the blood flow to different zones of the cortex was influenced by endogenous prostaglandin synthesis produced by arachidonate infusion at rates of infusion which alter renal function and to compare these changes with those produced by PGE_2 and PGF_{2a}.

Circulation Research, Vol. 36, January 1975
Methods

A total of 12 mongrel dogs of either sex were used. The dogs were anesthetized with sodium thiopental which was prepared as a 0.1% solution and infused intravenously at a rate that maintained a light plane of anesthesia. The trachea was intubated, and the dogs were ventilated with a Harvard respiration pump. Catheters were placed in the left ventricle via the right carotid, the lower aorta via the femoral artery, and the vena cava via the femoral vein. Through a midline abdominal incision, one renal artery was cannulated with a 23-gauge needle, flow probes were placed around one or both renal arteries, and bilateral ureteral catheters were inserted. Systemic arterial blood pressure was monitored with a Hewlett-Packard 1280 pressure transducer (Hewlett-Packard Co.) and renal blood flow with a Statham SP2202 flowmeter. Accuracy of the electronic zero was verified by a brief mechanical occlusion of the renal artery prior to and following each experiment. All recordings were on a Hewlett-Packard 1788 direct-writing recorder.

The experiments were started when urine flow was stable. One group of six dogs received renal arterial infusions of saline, PGE_2, and PGF_2α in a random, balanced design to eliminate any order effect. PGE_2 was infused at 10^{-7} g/kg min^{-1}, and PGF_2α was infused at 3 \times 10^{-7} g/kg min^{-1}. Infusions of both prostaglandins and of saline were given at 0.118 ml/min for 10 minutes, and each experimental infusion was separated by 15 minutes during which time the renal artery was infused with saline. The second group of dogs similarly received saline and sodium arachidonate at 3 \times 10^{-6} g/kg min^{-1} and 10^{-7} g/kg min^{-1} in random order. All doses were chosen based on our previous study (3) which indicated that such doses produce renal functional and hemodynamic changes. At the end of each 10-minute experimental infusion, the distribution of renal blood flow was measured with the microsphere technique using a batch (500,000–1,500,000) of 15 ± 5μm spheres (3M Company) labeled with ^{14}Ce, ^{51}Cr, or ^{85}Sr injected into the left ventricle over 15 seconds. At the end of the experiment, the dogs were killed with an excess of anesthetic, and the kidneys were dissected. The renal cortex was divided into four zones of equal thickness as described by McNay and Abe (5) with zone 1 being the outermost zone and zone 4 being the juxtamedullary zone. The sections were counted in a juxtamedullary zone. Resistance was calculated by dividing arteriolar blood pressure by zonal blood flow. The renal cortex was divided into four zones of equal thickness as described by McNay and Abe (5) with zone 1 being the outermost zone and zone 4 being the juxtamedullary zone. The sections were counted in a juxtamedullary zone. Resistance was calculated by dividing arteriolar blood pressure by zonal blood flow. The thickness of each zone was calculated assuming the kidney to be an ellipsoid (5). The counts from each zone were compared with the total counts in the kidney to determine the zonal distribution of blood flow. The methods for determining the counts from each isotope in the presence of the other isotopes have been published previously (7). Zonal blood flow was determined by multiplying the fractional distribution of flow to each zone by the total renal blood flow measured by the electromagnetic flowmeter. Zonal blood flow is presented as flow/100 g tissue for comparison of the different zones. Resistance was calculated by dividing arterial blood pressure by zonal blood flow.

The results for each intra-arterial infusion of prostaglandin or arachidonate were compared with those obtained during the control saline infusion in the same kidney, and statistics were calculated using Student's t-test for paired observations.

Sodium salts of PGE_2 and arachidonic acid (Nuchek Prep Inc.) were prepared fresh each day as described previously (3). PGF_2α was obtained as the tromethamine salt from the Upjohn Company.

Results

PGE_2 and sodium arachidonate had significant effects on renal hemodynamics, whereas PGF_2α had no significant effects. Distribution of renal blood flow was shifted to the juxtamedullary cortex during infusion of either PGE_2 or arachidonate (Tables 1 and 2), and the changes with arachidonate were dose dependent. PGE_2 produced much more marked changes in total renal blood flow (+60 ± 10%) (Fig. 1) than did arachidonate (+15 ± 4%) (Fig. 2), and despite the shift in fractional distribution of blood flow PGE_2 increased actual flow to all zones of the cortex (Fig. 1). In contrast, arachidonate produced dose-dependent increases in actual flow only to the inner cortical zones with no change in flow to zone 1 (Fig. 2). No changes were

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**Table 1**

Fractional Distribution of Renal Blood Flow with Prostaglandins

<table>
<thead>
<tr>
<th>Zone</th>
<th>Control (Fraction of RBF)</th>
<th>PGF_2α (Change)</th>
<th>PGF_2α (Change)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zone 1</td>
<td>0.402 ± 0.028</td>
<td>-0.093 ± 0.015</td>
<td>+0.014 ± 0.034</td>
</tr>
<tr>
<td>Zone 2</td>
<td>0.290 ± 0.014</td>
<td>-0.062 ± 0.007</td>
<td>+0.005 ± 0.008</td>
</tr>
<tr>
<td>Zone 3</td>
<td>0.169 ± 0.011</td>
<td>+0.046 ± 0.008</td>
<td>+0.001 ± 0.010</td>
</tr>
<tr>
<td>Zone 4</td>
<td>0.092 ± 0.017</td>
<td>+0.034 ± 0.007*</td>
<td>-0.007 ± 0.015</td>
</tr>
</tbody>
</table>

Values are means ± SE. RBF = renal blood flow. *P < 0.01.

