JCI The Journal of Clinical Investigation

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J Clin Invest. 1969;48(2):271-283. https://doi.org/10.1172/JCI105983.

Research Article

Rapid intravenous infusion of saline is known to suppress reabsorption of sodium and water in the proximal tubule. It has previously been shown that this suppression is accompanied by two changes which in combination might account for the over-all decrease in reabsorption: a reduction in the intrinsic reabsorptive capacity of the tubular epithelium ($C/\pi r^2$) and a reduction in the ratio between tubular volume and GFR ($\pi r^2 d/V_o$). The present micropuncture experiments were carried out in order to study the possible role of altered peritubular physical forces (hydrostatic and colloid oncotic pressure) in mediating these two changes. Proximal tubular reabsorptive capacity, transit time, fractional reabsorption of sodium and water, $\pi r^2 d/V_o$, and intratubular hydrostatic pressure were measured in saline-loaded rats during acute changes in renal perfusion pressure induced by intermittent constriction of the abdominal aorta.

We found that when renal perfusion pressure was lowered to 70-90 mm Hg, the usual effects of saline loading on $C/\pi r^2$, $\pi r^2 d/V_o$, and fractional reabsorption in the proximal tubule were greatly minimized. When the aortic clamp was released and renal perfusion pressure allowed to rise, $C/\pi r^2$, $\pi r^2 d/V_o$, and fractional reabsorption fell markedly to levels characteristically seen in saline diuresis. Reclamping of the aorta reversed all of these changes.

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Effect of Changes in Renal Perfusion Pressure on the Suppression of Proximal Tubular Sodium Reabsorption due to Saline Loading

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ABSTRACT Rapid intravenous infusion of saline is known to suppress reabsorption of sodium and water in the proximal tubule. It has previously been shown that this suppression is accompanied by two changes which in combination might account for the over-all decrease in reabsorption: a reduction in the intrinsic reabsorptive capacity of the tubular epithelium ($C/\pi r^2$) and a reduction in the ratio between tubular volume and GFR ($\pi r^2 d/V_o$). The present micropuncture experiments were carried out in order to study the possible role of altered peritubular physical forces (hydrostatic and colloid oncotic pressure) in mediating these two changes. Proximal tubular reabsorptive capacity, transit time, fractional reabsorption of sodium and water, $\pi r^2 d/V_o$, and intratubular hydrostatic pressure were measured in saline-loaded rats during acute changes in renal perfusion pressure induced by intermittent constriction of the abdominal aorta.

We found that when renal perfusion pressure was lowered to 70–90 mm Hg, the usual effects of saline loading on $C/\pi r^2$, $\pi r^2 d/V_o$, and fractional reabsorption in the proximal tubule were greatly minimized. When the aortic clamp was released and renal perfusion pressure allowed to rise, $C/\pi r^2$, $\pi r^2 d/V_o$, and fractional reabsorption fell markedly to levels characteristically seen in saline diuresis. Reclamping of the aorta reversed all of these changes.

In order to determine whether the changes in $C/\pi r^2$ accompanying changes in renal perfusion pressure were mediated by a circulating natriuretic hormone, we assayed in hydopenic rats the dialysate of plasma collected from saline-loaded rats during and after release of aortic constriction by the split oil drop method. No significant difference in reabsorptive half-time ($t_{\frac{1}{2}}$) was found between the two dialysates, and $t_{\frac{1}{2}}$ with both dialysates was approximately the same as was found when isotonic saline was injected in the tubules of hydropenic control animals. These observations suggest that the large changes in $C/\pi r^2$ which occurred with changes in renal perfusion pressure in saline-loaded rats were not mediated by a circulating hormone. We suggest that the reduction in $C/\pi r^2$, $\pi r^2 d/V_o$, and fractional reabsorption which occurs in the proximal tubule during a saline diuresis is related to the rise in hydrostatic pressure within the kidney.

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Received for publication 21 June 1968 and in revised form 9 October 1968.

INTRODUCTION

It is now well established that the increase in urinary excretion of sodium which occurs during acute saline loading is due to a decrease in sodium reabsorption by the tubules rather than to an increase in the amount of sodium filtered by the glomeruli (1–8). The mechanism (or mechanisms) responsible for this decrease in tubular reabsorption is not entirely clear. It has been shown by Rector, Sellman, Martinez-Maldonado, and Seldin (9) that acute saline loading in the rat is accompanied by two changes in the proximal tubule: a reduction in the intrinsic reabsorptive capacity of the epithelium ($C/\pi r^2$), and a reduction in the ratio between tubular volume and glomerular filtration rate ($\pi r^2 d/V_o$). The combined effect of these two changes were thought to account for the over-all decrease in proximal sodium reabsorption. These authors postulated that the reduction in $C/\pi r^2$ was due to a humoral substance secreted during saline loading, and that the decrease in $\pi r^2 d/V_o$ was due to altered peritubular physical forces which prevented the tubule from dilating in proportion to the increase in glomerular filtration rate (GFR).

More recently, it has been found that certain experi-

mental maneuvers designed to alter the hydrostatic or the colloid oncotic pressure within the peritubular capillaries can also produce significant changes in $C/\pi r^2$ of the proximal epithelium (10, 11). Thus, constriction of the renal vein (10) and acute arterial hypertension (11), both of which caused a rise in hydrostatic pressure in the peritubular capillaries, were found to inhibit proximal sodium reabsorption and to reduce $C/\pi r^2$. Because saline loading is usually accompanied by a decrease in renal vascular resistance (5, 12, 13) and often by an increase in blood pressure, it seemed possible that increased transmission of hydrostatic pressure from the renal artery to the peritubular capillaries, or a decrease in peritubular colloid oncotic pressure, (or both) may be responsible not only for the decrease in $\pi r^2 d/V_0$, but also for the reduction in $C/\pi r^2$.

