Inhibition of Prostaglandin E\textsubscript{2} Secretion

Failure to Abolish Autoregulation in the Isolated Dog Kidney

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SUMMARY We studied the role of renal prostaglandins in the regulation of glomerular filtration rate (GFR) and renal blood flow (RBF) in the isolated dog kidney. Indomethacin or meclofenamate, 2 mg/kg of body weight, suppressed renal prostaglandin E\textsubscript{2} (PGE\textsubscript{2}) secretion, measured by radioimmunoassay, to zero within 20 minutes; the effect persisted for the duration of the study. When renal arterial pressure (P\textsubscript{A}) was maintained at 104 mm Hg both drugs caused a sharp decrease in sodium excretion and RBF with redistribution of flow from inner to outer cortex. GFR was well maintained. In a separate group of experiments we examined autoregulation of GFR and RBF over the pressure ranges of 150-100 and 150-75 mm Hg, respectively, after inhibition of PGE\textsubscript{2} secretion and under control conditions. \(\Delta\text{GFR}/\Delta P\text{A}_{\text{a}}\) (ml/min per mm Hg) was 0.020 \(\pm\) 0.017 in the indomethacin group, 0.152 \(\pm\) 0.055 in the meclofenamate group, and 0.086 \(\pm\) 0.017 in the control group. The change in GFR for the indomethacin group was significantly less than that for meclofenamate \((P < 0.01)\) and control groups \((P < 0.025)\); the latter two groups were not statistically different from each other \((P > 0.1)\). There was no significant difference \((P > 0.1)\) between the three groups with respect to \(\Delta\text{RBF}/\Delta P\text{A}_{\text{a}}\), which measured 0.288 \(\pm\) 0.046, 0.370 \(\pm\) 0.112, and 0.438 \(\pm\) 0.123 ml/min per mm Hg in the indomethacin, meclofenamate and control groups, respectively. Renal vascular resistance changed to a similar degree in all groups as P\textsubscript{A} was lowered from 150 to 75 mm Hg. The observation that inhibition of prostaglandin synthesis promotes a redistribution of RBF from inner to outer cortex suggests that renal prostaglandins may participate in the regulation of medullary blood flow. However, since autoregulation of GFR and RBF remained intact despite inhibition of prostaglandin secretion, these data argue against a role for renal prostaglandins in regulating whole kidney GFR and RBF.

FOR MANY years it has been known that changes in renal arterial pressure (P\textsubscript{A}) are accompanied by parallel changes in renal vascular resistance but with little or no change in glomerular filtration rate (GFR) or renal blood flow (RBF). Various theories have been proposed to explain this phenomenon, which is referred to as autoregulation.\(^3\) In recent years attention has focused on the possibility that renal prostaglandins participate in the regulation of RBF. McGiff et al.\(^4\) detected an increased release of prostaglandin-like material in renal venous blood in response to renal artery constriction\(^5\) and to infusions of norepinephrine\(^6\) and angiotensin II.\(^4\) Lonigo et al.\(^4\) observed that indomethacin, an inhibitor of prostaglandin synthesis, depressed RBF in proportion to the decrease in prostaglandin E\textsubscript{2} (PGE\textsubscript{2}) secretion. In addition, it has been reported that indomethacin inhibition of prostaglandin synthesis impairs the recovery of RBF after hemorrhage.\(^6\) These data suggest that prostaglandins, and particularly PGE\textsubscript{2}, may function as a homeostatic mechanism for maintaining RBF in response to hypotension or vasoconstrictor stimuli.

