Effect of Acute Hypertension on Sodium Reabsorption by the Proximal Tubule

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ABSTRACT The effect of acute hypertension on sodium reabsorption by the proximal tubule was studied in rats by means of micropuncture methods. Hypertension was induced by bilateral carotid artery ligation and cervical vagotomy. Within a few minutes after blood pressure rose (30–60 mm Hg above control levels), a moderate natriuresis and diuresis began. Proximal sodium reabsorption, measured by two independent methods, was found to be markedly suppressed, both in absolute amount per unit length and per unit of tubular volume ($C/\pi r^2$). The ratio between tubular volume and glomerular filtration rate (GFR) ($\pi r^2 d/V_0$) was found to be increased. These observations indicate that the inhibition of proximal sodium reabsorption induced by hypertension cannot be explained by the tubular geometry hypothesis of sodium regulation.

Several possible hormonal mechanisms were investigated. Intravenous *d*-aldosterone did not prevent the suppression of sodium transport due to acute hypertension, nor did chronic oral saline loading to reduce the renal content of renin. Constriction of the suprarenal aorta, with maintenance of a normal renal perfusion pressure, did prevent the inhibition of proximal transport during carotid artery occlusion, thus excluding an extrarenally produced natriuretic hormone as the mechanism.

The observations are compatible with the view that sodium transport was inhibited either by an intrarenal natriuretic hormone or by an increase in the interstitial volume of the kidney produced by a transient hydrostatic pressure gradient across the peritubular capillaries. The latter seems more likely to us because of the rapidity of onset of the natriuresis, and because removing the renal capsule and releasing the surface interstitial fluid prevented the effect of hypertension on proximal sodium transport.

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INTRODUCTION

Experiments by several groups of investigators suggest that intrarenal pressure is one of the factors regulating sodium reabsorption by the renal tubules. Selkurt, Womack, and Dailey (1, 2), and Shipley and Study (3) found that acute increases in renal artery pressure induced in the perfused in situ dog kidney lead to a decrease in sodium reabsorption by the tubules. More recently, Earley, Martino, and Friedler (4, 5) have shown that drug-induced systemic hypertension reduces sodium reabsorption in the intact animal if the renal vasoconstricting effect of the pressor drug is counteracted by a locally injected renal vasodilating agent. That the proximal tubule participates in the response to hypertension was shown in experiments in which distal sodium reabsorption had been inhibited by appropriate diuretics before the induction of hypertension (5). Earley and his coworkers postulated that the reduction in sodium reabsorption was related to an increase in peritubular capillary hydrostatic pressure, transmitted from the renal artery, and a subsequent increase

in the interstitial volume of the kidney. The mechanism by which an increase in interstitial volume might reduce sodium reabsorption was not clear, but since it had previously been shown that sodium transport in the proximal tubule can vary directly with the intraluminal volume (6, 7), Earley and his coworkers suggested that the tubules were compressed by the expansion of the interstitial compartment.

In the present study, we have examined with micropuncture techniques the effect of acute hypertension induced by carotid artery occlusion on proximal reabsorption in the rat kidney. We found that proximal transport was suppressed out of proportion to tubular volume, and therefore the inhibition could not be explained by the tubular geometry hypothesis. The observations are compatible with the view that sodium transport was suppressed either by an intrarenal natriuretic hormone or by an increase in the interstitial volume of the kidney produced by a transient hydrostatic pressure gradient across the peritubular capillaries.

METHODS

Male white rats, weighing 250–350 g, were anesthetized with Inactin [sodium ethyl-(1-methylpropyl)-malonylthiorea], 100 mg/kg of body weight, placed on a heated animal table, and tracheotomized. The left external jugular vein was cannulated with Clay-Adams PE 50 polyethylene tubing, Clay-Adams, Inc., New York, for infusion. Blood pressure was measured continuously via a heparin-filled PE 50 catheter in the left common carotid artery, connected to a Statham strain gauge (model P 23 Dc), Statham Instruments, Inc., Los Angeles, Calif. The recording instrument was a Grass polygraph, model 5D, Grass Instrument Co., Quincy, Mass.

The left kidney was prepared for micropuncture as described previously (8). The kidney was bathed in continuously flowing mineral oil, warmed to 37°C by a circulating water bath, and was illuminated by a fiber optic system (Donner Electronics, Inc., Melrose, Mass.). Urine was collected from the experimental kidney through a PE 50 polyethylene catheter inserted directly into the renal pelvis. During surgical preparation of the animal, 3–4 ml of Ringer's lactate solution was given intravenously, to replace fluid losses, and the same solution was administered at a constant rate of 0.05 ml/min throughout the entire experiment.

After control data had been obtained in each animal, we elevated blood pressure acutely by ligating the remaining right common carotid artery and, in most instances, severing both cervical vagus nerves. Only those experiments in which the blood pressure rose by 30 mm Hg or more and was sustained at the new level have been included in the study. The total number of animals studied under the various protocols described below was 57.

Inulin and PAH clearance, PAH extraction ratio, and filtration fraction. In order to determine the effect of acute hypertension on renal hemodynamics under these experimental conditions, inulin clearance (GFR) was measured in nine animals together with *para*-aminohippurate (PAH) clearance and renal extraction of PAH in eight of them. The surgical preparation of the animals was the same as for the micropuncture experiments, but micropuncture was not carried out in this group of animals. After a priming dose of 12.5 μc of inulin-^{14}C and 0.2 mg of PAH intravenously, both substances were administered together in lactated Ringer's solution (0.05 ml/min) at a rate of 0.19 μc/min and 0.15 mg/min respectively for a 40–60 min equilibration period. One control urine collection and two or three urine collections during hypertension were then obtained in each animal. In order to minimize dead-space error, we started the urine collection for the first hypertensive period at least 10 min after urine flow was observed to increase abruptly. Arterial blood samples (0.4 ml) were taken from the femoral artery at the mid-point of each urine collection; for the determination of PAH extraction ratio, 0.4 ml blood was drawn from the left renal vein with a 27 gauge needle at the end of the control period and at the end of the experiment. The volume of each blood sample was immediately replaced with an equal volume of Ringer's solution injected through the femoral catheter. Inulin-^{14}C concentration in the urine and plasma was measured as previously described (9), and PAH concentration was measured by the method of Smith, Finkelstein, Aliminosa, Crawford, and Graber (10). Inulin and PAH clearances, PAH extraction ratio, and filtration fraction (FF) were calculated from standard equations (11).

