Mechanism of natriuresis and diuresis during elevated renal arterial pressure


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{\textsuperscript{\textfrac{1}{3}}}, 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{\textsuperscript{\textfrac{1}{3}}} 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.

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Hepatic and renal clearance of vasopressin from plasma of dogs


The fraction of vasopressin removed from portal venous plasma by liver (hepatic portal extraction ratio) was estimated in conscious, hydrated female dogs. Anti-diuretic responses to physiological doses of beef Pitressin (Parke-Davis) given as 5-min infusions via a splenic vein catheter were compared with responses to the same dose infused by way of a foreleg vein. The fraction of vasopressin removed during passage through left kidney was estimated in experiments of analogous design. Antidiuretic responses of right kidney to physiological doses given as 5-min infusions via a catheter implanted transaortically in left artery were compared with responses of right kidney to same dose given by way of foreleg vein. Infusions were given by the alternate routes at hourly intervals. Hepatic portal extraction ratio for vasopressin averaged 12%. Renal extraction ratio averaged 25%. Renal extraction ratio, estimated by bioassay of arterial and renal venous plasma, was somewhat smaller (20%) in anesthetized dogs in which concentration of vasopressin in plasma was raised to unphysiologically high values by a constant infusion of beef Pitressin. From measurements of plasma flow through these organs and extraction ratios, clearances of vasopressin in liver and both kidneys were calculated. Respective estimates, expressed as per cent of plasma volume cleared per minute, were: hepatic, 4.6; renal (physiological plasma concentrations), 9.4; and renal (high plasma concentrations), 5.8.

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Effect of renin, ischemia, and plasma protein loading on the isolated perfused kidney
Normal renal function has been maintained in an isolated artificial heart-lung, whole-blood perfused rabbit kidney for periods of 2-4 h. The isolated kidney responds to changes in perfusion pressure, changes in plasma protein concentration, and exposure to a 10-min period of ischemia, in a manner similar to that described for the kidney of the normal intact animal. Elevation of the plasma protein concentration produces a fall in the rate of urine flow, sodium excretion, and creatinine clearance, and a marked proteinuria. The administration of renin produces a marked diuresis, natriuresis, and proteinuria. This effect is also produced by the exposure of the isolated kidney to a 10-min period of ischemia, suggesting that this response may be mediated by a renin mechanism. The responses of the kidney to these two procedures differ only in that ischemia produces an increase in renal blood flow and renin produces a slight reduction in renal blood flow and a more pronounced proteinuria.
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Effect of catecholamines and the renal nerves on renin secretion in anesthetized dogs
Intravenous infusion of either epinephrine (5-6 µg/min) or norepinephrine (12-16 µg/min) during maintenance of a constant renal arterial blood pressure by means of suprarenal aortic constriction, or stimulation of the renal nerves produced essentially the same effects on renal function and renal venous plasma renin concentration, the latter being measured indirectly by bioassaying the pressor activity produced by plasma incubation under standardized conditions. Glomerular filtration rate (GFR), renal plasma flow (RPF), and sodium excretion were decreased, and renin concentration was increased. The induction of osmotic diuresis during catecholamine infusion or renal nerve stimulation reversed or prevented the increase in renin secretion but did not alter the changes in GFR or RPF. It is suggested that the increased renin secretion induced by catecholamines and renal nerve stimulation in nondiuretic dogs might be the indirect result of the decrease in filtered sodium produced by these procedures. However, a direct effect of the catecholamines and renal nerves on the renin-secreting cells cannot be ruled out.
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Role of transmural pressure in local regulation of blood flow through kidney
In the kidney of the anesthetized dog, the pressure in an occluded hilar lymphatic vessel was used as an index of tissue pressure. While elevation of renal vein pressure produced a large rise in lymphatic pressure, reduction of renal artery pressure had little effect. Similarly, while elevation of vein pressure at constant flow produced an almost equal rise in lymphatic pressure, large changes in blood flow and hence artery pressure had little effect, despite evidence of local regulation of resistance. Intrarenal injection of vasoactive agents at constant flow, which produced large changes in renal artery pressure, had little effect on lymphatic pressure. Sudden transient increase in renal blood flow sometimes produced changes in perfusion pressure which could have resulted from active
constriction subsequent to rise in transmural pressure. These findings provide little support for the tissue pressure theory of autoregulation but suggest that tissue pressure does participate in the vascular response to elevated vein pressure. The study also provides some evidence for a vascular myogenic response to change in renal vascular transmural pressure.