Recently Herbaczynska-Cedro and Vane\(^7\) implicated a role for renal prostaglandins in the autoregulation of whole kidney blood flow. They found that the autoregulatory response was abolished in the dog kidney after inhibition of prostaglandin synthesis by indomethacin. That inhibition of prostaglandin synthesis should abolish whole kidney autoregulation is somewhat surprising because the enzyme prostaglandin synthetase is located primarily in the medulla.\(^8\) Although prostaglandin synthetase has been identified in the cortex, cortical synthesis of biologically active PGE\textsubscript{2} was less than 1-2% of that of the renal medulla.\(^9\) Moreover, stimulation\(^10\),\(^11\) as well as inhibition\(^12\),\(^13\) of prostaglandin synthesis has been shown to preferentially affect inner cortical and medullary blood flow, whereas the predominant change in renal vascular resistance which characterizes the autoregulatory response must occur in the microcirculation of the outer cortex because this zone receives the highest fraction of blood flow.

Stimulated by these considerations, we studied in the isolated dog kidney the effects of inhibiting prostaglandin synthesis on the distribution and autoregulation of blood flow and on filtration rate.

Methods

Experiments were performed in mongrel dogs weighing 15-30 kg and fed a standard kennel ration. One dog served as a kidney donor; a second dog was used to perfuse the isolated kidney. On the morning of the study the perfusion dog received deoxycorticosterone acetate, 15 mg, im. Anesthesia was induced with sodium pentobarbital, 30 mg/kg, iv, and supplemental doses were given as required to maintain light anesthesia. An endotracheal tube was inserted and the dog was ventilated with a Harvard respirator adjusted to maintain arterial pH between 7.35 and 7.45. The isolated kidney was prepared as previously described.\(^14\) In brief, a kidney was removed from a donor dog, placed in a receptacle filled with 0.9% saline maintained at 38°C, and perfused with blood from the femoral artery of the perfusion donor.
dog. Renal venous blood flowed by gravity into a reservoir from which it was pumped to the perfusion dog's femoral vein. The perfusion dog rested on an adjustable platform; by raising or lowering the platform we could alter the hydrostatic pressure between the femoral artery and the isolated kidney and regulate the arterial pressure of the isolated kidney.

After blood flow to the isolated kidney had been established, the perfusion dog received a priming dose of inulin in 0.9% saline at 1.0 ml/min to achieve a plasma inulin concentration of 20 mg/100 ml. Aqueous vasopressin (Pitressin, Parke-Davis) was added to the infusion to deliver 0.1 mU/kg per min. A minimum interval of 60 minutes was allowed for stabilization of renal function before observations were made.

Five groups of experiments were performed. In group I (eight experiments) we studied the effect of indomethacin on the function of the isolated kidney under the condition of constant PRA. After collection of two 10-minute control urine and midpoint blood samples, indomethacin (2 mg/kg of body wt) was added to the reservoir. Twenty minutes later serial urine and blood samples were collected at 20-minute intervals for up to five periods. PRA and renal venous pressure were maintained constant at 104 and 0 mm Hg, respectively, throughout the experiment. At the end of the control period and of the first postindomethacin period, microspheres labeled with either 85Sr or 146Ce were injected into the renal arterial catheter to measure distribution of renal cortical blood flow. The experiments in group II (six experiments) were identical to those of group I except that meclofenamate (2 mg/kg of body wt) was added to the reservoir.

In group III (10 experiments) we examined the effect of indomethacin on autoregulation of GFR and RBF. After two 10-minute control periods indomethacin, 2 mg/kg of body wt, was added to the reservoir. Twenty minutes later two 10-minute urine collections were obtained with PRA maintained constant at 104 mm Hg. Then PRA was raised to approximately 155 mm Hg and, at intervals of 25 minutes, PRA was lowered by decrements of 25 mm Hg to 75 mm Hg. An interval of 5 minutes was allowed for renal function to stabilize after each change in PRA, before collection of either two 10-minute or a single 20-minute urine sample. At the end of the first postindomethacin period, while PRA was 104 mm Hg and after raising PRA to 155 mm Hg, radiolabeled microspheres were injected into the renal artery catheter to measure distribution of cortical blood flow. Experiments in group IV (six experiments) were identical to those in group III except that meclofenamate (2 mg/kg of body wt) was added to the reservoir. In groups I–IV arterial and renal venous blood samples were collected at the end of the control period, 20–40 minutes after the prostaglandin synthetase inhibitor had been administered, and at the end of the experiment; these samples were assayed for PGE₂. For 5 minutes prior to drawing the last blood samples PRA was lowered to 50 mm Hg to stimulate PGE₂ secretion.