Proximal tubular fluid pressure. In 11 rats, the hydrostatic pressure in the surface proximal tubules was measured before and during arterial hypertension. The method used was essentially the same as that described by Gottschalk and Mylle (12, 13) except that the probing micropipet was filled with Lissamine green–colored saline, and the recording manometer was filled with water rather than mercury. No pressure reading was accepted unless clear tubular fluid flowed freely into the micropipet when the externally applied pressure was reduced slightly, and unless Lissamine green flowed into the tubular lumen when the applied pressure was raised slightly. In 4 of the 11 animals, the renal capsule was stripped off before pressure measurements, and in the remaining seven it was left intact.

Split-drop experiments. The rate of sodium reabsorption per unit volume of the proximal tubule was measured in 27 rats by means of the "split-drop" technique of Gertz (14). With this method, a column of colored castor oil is injected into the tubular lumen through one barrel of a double-barreled pipet, and is then "split" by injection of NaCl (150 mEq/liter) through the second barrel. The reabsorptive rate of the saline is estimated by measuring the velocity at which the two oil columns approach one another with rapid sequence photography. The photo-

graphic equipment was the same as described previously (15), except for the following modifications: (*a*) the "dipping cone" on the Ultropak objective (E. Leitz, Inc., New York) was removed to allow greater working space for the micropipet; and (*b*) the camera shutter was triggered by an automatic timer (Industrial Timer Corporation, Parsippany, N. J.) that also activated the electronic flash unit and the film advance motor. Pictures were taken every 4 sec with high speed Ektachrome film (ASA 160), Eastman Kodak Co., Rochester, N. Y. The progressive changes in the length of the saline column in the tubular lumen were determined by projecting the transparencies on a smooth-surfaced white board and measuring the distance between the two oil blocks with a map measure wheel. The percent change in the length of the saline column was plotted semilogarithmically against time in order to obtain the half-time of reabsorption ($t_{\frac{1}{2}}$). The reabsorptive rate per unit of tubular volume ($C/\pi r^2$) was calculated from the expression:

$$C/\pi r^2 = 0.693/t_{\frac{1}{2}} \quad (6, 7). \tag{1}$$

The internal diameter of both the free-flow tubules and of the isolated saline column between the two oil blocks was also measured in these experiment from the projected transparencies. A transparency of a red blood cell counting chamber, photographed at the same magnification as the kidney surface, served for calibration. With this method, the internal diameter of the tubule can be measured to the nearest 0.5 μ. Because there is considerable variation in the diameter of different surface convolutions, at least 10 convolutions were measured at the periphery of the field surrounding each oil-blocked tubule.

Several different protocols were followed in the split-drop experiments. (*a*) In eight rats, reabsorptive half-time was measured during control periods and after induction of acute hypertension, and in an additional two animals during hypertension only. In 3 of the 10 animals, *d*-aldosterone (CIBA Pharmaceutical Co., Summit, N. J.) was administered intravenously in a dose of 0.25 μg/min throughout the control and hypertensive periods. (*b*) In order to study the possible effect of hydration on $t_{\frac{1}{2}}$, in two animals split-drop measurements were made over a prolonged period (4 hr) of Ringer's infusion at 0.05 ml/min. In one of these animals, hypertension was induced at the end of the 4 hr period, and split-drop measurements continued. (*c*) Four rats were given isotonic saline ad lib. as drinking solution for 5 wk before study in order to reduce the renal content of renin (and presumably angiotensin) (16, 17). Since aldosterone secretion may have been suppressed by the high salt intake, *d*-aldosterone was infused at 0.25 μg/min in these four animals. (*d*) In four normal rats, the renal capsule of the experimental kidney was removed completely before the induction of hypertension and reabsorptive half-time measurements. (*e*) In seven rats, renal perfusion pressure was maintained at normal levels during carotid artery occlusion by means of an adjustable clamp on the aorta just cephalad to the renal arteries. Blood pressure below the clamp was measured via a catheter in the right femoral artery and was kept at levels between 90 and 130 mm Hg. In five of the seven rats, the cervical vagus nerves were severed, but in the other two they were left intact.

Proximal tubular fluid/plasma inulin ratios $(TF/P)_{In}$, *and Lissamine green transit time* (T). In 10 rats, $(TF/P)_{In}$ ratios were measured at the end of the accessible portion of the proximal tubule before and during arterial hypertension. Inulin-^{14}C was given in a priming dose of 25 μc/min and 0.4 μc/min was administered via the infusion. The terminal segments of the proximal tubule were selected for micropuncture on the basis of three criteria: (*a*) they converged about a vascular "star" (6); (*b*) they were the last proximal convolutions in which intravenously injected Lissamine green appeared before disappearing from the surface of the kidney; and (*c*) colored castor oil injected into their lumen disappeared from the surface and did not reappear in any other surface convolution. Previous studies have shown that convolutions selected on this basis are located between 50 and 65% of the total proximal tubular length (6, 15).

