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Research Article

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Inhibition of Renal Tubular Sodium Reabsorption by Hypernatremia *

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In a recent study (1), we confirmed the observation of Bresler (2) and Toussaint and Vereerstraeten (3) that tubular sodium reabsorption (T_{Na}) in dogs increases following plasma sodium (P_{Na}) elevation. However, when the increase in filtered sodium (F_{Na}) that usually accompanied an elevated P_{Na} was eliminated by reducing glomerular filtration rate (GFR) with an aortic clamp, hypernatremia appeared to inhibit rather than stimulate T_{Na}. Similar results have been obtained by Blythe and Welt (4), who found that sodium excretion during the infusion of hypertonic saline was above control when filtered sodium was reduced below control by inflating a balloon in the inferior vena cava. The micropuncture studies of Giebisch, Klose, and Windhager (5) in rats have also demonstrated that T_{Na} is decreased by hypertonic saline infusions.

In all these studies the depression of T_{Na} was considered to be a consequence of hypernatremia per se. In each case, hypernatremia was induced by loading with hypertonic saline. The infusion of similar volumes of isotonic saline has been shown to inhibit T_{Na} to a comparable degree (6–9). Therefore, the studies cited do not clearly differentiate between volume expansion and hypernatremia as the cause of the decreased T_{Na}, nor, indeed, do they clearly establish that hypernatremia itself has any direct effect on T_{Na}. In the present experiments, we have attempted to isolate the effects of hypernatremia on T_{Na} by unilaterally elevating renal arterial P_{Na}, using the opposite kidney as a simultaneous control. Since any effect of volume expansion is presumably equal in the two kidneys, changes in T_{Na} in the experimental kidney relative to the control should be a function of hypernatremia per se. The results demonstrate that hypernatremia specifically inhibits T_{Na} by means of a direct intrarenal action.

Methods

Female mongrel dogs were anesthetized with pentobarbital, 30 mg per kg intravenously, and small supplementary doses were given as necessary to maintain light anesthesia. A sustaining infusion containing appropriate concentrations of inulin and *p*-aminohippurate (PAH) in 0.82% NaCl was given throughout each experiment at 8.0 ml per minute. The dogs were last fed about 20 hours before an experiment; water was usually allowed ad libitum. In some studies, water was withdrawn 18 hours before the experiment, and the dogs were given 5 U vasopressin tannate in oil intramuscularly 18 hours and again ½ hour before the experiment; aqueous Pitressin, 50 mU per kg per hour, was added to the sustaining infusion. Urine was collected separately from each kidney through polyethylene tubing that had been inserted into the ureters through a lower mid-line abdominal incision.

The experimental kidney was supplied with femoral arterial blood through a modification of the surgical procedure used by Goodman and Fuisz (10). The ipsilateral femoral artery was cannulated and connected to ¼-inch (i.d.) polyethylene tubing. Through a flank incision, the proximal segment of the artery to the experimental kidney was carefully dissected free from the surrounding connective tissue. After the intravenous administration of 50 mg of heparin, the renal artery was ligated at its origin and cannulated. Care was taken that the cannula was aligned properly with the direction of the artery and that the tip was proximal to the bifurcation. The renal arterial cannula was then connected to

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the tubing in the femoral artery, and circulation to the experimental kidney was thus completed. The period of renal ischemia during the creation of the shunt varied from 1 to 4 minutes.

Infusions into the shunt were accomplished by direct puncture of rubber tubing near its femoral end with the needle directed against the flow of blood to enhance mixing. Blood samples for the experimental kidney were obtained via a sidearm close to the renal end of the shunt. The length of the tubing between the site of infusion and the point at which blood samples were drawn was approximately 40 cm. Blood samples for the control kidney were obtained from a retention needle in the jugular vein.