In order to study this problem, we measured proximal tubular $C/\pi r^2$, Lissamine green transit time, fractional reabsorption of sodium and water, the ratio $\pi r^2 d/V_0$, and hydrostatic pressure in saline-loaded rats during acute changes in renal perfusion pressure induced by intermittent constriction of the abdominal aorta. We found that when renal perfusion pressure was lowered to 70–90 mm Hg, the usual effects of saline loading on $C/\pi r^2$, $\pi r^2 d/V_0$, and fractional reabsorption in the proximal tubule were greatly minimized. When the aortic clamp was released and renal perfusion pressure allowed to rise, $C/\pi r^2$, $\pi r^2 d/V_0$, and fractional reabsorption fell markedly. Reclamping the aorta reversed these changes.

Because of the possibility that the changes in $C/\pi r^2$ were mediated by a circulating natriuretic hormone, we assayed the plasma of saline-loaded rats, collected during and after release of aortic constriction, for an inhibitor of sodium transport by the split oil drop method. No inhibitor was demonstrable in the plasma dialysate of such animals. Our observations are most compatible with the view that the decrease in both $C/\pi r^2$ and $\pi r^2 d/V_0$ during a saline diuresis is mediated by an increase in hydrostatic pressure within the kidney.

METHODS

Reabsorptive half-time and Lissamine green transit time measurements. 12 male white rats, weighing 250–350 g, were anesthetized with intraperitoneal Inactin, 100 mg/kg body weight, and prepared for micropuncture as previously described (14). Intravenous infusions were administered via a PE 50 catheter in an external jugular vein, and blood pressure was measured in a femoral artery by a Statham strain gauge (model P 23 Dc), with a Grass polygraph (model 5 D) as recording instrument. Urine was collected from the micropuncture kidney (left) via a PE 50 catheter threaded into the renal pelvis. The abdominal aorta cephalad to the origin of the renal arteries was freed by blunt dissection and an adjustable clamp placed around it. The clamp was then tightened until femoral artery blood pressure stabilized between 70 and 90 mm Hg. During the surgical preparation of the animal, 3 ml of Ringer's lactate solution was given intravenously to replace fluid losses.

After the surgical preparation was completed and the aortic clamp adjusted, priming doses of inulin-^{14}C (25 μc) and *p*-aminohippurate (PAH) (0.2 mg) were given intravenously in 1 ml of Ringer's solution each. This was followed by a constant infusion of Ringer's lactate solution containing 0.8 μc/ml of inulin-^{14}C and 0.3 mg/ml of PAH at a rate of 0.5 ml/min. After a 50 min period of infusion at this high rate, the first of three urine clearance periods was started. During the first clearance period, renal perfusion pressure was maintained between 70 and 90 mm Hg. During the second period, the aortic clamp was loosened and femoral artery pressure allowed to rise. In the third period the clamp was retightened to the same level of blood pressure as in the first period. Arterial blood samples (0.4 ml) were taken from a carotid artery at the midpoint of each urine collection, the volume of blood being immediately replaced with an equal volume of Ringer's solution. Inulin-^{14}C concentration in the urine and plasma was measured by liquid scintillation counting, as previously described (15), and PAH concentration in the same samples was measured by the method of Smith, Finkelstein, Aliminosa, Crawford, and Graber (16). Inulin, and PAH clearances and filtration fraction (FF) were calculated from standard equations (17).

During each of the three clearance periods described above, the reabsorptive half-time ($t_{\frac{1}{2}}$) of isolated columns of isotonic NaCl (150 mEq/liter) injected into the lumen of surface proximal convolutions was measured by the split oil drop method of Gertz (18). During the second and third clearance periods, $t_{\frac{1}{2}}$ measurements were started within 2–3 min after renal perfusion pressure had been changed abruptly by adjustment of the clamp. The method used for measurement of $t_{\frac{1}{2}}$ was the same as that described previously (11), except that special care was taken that the length of the saline column was at least 5 tubule diameters (approximately 100 μ) before the injection was stopped and shrinkage of the column allowed to start. Measurements of saline columns were made from projected Ektachrome transparencies taken by timed-sequence photography.

In addition to the split drop data obtained from saline-loaded animals, control reabsorptive $t_{\frac{1}{2}}$ measurements were made in seven normal rats deprived of food and water overnight, given no fluid to replace surgical losses, and infused with Ringer's lactate at the slow rate of 0.025 ml/min. As in the saline-loaded animals, care was taken to measure saline columns with an initial length of at least 100 μ.

From the measured $t_{\frac{1}{2}}$ values the reabsorptive rate per unit of tubular volume ($C/\pi r^2$) was calculated from the expression (19):

$$C/\pi r^2 = 0.693/t_{\frac{1}{2}}. \quad (1)$$

In addition, the transit time (T) of intravenously injected Lissamine green from the glomerulus (taken as the initial diffuse discoloration of the kidney) to the terminal proximal convolutions on the surface of the kidney was measured at least twice at the beginning and end of the three clearance periods in the saline-loaded animals. From the average T for each period and the average value for $C/\pi r^2$, the tubular fluid : plasma inulin ratio, $(TF/P)_{In}$, at the terminal proximal convolutions was calculated from the equation of Gertz, Mangos, Braun, and Pagel (19):

$$\log(TF/P)_{In} = \frac{CT/\pi r^2}{2.3}. \quad (2)$$

From the values for $(TF/P)_{In}$ and $C/\pi r^2$, the average ratio between tubular volume and GFR for each clearance period

was calculated by the expression (9):

$$\pi r^2 d/V_0 = \frac{\text{per cent reabsorbed}}{C/\pi r^2}. \quad (3)$$

In each experiment the internal diameter of the isolated columns of saline between the two oil blocks was measured from the projected photographic transparencies by a previously described method (11).