Just before each tubular fluid collection, the transit time (T) of intravenously injected Lissamine green from the glomerulus (taken as the first diffuse discoloration of the kidney) to the selected convolution was measured, as described by Steinhausen (18). The pipet was then inserted into the lumen, the tubule blocked distal to the pipet with castor oil, and a collection of tubular fluid obtained. The volume of the tubular sample was measured, as previously described (9), and inulin-^{14}C concentration in tubular fluid, plasma, and urine was determined by liquid scintillation counting (9). Plasma inulin concentration was corrected for a plasma water content of 94%. The reabsorptive rate per unit of tubular volume ($c/\pi r^2$) was calculated from the paired $(TF/P)_{In}$ and T measurements, using the equation of Gertz, Mangos, Braun, and Pagel (6):

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

The ratio between tubular volume and GFR was calculated for each nephron sampled from the expression:

$$\pi r^2 d/V_0 = \frac{\text{per cent reabsorbed}}{C/\pi r^2} \quad (19). \tag{3}$$

Urinary sodium concentration was measured by flame photometry, with lithium as an internal standard.

In all of the statistical analyses presented below, the data from each animal were averaged and the single average value used in the calculation of over-all mean, standard deviation (SD), and standard error (SE) for the group (20). Since n is reduced to the number of animals and becomes relatively small, a "pooled" standard deviation was determined whenever two groups of data were tested for significant difference, using the equation:

$$s^2 = \frac{(x_1 - \bar{x}_1)^2 + (x_2 - \bar{x}_2)^2}{n_1 + n_2 - 2} \quad (21).$$

The t value was then calculated from the equation:

$$t = \frac{\bar{x}_1 - \bar{x}_2}{s}\sqrt{\frac{n_1 n_2}{n_1 + n_2}} \quad (21).$$

RESULTS

Blood pressure, urine flow, and sodium excretion. During the control period, mean blood pressure was usually between 105 and 130 mm Hg in all animals but in individual animals varied over a relatively narrow range (5–15 mm Hg). Bilateral carotid artery ligation and cervical vagotomy resulted in a sharp rise in blood pressure, usually within a few minutes of the procedure. The minimal increase which we accepted for inclusion in the study was 30 mm Hg, but in many of the animals, a sustained pressure rise of 40–60 mm Hg occurred. Although it was not measured systematically, the pulse pressure was noted to increase strikingly in most animals. In the 22 animals presented in Tables I and VI below, in which proximal sodium reabsorption was also measured, and the experimental protocols were comparable, the average rate of urine flow for the experimental kidney was 11.1 μl/min per kg ($\pm$ 5.7 SD) during the control period, and the average rate of sodium excretion was 1.09 μEq/min per kg ($\pm$ 0.95 SD). In every animal, starting within a few minutes after the blood pressure rise, urine flow increased abruptly, the average urine flow being 86.7 μl/min per kg ($\pm$ 63.4 SD) ($P < 0.001$) during hypertension. Urinary sodium concentration also increased from an average of 110 mEq/liter in the control period to 176 mEq/liter during hypertension, and sodium excretion rose to a mean value of 12.2 μEq/min per kg ($\pm$ 8.5 SD) ($P < 0.001$).

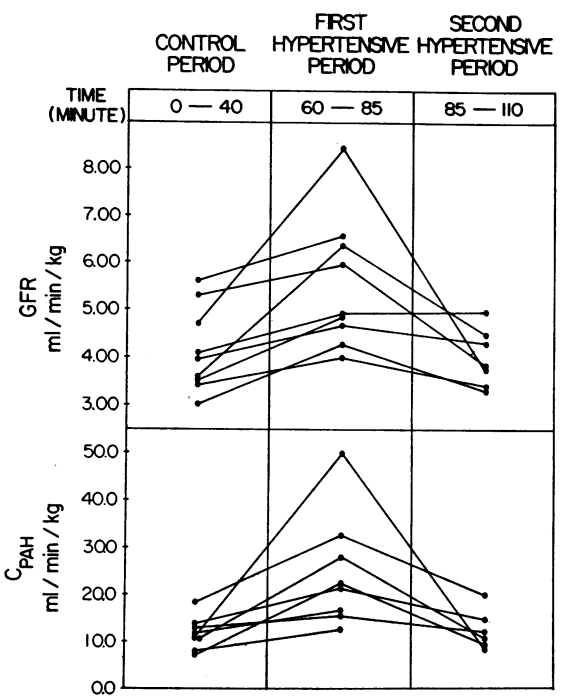

FIGURE 1 Inulin clearance (*GFR*), and *para*-aminohippurate (PAH) clearance (C_{PAH}) during control and hypertensive periods. The approximate time course of the experiments is shown at the top of the figure.

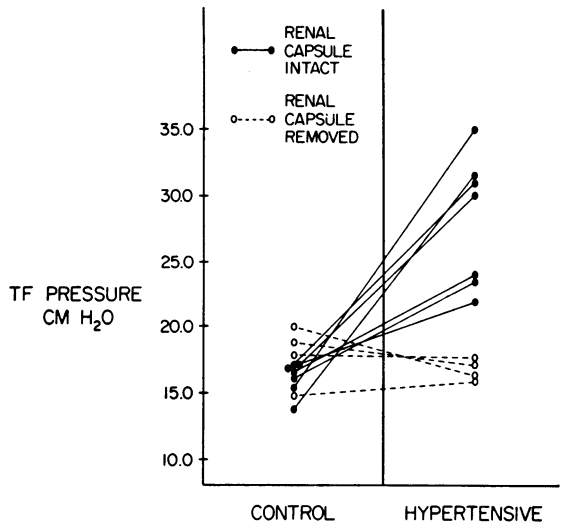

FIGURE 2 Proximal tubular hydrostatic (*TF*) pressure (*CM H_2O*) during control and hypertensive periods. Each point represents the average of two to five measurements in different tubules.

