Enhanced Renal Prostaglandin Production in the Dog

The Effect of Sodium Arachidonate in Nonfiltering Kidney

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Summary

Sodium arachidonate, 10⁻⁵ g/kg per minute, was infused into the renal artery of a nonfiltering canine kidney in situ in order to determine the effects of enhanced prostaglandin synthesis on renal blood flow and its distribution in circumstances where prostaglandins produced in the medulla could not gain access to the cortex via tubular fluid. The contralateral normal kidney was also infused with sodium arachidonate and served as control. Radiopaque microspheres were used to calculate the hemodynamic effects. In the nonfiltering kidney, the total renal blood flow increased after sodium arachidonate from a mean of 105 ml/min per 100 g to 146 ml/min per 100 g (P < 0.01). This increase was completely abolished by prior treatment with indomethacin, 8 mg/kg, intravenously. The normal kidney responded qualitatively the same as the nonfiltering side. In both kidneys, blood flow increased significantly to all cortical zones except the outermost (zone 1), but the fractional distribution of renal blood flow was significantly increased only in the innermost cortex (zone 4). Since the kidneys were nonfiltering, the increase of renal blood flow during infusion of arachidonic acid cannot be explained by prostaglandins being transported from renal medulla to the cortex through renal tubules. Most likely prostaglandins are produced locally in the cortex and have only local effects.

Methods

Six mongrel dogs of either sex weighing 20–30 kg were initially operated under aseptic condition, using pentobarbital anesthesia (25 mg/kg, iv). Through a left flank incision the left ureter was ligated, and the left renal artery was occluded for 2 hours as described by Blaine et al. to make the kidney nonfiltering. Two days later the dogs were reoperated, this time through an abdominal incision; both renal arteries were exposed and cannulated with a 23-gauge needle. Catheters were inserted into both femoral arteries for blood pressure monitoring and blood withdrawal and into a femoral vein for drug administration. A catheter was passed retrograde from the left carotid artery into the left ventricle for injection of microspheres. Throughout the experiment the dogs were ventilated through an endotracheal tube with a Harvard
respirator pump. After a 60-minute stabilization period, the experiment was divided into four periods. Period 1 was the control period in which both renal arteries were infused with normal saline at 0.1 ml/min. One batch of radioactive microspheres was injected at this time. During period 2, both renal arteries were infused with sodium arachidonate, \(10^{-5}\) g/kg per minute, for 15 minutes, and another batch of radioactive microspheres was injected. After period 2, indomethacin, 8 mg/kg [a dose known to inhibit prostaglandin production in the kidney by more than 90\% (unpublished observations)] was given intravenously. After a 30-minute equilibration period, another batch of radioactive microspheres was given while saline was infused into both renal arteries as in period 1. Period 4 was a repeat of period 2 with infusion of sodium arachidonate into both renal arteries.

Radioactive microspheres 15 ± 5 \(\mu\)m in diameter labeled with \(^{95}\text{Nb}, \; ^{85}\text{Sr}, \; ^{51}\text{Cr}, \; ^{141}\text{Ce}, \; \text{or} \; ^{125}\text{I} \) (3M Co.) were used to measure cardiac output, total renal blood flow, and regional blood flow distribution. Between 400,000 and 1,000,000 microspheres were suspended in 1 ml of saline in an injection chamber and injected into the left ventricle over 10 seconds. At the same time, a reference blood sample was withdrawn at a rate between 10 and 20 ml/min for 60 seconds with a constant rate withdrawal pump. Cardiac output was calculated by multiplying the radioactivity injected by the reference sample flow rate divided by reference sample radioactivity.13

At the end of the experiments, the kidneys were removed, sectioned, and counted in a \(\gamma\) scintillation counter. The cortex was divided into four zones of equal thickness with zone 1 being the outermost and zone 4 being juxtamedullary, according to the methods of McNay and Abe.14 Renal blood flow was determined from cardiac output multiplied by the fraction of the total radioactivity in the kidney. The method for calculating the radioactivity for a given nuclide in the presence of other nuclides has been published.15 Prior to period one, we injected 3 ml of indigo carmine, iv, to assure that the left kidney was indeed nonfiltering. During renal dissection, if there was any blue discoloration of the renal tubules or of the filtrate remaining in the pelvis on the left side, the dog was excluded from the study.