After the collection of three to five control periods, 20% saline was infused into the shunt at 0.5 to 3.0 ml per minute. After 5 to 10 minutes for equilibration, the "hypernatremic" periods were collected. In some experiments the degree of hypernatremia on the experimental side was then altered by changing the rate of the hypertonic infusion, and additional groups of hypernatremic periods were obtained. In some cases hypernatremic periods were collected with the shunt partially occluded by a clamp, so that clearance measurements could be made with sodium excretion from the experimental kidney equal to or only slightly greater than the value on the control side. In some experiments, additional control periods, during which no saline was infused into the shunt, and "isotonic" periods, during which 0.82% saline was infused into the shunt, were obtained between or after the groups of hypernatremic periods.

Inulin clearance (C_{In}) was used as a measure of GFR, and F_{Na} was calculated as equal to $P_{Na} \cdot C_{In}$ without a Donnan correction. The analytical methods used in this study have been listed elsewhere (6). Except where individual experiments are shown, each clearance value in this paper is the mean of three to seven consecutive clearance periods. Experiments were discarded if the filtration rates of the two kidneys differed by more than 10% in the initial control periods.

TABLE I

*Protocol of a representative experiment**

Time	C_{PAH}		C_{In}		P_{Na}		F_{Na}		$U_{Na}V$		T_{Na}	
	Exp.	Cont.	Exp.	Cont.	Exp.	Cont.	Exp.	Cont.	Exp.	Cont.	Exp.	Cont.
	ml/min		*ml/min*		*mEq/L*		*mEq/min*		*mEq/min*		*mEq/min*	
0	Primes given: 400 mg PAH, 600 mg inulin; infusion I started: 0.82% saline at 12 ml per minute											
40	Ureters catheterized											
110	Right femoral artery cannulated											
120	Infusion I stopped and infusion II started: inulin 2.25 mg per ml, PAH 0.75 mg per ml, and aqueous Pitressin 2 mU per ml in .82% saline at 8 ml per minute											
130	Right renal artery ligated											
132	Right femoral-renal shunt completed											
191–196	59	62	30.0	30.8		150	4.50	4.62	0.368	0.355	4.13	4.25
196–201	57	60	28.7	29.6		152	4.36	4.50	0.364	0.338	4.00	4.16
201–207	60	59	27.7	27.5		151	4.18	4.15	0.368	0.321	3.81	3.83
210	Infusion III started: 20% saline into shunt at 0.9 ml per minute											
221–226	49	59	25.2	30.1	171	152	4.31	4.58	0.699	0.410	3.61	4.17
226–231	57	57	24.0	27.1	163	153	3.91	4.15	0.711	0.414	3.20	3.74
231–236	62	59	24.4	28.8	167	154	4.07	4.44	0.722	0.442	3.35	4.00
243	Shunt constricted with clamp											
248–253	53	53	24.1	28.3	180	157	4.34	4.44	0.652	0.499	3.69	3.94
253–258	53	59	23.6	30.4	183	158	4.32	4.80	0.668	0.537	3.65	4.26
258–263		59	25.4	29.1	182	160	4.62	4.66	0.672	0.537	3.95	4.12
263–268	56	59	23.1	27.9	183	161	4.23	4.49	0.674	0.537	3.56	3.95
269	Clamp around shunt released											
270	Infusion III stopped and infusion IV started: 0.82% NaCl into shunt at 2.9 ml per minute											
288–294	54	52	24.4	25.1	158	157	3.86	3.94	0.214	0.195	3.65	3.74
294–301	48	52	23.3	26.7	157	159	3.66	4.25	0.186	0.190	3.47	4.06
301–309	47	48	22.9	24.3	154	159	3.53	3.86	0.172	0.171	3.36	3.69
309–316	46	48	23.2	22.8	154	159	3.57	3.63	0.160	0.155	3.41	3.47
325	Infusion IV stopped; infusion III restarted into the shunt at 1.5 ml per minute, shunt constricted with clamp											
337–342	33	48	15.8	24.9	250	165	3.95	4.11	0.761	0.345	3.19	3.76
342–348	35	50	17.4	25.6	249	169	4.33	4.32	0.850	0.422	3.48	3.90
354–359	38	41	17.9	22.4	240	174	4.30	3.90	1.080	0.543	3.22	3.36
359–364	35	43	18.1	24.8	248	177	4.49	4.39	1.100	0.603	3.39	3.79
365	Clamp around shunt released											
366	Infusion III stopped; infusion IV restarted into shunt at 2.9 ml per minute											
380–385	39	41	17.4	22.3	173	175	3.01	3.90	0.263	0.325	2.75	3.57
385–390	41	41	17.9	21.6	170	172	3.04	3.72	0.234	0.298	2.81	3.42
390–398	31	41	16.3	21.9	171	173	2.79	3.79	0.167	0.239	2.62	3.55

