Mechanism of natriuresis and diuresis during elevated renal arterial pressure

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Continuous perfusion of the dog's renal artery at pressures averaging 200 mm Hg resulted in natriuresis, increased osmolar clearance, and increase in urine volume. The diuresis was typified by a decrease in T\textsubscript{\textit{H}2\textit{O}}, and in some instances positive free water clearance resulted. U/P of osmolality also declined, in some cases below unity. The above changes were observed in the absence of increase in glomerular filtration rate, as measured by creatinine clearance. The reductions in T\textsubscript{\textit{H}2\textit{O}} and U/P osmolality were correlated with decrease in the papillary to cortical sodium gradient. Thus, a washout of the osmotic gradient appeared to be the mechanism responsible for the decrease in ability of ADH to concentrate the urine. Because sodium and total osmolar load did not increase during the elevated pressure perfusion, decreased tubular reabsorption must have accounted for the natriuresis and enhanced osmolar clearance. It is speculated that the papillary sodium washout might indirectly influence sodium reabsorption by the ascending limb of the loop of Henle. The possibility is also considered that a mechanism of intrarenal hormonal regulation, responsive to changes in arterial pressure, might be responsible for the increased sodium clearance.

methods

Experiments were performed in 12 dogs anesthetized with 30 mg/kg pentobarbital given intravenously. The technique for elevating renal arterial perfusion pressure was that previously employed (9). The perfusion pump (Dale-Shuster) and connections were designed so that blood never contacted metal or glass: Teflon valves, plastic connections and fittings, Tygon tubing, and polyethylene catheters were used throughout. The left kidney was continuously perfused by blood supplied to the pump by the carotid artery, while the opposite kidney served as the control.

The experimental protocol was as follows: Infusion of 0.85% NaCl was begun at a rate of 4 ml/min with a motor-driven syringe ca. 2 hr before the beginning of urine collection. A priming dose of creatinine was given 50 min prior to clearance measurement and continuously infused throughout the experiment. Two paired control periods of 10 min each were followed by elevation of the pump pressure of the experimental kidney from an out of the medullary osmotic gradient needed for the process of urinary concentration. In support of this, with prolonged perfusion of the dog kidney at elevated arterial pressure, they observed that C\textsubscript{\textit{H}2\textit{O}} became positive in their experiments. Analysis of the renal osmolar gradient was not made, however. Tobian et al. (15) have speculated on the possibility of a hormonal mechanism accounting for the natriuresis, activated by increased perfusion pressure. They discounted the possibility of increased medullary blood flow, but also did no tissue slice analysis to see if possible alteration of the gradient of osmolarity might have occurred in their experiments.

The present experiments were designed to correlate changes in concentrating ability with possible alterations in the cortical to papillary sodium gradient resulting from increased renal arterial pressure. Alterations in osmolar clearance and C\textsubscript{\textit{H}2\textit{O}}, and in U/P osmolality and U/P creatinine served as indices of changes in concentrating ability, as related to the sodium cortical to papillary gradient. Na and K clearances were also examined.

The mechanism of the natriuresis and diuresis which accompanies acute elevation of renal arterial pressure has been of particular interest because of occurrence of such alterations in the presence of apparent constancy of glomerular filtration rate (9). Thurau and Deetjen (13) have presented evidence that, despite constancy of the cortical blood flow due to autoregulation, medullary blood flow increases, allowing for the possibility of wash-out of the medullary osmotic gradient needed for the process of urinary concentration. In support of this, with prolonged perfusion of the dog kidney at elevated arterial pressure, they observed that C\textsubscript{\textit{H}2\textit{O}} became positive in their experiments. Analysis of the renal osmolar gradient was not made, however. Tobian et al. (15) have speculated on the possibility of a hormonal mechanism accounting for the natriuresis, activated by increased perfusion pressure. They discounted the possibility of increased medullary blood flow, but also did no tissue slice analysis to see if possible alteration of the gradient of osmolarity might have occurred in their experiments.

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pressur e diuresis free water clearance osmolar clearance corticomedullary sodium gradient corticomedullary potassium gradient sodium clearance creatinine clearance urinary concentrating ability

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average of 154 mm Hg to a level of ca. 200 mm. After a 10-min discard period, urine was collected in three paired periods of 10 min each. The left kidney was then removed and paired slices rapidly taken from the cortex, outer medulla, and papilla. An additional period was taken for the control kidney, then slices of the control kidney were likewise obtained.

Chemical procedures employed, including the method used for tissue sodium analysis, have been previously described (10).