In this group of experiments, urinary and plasma sodium concentrations were measured by flame photometry, with lithium as an internal standard, and sodium excretion rate ($U_{Na}V$) and fractional reabsorption of sodium were calculated for each clearance period.

Proximal hydrostatic pressure measurements. In four additional rats loaded with Ringer's solution at the same rapid rate of 0.5 ml/min, proximal tubular hydrostatic pressure was measured during three consecutive periods in which the aorta was constricted, released, and reconstricted, as described above. The method used for intraluminal pressure measurement was similar to that described by Gottschalk and Mylle (20, 21). Inulin and PAH clearances were also measured in these four animals and filtration fraction calculated as above.

Assay for natriuretic hormone. In four normal rats, the abdominal aorta above the renal arteries was constricted with a clamp and femoral artery blood pressure lowered to 70–90 mm Hg. Ringer's infusion was then started at 0.5 ml/min. At the end of 90 min of infusion, 2 ml of blood was collected from the femoral artery for hormone assay. The aortic clamp was then released, the rapid infusion continued for another 30 min, and a second blood sample collected for hormone assay. All plasma samples were dialyzed against an equal volume of isotonic saline for 18–24 hr at 5°C in acrylic plastic cells (Chemical Rubber Co., Cleveland, Ohio) with a Visking semipermeable membrane (Union Carbide Corp., Chicago, Ill.) separating the two half cells. Neither the plasmas nor the dialysates were pooled. In every experiment, the individual dialysates from a single donor rat were tested in a single normal hydropenic assay rat on the day after the plasma had been obtained from the donor animal. The method used for assay of an inhibitor of sodium transport was reabsorptive $t_{\frac{1}{2}}$ measurements, with the plasma dialysate as the oil-splitting solution (22).

In all of the statistical analyses, the data from individual animals have been averaged and the single average values used to calculate over-all mean and standard deviation for the group (11).

RESULTS

$t_{\frac{1}{2}}$ measurements made in 12 saline-loaded rats during intermittent constriction of the abdominal aorta are shown in Table I. Also shown in the Table are the values for Lissamine green transit time (T) and the calculated $(TF/P)_{In}$ ratios at the end of the proximal tubule. It is clear that in every animal $t_{\frac{1}{2}}$ became much longer, transit time fell, and the calculated value for $(TF/P)_{In}$ decreased during the second clearance period when the aortic clamp was released and renal perfusion pressure allowed to rise. These changes were observed in the first measurements made after release of the aortic clamp, within 2–3 min after the rise in renal perfusion pressure, and persisted throughout the period. The differences between the means for $t_{\frac{1}{2}}$, T, and $(TF/P)_{In}$ in the first and second clearance periods are highly significant ($P < 0.001$). In 7 of the 12 experiments, these changes were reversed during a third clearance period when renal perfusion pressure was again lowered to a level comparable with the first period, thus demonstrating that neither the amount of saline infused nor the sequence of the clamping was critical in determining the results. Brenner, Bennett, and Berliner (23) and Lassiter, Arrizurieta de Muchnik, Lipham, and Gottschalk (24) have recently reported that proximal $(TF/P)_{In}$ ratios, measured directly, increase significantly in saline-loaded rats when renal perfusion pressure is reduced by aortic constriction, in agreement with the calculated $(TF/P)_{In}$ values in the present study. Our data show in addition a consistent inverse relationship between renal perfusion pressure and $C/\pi r^2$ during a saline diuresis. In the study by Brenner, Bennett, and Berliner (23), an inverse relationship between renal perfusion pressure and $C/\pi r^2$, calculated from free-flow $(TF/P)_{In}$ and T measurements, was also evident in both saline-loaded and nondiuretic rats, although the effect was not as consistent as in the present experiments. The average diameter of the isolated saline columns during reabsorptive $t_{\frac{1}{2}}$ determinations, measured from the photographic transparencies, was 28.3 μ ($\pm$2.6 SD) in the two aortic constriction periods and was 28.0 μ ($\pm$2.0 SD) in the second period when the clamp was released. Since these values are statistically identical, we conclude that the observed changes in reabsorptive $t_{\frac{1}{2}}$ reflect changes in the capacity for sodium reabsorption per unit length of tubule (C), as well as in the capacity per unit of tubular volume ($C/\pi r^2$). Our observations differ from those of Rector, Sellman, Martinez-Maldonado, and Seldin (9), who found $t_{\frac{1}{2}}$ and T to be unaffected by aortic constriction in three rats undergoing saline diuresis. However, since they did not measure blood pressure distal to the aortic constriction, and since the reduction in GFR produced in their animals was somewhat less than in ours, it is possible that renal perfusion pressure had not been lowered enough to induce the changes which we observed in our animals.