* Abbreviations: Exp. = experimental kidney; cont. = control kidney; C_{PAH} = clearance of *p*-aminohippurate; C_{In} = clearance of inulin; P_{Na} = plasma sodium; F_{Na} = filtered sodium; $U_{Na}V$ = excreted sodium; T_{Na} = tubular sodium reabsorption.

TABLE II

*Summary of all experiments**

Exp. no.	Collection periods	Infusion*	C_{In}		P_{Na}		F_{Na}		$U_{Na}V$	
			Exp.	Cont.	Exp.	Cont.	Exp.	Cont.	Exp.	Cont.
		ml/min	*ml/min*		*mEq/L*		*mEq/min*		*mEq/min*	
1.	Control	0	25	28		152	3.78	4.18	0.109	0.114
	Hypernatremic	1.2	25	31	189	165	4.60	5.13	0.563	0.525
2.	Control	0	41	37		150	6.18	5.63	0.130	0.125
	Hypernatremic†	1.2	23	41	221	176	5.08	7.16	0.245	0.205
3.	Control	0	31	34		144	4.46	4.83	0.178	0.221
	Hypernatremic	0.5	25	32	166	148	4.20	4.70	0.245	0.226
4.	Control	0	25	25		152	3.85	3.82	0.157	0.143
	Hypernatremic†		17	25	213	170	3.59	4.16	0.399	0.240
	Hypernatremic†		14	24	238	184	3.36	4.31	0.585	0.576
5.	Control	0	38	42		160	6.02	6.63	0.201	0.243
	Isotonic	3.0	39	42	164	158	6.39	6.62	0.263	0.271
	Isotonic	3.0	36	43	163	158	5.94	6.83	0.243	0.416
	Hypernatremic†	3.0	25	41	238	177	5.95	7.31	1.38	0.987
6.	Control	0	40	43		152	6.13	6.48	0.242	0.272
	Hypernatremic	0.5	37	43	160	153	5.94	6.55	0.465	0.465
	Isotonic	2.9	43	46	151	151	6.45	6.91	0.453	0.475
	Hypernatremic	0.6	37	41	184	155	6.73	6.33	1.19	0.600
	Control	0	42	47		157	6.58	7.37	0.460	0.494
7.	Control	0	28	31		147	4.15	4.49	0.261	0.249
	Hypernatremic†	0.7	27	30	173	156	4.60	4.62	0.521	0.384
	Isotonic	2.8	27	30	153	153	4.21	4.60	0.239	0.241
	Hypernatremic†	0.9	24	30	193	164	4.57	4.88	0.699	0.490
	Isotonic	2.8	25	31	161	162	4.05	5.02	0.284	0.335
	Control	0	28	31		163	4.49	4.96	0.221	0.253
	Hypernatremic	1.2	24	32	196	169	4.71	5.44	0.745	0.399
	Hypernatremic	1.7	23	29	220	174	5.10	5.01	1.511	0.577
	Control	0	16	20		178	2.77	3.54	0.246	0.289
8.	Control	0	29	29		151	4.35	4.42	0.367	0.338
	Hypernatremic	0.9	25	29	167	153	4.10	4.39	0.710	0.422
	Hypernatremic†	0.9	24	29	182	159	4.38	4.60	0.667	0.527
	Isotonic	2.9	24	25	156	159	3.66	3.92	0.183	0.178
	Hypernatremic†	1.5	17	24	247	171	4.27	4.18	0.948	0.478
	Isotonic		17	22	171	173	2.95	3.81	0.221	0.287

* Abbreviations as in Table I. Infusion = rate of infusion into shunt. Twenty per cent saline was infused during hypernatremic periods, 0.82% saline during isotonic periods. Each value in this Table is the mean of three to seven clearance periods.

