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Effects of Prostaglandin Inhibition on Intrarenal Hemodynamics in Acutely Saline-Loaded Rats

RAINER DÜSING, BERNWARD MELDER, AND HERBERT J. KRAMER

SUMMARY We studied the effect of inhibition of the prostaglandin (PG)-synthesizing enzyme system in female Sprague-Dawley rats following acute expansion of the extracellular fluid volume (ECV). In 57 conscious rats expansion of the ECV with isotonic saline corresponding to an increase in body weight of 10% was induced. Prior to ECV expansion 31 rats received indomethacin (10 mg/kg of body wt) by stomach tube. In six non-ECV-expanded rats indomethacin had no effect on glomerular filtration rate (GFR) and renal plasma flow (RPF). In ECV-expanded rats pretreated with indomethacin, GFR was unaltered but 125I-hippuran clearance decreased, and filtration fraction significantly increased. Intrarenal 86Rb distribution was similar in control and ECV-expanded rats. Indomethacin caused a slight increase in relative cortical 86Rb activity in non-ECV-expanded rats, but had no effect on intrarenal 86Rb distribution in ECV-expanded rats. No difference in intracortical glomerular perfusion was noted between control and ECV-expanded rats. In indomethacin-treated ECV-expanded rats an increase in relative inner cortical perfusion was observed. Absolute perfusion remained unaltered. Thus the decrease in total RPF was entirely due to decreased perfusion of outer cortical nephrons. Renal prostaglandins therefore may play a permissive role for physical factors to promote renal sodium excretion in acute ECV expansion via changes in intrarenal hemodynamics.

THE ADAPTATION of renal tubular function with its resulting natriuresis following intravenous infusion of isotonic saline may be independent of changes in glomerular filtration rate (GFR) or aldosterone activity. Therefore other determinants of tubular reabsorption of sodium, such as a natriuretic hormone, have been postulated. In addition, the important role of peritubular physical fac-

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tors, i.e., onotic and hydrostatic pressure, has been recognized in acute expansion of the extracellular fluid volume (ECV) with isotonic saline. Previous studies concerning the role of changes in intrarenal and intracortical distribution of blood flow in the renal response to acute saline loading have so far led to conflicting results. If such alterations in renal hemodynamics do play a role they may be mediated by intrarenal hormonal action.

Thus, infusions of either prostaglandin (PG) A or E have been shown to result in intrarenal hemodynamic changes accompanied by a marked increase in urinary sodium and water excretion in animals and in man (for review see Anderson et al. and Lee et al.). It therefore

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has been proposed that these substances might act as intrarenal or systemic natriuretic agents. Infusions of PGs, however, might not mimic their physiological action, because renal PGs are mainly synthesized within the inner medullary tissue and high PG metabolizing enzyme activity is present in the renal cortex (for review see Lee et al.24). Furthermore, it has been shown that intrarenal PGE_2 in the rat15 and peripheral venous PGA concentrations in normal humans18,19 decrease during high salt intake. This has been interpreted as evidence against the hypothesis that PGs are involved in the natriuresis of chronic salt load.

In contrast to the infusion of PGs, the experimental model of inhibiting PG synthetase with nonsteroidal anti-inflammatory drugs such as indomethacin or the use of substances which compete with arachidonic acid for PG synthetase activity, such as RO-20 5720,20-22 appear more appropriate to elucidate the biological function of renal PG. Previous results from this laboratory have demonstrated that inhibition of PG synthesis with indomethacin has no effect on renal function in rats on a normal salt intake but significantly reduces urinary flow rate and sodium and potassium excretion in rats which are acutely expanded with isotonic saline.23 The present results demonstrate that this retention of sodium and water occurs in the absence of changes in GFR but is associated with a significant decrease in total renal plasma flow (RPF). To further elucidate the mechanism determining renal sodium excretion after inhibition of PG synthesis in the present study the effects of indomethacin on total RPF and its intrarenal distribution as well as on GFR and glomerular perfusion of superficial and deep cortical nephrons were studied in control rats and in rats undergoing acute expansion of the ECV with isotonic saline.