Statistical analysis was performed using Student's \(t\)-test for paired comparisons. Period 2 results were compared to those of period 1, and period 4 results were compared to those of period 3. Results are reported as mean ± standard error of the mean. A \(P\) value of less than 0.05 was considered significant.

Results

The results are shown in Table 1 and Figure 1. Sodium arachidonate infusion increased the renal blood flow and decreased the renal arteriolar resistance in both the nonfiltering and normal kidneys. These effects of arachidonate were inhibited by prior administration of indomethacin (8 mg/kg), a potent cyclooxygenase inhibitor. The percent increase in blood flow produced by arachidonate was greater in the nonfiltering kidney than in the normal kidney (Table 1), probably because the concentration of arachidonic acid reaching the nonfiltering side was higher as a result of the much lower renal blood flow on that side. The intrarenal distribution of blood flow (Fig. 1, Table 1) showed a shift to zones 3 and 4. This change was again inhibited by prior administration of indomethacin.

Discussion

Although the renal cortex has only one-tenth the capacity of the medulla to produce prostaglandins from arachidonic acid in vitro,5 our data indicate that cortical prostaglandin synthesis can influence renal hemodynamics. In the kidneys rendered nonfiltering, there is no possibility that prostaglandins produced in the medulla could be transported to the cortex in the tubular fluid. Nonetheless, the hemodynamic changes produced by enhanced prostaglandin synthesis in the nonfiltering kidney were at least as large as those produced in the normal kidney that was also infused with sodium arachidonate. The fact that these hemodynamic effects of arachidonate were blocked by indomethacin is good evidence that they are mediated by prostaglandin synthesis. Although there are alternate

### Table 1  Effects of Arachidonate on Renal Hemodynamics

<table>
<thead>
<tr>
<th>Period</th>
<th>Renal blood flow (ml/min per 100 g)</th>
<th>Renal resistance (mm Hg/ml per min)</th>
<th>Zonal distribution of renal blood flow</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Zone 1</td>
</tr>
<tr>
<td>1</td>
<td>105±20</td>
<td>1.55±0.19</td>
<td>0.3591±0.0217</td>
</tr>
<tr>
<td>2</td>
<td>146±25*</td>
<td>1.07±0.16*</td>
<td>0.2890±0.0247</td>
</tr>
<tr>
<td>3</td>
<td>92±31</td>
<td>2.92±1.07*</td>
<td>0.4764±0.1097</td>
</tr>
<tr>
<td>4</td>
<td>95±30</td>
<td>2.62±0.80</td>
<td>0.3158±0.0353</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± sem. Period 1 = baseline; period 2 = arachidonate infusion; period 3 = baseline after indomethacin; period 4 = arachidonate after indomethacin.

* \(P < 0.01\)

† \(P < 0.05\).
prostaglandin synthesis, it is possible that there is qualitative compartmentalization of synthesis as well. The highly vascular renal cortex is a good candidate for the synthesis of the newly described prostacyclin, but the renal medulla has been shown to be devoid of prostacyclin synthesis.21

It seems very logical to have prostaglandins produced and act locally if their main action is to cushion the excesses of other hormones, e.g., angiotensin, norepinephrine, and vasopressin. Our data show that flow of tubular fluid is not necessary for the cortical hemodynamic effects of enhanced prostaglandin production when the precursor is infused. Most likely the prostaglandins are formed locally in the cortex to affect hemodynamics.

References


FIGURE 1  Mean flow change (ml/100 g per minute) after arachidonic acid in the four zones, before and after indomethacin. Zone I (Z1) represents the outer cortex and zone 4 (Z4) the juxtamedullary cortex.
Enhanced renal prostaglandin production in the dog. The effect of sodium arachidonate in nonfiltering kidney.
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Circ Res. 1978;42:43-45
doi: 10.1161/01.RES.42.1.43

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/42/1/43

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