RESULTS

Relationship of clearance to hemodynamic alterations. In Fig. 1, average changes in urine volume, CH₂O, COsm, and CNa are related to CCr, taken to measure glomerular filtration rate, and to the renal arterial pressure. Use of a compression chamber helped to minimize pulse-pressure increase as the pump action was increased during the experimental periods. The control pulse pressure averaged 36 mm Hg, which increased to 50 mm. GFR did not increase in the face of increase in arterial perfusion pressure, but rather showed a small, nonspecific decrease paralleling a slight decrease in the control. Although the experimental kidney clearance for creatinine averaged 10 ml/min less than the intact control, the average value of 0.75 ml/g kidney tissue per min (0.54–1.08) was well within the expected normal range for the canine kidney (12).

C₀sm and C₅Na increased during period 3, then decreased toward control with further perfusion at elevated pressure. The increase in C₅Na occurred with no increase in GFR and relatively constant plasma sodium concentration. The following average values for plasma Na were found during periods 1–5: 149, 148.3, 148.6, 147.3, and 147.3 mEq/liter. The changes in C₀sm were also accompanied by significant alterations in plasma osmolality. K clearance (not shown in the figure) showed a decrease from the control average of 7.1 ml/min to 4.9 during the pump perfusion. The corresponding paired control kidney values were 8.7 and 8.3 ml/min, respectively.

Urine volume of the pressure-elevated kidney increased from the control average of 0.73 to 1.31 ml/min (P = .05–.01) during period 3, decreasing somewhat to 1.25 and 1.12 during the next two periods (P = .05 and .10–.05, respectively, when compared to the ipsilateral control values). T₉/H₂O averaged 0.52 ml/min, then progressively decreased to 0.31, 0.22, and 0.20, the latter two values highly significantly reduced from the control average (P = .01 or less). However, although T₉/H₂O decreased in all experiments, it approximated zero in only two animals, and became positive in only three others of the entire series.

Changes in tissue sodium and potassium distribution. These are summarized for sodium in Fig. 2 for cortex, outer medulla, and papilla. It can be seen that only in the papilla is the sodium content significantly reduced by the elevated arterial pressure, maintained for a total of 40 min. The decrease averaged 19.3% (143 to 115.6 mEq/kg wet tissue) when compared to the paired kidney’s papillary sodium content. However, this represented 3% of the papillary to cortical gradient (143 to 72 mEq/kg wet tissue).

Potassium showed no significant differences in the regional distribution as the result of pressure elevation, the average values for the papilla, outer medulla, and cortex being 44.9, 50.1, and 61.8 mEq/kg wet tissue, respectively, for the experimental kidney as compared to 42.7, 53.7, and 64.1 for the control.

Relation of CH₂O and U/Pₐsm to tissue sodium content. Osmolar U/P of the last two periods of increased arterial pressure is related to papillary sodium content in Fig. 3. Also shown are the values for the last two periods of the paired control kidney. T₉/H₂O averaged 0.21 ml/min for the experimental kidney at this time, and 0.52 for the control, at the average papillary sodium concentrations of 115.6 and 143 mEq/kg wet tissue, respectively. It is apparent that the lower values of osmolar U/P and T₉/H₂O are related to the lower papillary sodium concentra-
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FIG. 2. Distribution of renal tissue sodium (per kg wet tissue) in pump-perfused kidney as compared with simultaneous control. Mean values ± 1 se. P: papilla; M: outer medulla; C: cortex.

FIG. 3. Relationship of U/P osmol to papillary sodium content of pump-perfused kidney (solid symbols) and paired control (open). Last two periods only of the elevated pressure are included.

The exact mechanism of impairment of reabsorption still eludes definition. The possibility that physical forces might be involved which modify the transit of electrolytes and water from the tubular lumina through the interstitium into peritubular capillaries and vasa recta seems to be ruled out by the demonstration that proximal tubular intraluminal and peritubular capillary pressures remain constant when blood pressure is elevated (14). This comes about because of afferent arteriolar constriction—the autoregulatory response, buffering the effect that the elevated arterial pressure might have on intrarenal pressure relationships.

A more likely explanation of the decrease in sodium reabsorption may involve the papillary washout of sodium. In the descending limb of the loop of Henle, there is passive loss of water into the hypertonic interstitium. If medullary blood flow is increased and there is a washout of sodium, the medullary hypertonicity would be decreased, and the volume of water leaving the descending limb would decrease. As a result, the volume of flow through the ascending limb would be enhanced, and the concentration of sodium reaching this segment would decrease. As the result of this, the net transport of sodium out of the ascending limb would decrease. Even if the transport rate could achieve some minimal concentration of sodium in the tubular fluid, net reabsorption would be decreased as an increased rate of flow of less concentrated fluid entered the ascending limb.

