Enhanced Renal Prostaglandin Production in the Dog

The Effect of Sodium Arachidonate in Nonfiltering Kidney

JOHN G. GERBER, JOANN L. DATA, AND ALAN S. NIES

SUMMARY Sodium arachidonate, $10^{-6}$ 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.

THE physiological function of prostaglandins in the kidney is unknown. The major renal prostaglandin, PGE$_2$, is a potent vasodilator and causes natriuresis and diuresis in dogs. Similar effects can be produced from the precursor of the renal prostaglandins, arachidonic acid. The fact that inhibition of prostaglandin synthesis in awake dogs neither alters renal autoregulation to aortic clamping nor decreases basal renal blood flow makes a primary role in renal hemodynamics seem unlikely. Nonetheless, prostaglandins do appear to modulate renal hemodynamics by opposing vasoconstriction produced by angiotensin, sympatheticmetics, and renal nerve stimulation, all of which have been shown to be stimuli for PG synthesis. It is probably by “fine tuning” of the vasoconstrictive forces that prostaglandins affect renal hemodynamics.

Initially it was thought that the renal cortex was devoid of prostaglandin synthetic capability. In vitro studies have demonstrated that prostaglandins are produced in much larger quantities in the renal medulla than in the cortex. We and others proposed that prostaglandins, produced in the medulla, might be transported in tubular fluid to the cortex where hemodynamic effects could be produced. However, when Larsson and Anggard showed that the renal cortex could produce prostaglandins at about 10% the rate of the renal papilla, it became necessary to determine the function of the cortical prostaglandins. One role might be to control renin release; another might be to modulate renal hemodynamics.

Indeed, it seemed unlikely that a portal system transporting medullary prostaglandins to the cortex would be an efficient mechanism to fine tune renal hemodynamics. In order for prostaglandins to be effective immediately, their synthesis should occur near or at the resistance vessels in the cortex. It is for this reason that we decided to study the effect of arachidonic acid infusion in the renal artery of the nonfiltering kidney. Since the kidneys were nonfiltering, prostaglandins could not be transported from medulla to the cortex in tubular fluid, and any hemodynamic alterations would probably result from local cortical prostaglandin synthesis.

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 µm in diameter labeled with $^{95}$Nb, $^{85}$Sr, $^{51}$Cr, $^{141}$Ce, or $^{125}$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.$^{15}$

At the end of the experiments, the kidneys were removed, sectioned, and counted in a γ 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 divided by reference sample radioactivity. $^{15}$

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, 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>Nonfiltering Kidney</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>105±20</td>
<td>1.55±0.19</td>
<td>0.359±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>
<tr>
<td>Normal Kidney</td>
<td></td>
<td></td>
<td>0.3301±0.0172</td>
</tr>
<tr>
<td>1</td>
<td>302±40</td>
<td>0.50±0.06</td>
<td>0.3196±0.0123</td>
</tr>
<tr>
<td>2</td>
<td>344±52*</td>
<td>0.44±0.06*</td>
<td>0.3485±0.0256</td>
</tr>
<tr>
<td>3</td>
<td>274±46</td>
<td>0.65±0.14</td>
<td>0.3367±0.0251</td>
</tr>
<tr>
<td>4</td>
<td>236±37</td>
<td>0.74±0.4</td>
<td>0.3457±0.0158</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.

* $P < 0.01$

† $P < 0.05$. 

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.
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pathways from the medulla to the cortex in the nonfiltering kidney, they seem unlikely to play a significant role. Lymphatic flow is very sluggish and an unlikely channel to account for immediate changes in hemodynamics. Neither venous flow nor vasa recta flow would seem likely because an active transport mechanism would be required for the prostaglandins to diffuse out of the blood to reach the resistance vessels. Prostaglandins, being organic acids with a pK near 6, would circulate mainly in the ionized form. Bito et al.\(^{16,17}\) have shown that primary prostaglandins do not simply diffuse across membranes but have to be actively transported by an organic acid pump.

Our data also suggest the possibility that there are at least two distinct compartments of prostaglandin synthesis in the kidney, each with a separate function. It is quite possible that the cortex and medulla produce prostaglandins independently in response to different stimuli. A vascular stimulus, including angiotensin, norepinephrine, and hemorrhagic shock, would tend to favor cortical prostaglandin release which would result in a decreased renovascular resistance and a shift in renal blood flow to the juxtamedullary nephrons. On the other hand, a tubular stimulus such as vasopressin would tend to favor collecting duct release of prostaglandin to "fine tune" the free water reabsorptive effect of vasopressin. Although there is no direct proof for compartmentalization of prostaglandin synthesis, angiotensin, a strong stimulator of prostaglandin release in vivo and in vitro, does not usually produce natriuresis or diuresis,\(^ {18}\) but endogenously stimulated prostaglandins oppose angiotensin's vascular effect. Vasopressin, which has been shown in vitro to release prostaglandins\(^ {19}\) and in vivo to have an increased effect on water reabsorption after prostaglandin inhibitors,\(^ {20}\) does not affect renal distribution of blood flow in subpressor doses (unpublished data). Aside from quantitative and stimulus-dependent compartmentalization of 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 1 (Z1) represents the outer cortex and zone 4 (Z4) the juxtamedullary cortex.
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