In group V (eight experiments) the experimental design was identical to that of groups III and IV except that the prostaglandin synthetase inhibitor was not added to the reservoir and distribution of cortical blood flow was not measured. At the end of the experiment, with PRA at 50 mm Hg, arterial and renal venous bloods were collected and assayed for PGE₂.

We measured PGE₂ by the radioimmunoassay method of Van Orden and Farley. In brief, plasma was extracted with ethyl acetate and the extract was subjected to column chromatography on a silicic acid column to achieve separation of the prostaglandin classes. Recovery of ³H-PGE₂ through the extraction step averaged 83.2 ± 0.8% (n = 13). Column recovery of ¹⁴C-PGE₂ averaged 67.7 ± 1.2% (n = 13). Less than 3% of ³H-labeled prostaglandin F₂α (PGF₂α) was eluted with the PGE fraction. For the radioimmunoassay we used an antibody raised against PGF but which cross-reacts with PGE. The standard curve (Fig. 1) was constructed by plotting the ratio of bound counts (B) in tubes containing known amounts of cold PGE₂ to that of tubes containing no cold PGE₂ (B₀). The percent B/B₀ was calculated for each unknown and the PGE₂ content was determined from the standard curve. The coefficient of variation for a three-point parallel assay was 13.1 ± 0.6% (n = 100). The coefficient of variation for replicate assays performed on 24 samples on 4 separate days was 18.8 ± 2.1%. For the most part, samples were extracted and fractionated only once and the concentration of PGE₂ was determined from the mean value of the three-point parallel radioimmunoassay for correction after an average recovery of 56.3% as determined for the combined extraction and fractionation steps.

Renal arterial and venous pressures of the isolated kidney were monitored with Statham pressure transducers (model

![Figure 1](http://circres.ahajournals.org/)

**Figure 1. Standard curve for the radioimmunoassay of prostaglandin E₂.** Curve represents the mean ± SE of 10 standard curves. For explanation of % B/B₀, see the text.
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23 AA) connected about 8 cm from the kidney to the arterial and venous catheters and recorded on a Beckman Dynograph. RBF was measured directly by timing the flow from the renal vein. Renal plasma flow (RPF) was calculated by the formula RPF = RBF × (1 - PCV) where PCV is packed cell volume determined with a microhematocrit centrifuge. GFR was determined from the clearance of inulin (C<sub>IN</sub>). The technique for measuring fractional cortical blood flow distribution was identical to that previously reported. Absolute blood flow to the four cortical zones, expressed as ml/min per g per zone, was calculated by dividing whole kidney blood flow by the estimated cortical weight and multiplying by the fraction of blood flow delivered to each zone. The cortical weight was estimated to be 78% of whole kidney weight. The autoregulation index for GFR was defined as the slope of the regression of C<sub>IN</sub> on P<sub>RA</sub> over the interval of 150-100 mm Hg. The autoregulation index for RBF was defined as the slope of regression of RBF on P<sub>RA</sub> over the interval of 150-75 mm Hg. Renal vascular resistance (RVR) was calculated according to the formula RVR = P<sub>RA</sub>/RBF expressed in peripheral resistance units (PRU) of ml/min per mm Hg. Renal PGE<sub>2</sub> secretion was calculated as the product of Δ renal PGE<sub>2</sub> (renal venous minus arterial PGE<sub>2</sub> concentration) and RPF.

Analysis of variance was used to test for significance of differences within each group, and Student's t-test was used to analyze differences between groups. Regression analysis was performed by the method of least squares. The data in the text, table, and figures are expressed as the mean ± the standard error of the mean.