† Shunt constricted with clamp during collection of this group of periods.

Results

The detailed protocol of a single experiment is presented in Table I. In the control periods filtered sodium was equal in the two kidneys; sodium excretion was slightly higher on the experimental side. Hypertonic saline (20%) was then infused into the right femoral-renal arterial shunt at about 0.9 ml per minute, elevating P_{Na} in the shunt blood 10 to 20 mEq per L above systemic P_{Na}. After one set of hypernatremic periods at the spontaneous rates of sodium excretion had been obtained, excretion from the experimental kidney was brought closer to the rate of the control kidney by partial occlusion of the shunt, and a second set of hypernatremic periods was obtained. Despite modest but definite reduction of F_{Na} in the experimental kidney during both of these collections, sodium excretion from the experimental kidney exceeded that from the control by 0.130 to 0.300 mEq per minute. The clamp was released and the 20% saline infusion stopped. A 0.82% concentration of saline was then infused into the shunt at 2.9 ml per minute, a rate well in excess of that at which the 20% saline had been given. In the isotonic periods, which were next collected, sodium excretion was approximately equal in the two kidneys, although a modest reduction in F_{Na} of the experimental kidney was still present. The isotonic infusion was then stopped, 20% NaCl was restarted into the shunt at nearly twice the earlier rate, and the shunt was again partially occluded. The reduction in GFR of the experimental kidney due to clamping of the shunt compensated almost exactly for the elevation of 65 to 85 mEq per L in P_{Na} in the shunt blood, so that

filtered sodium was approximately equal in the two kidneys. Mean sodium excretion from the experimental kidney now exceeded mean excretion from the control kidney by 0.475 mEq per minute. Finally the clamp was released, and isotonic saline was infused into the shunt in place of hypertonic. The GFR of the experimental kidney did not quite return to control in the ensuing isotonic periods; F_{Na} and sodium excretion were both lower on the experimental side. Thus, during all three sets of hypernatremic periods, sodium excretion from the experimental kidney was significantly greater than that from the control kidney, despite equal or decreased F_{Na} in the experimental kidney. This increase in sodium excretion did not occur when a larger volume of isotonic saline was infused into the shunt.

The results of all eight experiments are summarized in Table II. In seven studies, sodium excretion from the experimental kidney was elevated during the infusion of hypertonic saline, despite a lower F_{Na}. In the remaining experiment (no. 6), sodium excretion in the first set of hypernatremic periods was equal when F_{Na} was 0.6 mEq per minute lower in the experimental kidney; in the second group of hypernatremic periods, experimental sodium excretion exceeded control excretion by 0.59 mEq per minute when filtered sodium was only 0.4 mEq per minute greater on that side. These results are illustrated in Figure 1. Each point represents the mean difference, experimental minus control kidney, in filtered and excreted sodium during one group of periods. Eleven control, seven isotonic, and fifteen hypernatremic periods are plotted. In the control periods, during which there was no infusion into the shunt, F_{Na} on the experimental side was higher than on the control side in one, the same in two, and 0.3 to 2.1 mEq per minute lower in eight collections. Differences in sodium excretion between the kidneys were slight, varying from + 0.05 to − 0.05 mEq per minute; on the whole, differences in excretion paralleled differences in F_{Na}, so that mean excretion was slightly less on the experimental side. The results of the isotonic periods, during which 0.82% saline was infused into the shunt, were similar to those obtained during control collections. Sodium excretion from the experimental kidney was generally slightly lower than that from the control kidney; filtered sodium was 0.2 to 1.0 mEq per minute lower on the experimental side. In nine of fifteen hypernatremic collections, sodium excretion from the experimental kidney was 0.04 to 0.34 mEq per