Methods

Female Sprague-Dawley rats weighing 250–320 g were fed a normal rat chow diet (0.25% Na; 0.6% K) (Altromin) with free access to water. The rats were anesthetized with methohexital-Na (12 mg/kg), and polyethylene catheters were inserted into the jugular vein, the aorta via the carotid artery, and transabdominally into the bladder. Two hours after recovery from anesthesia and surgery the rats were placed in restraining cages mounted on a triple-beam balance. In 57 conscious rats infusion of isotonic saline was started at a rate of 0.5 ml/min until an increase in body weight of 10% was achieved.23 At this time a priming dose of 51Cr-EDTA or 125I-hippuran was given followed by a sustaining infusion to maintain body weight constant. After an equilibration period of 45 minutes urine was collected during three 15-minute periods. The rats were then killed by intraaortal injection of 131I-macroalbumin aggregates (131I-MAA). This method was previously described by Flohr and Hoppe25 and is based on the same experimental principle as the recently described use of microspheres to determine single glomerular perfusion.26 For determination of intrarenal 86Rb distribution and of intracortical glomerular perfusion, kidneys were removed 2 minutes after intravenous injection of 200 μCi of 86Rb and after intraaortal injection of 131I-MAA (500 μCi/kg of body wt), respectively. They were immediately frozen and tissue slices were prepared with a heavy sledge microtome. For autoradiography of intracortical 131I-MAA distribution tissue slices 0.5 mm thick were placed on Agfa Gevaert Graphic film 053 with an exposure time of approximately 48 hours. A representative example of intracortical 131I-MAA distribution in kidneys from expanded rats is shown in Figure 1. For quantitative evaluation 1.0-mm slices of renal cortex were dissected into an inner and outer half and 131I-MAA activities were determined and expressed per milligram of tissue wet weight. Relative inner and outer cortical tissue activity then was calculated as percent of activity in the total cortex.

Mean absolute inner and outer cortical blood flow was estimated from the mean intracortical 131I-MAA distribution and total 131I-hippuran clearance per gram of cortical tissue in individual rats. 86Rb activity in cortex, medulla, and papilla also was measured by direct tissue counting and expressed per milligram of tissue wet weight. Cortical, medullary, and papillary tissue activities then were calculated as percent of total activity in the three tissues. Activities of 51Cr-EDTA and 131I-hippuran in plasma and urine as well as 131I-MAA and 86Rb activities in renal tissue were measured in an automatic gamma counting system ( Nuclear-Chicago).

Statistical analysis of results was performed using a double-tail Student's t-test. Data are presented as mean ± SE.

Results

RPF AND GFR IN CONTROL AND ECV-EXPANDED RATS

Total RPF in non-ECV-expanded rats was not altered by inhibition of PG synthesis. Following acute ECV expansion RPF, estimated as 131I-hippuran clearance, de-
Intracortical distribution of 131I-labeled macroalbumin aggregates (131I-MAA).

creased significantly when rats were pretreated with indomethacin (Table 1). GFR in nonexpanded rats was unaffected by pretreatment with indomethacin and rose significantly during ECV-expansion to the same degree in animals that had and had not been pretreated with indomethacin (Table 1).

RELATIVE INTRARENAL DISTRIBUTION OF 86Rb IN CONTROL AND ECV-EXPANDED RATS

In nonexpanded rats indomethacin caused a slight but significant increase in relative 86Rb activity in cortical tissue with a concomitant decrease in medullary activity, while relative papillary activity remained unchanged (Table 1).

INTRACORTICAL GLOMERULAR PERFUSION IN CONTROL AND ECV-EXPANDED RATS

In nonexpanded control rats indomethacin had no effect on intracortical glomerular perfusion. The distribution of 131I-MAA was unaltered during acute expansion of the ECV with isotonic saline (Table 1). However, when ECV-expanded rats were pretreated with indomethacin a significant decrease in relative outer cortical perfusion and an increase in relative deep cortical perfusion was noted (Table 1). When intracortical perfusion was calculated from 131I-hippuran clearances obtained in ECV-expanded rats with and without pretreatment with indomethacin, absolute inner cortical perfusion was unaffected by PG inhibition. Thus the decrease in total RPF was entirely due to the decrease in absolute outer cortical perfusion (Fig. 2).