Inulin and PAH clearance, PAH extraction ratio, and filtration fraction (Fig. 1). Inulin clearance (GFR) measured in nine rats is shown in Fig. 1, together with PAH clearance (C_{PAH}) measurements made simultaneously in eight of them. As can be seen, both GFR and C_{PAH} rose during the initial hypertensive period, the average individual increase being 36% for GFR and 117% for C_{PAH}. Both GFR and C_{PAH} then returned to values which were approximately the same as in the control period, the average individual difference from the control being + 3% for GFR and + 1.5% for C_{PAH}. The mean filtration fraction (FF) for the group was 0.35 during the control period, 0.22 during the initial hypertensive period, and 0.32 during the last hypertensive period. PAH extraction (E_{PAH}) showed no consistent change

TABLE I

Effect of Acute Hypertension on Proximal Reabsorptive Half-Time

Experiment No.	Control			Hypertension		
	Blood pressure	Reabsorptive $t_{\frac{1}{2}}$	Reabsorptive capacity $C/\pi r^2$	Blood pressure	Reabsorptive $t_{\frac{1}{2}}$	Reabsorptive capacity $C/\pi r^2$
	mm Hg	*sec*	*sec*$^{-1}$	*mm Hg*	*sec*	*sec*$^{-1}$
21	110–117	7.0	0.099	145–150	13.6	0.051
		8.3	0.084		16.8	0.041
					15.6	0.044
		7.7	0.092		18.0	0.039
					16.0	0.044
22*	105–112	7.0	0.099	155–178	15.6	0.044
		8.5	0.082		12.6	0.055
					19.0	0.037
		7.8	0.091			
					15.7	0.045
23*	105–125	8.2	0.085	160–175	11.2	0.062
		9.0	0.077		13.0	0.053
					11.8	0.059
		8.6	0.081			
					12.0	0.058
24*	115–120	7.0	0.099	150–162	15.5	0.045
		8.0	0.087		12.2	0.057
					11.8	0.059
		7.5	0.093		11.0	0.063
					12.6	0.056
25	120–130	8.0	0.087	175–179	12.8	0.054
		7.5	0.092			
		7.8	0.090			
26	125–130	7.3	0.095	160–180	27.0	0.026
		10.5	0.066		13.5	0.051
		12.5	0.055		15.5	0.045
		6.8	0.102		13.0	0.053
					23.7	0.029
		9.2	0.080		17.0	0.041
					17.8	0.039
					12.5	0.055
					14.5	0.048
					17.7	0.043
27	110–120	9.5	0.073	155–167	12.8	0.054
		7.3	0.095		14.0	0.050
		7.8	0.096		10.5	0.066
					13.0	0.051
		8.0	0.088		12.0	0.058
					12.7	0.056
28	115–119	9.5	0.073	165–173	14.7	0.047

* Animal received 0.25 μg/min of *d*-aldosterone intravenously throughout the experiment.
‡ Control measurements started after 3 hr of infusion.

TABLE I (*Concluded*)

Experiment No.	Control			Hypertension		
	Blood pressure	Reabsorptive $t_{\frac{1}{2}}$	Reabsorptive capacity $C/\pi r^2$	Blood pressure	Reabsorptive $t_{\frac{1}{2}}$	Reabsorptive capacity $C/\pi r^2$
	mm Hg	*sec*	*sec*$^{-1}$	*mm Hg*	*sec*	*sec*$^{-1}$
29				140–164	9.8	0.071
					11.1	0.062
					12.6	0.055
					14.5	0.048
					10.6	0.065
					11.7	0.060
30				155–160	13.6	0.051
31‡	120–126	8.0	0.087	165–184	9.6	0.072
		8.0	0.087		20.5	0.034
		10.2	0.068		20.5	0.034
		7.5	0.092		22.6	0.031
		8.3	0.084		22.1	0.039
		11.8	0.059		18.0	0.031
		10.7	0.065		21.9	0.032
		10.1	0.069		21.2	0.033
		9.4	0.074		19.9	0.035
		10.5	0.066		14.3	0.049
		9.5	0.075		14.4	0.048
					20.2	0.034
					18.8	0.039
32‡	115–120	9.2	0.075			
		8.8	0.079			
		8.0	0.087			
		12.0	0.058			
		8.0	0.087			
		9.2	0.077			
Mean ± standard deviation		8.5 ± 0.8	0.084		14.3 ± 2.4	0.050

from the control to the last hypertensive period, the average ratio being 0.87 for both periods.

Since precisely the same protocol was followed with few exceptions in the experiments described below, we assume that the renal hemodynamic changes measured in this group of animals are representative of most of the rats in this study. Most of the micropuncture data presented below were obtained during a time interval which corresponds best with the second hypertensive period in this group, i.e., when GFR and C_{PAH} had returned to or toward control levels.

Proximal tubular hydrostatic pressure (Fig. 2). The mean proximal hydrostatic pressure during the control period was 16.2 cm H_2O (± 1.4 SD). This value is in close agreement with those reported by Gottschalk and Mylle (12, 13) and Thurau and Wober (22). With the onset of hypertension and diuresis, the kidney was noted to swell, and in seven rats with the renal capsule intact, proximal tubular pressure rose to 28.1 cm H_2O (± 4.9 SD) ($P < 0.001$). This finding is in agreement with Gertz, who also observed a significant rise in proximal tubular pressure during hypertension induced by carotid artery occlusion,[1] but is in disagreement with Thurau and Wober (22) who found no change in proximal pressure over a wide range of blood pressure. We have no explanation for this disagreement.

In sharp contrast to the animals with their renal capsule intact, no rise in proximal hydrostatic

[1] Personal communication.