In the seven control hydropenic rats, reabsorptive $t_{\frac{1}{2}}$ measured in 21 tubules was 11.0 sec ($\pm$0.7 SD), a value which is not significantly different from that observed in the saline-loaded rats during the first period of aortic clamping (11.0 vs. 11.2). However, it is slightly longer than normal control values previously reported from this laboratory (11) (11.0 vs. 8.5). We believe the longer values to be more nearly correct and are attributable to the use of longer columns of saline in the split droplet. With shorter columns of saline, as was used in our previous study (11), the volume of fluid at the oil-saline meniscus constitutes a significant fraction of the whole column. Since the cross-sectional diameter of

TABLE I

The Effect of Aortic Constriction on Proximal

Animal No.	Aorta constricted					Aorta	
	Femoral blood pressure	Reabsorptive $t_{\frac{1}{2}}$	Reabsorptive capacity $C/\pi r^2$	Transit time	Calculated $(TF/P)_{In}$	Femoral blood pressure	Reabsorptive $t_{\frac{1}{2}}$
	mm Hg	*sec*	*sec*$^{-1}$	*sec*		*mm Hg*	*sec*
1	82–88	10.3	0.067			130–140	20.8
		10.8	0.064				22.3
		12.5	0.056				19.3
		11.3	0.061				24.3
							17.7
							21.0
Average		11.2	0.062	17.0	2.86		20.9
2	81–84	9.0	0.077			120–125	14.5
		9.6	0.072				15.2
		7.7	0.090				11.7
		10.7	0.065				17.4
							13.5
Average		9.3	0.076	10.4	2.21		14.5
3	80–84	13.8	0.050			120–132	12.3
		13.1	0.053				15.3
							18.2
Average		13.5	0.052	14.4	2.12		15.3
4	80–85	8.7	0.080			150–160	10.2
		10.4	0.067				14.4
		10.5	0.066				14.4
		11.0	0.063				16.5
		10.9	0.064				17.1
Average		10.3	0.068	15.5	2.87		14.5
5	80–90	12.3	0.056			111–118	15.4
		11.4	0.061				16.1
		11.2	0.062				13.1
		12.4	0.056				12.8
							17.3
Average		11.8	0.059	11.9	2.02		15.0
6	72–83	15.0	0.046			139–140	18.6
		13.1	0.053				21.2
		12.1	0.057				
		15.7	0.044				
		12.1	0.057				
Average		13.6	0.051	12.1	1.85		19.9
7	82–91	11.1	0.062			119–129	19.4
		10.6	0.065				22.3
Average		10.9	0.064	11.4	2.08		20.9

$[TF/P)_{In}$, tubular fluid–to–plasma inulin ratio.

released			Aorta constricted				
Reabsorptive capacity $C/\pi r^2$	Transit time	Calculated $(TF/P)_{In}$	Femoral blood pressure	Reabsorptive $t_{\frac{1}{2}}$	Reabsorptive capacity $C/\pi r^2$	Transit time	Calculated $(TF/P)_{In}$
sec^{-1}	*sec*		*mm Hg*	*sec*	sec^{-1}	*sec*	
0.033			82–87	9.8	0.071		
0.031				9.5	0.073		
0.036				13.5	0.051		
0.029							
0.039							
0.033							
0.034	8.9	1.35		10.9	0.065	12.7	2.29
0.048			80–84	12.2	0.057		
0.046				11.5	0.060		
0.059				9.7	0.071		
0.040				12.6	0.055		
0.051				14.0	0.050		
				9.3	0.075		
0.049	7.6	1.45		11.6	0.061	9.2	1.75
0.056			81–90	17.0	0.041		
0.045				14.0	0.050		
0.038				13.8	0.050		
				14.8	0.047		
				10.0	0.069		
0.046	9.4	1.54		13.9	0.051	14.9	2.14
0.068			79–81	9.9	0.070		
0.048				8.3	0.083		
0.048				11.3	0.061		
0.042							
0.041							
0.049	8.5	1.52		9.8	0.071		
0.045			70–83	14.8	0.047		
0.043				13.5	0.051		
0.053				12.0	0.058		
0.054							
0.040							
0.047	8.0	1.46		13.4	0.052	10.5	1.73
0.037			90	10.5	0.066		
0.033				13.4	0.052		
				19.7	0.035		
				21.1	0.057		
0.035	8.1	1.33		13.9	0.053	10.8	1.78
0.036			82–90	9.9	0.070		
0.031				16.7	0.041		
				8.3	0.083		
				11.2	0.062		
0.033	8.2	1.31		11.5	0.060	10.5	1.88

TABLE I—(Continued)

Animal No.	Aorta constricted					Aorta	
	Femoral blood pressure	Reabsorptive $t_{\frac{1}{2}}$	Reabsorptive capacity $C/\pi r^2$	Transit time	Calculated $(TF/P)_{In}$	Femoral blood pressure	Reabsorptive $t_{\frac{1}{2}}$
	mm Hg	*sec*	*sec*$^{-1}$	*sec*		*mm Hg*	*sec*
8	80–89	9.4	0.074			120–145	17.7
		11.7	0.059				16.5
		9.6	0.072				16.7
		12.0	0.058				16.1
		12.0	0.058				18.5
							25.0
Average		10.9	0.064	12.2	2.19		18.4
9	78–84	11.6	0.060			110–119	22.4
		12.4	0.056				18.0
		12.1	0.057				15.5
Average		12.0	0.058	13.1	2.14		18.6
10	80–88	10.1	0.069			132–142	16.0
		10.2	0.068				19.3
							17.8
Average		10.2	0.068	13.5	2.51		17.7
11	80–90	7.8	0.089			102–107	12.7
		12.4	0.056				25.7
		9.2	0.075				
Average		9.5	0.073	13.2	2.62		19.2
12	78–80	8.4	0.083			116–125	15.0
		9.4	0.074				
		11.7	0.059				
		13.8	0.050				
		11.9	0.058				
		9.3	0.075				
		11.7	0.059				
Average		10.9	0.065	15.3	2.71		15.0
Over-all mean ± standard deviation		11.2 ±1.4	0.063 ±0.008	13.3 ±1.9	2.35 ±0.35		17.5 ±2.5

the fluid-occupying space is reduced at the meniscus, an error is introduced which tends to yield high values for $C/\pi r^2$ and shorter values for $t_{\frac{1}{2}}$.

