RENAL PROSTAGLANDINS: DETERMINANTS OF INTRARENAL DISTRIBUTION OF BLOOD FLOW IN THE DOG

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SUMMARY

1. Indomethacin inhibited the synthesis of prostaglandins in isolated blood-perfused canine kidneys.
2. Blood flow to the inner cortex was reduced to a greater degree by indomethacin than blood flow to the outer cortex, resulting in redistribution of fractional blood flow to the outer cortex.
3. A prostaglandin, probably PGE₂, appears to participate in the regulation intrarenally of medullary vascular resistance and thereby inner cortical blood flow.

Key words: prostaglandins, intrarenal distribution of blood flow, indomethacin, isolated perfused kidneys.

The capacity of the renal medulla to synthesize prostaglandins is surpassed only by that of the seminal vesicles (Ånggärd, Bohman, Griffin, Larsson & Maunsbach, 1972). Inhibition of synthesis of renal prostaglandins results in a prompt reduction in renal blood flow (Lonigro, Itskovitz, Crowshaw & McGiff, 1973). These anatomical, biochemical and physiological considerations lead us to postulate that the rate of production of prostaglandins by the kidney is an important determinant of renal medullary vascular resistance. By this action prostaglandins could participate in the regulation of blood flow to the renal medulla and thereby influence concentrating mechanisms and excretion of salt and water.

In the present study, in isolated blood-perfused canine kidneys, we assessed the role of prostaglandins in the regulation of the renal circulation by measuring the intrarenal distribution of blood flow before and after inhibition of prostaglandin synthetase by indomethacin (Vane, 1971). The isolated kidney was chosen for this study because it excludes the operation of cardiac, nervous and extrarenal hormonal influences which might affect fractional distribution of renal blood flow. Further, the response of the isolated kidney to prostaglandins is indistinguishable from that of the kidney in situ.

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METHODS

Our method of isolated renal perfusion (Berkowitz, Miller & Itskovitz, 1967) was modified by substituting a Waters pulsatile pump (64 pulsations/min) and membrane oxygenator for the Klung oxygenator and Bluemle pump. Kidneys were obtained from male mongrel dogs weighing approx. 20 kg. The perfusate consisted of 700–800 ml of autologous dog blood. Renal blood flow was measured directly by timed collections of the renal venous effluent. Renal perfusion pressure was maintained at 140 mmHg systolic and from 110 to 116 mmHg diastolic. The intrarenal distribution of blood flow was assessed by using radioactively labelled microspheres ($^{85}$Sr, $^{169}$Yb and $^{141}$Ce) according to the technique of McNay & Abe (1970). To this purpose, a radionuclide (1–4 μCi) was injected into the perfusion circuit before and 30 min after injection of 2–5 mg of indomethacin. We divided the cortex into two zones of equal thickness rather than four zones. Thus, our outer and inner cortex corresponded to the cortical zones designated by McNay & Abe (1970) as $C_1$, $C_2$ and $C_3$, $C_4$, respectively. In five experiments, we obtained blood at various intervals from the renal outflow of the perfusion circuit and determined its concentration of prostaglandins of the E series ('PGE') by parallel bioassay after extracting acidic lipids from the blood and chromatographing the lipid extract (McGiff, Crowshaw, Terragno, Malik & Lonigro, 1972). By this method we can detect 'PGE' in concentrations of 0·02 ng/ml of blood, or greater, assayed as PGE$_2$ equivalents. The Student’s $t$-test was used to determine statistical significance.