TABLE II

Representative Experiment Demonstrating the Effect of Acute Hypertension on Reabsorptive Half-Time, Tubular Diameter, and Urinary Sodium Excretion

Time	Blood pressure	Tubule No.	UV	U_{Na}	$U_{Na}V$	Diameter		Reabsorptive $t_{\frac{1}{2}}$	Reabsorptive capacity $C/\pi r^2$
						Free flow*	Split drop		
min	*mm Hg*		*μl/min per kidney*	*mEq/liter*	*μEq/min per kidney*	*μ*	*μ*	*sec*	*sec*$^{-1}$
0	Infusion of Ringer's solution started at 0.05 ml/min.								
20–25	4 ml Ringer's solution given intravenously to replace fluid losses during surgery.								
130–220			3.39	44	0.15				
	122	1				18.0	29.0	8.0	0.087
	120	2				17.5	22.0	8.0	0.087
	120	2				19.0	29.5	10.2	0.068
	121	2				17.5	25.0	7.5	0.092
	120	2				17.0	26.0	8.3	0.084
	125	3				17.5	29.0	11.8	0.059
	126	4				17.0	23.0	10.7	0.065
	125	5				17.0	26.5	10.1	0.069
	125	5				17.0	28.5	9.4	0.074
	125	5				17.5	28.5	10.5	0.066
223	Carotid arteries clamped and cervical vagus nerves cut.								
	165	6				22.0	28.5	9.6	0.072
	166	7				21.0	28.5	20.5	0.034
	172	8				20.5	29.0	20.5	0.034
	172	8				21.5	28.0	22.6	0.031
	180	9				25.0	27.5	22.1	0.031
	180	9				23.0	29.5	18.0	0.039
268–315			62.9	144	9.96				
	174	10				21.0	30.0	21.9	0.032
	174	11				21.5	27.5	21.2	0.033
	178	12				21.5	26.5	19.9	0.035
	180	13				20.0	25.0	14.3	0.049
	184	14				19.0	28.0	14.4	0.048
	184	14				20.0	27.5	20.2	0.034

UV, rate of urine flow; U_{Na}, urine sodium concentration; $U_{Na}V$, rate of sodium excretion.
* Mean of 10–12 measurements of tubules not blocked by oil.

pressure was found during comparable degrees of hypertension in four rats in which the renal capsule had been removed. The data are presented in Fig. 2, in which each symbol represents the average pressure during the control or hypertensive period for individual animals.

Split-drop reabsorptive half-time measurements and tubular diameter (Tables I–V). The split-drop data from 12 normal rats are shown in Table I. 3 of the 12 animals received intravenous *d*-aldosterone throughout the experiment, but since no differences were observed in reabsorptive half-time between these animals and the remainder of the group, all the data have been considered together. The mean $t_{\frac{1}{2}}$ during the control periods was 8.5 sec (± 0.8 SD) and during acute hypertension became significantly prolonged to 14.3 sec (± 2.4 SD) ($P < 0.001$). In columns 4 and 7, $C/\pi r^2$ has been calculated from equation 1, and as can be seen, this ratio fell markedly during acute hypertension. Experiment 31 is shown in further detail in Table II. This animal received more than the usual amount of infusion (approximately 16 ml over a 4 hr period) before the induction of hypertension. Reabsorptive half-time remained within the normal range before hypertension was induced and then became greatly prolonged. The internal diameter of the free-flow tubules increased during hypertension and diuresis, but no consistent difference in the diameter of the isolated saline column in the split-drop was found between the control and hypertensive periods.

TABLE III

*Effect of Chronic Oral Saline Loading on Reabsorptive Half-Time before and during Acute Hypertension**

Experiment No.	Control			Hypertension		
	Blood pressure	Reabsorptive $t_{\frac{1}{2}}$	Reabsorptive capacity $C/\pi r^2$	Blood pressure	Reabsorption $t_{\frac{1}{2}}$	Reabsorptive capacity $C/\pi r^2$
	mm Hg	*sec*	*sec*$^{-1}$	*mm Hg*	*sec*	*sec*$^{-1}$
33	139–145	10.9	0.064	168–170	11.5	0.060
		8.0	0.087		13.9	0.050
		11.9	0.058		—	—
		—	—		12.7	0.055
		10.3	0.070			
34	104–112	7.5	0.092	140–150	13.8	0.050
		9.3	0.075		17.2	0.040
		9.6	0.072		15.0	0.046
		9.7	0.071		—	—
		9.8	0.071		15.3	0.045
		—	—			
		9.2	0.076			
35	104–110			173–180	14.5	0.048
					12.7	0.055
					13.6	0.051
					17.1	0.041
					19.2	0.036
					13.2	0.053
					16.1	0.043
					20.4	0.034
					19.8	0.035
					18.3	0.038
					18.2	0.038
					15.4	0.045
					—	—
					16.5	0.043
36	125–130	9.9	0.070	167–180	14.6	0.048
		10.7	0.065		13.7	0.051
		—	—		—	—
		10.3	0.068		14.2	0.050
Mean ± standard deviation		9.9 ± 0.6	0.071		14.7 ± 1.62	0.048

* All animals received 0.25 μg/min of *d*-aldosterone intravenously throughout the experiment.

The internal diameters of the free-flow tubules and of the segments of tubules containing the injected saline column were measured from the photographic transparencies of the experiments in Table I. The mean diameter of the free-flow tubules was 18.5 μ (± 1.2 SD) during control periods and increased to 23.5 μ (± 1.6 SD) during hypertension. The difference is highly significant ($P < 0.001$). In contrast, no significant difference in the internal diameter of the isolated saline columns was found before and during hypertension (27.1 μ ± 2.2 SD vs. 27.3 μ ± 2.0 SD).

The absolute rate of sodium reabsorption calculated from split-drop measurements depends upon the volume of fluid in the droplet as well as on the reabsorptive half-time. Steinhausen (23) and Hayslett, Kashgarian, and Epstein (17) found that the diameter of the tubule segment containing the isolated droplet seems to be maximally enlarged, and is not further affected to any appreciable extent by experimental conditions which may affect the diameter of the free-flow tubules. Our observations agree with the findings of these authors. The prolongation of the half-time of

TABLE IV

Effect of Decapsulation of the Kidney on Reabsorptive Half-Time during Acute Hypertension