Discussion

Previous results from this laboratory have demonstrated that acute expansion of the ECV in the rat by intravenous infusion of isotonic saline equal to a 10% increase in body weight causes a significant increase in fractional excretion of sodium up to 20%. In addition, we have shown that inhibition of the PG synthesizing enzyme system with indomethacin reduces this fractional excretion by more than 40%. Although previous studies in vitro suggested that PGF2 but not PGE2 may reduce active tubular reabsorption of sodium via inhibition of Na-K-ATPase, our data did not demonstrate any change in cortical, medullary, and papillary Na-K-ATPase activity in ECV-expanded rats following inhibition of PG synthesis. In the present study we therefore further investigated the possi-

Table 1 Glomerular Filtration Rate (GFR), Total Renal Plasma Flow (RPF), Intrarenal 86Rb Distribution and Intracortical 131I-Labeled Macroalbumin Aggregates (MAA) Distribution in Rats with and without Extracellular Fluid Volume (ECV) Expansion, and with and without Pretreatment with Indomethacin (INDO)

<table>
<thead>
<tr>
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<th>Non-ECV-expanded</th>
<th>ECV-expanded</th>
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<tr>
<td></td>
<td>Without INDO</td>
<td>With INDO</td>
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<tr>
<td>RPF (ml/min/kg body wt)</td>
<td>27.8 ± 2.4 (n = 6)</td>
<td>26.0 ± 2.2 (n = 6)</td>
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<tr>
<td>GFR (ml/min/kg body wt)</td>
<td>6.1 ± 0.4 (n = 6)</td>
<td>5.2 ± 0.4 (n = 6)</td>
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<tr>
<td>86Rb distribution (%)</td>
<td></td>
<td></td>
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<tr>
<td>Cortex</td>
<td>53.5 ± 0.7 (n = 5)</td>
<td>60.7 ± 2.4 (n = 5)</td>
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<tr>
<td>Medulla</td>
<td>28.5 ± 0.7 (n = 5)</td>
<td>23.3 ± 1.4 (n = 5)</td>
</tr>
<tr>
<td>131I-MAA distribution (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortex</td>
<td>18.0 ± 0.3 (n = 5)</td>
<td>16.0 ± 1.5 (n = 5)</td>
</tr>
<tr>
<td>Outer cortex</td>
<td>77.2 ± 1.1 (n = 5)</td>
<td>73.4 ± 1.8 (n = 5)</td>
</tr>
<tr>
<td>Inner cortex</td>
<td>22.8 ± 1.1 (n = 5)</td>
<td>26.6 ± 1.8 (n = 5)</td>
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* Expanded vs. nonexpanded rats: P < 0.01.
creases following the administration of arachidonic acid, of 86Rb in cortical, medullary, and papillary tissue. Associated with significant changes in relative distribution was 53.5:28.5:18.0. A slight relative increase in cortical 86Rb content with a corresponding decrease in medullary and papillary 86Rb activity were noted following indomethacin (for review see Anderson15). This would be in agreement with previous observations that inner cortical blood flow in anesthetized dogs increased during ECV-expansion, was unaffected by inhibition of PG synthesis during acute saline loading suggests a role of PG in the natriuresis of acute saline loading22,36 this effect of indomethacin observed in ECV-expanded rats, no effect of this substance on intracortical 131I-MAA distribution could be demonstrated. However, in ECV-expanded rats decreased outer cortical blood flow accompanied by a significant relative increase in juxtamedullary glomerular perfusion was observed after pretreatment with indomethacin. Since PGs seem to be involved in the natriuresis of acute saline loading25,26 this effect of indomethacin observed in ECV-expanded rats may be interpreted as analogous to the observation that saline infusion in the dog is associated with a fall in filtration fraction in deep cortical nephrons.23 In conclusion, our data support the concept that a major role of renal PGs may be to act as local vasodilators of efferent juxtamedullary arterioles. In addition, the reduction in outer cortical perfusion following inhibition of PG synthesis during acute saline loading suggests a role of PG in regulating outer cortical resistance possibly via modulation of pressor stimuli.

Thus, PGs may at least in part play a permissive role for physical factors to promote renal sodium excretion via changes in intrarenal hemodynamics. However, since no significant changes in intrarenal and intracortical blood flow distribution were observed with acute ECV expansion only, it may be that the hemodynamic changes following administration of indomethacin are to some degree a pharmacological rather than a physiological effect of the inhibition of PG biosynthesis.
Acknowledgments

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