Results

Figure 2 depicts the effect of indomethacin and meclofenamate on Δ renal PGE<sub>2</sub> and PGE<sub>2</sub> secretion. In 15 experiments using indomethacin (five experiments in group I and 10 experiments in group III) control Δ renal PGE<sub>2</sub> was 0.35 ± 0.08 ng/ml, a value not significantly different (P > 0.5) from the control value (0.39 ± 0.08 ng/ml) of the 12 meclofenamate experiments. Similarly, there was no difference in PGE<sub>2</sub> secretion during the control period (51.8 ± 9.6 and 55.5 ± 14.3 ng/min in the indomethacin and meclofenamate groups, respectively; P > 0.5). After administration of indomethacin or meclofenamate Δ renal PGE<sub>2</sub> and PGE<sub>2</sub> secretion fell to levels that were not significantly different from zero (P > 0.4) and remained at this level at the end of the experiment even after P<sub>RA</sub> had been reduced to 50 mm Hg to stimulate PGE<sub>2</sub> secretion. In group V, the PGE<sub>E</sub> secretion was 90.3 ± 24.8 ng/min when P<sub>RA</sub> was reduced to 50 mm Hg. The absence of PGE<sub>2</sub> secretion in response to a decrease in P<sub>RA</sub> indicates that prostaglandin synthesis remained inhibited throughout the study. A significant decrease (P < 0.01) in C<sub>IN</sub> occurred during the first postindomethacin period; thereafter, C<sub>IN</sub> returned to a level not significantly different from the control (P > 0.05). C<sub>IN</sub> tended to decrease during the first and second postmeclofenamate periods but these changes were not statistically significant (P > 0.05).

Figure 3 illustrates the effects of these agents on renal function when P<sub>RA</sub> was maintained at 104 mm Hg. Both drugs caused a significant decrease (P < 0.01) in absolute sodium excretion (U<sub>Na</sub>V) and fractional sodium excretion (FE Na<sub>V</sub>); this was evident by the first postdrug period and persisted for the duration of the experiment. Urine volume, not shown, also decreased in parallel with sodium excretion in both groups. Urine volume fell from control levels of 1.3 ± 0.4 and 1.3 ± 0.3 ml/min to 0.4 ± 0.3 and 0.2 ± 0.01 ml/min after administration of indomethacin and meclofenamate, respectively, and remained at these levels for the duration of the experiment. A significant decrease (P < 0.01) in C<sub>IN</sub> occurred during the first postindomethacin period; thereafter, C<sub>IN</sub> returned to a level not significantly different from the control (P > 0.05). C<sub>IN</sub> tended to decrease during the first and second postmeclofenamate periods but these changes were not statistically significant (P > 0.05).
prostaglandin synthesis on fractional and absolute blood flow to the cortex. Distribution of cortical blood flow was measured during the control and first postdrug period. RBF = renal blood flow; C₁ = outermost cortex; C₂ = juxtamedullary cortex.

Both drugs caused a significant fall (P < 0.01) in RBF that was evident by the first postdrug period; no further change occurred over the ensuing period of observation.

Figure 4 summarizes the effects of indomethacin and meclofenamate on the distribution of fractional and absolute blood flow to the cortex. Both drugs promoted a significant redistribution of fractional blood flow from inner to outer cortical zones. Although absolute blood flow to all cortical zones decreased, outer cortical blood flow was depressed proportionately less than inner cortical blood flow. In group I, indomethacin caused a decrease of 37% in total RBF; absolute blood flow to the outer cortex (C₁) decreased by 20%, whereas flow to the inner cortex (C₂) decreased by 64%. Similarly, in group II meclofenamate depressed total RBF by 45% below the control level; absolute blood flow to C₁ decreased by only 28% in contrast to the 77% decrease in flow to C₂. These changes in blood flow distribution are similar to those found for the intact dog kidney. 