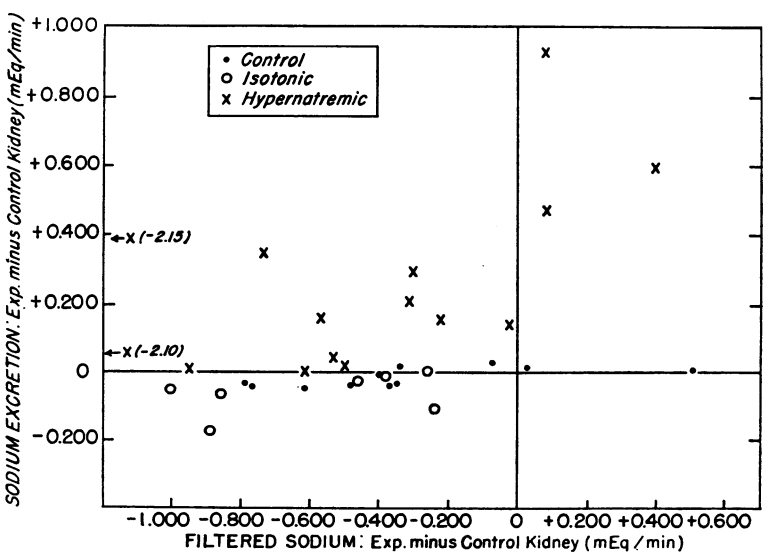

FIG. 1. DIFFERENCE IN SODIUM EXCRETION BETWEEN THE KIDNEYS PLOTTED AGAINST THE CORRESPONDING DIFFERENCE IN FILTERED SODIUM. Each point represents the mean of three or more periods, taken without infusion (control) or during infusion of 0.82% saline (isotonic) or 20% saline (hypernatremic) into the shunt supplying blood to the experimental kidney.

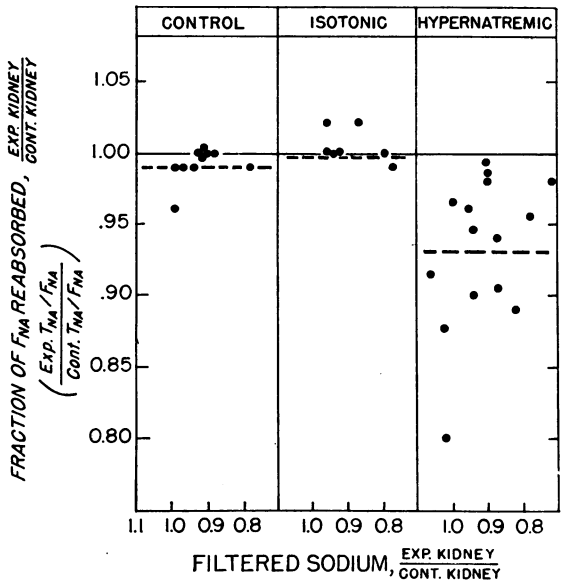

FIG. 2. COMPARISON OF FRACTIONAL SODIUM REABSORPTION (T_{Na}) IN THE TWO KIDNEYS, WITHOUT INFUSION (CONTROL) OR DURING INFUSION OF 0.82% SALINE (ISOTONIC) OR 20% SALINE INTO THE SHUNT SUPPLYING BLOOD TO THE EXPERIMENTAL KIDNEY. Relative filtered sodium (F_{Na}) in the two kidneys is shown on the abscissa. Each point is the mean of three or more periods.

minute greater than from the control despite a F_{Na} 0.02 to 2.1 mEq per minute lower in the hypernatremic kidney. In three hypernatremic collections, the experimental kidney excreted sodium at the same rate as the control side in spite of a F_{Na} 0.5 to 1.0 mEq per minute less than the control value. In the three remaining hypernatremic collections, both filtered and excreted sodium were greater on the experimental side, but the difference in sodium excretion was 0.2 to 0.8 mEq per minute more than the difference in F_{Na}. The mean differences in F_{Na} between the kidneys (experimental − control) in the control, isotonic, and hypernatremic periods, respectively, were − 0.235, − 0.580, and − 0.506 mEq per minute. These numbers are not significantly different from one another. The mean differences in excretion were − 0.015, − 0.045, and + 0.251 mEq per minute in the control, isotonic, and hypernatremic periods, respectively. The hypernatremic value differs statistically from each of the other two ($p < 0.01$ by t test); the control and isotonic values do not differ from each other.