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Role of chemical factors in regulation of flow through kidney, hindlimb, and heart

In the anesthetized dog, blood flow or metabolic rate was varied in kidney, hind-limb, or heart (experimental organ) while simultaneously diverting a portion of the venous outflow through forelimb or kidney (bioassay organ). The resistance to blood flow through the experimental organ gradually rose in the first few minutes following a large increase in flow and gradually fell following a large decrease in flow. Resistance to blood flow through an experimental organ (hindlimb) fell following increase in metabolic rate. In each case, bioassay organ resistance changed in the same direction when the assay organ was the forelimb and in the opposite direction when the assay organ was the kidney. These findings suggest that active hyperemia, reactive hyperemia, and autoregulation of blood flow result, at least in part, from alteration in the chemical environment of the blood vessels. Other findings in this study support the possibility that adenosine triphosphate contributes to the change in environment.

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Circulation times in the dog kidney measured by an external counting technique and by a dye dilution method

The aim of the study was to compare renal circulation times measured by an external isotope counting technique with the circulation times obtained by means of a photoelectric dye dilution technique. The fastest circulation time, the mean circulation time, and the cortical mean passage time for cardiogreen were measured in the dog kidney by a photoelectric dye dilution technique. At the same time measurements of the fastest circulation time and the mean circulation time for labelled red cells and plasma were performed by an external counting technique. The results obtained by the two methods showed good linear correlations. However, a significant difference between the fastest circulation times was found. The ratio between the two sets of values was 0.75, S.D. was 0.18, n = 26. The difference was supposed to be due to the use of a too wide collimator opening. The ratio between the mean circulation times was 1.18, S.D. was 0.12, n = 22. The mean circulation time measured by the photoelectric technique was the longest. Possible explanations for this discrepancy are discussed. The ratio between the mean passage time for dye passing through the cortex and the mean circulation time for red cells and plasma measured by the external counting technique was 0.54, S.D. was 0.10, n = 19. This indicates that the graphical analysis and the mathematical model used for the external counting curve probably are correct, and that the mean circulation time calculated in this way is valid for blood passing the renal cortex.
Renal tubular microinjection studies in normal and potassium-depleted rats


Microinjections of inulin-methoxy-\(^3\)H and \(^{14}\)C-urea were made into renal tubules of normal and potassium-depleted rats during mannitol diuresis. Inulin transit times along the nephron were prolonged and more variable in potassium-depleted animals following injections into proximal and distal tubules. The recovery of \(^{14}\)C-urea after proximal tubular injections was closely correlated with inulin transit time and less urea was recovered in the potassium-deficient animals. \(^{14}\)C-urea recovery after distal tubular injections was not influenced by potassium depletion. The results indicate that in the potassium-deficient animals delivery of solute to the renal medulla was reduced and transit time through Henle’s loop and the remainder of the nephron was prolonged. The former finding may partly explain the reduction in medullary osmolality and the limitation of urine concentration produced by potassium deficiency.

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Osmolality of renal tubular fluids in potassium-depleted rodents


The early distal tubular fluid of K-depleted rats was as hypo-osmotic as in normal rats, indicating a normal sodium concentration gradient across the epithelium of the thick ascending limb of the loop of Henle under the conditions of these experiments. Osmotic equilibration between collecting duct fluid and loop of Henle fluid or vas rectum blood was preserved in the papilla of K-depleted hamsters both in the nondiuretic and mannitol-diuretic states. It thus appears that the defective ability to concentrate the urine produced by K depletion in rodents is not due to reduced water permeability of the collecting ducts but is a result of reduced medullary interstitial osmotic pressure. The latter occurs despite normal ability of the sodium pump in the thick ascending limb of the loop of Henle to generate a trans-tubular concentration gradient and is probably due, at least in part, to reduced delivery of solute to the medulla. However, reduction in medullary osmotic pressure would also result if medullary blood flow were increased in K depletion either absolutely or relatively compared with tubular fluid flow rate. Information concerning this possibility is not available.