Figure 5 illustrates the response of the isolated kidney to alterations in P RA after administration of indomethacin (group III) or meclofenamate (group IV). Both groups U Na V, F ENa, C IN, and RBF were depressed after administration of the drug and the pattern was similar to that observed for groups I and II, i.e., C IN decreased slightly whereas sodium excretion and RBF decreased sharply. When P RA was increased to 155 mm Hg there was a significant increase (P < 0.01) in U Na V and F ENa above the level of the first postdrug period in both groups. Thereafter sodium excretion decreased in parallel with the decrease in P RA. In the indomethacin experiments C IN remained relatively constant until P RA was reduced to 75 mm Hg; this pressure is below the autoregulatory range for GFR in this preparation. A slightly greater dependency of C IN on P RA was evident in the meclofenamate experiments. In both groups RBF remained relatively constant as P RA was lowered from 150 to 75 mm Hg. This finding demonstrates that the autoregulatory capacity of the isolated kidney was intact at the time prostaglandin secretion was inhibited.

Since in groups I and II indomethacin and meclofenamate promoted an antinatriuresis in association with a decrease in RBF and redistribution of flow from inner to outer cortex, it was of interest to determine whether the natriuresis induced in groups III and IV by raising P RA was accompanied by redistribution of blood flow from outer to inner cortex. These data are summarized in Figure 6. In the indomethacin-treated kidneys, when P RA was raised from approximately 100 to 150 mm Hg, fractional blood flow to the outer cortex (C₁) increased from 41.5 ± 1.4 to 46.7 ± 1.8% (P < 0.01) in association with slight decreases in fractional flow to C₂-C₄. Thus, absolute cortical blood flow to C₂ increased from 1.70 ± 0.16 to 1.97 ± 0.19 ml/min per g (P < 0.05). Changes which were similar in direction but not significant were observed in the meclofenamate experiments. These data indicate that the pressure natriuresis is not dependent on restoration of blood flow to the inner cortex.

Figure 7 illustrates the response of the isolated kidney, in the absence of prostaglandin synthetase inhibition, to alterations in P RA over the range of 150–75 mm Hg. The pattern of response is similar to that observed in groups III and IV. Sodium excretion exhibited a high degree of pressure dependency while C IN and RBF remained relatively constant as P RA was reduced from 155 to 75 mm Hg. Figure 8 compares the changes in C IN, RBF, and renal vascular resistance as a function of P RA for groups III, IV, and V, and Table I summarizes the mean of the slopes of the lines computed by regression analysis for individual experiments in each group. Indomethacin-treated kidneys (group III) exhibited a greater capacity to autoregulate GFR compared to control kidneys (group V). ΔC IN/ΔP RA in group III was 0.020 ± 0.017 ml/min per mm Hg in group V (P < 0.025). Meclofenamate-treated kidneys (group IV) exhibited a slightly impaired capacity to autoregulate GFR compared to the control group; however, the difference in slopes was not statistically significant (P > 0.1). Although
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Figure 6
Effect of indomethacin and meclofenamate inhibition of prostaglandin synthesis on fractional and absolute blood flow to the cortex with renal arterial pressure (P_RA) at 100 and 150 mm Hg. RBF = renal blood flow; C₁ = outermost cortex; C₄ = juxtamedullary cortex.

in the indomethacin and meclofenamate groups ∆RBF/∆P_RA tended to be lower than that in control group, the differences in slopes were not statistically significant (P > 0.1). Similarly, in the two drug groups ∆RVR/∆P_RA tended to be greater than that of the control group but the difference was not statistically significant (P > 0.1). The essential observation is that, in both the indomethacin and meclofenamate groups, RVR changed appropriately as P_RA was altered over the range of 75 to 150 mm Hg; this demonstrates that autoregulation was intact.