In Table II are presented the inulin and PAH clearance data (C_{In} and C_{PAH}), sodium excretion, over-all fractional reabsorption of sodium, fractional reabsorption of the glomerular filtrate in the proximal tubule, and the calculated values for $\pi r^2 d/V_0$ (equation 3) for the same 12 rats as shown in Table I. The average GFR for this group of animals, and for four additional animals shown in Table III, was 2.70 ml/min per kg (±0.83 SD) during the first clearance period, 4.05 ml/min per kg (±0.99 SD) when the aortic clamp was released, and 2.90 ml/min per kg (±1.12 SD) during the second aortic constriction period. C_{PAH} for the same animals was 8.9 ml/min per kg (±3.6 SD), 12.8 ml/min per kg (±4.1 SD), and 9.1 ml/min per kg (±4.0 SD) during the first, second, and third periods respectively. The changes in GFR and C_{PAH} between the first and second periods are highly significant ($P < 0.01$). Filtration fraction was 0.32 ±0.13, 0.32 ±0.11, and 0.26 ±0.11 during the three clearance periods and showed no consistent pattern of change during the course of individual experiments. This finding is in agreement with the findings of Selkurt, Hall, and Spencer (25) and data calculated from the experiments of Earley, Martino, and Friedler (26) in which the experimental protocol included saline loading and changes in renal perfusion pressure induced by aortic or

released			Aorta constricted				
Reabsorptive capacity $C/\pi r^2$	Transit time	Calculated $(TF/P)_{In}$	Femoral blood pressure	Reabsorptive $t_{\frac{1}{2}}$	Reabsorptive capacity $C/\pi r^2$	Transit time	Calculated $(TF/P)_{In}$
sec^{-1}	*sec*		*mm Hg*	*sec*	sec^{-1}	*sec*	
0.039							
0.042							
0.041							
0.043							
0.037							
0.028							
0.038	6.7	1.29					
0.031							
0.039							
0.045							
0.038	9.1	1.41					
0.043							
0.035							
0.039							
0.039	7.4	1.34					
0.055							
0.027							
0.036							
0.046							
0.046	10.5	1.62					
0.041 ±0.006	8.4 ±1.0	1.42 ±0.11		12.1 ±1.6	0.059 ±0.007	11.4 ±2.0	1.93 ±0.23

renal artery constriction. Fractional reabsorption of sodium, however, changed significantly ($P < 0.01$) in the 16 animals from 97.4% (±4.3 SD) during the first aortic constriction period to 90.7% (±4.7 SD) when the clamp was released, to 96.0% (±4.3 SD) during the second aortic constriction period. Earley and his coworkers (26) have reported similar changes in fractional reabsorption induced by aortic constriction in the saline loaded dog. As can be seen from the data presented in columns 8, 15, and 22 of Table II, a consistent change in the ratio $\pi r^2 d/V_0$ occurred in every animal as renal perfusion pressure was changed. The mean values for the three periods were 8.8 sec (±1.4 SD), 7.0 sec (±0.8 SD), and 8.4 sec (±1.4 SD) respectively. The difference between the two constriction periods and the unconstricted period is highly significant ($P < 0.01$).

In Table III are shown proximal tubule hydrostatic pressure measurements made in 4 rats undergoing saline loading and intermittent constriction of the abdominal aorta. C_{In}, C_{PAH}, and calculated filtration fractions are also included. The mean proximal intratubular pressure was 15.5 cm H_2O during the first aortic constriction period, rose significantly to 25.3 cm H_2O when the clamp was released, and returned to 15.2 cm H_2O during the second aortic constriction period. Of interest is the fact that the absolute level of hydrostatic pressure in the proximal tubule was approximately the same in the presence of aortic constriction and saline loading as is

TABLE II

The Effect of Aortic Constriction on Fractional Reabsorption

Animal No.	Aorta constricted							Aorta		
	GFR	C_{PAH}	Filtration fraction	$U_{Na}V$	Fractional Na Reabsorption	Proximal fractional reabsorption	$\frac{\pi r^2 d}{V_0}$	GFR	C_{PAH}	Filtration fraction
	ml/min per kg	*ml/min per kg*		*μEq/min per kg*	%	%	*sec*	*ml/min per kg*	*ml/min per kg*	
1	3.23			19.6	95.6	65	10.4	4.67		
2	2.88	6.6	0.44	22.2	94.5	55	7.2	4.99	10.8	0.45
3	2.07	7.8	0.27	0.5	99.8	53	10.2	2.93	11.3	0.26
4		9.5		0.8		65	9.6		17.9	
5	1.98	10.8	0.18	35.3	87.3	50	8.6	2.92	14.5	0.20
6	1.82			1.5	99.4	46	9.0	3.59		
7	2.81	15.2	0.18	22.2	94.4	52	8.1	3.30	15.1	0.22
8	3.19	9.9	0.32	6.0	98.7	44	6.9	3.91	9.9	0.39
9	1.00	2.1	0.48	3.4	97.6	53	9.1	3.00	18.9	0.16
10	3.10	10.6	0.29	1.1	99.8	60	8.8	3.53	7.7	0.46
11	3.31	7.7	0.43	2.6	99.4	62	8.5	3.72	9.4	0.40
12	2.94			29.6	97.8	63	9.7	5.02		
Over-all mean ± standard deviation							8.8 ±1.4			

GFR, glomerular filtration rate; C_{PAH}, clearance of *p*-aminohippurate; $U_{Na}V$, rate of sodium excretion; $\pi r^2 d/V_0$, ratio of

seen in nondiuretic rats without aortic constriction (20, 21).