RESULTS

Measurement of 'PGE'

The concentration of 'PGE' in the blood perfusing the kidney increased progressively. Thus, during the initial 100 min the mean blood level of 'PGE' was 0·06±0·02 ng/ml which increased to 1·04±0·53 ng/ml between 100 and 200 min and reached 2·67±0·81 ng/ml after 200 min. In three experiments concentrations of 'PGE' were measured before and after indomethacin. In two experiments, the concentration of 'PGE' in blood fell from 3·03 and 1·20 ng/ml to 0·97 and 0·07 ng/ml, respectively, within 15–30 min of injection of indomethacin. In the remaining experiment in which we obtained the lowest control level of 'PGE', 0·30 ng/ml of blood, 15 min after giving indomethacin, 'PGE' was not detected.

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<tr>
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<th>Outer cortex</th>
<th>Inner cortex</th>
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<tr>
<td></td>
<td>Total RBF (ml/min)</td>
<td>RBF (ml/min)</td>
</tr>
<tr>
<td>Pre-indomethacin</td>
<td>187±19</td>
<td>135±19</td>
</tr>
<tr>
<td>Post-indomethacin</td>
<td>137±21</td>
<td>114±16</td>
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<tr>
<td>(Mean ± SEM)</td>
<td>(n = 8)</td>
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RBF = renal blood flow. Significant effect of indomethacin: * ($t = 2·31$, 0·02 < $P < 0·05$); † ($t = 2·78$, 0·01 < $P < 0·02$).
Renal blood flow and its fractional distribution

Before indomethacin, renal blood flow and its fractional distribution in the cortex were within the range described for dog kidneys in vivo (McNay & Abe, 1970); namely, renal blood flow was 187 ml/min of which 74% was directed to the outer cortex and 26% to the inner cortex (Table 1). Within 30 min of the administration of indomethacin, renal blood flow diminished by 50 ml/min. Inner cortical blood flow decreased by greater than 50%, whereas outer cortical blood flow did not decrease significantly. Indomethacin, thereby, resulted in redistribution of fractional renal blood flow from the inner to the outer cortex, the fraction to the inner cortex decreasing by 11%.

DISCUSSION

Prostaglandins are believed to be synthesized but not stored in the renal medulla (Änggård et al., 1972). Therefore, our demonstration of progressive increases in the concentration of 'PGE' in the blood perfusing isolated kidneys presumably represents continued synthesis as well as diminished degradation in the absence of the lung which normally removes greater than 90% of prostaglandins of the E series presented to it (Ferreira & Vane, 1967). At 30 min after inhibition of prostaglandin synthesis by indomethacin, blood flow to the inner cortex invariably decreased, whereas outer cortical blood flow did not decrease significantly. This was associated with a rapid decline in the concentration of 'PGE' and redistribution of blood flow intrarenally to effect greater fractional blood flow to the outer cortex and corresponding decrease to the inner cortex. The latter changes in distribution of renal blood flow produced by indomethacin assume additional significance in view of the progressive increase in blood flow to the inner cortex observed in this preparation when indomethacin is withheld (Itskovitz, Hebert & McGiff, 1973). We interpret these haemodynamic events produced by indomethacin to be a consequence of increased renal medullary vascular resistance secondary to the diminished production of PGE₂ in the renal medulla.

The deep cortical blood vessels continue into the renal medulla where they give rise to the vasa recta (Fourman & Moffat, 1971). Therefore, alterations in renal medullary vascular resistance may be reflected by changes in blood flow to the deep cortex. On the basis of these anatomical relationships, release of the vasodilator PGE₂, after its synthesis in the renal medulla, could affect medullary blood vessels and thereby alter blood flow to the inner cortex. The low activity of the major degrading enzyme, 15-hydroxy-prostaglandin dehydrogenase, in the renal medulla (Änggård et al., 1972) should assure this vascular action of PGE₂ after its release. Our demonstration of diminished blood flow to the inner cortex after inhibition of prostaglandin synthesis by indomethacin supports the proposal that PGE₂ dilates medullary blood vessels. Thus, we are led to conclude that PGE₂ functions in the canine renal medulla as a tissue hormone which participates in the regulation of deep cortical and medullary blood flow with all its attendant effects on renal function.

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REFERENCES