The effect of hypernatremia on T_{Na} is illustrated in Figure 2. Fractional reabsorption of sodium in the experimental kidney, divided by the value for the control kidney [(exp. T_{Na}/F_{Na})/(cont. T_{Na}/F_{Na})], is shown on the ordinate for the control, isotonic, and hypernatremic collections of all eight experiments. During the control and isotonic collections, fractional reabsorption was approximately equal in the two kidneys; the mean ratios were 0.99 and 1.0, respectively. As shown in the third column, during the hypernatremic periods the mean reabsorption ratio fell to 0.93, a value significantly different ($p < 0.01$) from both the control and the isotonic ratios. The decrease in fractional T_{Na} in the experimental kidney during hypernatremia is not due to differences in relative F_{Na} of the two kidneys in the hypernatremic as compared to the other periods. Inspection of the abscissa of Figure 2 shows that the ratio of F_{Na} in the kidneys (F_{Na} exp./cont.) was similar during the control (0.94), isotonic (0.89), and hypernatremic (0.91) collections, and this was confirmed by statistical analysis.

Discussion

These studies were designed to isolate the effect of hypernatremia on T_{Na}. It was found that elevation of P_{Na} depresses T_{Na}, so that Na excretion is increased approximately 0.3 mEq per minute in a hypernatremic kidney as compared to a control at the same F_{Na} (Figure 1). The decrease in T_{Na} is equivalent to approximately 7% of F_{Na} (Figure 2). The depression of T_{Na} in the studies of Blythe and Welt (4) in dogs and of Giebisch, Klose, and Windhager (5) in rats is roughly comparable to that found in the present study. In our previous experiments (1), there was a smaller effect of hypertonic loading (sodium excretion from both kidneys was increased 0.18 mEq per minute at a given F_{Na}).

The experimental kidney functioned normally, and there is no reason to believe that the shunting technique introduced an artifact that depressed T_{Na}. During control and isotonic collections T_{Na} in the two kidneys was quite comparable (Figure 2). Since control, isotonic, and hypernatremic periods were intermixed throughout most experiments, gradual deterioration of the experimental kidney cannot account for the decrease in T_{Na} during the hypernatremic collections. The results were comparable in the experiments in

which GFR fell spontaneously and those in which it was necessary to clamp the shunt to reduce GFR during the hypernatremic periods. Hence, the clamping procedure itself does not depress fractional T_{Na}. During control and isotonic periods, sodium excretion from the experimental kidney was decreased when GFR was lower on the experimental side, demonstrating that reduction of GFR per se does not account for the increased excretion during hypernatremia (Figure 1).

It is assumed that all the variables (other than hypernatremia) that undoubtedly changed during the course of these experiments affected T_{Na} in both kidneys equally. In particular, any depression of T_{Na} induced by volume loading (6–9) presumably was equal in the two kidneys. Hence, the depression of T_{Na} in the experimental kidney during hypernatremia represents a specific effect of the elevated P_{Na}. The decrease in T_{Na} during hypertonic saline infusion noted in previous studies (1, 4, 5) may represent the combined effects of volume loading and hypernatremia, each of which independently depressed T_{Na}. Alternatively, the data are consistent with the possibility that loading with hypertonic saline does not induce a "volume loading" effect on T_{Na} comparable to that induced by isotonic loading. The micropuncture studies of Giebisch and his colleagues (5) demonstrate that hypertonic saline infusion depresses distal sodium reabsorption but does not decrease proximal or loop of Henle sodium transfer, provided sodium excretion is less than 12% of F_{Na}. The micropuncture experiments of Cortney, Mylle, and Gottschalk (11), however, indicate that isotonic saline loading decreases fractional sodium reabsorption in the proximal tubule. It may be, therefore, that the volume loading effect is proximal whereas the effect of hypernatremia per se is exerted on distal tubular sodium transfer. The depression of proximal T_{Na} noted by Giebisch and co-workers (5) when sodium excretion was in excess of 12% might represent a volume loading effect added to the action of hypernatremia itself in depressing distal T_{Na}. It should be noted that all these micropuncture data were obtained in rats and may not be applicable in detail to the interpretation of our clearance experiments in dogs.