In Table IV are presented the results of reabsorptive $t_{\frac{1}{2}}$ measurements carried out with the dialysate of plasma obtained from four saline-loaded rats during and after release of aortic constriction. As can be seen, no significant differences in $t_{\frac{1}{2}}$ were observed between any of the paired dialysates. It should also be noted that almost all of the $t_{\frac{1}{2}}$ values observed with these plasma dialysates were within the range found in the normal hydropenic control rats (11.0 ±0.7 sec); moreover, they were significantly shorter than was found when $t_{\frac{1}{2}}$ was measured directly in the kidneys of saline-loaded rats during the declamped period (11.0 vs. 17.5 sec).

DISCUSSION

The results of the present experiments demonstrate that the effect of a rapid saline infusion on proximal tubule sodium reabsorption can be modified to a large extent by changes in renal perfusion pressure. Thus, when perfusion pressure was lowered to the range of 70–90 mm Hg in saline-loaded rats, the reabsorptive $t_{\frac{1}{2}}$ of a column of isotonic NaCl injected into the proximal tubule was only moderately prolonged in some animals and in others (rat Nos. 2, 4, 7, and 10) was entirely within the range found by others in nondiuretic rats (9, 10, 18, 19, 27). The over-all mean for $C/\pi r^2$ during the first constriction period (0.063/sec), calculated from equation 1, is very similar to that reported by Brenner, Bennett, and Berliner (23) for nondiuretic rats (0.062/sec). Thus, there was no evidence for a marked reduction in $C/\pi r^2$ during the first period when perfusion pressure was lowered by aortic constriction. In sharp contrast, when the aortic clamp was released and renal perfusion pressure allowed to rise, a very striking prolongation of $t_{\frac{1}{2}}$ was observed, indicating a large reduction in $C/\pi r^2$. In addition to these effects, $\pi r^2 d/V_0$ was also altered by the changes in renal perfusion pressure, i.e., $\pi r^2 d/V_0$ was significantly higher when perfusion pressure was lowered than when perfusion pressure was allowed to rise. Associated with these changes was a significant increase in the calculated value for fractional reabsorption in the proximal tubule when the aorta was constricted as compared with the value when the aorta was released. The alterations in proximal reabsorption induced by aortic constriction were accompanied by concordant changes in fractional reabsorption of sodium in the urine.

It has been proposed by Rector, Sellman, Martinez-Maldonado, and Seldin (9) that the inhibition of proximal sodium transport which occurs during a saline diuresis is due to the combined effects of a decrease in $C/\pi r^2$ and a decrease in $\pi r^2 d/V_0$. With regard to this latter change, they suggested that the distensibility of the proximal tubule might be limited during rapid saline infusion because of an increase in hydrostatic pressure, or a fall in colloid oncotic pressure in the peritubular capillaries, and a resultant increase in interstitial volume

released				Aorta constricted						
$U_{Na}V$	Fractional Na reabsorption	Proximal fractional reabsorption	$\frac{\pi r^2 d}{V_0}$	GFR	C_{PAH}	Filtration fraction	$U_{Na}V$	Fractional Na reabsorption	Proximal fractional reabsorption	$\frac{\pi r^2 d}{V_0}$
μEq/min per kg	*%*	*%*	*sec*	*ml/min per kg*	*ml/min per kg*		*μEq/min per kg*	*%*	*%*	*sec*
89.2	86.4	26	7.5	4.46			27.1	95.6	57	8.8
76.3	88.9	31	6.3	2.55	7.7	0.33	16.8	95.3	43	7.0
15.9	96.1	35	7.7	1.71	8.6	0.20	2.5	99.0	54	10.6
106.9		34	6.9		5.1		3.7			
36.5	90.0	32	6.7	1.43	7.8	0.18	11.0	94.5	42	8.0
50.5	90.0	25	6.6	1.46			12.9	94.0	44	8.3
69.0	85.1	24	7.3	3.05	16.9	0.18	41.9	90.2	47	7.8
87.7	83.9	22	5.8							
33.8	92.0	29	7.6							
59.3	88.0	25	6.4							
16.6	96.8			3.56	8.4	0.42	8.6	98.3		
176.5	92.4	38	8.3							
			7.0 ±0.8							8.4 ±1.4

proximal tubular volume to GFR/nephron.