**Table 2**

Fractional Distribution of Renal Blood Flow with Arachidonate

<table>
<thead>
<tr>
<th>Zone</th>
<th>Control (Fraction of RBF)</th>
<th>Arachidonate (Change)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zone 1</td>
<td>0.462 ± 0.029</td>
<td>-0.027 ± 0.008*</td>
</tr>
<tr>
<td>Zone 2</td>
<td>0.298 ± 0.013</td>
<td>+0.006 ± 0.004</td>
</tr>
<tr>
<td>Zone 3</td>
<td>0.150 ± 0.012</td>
<td>+0.007 ± 0.004</td>
</tr>
<tr>
<td>Zone 4</td>
<td>0.072 ± 0.012</td>
<td>+0.012 ± 0.005*</td>
</tr>
</tbody>
</table>

Values are means ± SE. RBF = renal blood flow. *P < 0.05. †P < 0.01.

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1 A gift from The Upjohn Co., Kalamazoo, Michigan.
seen in the zonal perfusion rates of the noninfused kidney with saline, the prostaglandins, or the low dose of arachidonate. With the high arachidonate dose, perfusion of zone 4 increased slightly (+39 ± 15 ml/100 g min⁻¹, P < 0.05), but the difference between the infused and the noninfused side was significant (P < 0.05) with the greater response occurring on the infused side. No other changes in the noninfused side occurred.

The arterial blood pressure was not altered significantly by any of the agents, and thus the changes in flow were reflected by reciprocal changes in zonal resistance which were seen in all zones with PGE₂ (Fig. 3) but only in the inner cortical zones with arachidonate (Fig. 4).

**Discussion**

We have previously shown that infusion of arachidonate into the renal artery produces renal functional and hemodynamic effects which can be abolished by blockade of prostaglandin synthetase. The present experiments indicated that the site of the renal hemodynamic effects produced by endogenously synthesized prostaglandins is the juxtamedullary cortex; no changes in flow were observed in the outer cortical zone. In contrast, exogenously administered PGE₂ increased flow to all cortical zones and PGF₁α had no effect. The more selective action of arachidonate on the juxtamedullary flow explains why it produces less increase in total renal blood flow than does PGE₂. Direct-acting vasodilators, such as PGE₂, administered into the renal artery would have access to all glomeruli and could change glomerular resistance in all zones of the kidney. The fact that the resistance fall was relatively greater in the juxtamedullary nephrons with PGE₂, a pattern also seen with other vasodilators (6, 8), possibly indicates that the resistance vessels in the inner cortical zones are more reactive to any vasodilator. However, when prostaglandin is formed endogenously at the sites of synthesis in the kidney during the arachidonate infusion, the outer cortical nephrons are not affected at all and the entire increase in blood flow and decrease in resistance occurs in the inner cortex. Thus, although the distribution of renal blood flow is altered by both PGE₂ and arachidonate infusions, only arachidonate causes a selective increase in the inner cortical nephrons.

Renal prostaglandins are synthesized primarily in the renal medulla (9, 10). The mechanisms whereby prostaglandins formed and released at this site can affect the blood flow through the inner cortical nephrons are unknown. However, it is of interest that these inner cortical nephrons are the ones whose postglomerular blood flow supplies the medulla and whose tubules reach into the medulla (11). The effect of prostaglandins may involve a direct action on the vessels reaching into the medulla, or alternatively they may result because prostaglandins enter the tubules in the medulla and are transported in the tubular fluid to the cortex. Since the tubule and the resistance vessels are in close proximity at the macula densa, it is...
conceivable that prostaglandins in the tubular fluid affect renal blood flow to those nephrons whose tubules descend into the medulla. The fact that prostaglandins are found in the urine makes this suggestion tenable (12).

Our data are consistent with those for the rabbit; in that species arachidonate infusion into the aorta causes a redistribution of microspheres toward the juxtamedullary cortex and indomethacin distributes the spheres away from the inner cortex (actual flow was not measured) (13). Our data are also consistent with experiments in isolated perfused dog kidneys in which indomethacin distributes flow away from the juxtamedullary nephrons (1). Prostaglandins have been implicated as being important in the kidney's ability to autoregulate blood flow during reductions in renal perfusion pressure (4). The autoregulation occurs almost exclusively in the inner cortex and is not affected by inhibitors of the sympathetic or the parasympathetic nervous system but is blunted by indomethacin (4, 5). The present experiment supports the hypothesis that prostaglandins produced in the kidney can have effects on blood flow of the juxtamedullary nephrons of that kidney and could thus also influence by endogenous prostaglandin formation, as has been suggested to explain the effect of large doses of indomethacin on total renal blood flow (2), is not given any support by the present data but is certainly not refuted.

References
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Circ Res. 1975;36:204-207
doi: 10.1161/01.RES.36.1.204

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