The possibility that a humoral mechanism could be responsible ought to be considered. Tobian et al. (15) have sought to explain the impaired sodium reabsorption in the distal nephron of the rat kidney during arterial pressure elevation by such a mechanism. They hypothesize that the elevated pressure acts on stretch receptors, possibly in the juxtaglomerular complex, resulting
in the release of a humoral substance which in turn passes to the distal tubular cells involved in the active transfer, acting here to inhibit sodium reabsorption. The humoral substance which might be responsible was not identified, although angiotensin has been viewed as a possibility by others. Stop-flow studies in the dog (17) appear to demonstrate inhibition of sodium reabsorption in the distal nephron by angiotensin, agreeing with Tobian’s findings, although dosages employed could be considered pharmacologic. De Wardener et al. (4) have also postulated a hormonal factor, other than aldosterone, which is responsible for increased excretion of sodium following expansion of the ECF volume. The receptor site, as well as the site of production of the alleged hormone, was not elucidated, however.

If angiotensin proves to be the regulatory humoral factor, some difficulty is presented by the recent findings of Skinner, McCubbin, and Page (11) that elevated pressure in the renal artery results in inhibition of renin production, whereas reduced pressure is a stimulus to production, the site being the juxtaglomerular apparatus. If this directly influences angiotensin production, then elevation of pressure would decrease angiotensin influence on tubular reabsorption, and if it is natriuretic, favor sodium retention. On the other hand, if angiotensin might cause sodium retention, then the findings of Skinner et al. could be resolved, for inhibition of angiotensin production by elevated renal arterial pressure would then favor sodium loss. The exact role of angiotensin on tubular sodium handling, however, still remains controversial, complicated by renal hemodynamic influences, and manifesting species differences (2, 3, 5, 6, 8, 16, 17). Angiotensin, added alone or in conjunction with Pitressin, did not influence sodium transport by the toad skin (1).

The stop-flow studies of Tobian et al. (15) rather strongly support the conclusion that the distal convolution and collecting duct are the loci of impaired sodium reabsorption; proximal tubular handling of the ion appears to be unaltered by elevated pressure, at least in the rat. It is possible that a similar mechanism accounts for the sodium and solute diuresis in the dog. However, the manifestations of loss of concentrating power (decrease in \( T_{\text{H}_2\text{O}} \) and U/P osmolality) require another explanation. Here the washout of sodium, and presumably other osmotic constituents, from the papilla may play a significant role in the over-all mechanism.

It is of interest that the present experiments gave evidence of loss of concentrating ability without alteration of the sodium gradient other than in the papilla. This was reduced to the level of that found in the outer medulla; sodium content here was the same as in the control. It is conceivable that more prolonged perfusion at elevated pressure might have reduced the gradient further, including that in the outer medulla, and might have led to even greater output of free water and further reduction in the U/P osmolality. Thurau and Deetjen (13) observed in their series of elevated-pressure kidneys a more significant increase in \( C_{\text{H}_2\text{O}} \) than was found in the present series. However, it is noteworthy that their control \( T_{\text{H}_2\text{O}} \) averaged considerably less than the present group, 2 \( \mu \)lter/g per kidney tissue as compared to 10 \( \mu \)lter/g per min. In addition, their U/P osmolal values were lower in the control, ca. 1.5 compared to 1.8. Thus, it appears that their base-line urines were closer to isotonicity before the pump perfusion was initiated. However, the trends were similar in both sets of experiments, as Fig. 4 indicates.

Finally, the possibility that decrease in ADH levels might be operative in accounting for the excretion of the more dilute urine must not be overlooked. In the present experiments, the constancy of the plasma osmolality would tend to rule out a dilutional stimulus to the hypothalamic nuclei, although operation of a volume receptor might still be possible in response to the saline infusion. It has been speculated that such receptors, possibly located in the large intrathoracic veins and cardiac atria, are responsive to increments in plasma or extracellular volume, or both, blocking the release of ADH (7). However, examination of the response of the control kidneys indicates that this type of modification must have been slight, as noted by the negligible change in \( C_{\text{H}_2\text{O}} \). Thus, the continuously elevated arterial pressure supplied the adequate stimulus for creating the observed

**FIG. 4.** Relationship of \( U/P_{\text{creatinine}} \) to \( U/P_{\text{creatinine}} \) in experimental kidney. Control values shown are for experimental (pump-perfused) kidney. Paired control values were essentially similar in distribution. Solid curve depicts for comparative purposes the trend of the data of Thurau and Deetjen (13).
dilution of the urine. It is believed that washout of the papillary osmotic gradient appeared to be the mecha-

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