Discussion
The purpose of our study was to evaluate the role of renal prostaglandins as mediators of autoregulation of GFR and RBF in the isolated dog kidney. We have previously reported that intra-arterial infusions of prostaglandins did not affect autoregulation in this preparation. However, since renal prostaglandins are thought to function as intrarenal hormones, it is admittedly difficult to assess their contribution to the autoregulatory response from observations on the effects of intra-arterial infusions of prostaglandins on renal function. The problem is analogous to that encountered in assessing the role of the renin-angiotensin system in renal autoregulation; intra-arterial infusions of angiotensin II may not mimic the effect of angiotensin II released intrarenally. Similarly, intra-arterial infusions of prostaglandins may not mimic the effect of prostaglandins synthesized and released within the kidney. Therefore, we employed an experimental design analogous to one we have used previously to evaluate the role of the renin-angiotensin system in renal autoregulation and which is similar to that used by Herbaczynska-Cedro and Vane. Two known inhibitors of prostaglandin synthetase, indomethacin and meclofenamate, were administered in doses reported by other investigators to inhibit renal prostaglandin synthesis and secretion. Since Lonigro et al. have shown that the depression in RBF which is associated with indomethacin administration correlates directly with the decrease in renal PGE₂ secretion, we monitored renal PGE₂ release by radioimmunoassay to determine the degree and duration of inhibition of prostaglandin secretion achieved in our experiments. Both indomethacin and meclofenamate depressed renal PGE₂ secretion to zero within 20 minutes and this effect persisted for the duration of the study. Additional evidence of inhibition of prostaglandin synthesis is provided by the observation that no PGE₂ secretion occurred in response to lowering P_RA to 50 mm Hg at the end of the experiment. This contrasts with the high level of PGE₂ secretion observed in the control group in response to
the same hypertensive stimulus. Since there is little evidence that prostaglandins are stored within the kidney, prostaglandin secretion reflects the rate of prostaglandin synthesis. Therefore, the absence of prostaglandin secretion in our experiment implies that prostaglandin synthesis was completely inhibited.

Both indomethacin and meclofenamate produced similar alterations in the function of the isolated dog kidney. These changes were characterized by a sharp decline in sodium excretion and RBF, whereas GFR was relatively well preserved. This finding suggests that effenter arteriolar resistance had increased to a greater extent than afferent arteriolar resistance. In addition, both agents effected a similar pattern of blood flow redistribution from inner to outer cortex, a finding that is in agreement with the observations of others.

After we had shown that the isolated dog kidney responds to these inhibitors in a manner qualitatively similar to that reported for the intact dog kidney, we assessed the effect of inhibiting prostaglandin synthesis on autoregulation of GFR, RBF, and RVR. Inhibition of prostaglandin synthesis by indomethacin did not impair the ability of the isolated kidney to autoregulate GFR in relation to the control group. In fact, the data suggest that autoregulation of GFR was improved by indomethacin, because the change in CIN over the pressure range from 150 to 100 mm Hg was significantly less than that of the control group (P < 0.025). However, we do not consider this difference to be of physiological significance.

Autoregulation of GFR in the meclofenamate experiments was not as efficient as that found for the indomethacin experiments. This difference reflects in large measure the influence of an atypical experiment in the meclofenamate group: one in which GFR decreased by 43%. Nevertheless, autoregulation of GFR in the meclofenamate group was not significantly different from that of the control group (P > 0.1).

In contrast to data describing GFR, the effects of indomethacin and meclofenamate on RBF autoregulation were more consistent. Although RBF was lower and renal vascular resistance was higher than in the control group, both the indomethacin and meclofenamate groups exhibited excellent autoregulation. Indeed, as PRA was lowered from 150 to 75 mm Hg, renal vascular resistance tended to decrease to a greater extent in the absence of PGE2 secretion than in the control group in which prostaglandin secretion remained intact. The fact that excellent autoregulation was preserved in the absence of prostaglandin synthesis and secretion provides cogent evidence against the hypothesis that renal prostaglandins mediate the autoregulatory response.