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Summaries – Resumes

Tracer microinjection studies of renal tubular permeability


Renal tubular permeability was studied in rats with a tracer microinjection technique in which radioactive inulin and another isotope were simultaneously micro-injected into proximal or distal convoluted tubules during osmotic diuresis and their excretion by that kidney measured. Noninulin radioactivity excreted with a time course similar to that of inulin is termed direct recovery and that excreted more slowly, delayed recovery. The absence of inulin excretion by the contra-lateral kidney demonstrated that there was no transtubular efflux of this substance under these conditions. Inulin transit time averaged 0.84 min and 0.33 min following proximal and distal microinjection, respectively. Excreted sodium 22 molecules apparently followed closely
the path of inulin molecules, since they appeared in the urine simultaneously. There was no delayed recovery of sodium 22. There was considerable direct and delayed recovery of urea-14C, indicating its diffusion into the tubular epithelial cells and subsequent return to the lumen. There was very little delayed and almost no direct recovery of tritiated water under these conditions in which physiologically maximally effective amounts of ADH were probably present. The injected quantity of isotope minus its direct recovery is believed to approximate its total tubular efflux.

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Tracer microinjection studies of effect of ADH on renal tubular diffusion of water
The tracer microinjection technique was utilized to study the effect of vasopressin (ADH) on transtubular water diffusion in rats with diabetes insipidus. Inulin-14C and titrated water (HTO) were simultaneously injected into the same distal convolutions before and after intravenous administration of ADH, and their recovery in the urine of the injected kidney measured. Urine flow was maintained constant by intravenous infusion of mannitol. ADH had no effect on inulin recovery, but delayed and reduced HTO excretion. Total HTO recovery averaged 19% before and 11% after ADH, and direct HTO recovery averaged 8% before and 1% afterward. A theoretical treatment of the data is presented which leads to the conclusion that ADH increases the permeability to water diffusion of the luminal surface of the cellular membranes of the distal convolutions and/or collecting ducts, but has no effect on permeability to water diffusion of their basal surfaces.

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Analysis of electrolyte movement in thin Henle’s loops of hamster papilla
The sine qua non of the countercurrent multiplier hypothesis is the assumption that ascending limbs transport salt hypertonically. We used the stopped-flow micro-perfusion technique to examine this question. Saline solutions isolated between oil droplets within the lumen of thin limbs of Henle’s loops remained at constant volume, while raffinose solutions underwent a continuous volume increase with time. After equilibrating, the Na and Cl concentrations of the saline perfusates were similar to those of vasa recta plasma; their osmolalities were also the same. These results were identical for both ascending and descending limbs and suggest that neither segment transports salt actively. Descending limbs and vasa recta were water-potential under all conditions; the ascending limb during antidiuresis is 9 mV negative, the collecting ducts 17 mV negative. Ascending limb negativity was abolished by osmotic diuresis or stopped-flow micropertfusion with saline. Measurement of ion concentrations showed that the ascending limb potential of anti-diuresis is not a diffusion potential, and that its disappearance during osmotic diuresis is not due to the appearance of a diffusion potential of countersign. We suggest that the ascending limb potential is a streaming potential, but that the collecting duct potential reflects active ion transport. Moreover the clear implication of this study is that the collecting duct is the only tubular structure in the inner medulla capable of performing the osmotic work necessary to establish interstitial hyperosmolality.

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Reliability of inulin for determining volume flow in rat renal cortical tubules
Recent assertions by others that inulin is reabsorbed from the proximal tubule of the rat and Necturus led to these experiments which were designed to measure the recoverability of inulin in rat tubules. A microperfusion pump delivered Ringer solution containing inulin into a single proximal tubule at a constant rate. The perfusate was collected from the distal tubule for a specified period. The inulin content of the distal sample was then measured with the microanthrone method and compared with the amount of inulin delivered by the pump in that time. The distal recovery of inulin in such experiments was 99.3 ± 2.3%, indicating no re-absorption. Similar experiments were performed on rats receiving inulin intravenously. The inulin recovery was 99.6 ± 2.9%, and there is no secretion of inulin. Finally, inulin 14C was injected into proximal tubules and measured in the urine; the recovery of 98.4 ± 1.4% makes it unlikely that there is significant reabsorption in the collecting ducts, and we conclude that inulin is conserved in the tubule lumen.
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