(26, 28, 29). The rise in GFR which often occurs in the rat during saline loading would thus not be accompanied by a proportionate increase in the volume of the proximal tubule. According to the tubular geometry hypothesis of regulation of sodium transport (9, 19, 27, 30), a decrease in the ratio $\pi r^2 d/V_0$ could contribute to a fall in fractional reabsorption of sodium and water in the proximal tubule. The present observations are compatible with the view that a change in peritubular physical forces is responsible for the decrease in $\pi r^2 d/V_0$ which normally occurs during a saline diuresis, since when renal perfusion pressure was reduced acutely by aortic constriction, this ratio remained within the normal or even high-normal range (9, 11). It would seem from our data that the colloid oncotic pressure in the peritubular capillaries was not of paramount importance in this effect, since the variations in $\pi r^2 d/V_0$ were not related to the amount of saline infused, and FF did not change significantly throughout the three periods of the experiment (Table II). On the other hand, hydrostatic pressure was definitely varied by the experimental procedures, and changes in this pressure within the peritubular capillaries may have been important in determining the ratio $\pi r^2 d/V_0$. An alternative explanation is afforded by the model for flow and pressure relationships in the proximal tubule proposed by Bossert and Schwartz (31). According to their model, the loop of Henle responds to a decrease in GFR by constricting and thereby increasing the resistance to outflow of fluid from the proximal tubule. The increase in loop resistance results, in turn, in a smaller reduction in hydrostatic pressure and radius in the proximal tubule than might otherwise be expected from the fall in GFR. A mechanism such as this could also account for the relatively normal or increased value for $\pi r^2 d/V_0$ observed during the periods of aortic constriction and reduced GFR.

With regard to the effect of changes in renal perfusion pressure on $C/\pi r^2$, several different mechanisms can be considered. Rector and his coworkers (22) have presented evidence that a dialyzable humoral inhibitor of sodium transport is responsible for the decrease in $C/\pi r^2$ which occurs during rapid saline infusion. They postulated that the stimulus for the release of this hormone was expansion of extracellular fluid (ECF) volume at some critical receptor site. It is difficult, however, to reconcile the present observations with this hypothesis. First, if $C/\pi r^2$ were under hormonal regulation during saline diuresis, a reduction in renal perfusion pressure ought not to interfere with the effect of such a hormone. While it is conceivable that a crucial rate of delivery of hormone to the tubules is necessary for its effect to be observed, and that lowering renal blood flow in the present experiments reduced the delivery of hormone below this rate, the greater expansion of ECF volume during the period of aortic clamping should have compensated for this by raising the plasma hormone concentration to even higher levels. It is also possible that the trigger mechanism causing release of a humoral inhibi-

TABLE III

Effect of Aortic Constriction on Proximal Tubular Hydrostatic Pressure

	Aorta constricted					Aorta released					Aorta constricted				
Animal No.	Femoral blood pressure	Intratubular pressure	GFR	C_{PAH}	FF	Femoral blood pressure	Intratubular pressure	GFR	C_{PAH}	FF	Femoral blood pressure	Intratubular pressure	GFR	C_{PAH}	FF
	mm Hg	*cm H_2O*	*ml/min per kg*	*ml/min per kg*		*mm Hg*	*cm H_2O*	*ml/min per kg*	*ml/min per kg*		*mm Hg*	*cm H_2O*	*ml/min per kg*	*ml/min per kg*	
13		16.6					21.9					12.0			
	68–70	13.8				129–135	21.4				71–78	13.0			
		15.9					22.2					14.1			
							23.6								
Average		15.4	1.58	6.0	0.26		22.3	3.11	11.6	0.27		13.0	2.11	8.3	0.25
14		15.2					25.8					18.0			
	65–71	16.0				114–116	26.8				65–70	15.8			
		14.8					27.2					17.4			
		14.4					26.4					17.2			
		14.2					25.6					17.3			
Average		14.9	4.19	11.9	0.35		26.4	4.74	14.9	0.32		17.1	3.93	12.0	0.33
15		18.1					27.8					18.0			
	73–80	15.7				135–143	24.8				66–75	16.1			
		16.3					25.8					16.8			
		13.2					27.4					16.6			
		14.7										16.3			
												15.8			
												15.2			
Average		15.6	3.53	8.6	0.41		26.5	5.36	14.1	0.38		16.4	4.39	11.4	0.39
16		14.8					23.7					15.0			
	72–78	15.0				118–124	27.0				70–76	14.0			
		15.4					30.8					13.8			
		16.8					24.0					14.2			
		17.4					25.4					13.8			
							25.5					16.0			
							24.6					11.6			
Average		15.9	2.83	10.9	0.26		25.9	5.96	15.8	0.38		14.1	3.21	11.3	0.28
Over-all average		15.5					25.3					15.2			

FF, filtration fraction. See Table II for explanation of other abbreviations.

TABLE IV

*Assay of Plasma Dialysate for Natriuretic Hormone Activity**

Assay rat No.	Plasma collected during aortic constriction: Reabsorptive $t_{\frac{1}{2}}$	Plasma collected after release of aortic clamp: Reabsorptive $t_{\frac{1}{2}}$
	sec	*sec*
1	10.6	10.6
	10.4	9.8
	10.6	11.3
	10.9	12.5
	10.5	12.3
	11.3	12.3
		12.3
		13.5
Average	10.7	11.8
2	12.3	10.7
	10.0	11.0
	10.6	11.0
	10.5	11.8
	10.7	10.5
		11.0
		10.5
		10.5
		10.7
		12.3
		8.5
Average	10.8	10.8
3	11.6	10.5
	11.6	12.5
	11.3	10.5
	9.0	10.5
		10.4
Average	10.9	10.9
4	11.6	10.5
	9.6	10.2
	11.0	10.2
	10.0	10.2
		9.8
		11.3
		10.2
		9.8
Average	10.6	10.3
Over-all mean ± standard deviation	10.8 ±0.1	11.0 ±0.6