The results of our experiments on the isolated dog kidney are in agreement with the studies of Anderson et al. on the intact dog but at variance with those of Herbacynska-Cedro and Vane, who found that inhibition of prostaglandin synthesis almost completely abolished autoregulation of blood flow. The reason for the disparity in results between these studies is not readily apparent. In our studies and those of Herbacynska-Cedro and Vane similar doses of indomethacin and meclofenamate were used and similar effects on prostaglandin secretion were observed. In contrast to our isolated kidney preparation, Herbacynska-Cedro and Vane examined autoregulation in a perfused-perfused kidney; in some instances constant flow and in others constant pressure was maintained. These authors presented no data on the functional characteristics of their model, such as sodium excretion, GFR, or blood flow distribution. In addition, they provided no information on the stability of their preparation with respect to time. Thus, the possibility exists for their study that the absence of autoregulation after indomethacin administration reflects a time-dependent deterioration in renal function rather than a consequence of prostaglandin synthesis inhibition. In the absence of appropriate time-control experiments this possibility cannot be excluded.

Theoretical considerations also militate against the hypothesis that prostaglandins mediate autoregulation of whole kidney GFR and RBF. Since the outer cortex receives the largest fraction of blood flow, it is obvious that the predominant change in renal vascular resistance, which characterizes the autoregulatory response, must occur in the microcirculation of this zone and presumably at the afferent arterioles. However, prostaglandin synthesis occurs primarily in the medulla; the capacity of the cortex to synthesize biologically active PGE2 was found to be less than 1–2% of the capacity of the medulla. Moreover, the major enzyme of prostaglandin degradation, prostaglandin dehydrogenase, is localized primarily in the cortex. The anatomical distribution of prostaglandin synthetase and prostaglandin dehydrogenase would suggest that the action of intrarenally released prostaglandin is not primarily within the outer cortex. This conclusion is supported by the observations that stimulation and inhibition of prostaglandin secretion preferentially affect inner cortical and medullary blood flow. Although the latter findings
suggest a role for prostaglandins in regulating medullary blood flow, at present there is no compelling evidence for a similar role of prostaglandins in regulating blood flow to the outer cortex.

In contrast to the medullary location of prostaglandins, renin is confined to the cortex in the juxtamedullary cells of afferent arterioles. Furthermore, it has been shown that glomeruli of superficial cortical nephrons contain more renin than do glomeruli of juxtamedullary nephrons. These observations, plus the fact that converting enzyme activity has been demonstrated to be present in the juxtamedullar apparatus, provide the basis for the hypothesis that the renin-angiotensin system participates in the regulation of cortical blood flow. Thurau et al. proposed that the renin-angiotensin system mediates autoregulation of GFR and RBF by a feedback mechanism involving the macula densa and afferent arteriole. We have previously reported our studies which provide indirect support for the renin-angiotensin hypothesis. We observed that renin depletion significantly impaired the ability of the isolated dog kidney to autoregulate GFR and RBF; this finding is in sharp contrast to the preservation of autoregulation in prostaglandin-depleted kidneys. Thus, of the two theories, our studies on the isolated dog kidney are most consistent with the hypothesis that the renin-angiotensin system participates in the autoregulation of whole kidney GFR and RBF.

The contribution of RBF distribution to the renal regulation of sodium excretion has been a subject of controversy among renal physiologists in recent years. Stein and colleagues have summarized the evidence concerning a possible association between natriuresis and redistribution of cortical blood flow to inner cortical nephrons. It is of interest to note that, in our present studies, after indomethacin and meclofenamate administration there was a decrease in sodium excretion in association with a decrease in whole kidney blood flow and with redistribution of flow from inner to outer cortex. Since GFR was well maintained, the antinatriuresis reflected primarily an increase in tubular sodium reabsorption which possibly was secondary to the increase in filtration fraction and the associated changes in Starling forces operating across the peritubular capillaries. In groups III and IV, however, raising PRA, promoted an increase in sodium excretion when blood flow to the inner cortex either decreased further, albeit slightly (indomethacin experiments, group III), or remained unchanged (meclofenamate experiments, group IV). Therefore, it may be concluded that, under the conditions of our experiments, the natriuresis accompanying a rise in renal perfusion pressure is not dependent on redistribution of blood flow to the inner cortex. Our data also demonstrate that the natriuresis that accompanies a rise in renal perfusion pressure is not mediated by renal prostaglandins.

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