Experiment No.	Blood pressure	Reabsorptive $t_{\frac{1}{2}}$	Reabsorptive capacity $C/\pi r^2$
	mm Hg	*sec*	*sec*$^{-1}$
37	145–150	7.3	0.095
		11.7	0.059
		10.7	0.065
		9.9	0.073
38	154–170	9.5	0.073
		7.6	0.091
		7.2	0.096
		8.3	0.083
		10.2	0.068
		8.5	0.082
		8.6	0.082
39	150–172	8.3	0.083
		12.0	0.058
		9.9	0.070
		9.7	0.072
		7.9	0.088
		9.3	0.075
		8.9	0.078
		7.7	0.090
		8.9	0.078
		9.2	0.077
40	164–180	7.3	0.095
		8.1	0.086
		7.6	0.092
		8.3	0.084
		7.6	0.091
		8.6	0.081
		8.6	0.081
		8.9	0.078
		8.8	0.078
		8.2	0.085
Mean ± standard deviation		9.0 ± 0.7	0.079

TABLE V

Effect of Suprarenal Aortic Constriction on Reabsorptive Half-Time during Carotid Artery Occlusion

Experiment No.	Femoral artery blood pressure	Reabsorptive $t_{\frac{1}{2}}$	Reabsorptive capacity $C/\pi r^2$
	mm Hg	*sec*	*sec*$^{-1}$
41	105–120	9.0	0.077
		7.4	0.095
		7.7	0.090
		9.6	0.072
		8.4	0.084
42	102–123	7.3	0.095
		6.8	0.102
		7.7	0.089
		8.8	0.079
		9.0	0.077
		8.5	0.082
		9.6	0.087
43	100–105	7.3	0.095
		9.7	0.071
		10.7	0.065
		7.3	0.095
		9.2	0.075
		8.8	0.080
44	102–110	7.5	0.092
		7.5	0.092
		8.4	0.083
		7.8	0.089
45	90–114	8.8	0.079
		10.5	0.066
		7.9	0.088
		9.4	0.074
		10.8	0.064
		6.8	0.102
		8.3	0.084
		8.9	0.080
46*	99–114	8.6	0.081
		9.0	0.077
		7.9	0.088
		9.1	0.076
		8.5	0.082
		9.0	0.077
		8.7	0.080
47*	106–128	8.8	0.079
		7.6	0.091
		10.0	0.069
		9.3	0.075
		8.5	0.082
		10.3	0.067
		10.9	0.064
		9.3	0.075
Mean ± standard deviation		8.8 ± 0.6	0.082

* Cervical vagus nerves were left intact in these experiments.

reabsorption during acute hypertension suggests, therefore, that there was a fall in the absolute rate of proximal sodium transport per unit length of tubule as well as per unit volume.

In Table III are shown the reabsorptive half-time data obtained from four rats given isotonic saline ad lib as drinking solution for 5 wk. The average saline consumption was 80 ml/day. As can be seen, $t_{\frac{1}{2}}$ was comparable to that in nonsaline loaded rats during the control periods and became just as prolonged during acute hypertension as it did in the rats shown in Table I.

In contrast to the preceding observations, acute hypertension had no significant effect on $t_{\frac{1}{2}}$ in four normal rats in which the renal capsule of the experimental kidney had been removed ($0.4 > P > 0.3$). These data are presented in Table IV.

The data obtained from seven rats in which renal perfusion pressure was maintained between 90 and 128 mm Hg by a suprarenal aortic clamp are shown in Table V. Both carotid arteries were occluded in these animals and in five of the seven, the cervical vagus nerves were also severed. As can be seen, reabsorptive half-time remained within the normal range under these experimental conditions. At the conclusion of each of these experiments, femoral blood pressure was found to rise to hypertensive levels after the aortic clamp had been removed.

Tubular fluid/plasma inulin ratios $(TF/P)_{In}$, *and Lissamine green transit time* (T) *(Table VI).* In Table VI, the data from 10 rats are presented in which paired $(TF/P)_{In}$ ratios and Lissamine green transit time (T) measurements were made near the end of the proximal tubule before and during acute hypertension. In columns 5 and 10 the values for $C/\pi r^2$ are shown, calculated from equation 2, and in columns 6 and 11 are the values for $\pi r^2 d/V_0$, calculated from equation 3. In each experiment, the $(TF/P)_{In}$ ratio fell during the diuresis induced by hypertension, the mean value for the control and hypertensive periods being 2.64 ($\pm$ 0.35 SD) and 1.87 ($\pm$ 0.17 SD) respectively ($P < 0.001$). The calculated intrinsic reabsorptive capacity ($C/\pi r^2$) similarly fell significantly, from a mean of 0.085/sec ($\pm$ 0.015 SD) to 0.045/sec ($\pm$ 0.011 SD) ($P < 0.001$). These data are thus in agreement with the split-drop experiments shown in Table I and demonstrate by a second, independent method that sodium transport per unit of tubular volume was markedly reduced during acute hypertension. Although GFR per nephron was not measured in these experiments, the significant fall in fractional reabsorption during the period which corresponds with the return of over-all GFR to control levels, suggests that absolute reabsorption per unit length was also diminished. The ratio of tubular volume to GFR ($\pi r^2 d/V_0$), shown in columns 6 and 11, increased significantly during the hypertensive period, from a mean of 7.5 sec ($\pm$ 1.1 SD) to 10.6 sec ($\pm$ 2.7 SD) ($P < 0.01$).

DISCUSSION

The results of the present experiments demonstrate that in the rat, acute hypertension produced by carotid artery occlusion causes a marked suppression of proximal sodium transport and a natriuresis, even when autoregulation is present. In the dog, hypertension induced by systemic administration of vasopressor drugs results in a natriuresis if autoregulation is abolished by renal vasodilator drugs, but only inconsistently if autoregulation is intact (4). It is not clear whether this difference between the dog and rat is intrinsic to the species, or whether hypertension induced by exogenous vasopressor drugs has a more pronounced constrictor effect on the renal blood vessels than does hypertension induced by carotid artery occlusion. In any case, the effect on proximal sodium reabsorption in our animals appears to be similar to that described by Earley et al. in hypertensive dogs with renal vasodilatation (4, 5).