* The donor animals were loaded with Ringer's solution at 0.5 ml/min for 90 min before the first plasma sample was collected.

tor of sodium transport during saline loading is within the kidney itself, and that aortic constriction in some way interfered with this mechanism. If this were the case, then significantly greater amounts of hormone should have been detectable in the plasma of saline-loaded animals after the aortic clamp was released. The plasma assay experiments, however, failed to demonstrate any potent inhibitory substance appearing when the aortic clamp was released (Table IV). In fact, no definite evidence for an inhibitor of sodium transport was found in any of the plasma dialysates of the saline-loaded donors, since reabsorptive $t_{\frac{1}{2}}$ measured with the dialysates was essentially the same as was found when isotonic saline was injected into the proximal tubules of hydropenic control animals. It thus seems unlikely from these observations that the large changes in reabsorptive $t_{\frac{1}{2}}$ observed directly in the saline-loaded rats shown in Table I were hormonally mediated.

Other mechanisms which might account for the changes in $C/\pi r^2$ with changes in perfusion pressure are the variations in renal blood flow produced by the experimental procedure and the renin-angiotensin system. Lewy and Windhager (10) have shown that $C/\pi r^2$ falls in parallel with a fall in renal blood flow produced by partial constriction of the renal vein. Such a mechanism involving reduced renal blood flow seems unlikely in the present experiments, however, since the large decrease in $C/\pi r^2$ which occurred during the second clearance period was accompanied by a sharp rise in renal blood flow (Table II). Insofar as the renin-angiotensin system is concerned, this also seems unlikely because of the fact that prolongation of $t_{\frac{1}{2}}$ was observed within 2–3 min after the aortic clamp was released. Such a humoral mechanism might be expected to take a longer period of time to act. Furthermore, Thurau has presented convincing evidence that angiotensin is not a direct inhibitor of sodium transport in the proximal tubule of the rat (32).

Finally, it seems possible that changes in renal perfusion pressure altered $C/\pi r^2$ by the effect produced on hydrostatic pressure within the peritubular capillaries. In a previous study (11), we found that acute hypertension induced by carotid artery ligation is associated with a rise in peritubular capillary pressure and inhibition of proximal sodium reabsorption. We postulated that proximal $C/\pi r^2$ is responsive to changes in peritubular pressure and the volume of the interstitial compartment of the kidney (11). It seems possible that the reduction in renal perfusion pressure produced by aortic constriction in the present study might have had its effect on $C/\pi r^2$ via pressure changes within the peritubular capillaries. Thus when the aortic clamp was tightened and perfusion pressure lowered to 70–90 mm Hg, proximal intratubular pressure was approximately the same as is found in nondiuretic rats with a normal renal perfusion pressure (20, 21). When the clamp was released, proximal pressure rose strikingly to an average value of 25.3 cm H_2O. While these intratubular pressure measurements do not in themselves provide critical information

about possible pressure gradients across the various structures at the level of the proximal tubule, or changes in interstitial volume, they most likely do reflect directional changes in pressure in the peritubular capillaries (20, 21). It might therefore be postulated that the relatively normal reabsorptive $t_{\frac{1}{2}}$ found during aortic constriction and saline loading was in some way related to a relatively normal hydrostatic pressure in the peritubular capillaries. Further, the prolongation of $t_{\frac{1}{2}}$ found when the aortic clamp was released might have been related to the increase in hydrostatic pressure which presumably occurred within the peritubular capillaries during this period of the experiment.

The precise mechanism by which a rise in peritubular capillary pressure might inhibit proximal sodium transport is unknown. Earley, Martino, and Friedler (26, 28, 29) have postulated that increases in pressure within the capillaries delay the removal of the tubular reabsorbate, thus causing an increase in the interstitial volume of the kidney. Lewy and Windhager (10) and Nutbourne (33) suggested that an increase in renal interstitial volume might create a layer of high sodium concentration within the basal labyrinth adjacent to the transporting membrane of the tubular epithelium which might then interfere with the active sodium pump mechanism or enhance back-diffusion of sodium into the cells. However, it might be unnecessary to postulate a change in the volume of the interstitial compartment of the kidney in order to explain the effect of pressure on sodium transport. Recently it has been reported that small changes in hydrostatic pressure can markedly alter the rate of salt transport in isolated single cells of Valonia ventricosa (34). The effect on salt transport seemed to be specific since it was independent of water flux, and urea movement was not influenced at all. In this experimental situation, there was of course no change in the volume of the surrounding bathing medium. Compatible with the possibility that hydrostatic pressure per se may in some way be responsible for changes in sodium reabsorptive rate in the kidney is the observation of Brenner, Bennett, and Berliner (23) that $C/\pi r^2$ falls when proximal pressure is raised from the luminal side of the tubule by clamping the ureter. Under these conditions, an increase in renal interstitial volume would not be anticipated. Thus, a basic biologic mechanism might be involved in the relation between intrarenal hydrostatic pressure and proximal sodium transport. Whatever this mechanism eventually proves to be, the observations presented here are compatible with the view that the inhibition of sodium reabsorption which occurs in the proximal tubule during a saline diuresis is related to pressure changes within the kidney.

ACKNOWLEDGMENTS

We thank Mr. Bertrand F. Mutz for his excellent technical assistance.

This work was supported by a grant from the U. S. Public Health Service. Dr. Karl M. Koch was supported by a research fellowship from the National Kidney Foundation. Mr. Marc Aras was supported by a traineeship from the Ministry of Health, Quebec, Canada.

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