The precise mechanism responsible for the inhibition of proximal sodium transport during acute hypertension is uncertain, but several different possibilities can be considered. According to the tubular geometry hypothesis (6, 7, 24), some property of sodium transport correlated with the cross-sectional diameter of the proximal lumen, such as the size of pores within the membrane, influences the rate of net transport. Thus, the absolute rate of transport per unit length of tubule (C) has been shown to vary directly with tubular diameter under several different experimental conditions (6, 7, 24, 25). Therefore, a reduction in luminal diameter would be expected to cause a proportional decrease in C. In this case, the ratio $C/\pi r^2$ would remain constant. A second aspect to the tubular geometry hypothesis is that the ratio between tubular volume and GFR ($\pi r^2 d/V_0$) is an important determinant of fractional reabsorption of sodium and water in the proximal tubule (19). Any decrease in this ratio during acute hypertension might therefore be expected to result in a fall in fractional reabsorption. It is clear, however, that neither of these two mechanisms can account for the suppression of proximal sodium transport which occurred in the present experiments. In both the split-oil drop experiments and in the free-flow experiments (Tables I and VI), it was found that the rate of

TABLE VI

Effect of Acute Hypertension on $(TF/P)_{In}$ and Lissamine Green Transit Time

Experiment No.	Control					Hypertension				
	Blood pressure	$(TF/P)_{In}$*	Transit time	Reabsorptive capacity $C/\pi r^2$	Tubular volume per GFR‡ $(\pi r^2 d/V_0)$	Blood pressure	$(TF/P)_{In}$*	Transit time	Reabsorptive capacity $C/\pi r^2$	Tubular volume per GFR‡ $(\pi r^2 d/V_0)$
	mm Hg		*sec*	*sec*$^{-1}$	*sec*	*mm Hg*		*sec*	*sec*$^{-1}$	*sec*
48	125–132	2.15	13.0	0.059	9.0	158–180	2.60	10.0	0.068	9.1
		2.32	10.0	0.084	6.8		2.17	14.0	0.055	9.8
		2.09	10.5	0.070	7.4		2.54	16.0	0.058	10.5
							1.82	18.0	0.033	13.6
		2.19	11.2	0.071	7.7		1.41	23.0	0.015	19.5
							2.11	16.2	0.046	12.5
49	119–123	2.66	10.0	0.098	6.3	153–168	2.93	19.0	0.057	11.7
		2.16	10.5	0.073	7.4		1.14	19.5	0.007	17.9
							1.27	18.5	0.013	16.3
		2.41	10.3	0.086	6.9		1.29	16.0	0.017	12.9
							1.66	18.3	0.024	14.7
50	132–136	2.69	10.5	0.094	6.7	165–179	2.09	14.0	0.053	9.9
		3.06	12.0	0.093	7.2		2.17	16.0	0.048	11.2
		2.53	12.0	0.077	7.8		1.54	15.0	0.029	12.2
							2.29	17.5	0.047	11.8
		2.76	11.5	0.088	7.2		1.87	18.0	0.035	13.5
							1.99	16.1	0.042	11.7
51	117–123	2.46	9.0	0.100	5.9	149–167	1.75	26.0	0.022	20.0
							1.63	18.5	0.026	14.8
							2.65	17.2	0.057	11.0
							2.27	16.9	0.049	11.5
							1.66	17.0	0.030	13.4
							1.97	17.0	0.040	12.3
							1.99	18.8	0.037	13.8
52	111–120	2.44	16.0	0.056	10.6	158–160	1.76			
		2.39	9.0	0.097	6.0		2.03			
		2.42	12.5	0.077	8.3		2.03			
53	120–125	2.90	9.0	0.118	5.6	150–160	1.80	10.1	0.059	7.5
		2.71	10.0	0.100	6.3		2.15	10.2	0.075	7.1
							1.68	9.9	0.052	7.6
		2.81	9.5	0.109	6.0		1.76	10.1	0.056	7.7
							1.62	10.3	0.047	8.1
							2.05	9.8	0.073	7.0
							1.84	10.1	0.060	7.5
54	115–120	3.37	15.1	0.080	8.7	145–150	2.29	13.4	0.062	9.1
							1.29	10.0	0.025	8.7
							1.67	13.8	0.037	10.8
							1.68	13.5	0.038	10.4
							2.66	14.4	0.068	9.1
							1.92	13.0	0.046	9.6

* $(TF/P)_{In}$, tubular fluid-to-plasma inulin ratio.

‡ GFR, glomerular filtration rate per nephron in this ratio.

TABLE VI (*Concluded*)

Experiment No.	Control					Hypertension				
	Blood pressure	$(TF/P)_{In}$*	Transit time	Reabsorption capacity $C/\pi r^2$	Tubular volume per GFR‡ $(\pi r^2 d/V_0)$	Blood pressure	$(TF/P)_{In}$*	Transit time	Reabsorption capacity $C/\pi r^2$	Tubular volume per GFR‡ $(\pi r^2 d - V_0)$
	mm Hg		*sec*	*sec*$^{-1}$	*sec*	*mm Hg*		*sec*	*sec*$^{-1}$	*sec*
55	112–116	2.85	13.8	0.076	8.6	149–162	2.08	8.8	0.083	6.3
		2.00	13.4	0.052	9.7		1.87	10.4	0.060	7.8
							2.40	12.6	0.069	8.4
		2.43	13.6	0.064	9.2		1.35	14.3	0.021	12.4
							1.84	16.8	0.036	12.7
							1.91	12.6	0.054	9.5
56	112–126	4.65	9.4	0.163	4.8	162–172	1.63	11.0	0.044	8.8
		2.47	11.7	0.077	7.8		1.63	11.3	0.047	8.2
		1.96	10.6	0.063	7.7					
							1.63	10.7	0.046	8.5
		3.03	10.6	0.101	6.8					
57	113–115	2.49	13.2	0.069	8.7	150–179	1.55	9.1	0.048	7.3
		2.48	12.2	0.074	8.1		1.14	9.0	0.015	8.3
							2.29	9.3	0.089	6.3
		2.49	12.7	0.072	8.4					
							1.66	9.1	0.051	7.3
Mean ± standard deviation		2.64 ±0.35	11.6 ±1.9	0.085 ±0.015	7.5 ±1.1		1.87 ±0.17	13.9 ±3.6	0.045 ±0.011	10.6 ±2.7

sodium transport was depressed out of proportion to tubular diameter i.e., $C/\pi r^2$ fell markedly. Moreover, the ratio between tubular volume and GFR actually increased rather than decreased (Table VI). Finally, tubular diameter measurements showed a significant increase in size instead of the decrease which this hypothesis would require.[2] We conclude, therefore, that a mechanism other than that related to tubular geometry was responsible for the inhibition of proximal sodium transport which occurred during acute hypertension.

This conclusion does not mean, however, that the volume of the tubules played no part at all in adjusting the rate of sodium transport. In fact, there is some evidence in the present experimental data which suggests that cross-sectional diameter continued to influence the transport rate in spite of the over-all reduction in reabsorptive capacity. If we calculate the mean $(TF/P)_{In}$ ratio during hypertension by substituting in equation 2 the mean $C/\pi r^2$ value obtained from the split-drop experiments, and the value for T observed in the free-flow experiments, the ratio obtained is quite close to that which was actually measured in free-flow tubules (2.01 vs. 1.87). Since the cross-sectional diameter of the isolated saline column in the split-drop measurements was considerably larger than the free-flow diameters, this agreement in fractional reabsorption by the two methods suggests that both C and πr^2 were greater in the split-droplet tubules than in the free-flow tubules, although the ratio $C/\pi r^2$ was approximately the same. Thus, the larger tubular volume of the split droplet may have caused a higher absolute rate of transfer at the same time that the intrinsic reabsorptive capacity was reduced to an equivalent degree in both types of experiments by some other mechanism. It would seem from these considerations that tubular volume (or some function thereof) may continue to modify sodium reabsorption even under experimental conditions where it is not the primary cause of changes in transport rate.

[2] The conclusions reached about the tubular geometry hypothesis from equations 1–3 do not require diameter measurements but are supported by these measurements in this study.

In addition to tubular geometry, several hormonal mechanisms were investigated by the various experimental protocols described above, with essentially negative results. Thus, *d*-aldosterone did not seem to be involved, since large intravenous doses of this hormone did not prevent the effect of hypertension on proximal sodium transport. Similarly, the renal renin-angiotensin system did not appear to be responsible, since chronic oral saline loading, which is thought to significantly reduce the renin content of the kidney (16, 17, 26), did not alter the response to acute hypertension. While these latter observations are not conclusive, because small amounts of renin most likely remained in the kidney even after 5 wk of saline ingestion, recent split-drop micropuncture experiments by Thurau cast serious doubt on the ability of angiotensin to inhibit proximal sodium transport in the rat (27). Finally, the experiments in which suprarenal aortic constriction was found to completely prevent the inhibition of proximal sodium transport during carotid artery occlusion (Table V) tend to exclude an extrarenally produced natriuretic hormone as the mechanism. While it is conceivable that a severe reduction in renal perfusion pressure might modify the inhibitory effect of an extrarenal natriuretic hormone, such an explanation seems unlikely in the present experiments, since perfusion pressure was reduced only to the normal range.

At least two additional possibilities remain, but the present data do not distinguish conclusively between them. The first is that increased renal perfusion pressure may have caused the release of an intrarenal natriuretic hormone, perhaps prostaglandin (28). Since constriction of the aorta above the renal arteries prevented the inhibition of sodium transport, a high perfusion pressure at some point within the renal vasculature would presumably be the trigger mechanism for release of the hormone. A second possibility is that which has been proposed by Earley et al. (4, 5). They suggested that a hydrostatic pressure gradient from the peritubular capillaries to the interstitium might increase the interstitial volume of the kidney, and that this increase would then reduce the rate of sodium reabsorption. Several of our observations could be interpreted to support this mechanism. It seems likely that an increase in peritubular capillary hydrostatic pressure did occur in our animals, since intraluminal pressure was found to rise significantly during the hypertensive period (Fig. 2).[3] While no conclusion can be drawn about a pressure gradient from these measurements, it seems possible that during the initial phase of hypertension such a gradient did exist, since the rise in RPF was accompanied by a large fall in FF. This finding suggests that efferent arteriolar resistance fell, relative to afferent resistance, and thus pressure transmission to the postglomerular capillaries may have been relatively greater than to the tubular lumen. We suspect, however, that a new steady-state pressure level was quickly reached, since the tubules were noted to enlarge within a few minutes of the onset of hypertension. Nevertheless, an initial increase in interstitial volume produced by a transient pressure gradient might have persisted, since the entire kidney was noted to swell. While our data do not allow us to choose between a hormonal and a physical mechanism, two points weigh in favor of the latter. First, the rapidity of onset of the natriuresis and diuresis, which frequently occurred within a few minutes after the induction of hypertension, speaks against a hormonal action. Second, the experiments in which the renal capsule was stripped off (Fig. 2 and Table IV) favor a mechanism involving the interstitial volume, since the most likely effect of removing the renal capsule was to alter the normal anatomical limits of the interstitial fluid surrounding the surface nephrons. Finally, Lewy and Windhager (29) have recently reported that elevation of peritubular capillary pressure by partial clamping of the renal vein also suppresses proximal intrinsic reabsorptive capacity, presumably by a mechanism involving an increase in the interstitial volume of the kidney. Precisely how an increase in interstitial volume might reduce proximal sodium transport, whether by increasing the permeability of the tubular epithelium and thus allowing greater backflux, or by inhibiting the active sodium pump, remains to be determined.

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[3] Since no measureable steady-state pressure gradients have been found between the proximal lumen and the peritubular capillaries under conditions of both normal and elevated intrarenal pressure (12, 13, 22), we assume that pressure also rose in the peritubular capillaries during hypertension.

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