Our experiments show that T_{Na} can be depressed unilaterally by hypernatremia. This indicates that hypernatremia affects sodium transfer by a local action within the kidney, not indirectly via a systemic factor such as a hormone. Giebisch and co-workers (5) suggested that the decrease in distal sodium reabsorption in their experiments during hypernatremia was probably caused by a reduction in circulating mineralocorticoids. Our data indicate that this explanation cannot be correct, as least in the dog.

One possible mechanism, suggested by Blythe and Welt (4), is that back diffusion of sodium is enhanced because a steeper concentration gradient for passive diffusion of sodium from the interstitium into the tubular lumen exists during hypernatremia. The increased back diffusion might be sufficient to significantly diminish net transfer of sodium from lumen to interstitium, if the active transfer capacity in that direction were limited. The data of Giebisch and associates (5) demonstrating decreased net transfer of sodium in the distal tubule during hypernatremia would be compatible with this view, since it is known that sodium reabsorptive capacity in this segment is limited (12). It has recently been demonstrated that the sodium permeability of the mucosal surface of toad bladder (13) and the corresponding outer surface of frog skin (14) decreases as the sodium concentration in the bathing medium is increased. A similar effect of increased tubular fluid sodium concentration on the permeability of the luminal surface of the distal tubular epithelium to sodium might limit sodium reabsorption and account for the effect of hypernatremia on T_{Na}.

Thurau (15) has suggested that angiotensin release is stimulated by a high concentration of sodium in the tubular fluid passing the early distal segment in which the macula densa is located. Micropuncture data in rats (5) indicate that during hypertonic saline loading sodium concentration in early distal tubular fluid is probably increased. (Tubular fluid/plasma sodium ratios are unchanged from those in noninfused rats, but plasma sodium is higher in the loaded rats.) Several lines of evidence (16–18) suggest that angiotensin may directly inhibit T_{Na}. Thus it is possible that the depression of T_{Na} by hypernatremia is mediated by intrarenal release and action of angiotensin. The amount released would be small enough so that no significant concentra-

tion would reach the contralateral kidney through the systemic blood. No direct evidence for this mechanism was obtained in our experiments. It is interesting, however, that in each of the six hypernatremic periods in which the shunt was not clamped, GFR in the experimental kidney relative to the control fell as compared to the preceding control or isotonic period. The magnitude of this fall in these six periods was 3, 4, 3, 1, 5, and 4 ml per minute (Table I). It is conceivable that this fall in GFR due to hypernatremia per se is the result of intrarenal arteriolar vasoconstriction induced by angiotensin. Obviously, it may also represent a direct effect of hypernatremia on arterioles. Many alternative mechanisms can be proposed to account for the decrease in T_{Na} and GFR; final conclusions will depend on further data.

Summary

1. To study the effects of hypernatremia per se on sodium excretion, hypertonic saline was infused into one renal artery of dogs by means of a femoral to renal arterial shunt.

2. Even when filtered sodium in the experimental kidney was reduced below that in the control, sodium excretion from the experimental kidney was increased above that on the control side. The depression of tubular sodium reabsorption by hypernatremia was equivalent to about 7% of the filtered load.

3. The data indicate that hypernatremia per se decreases tubular reabsorption of sodium independently of any effect of systemic volume loading. This effect of hypernatremia is exerted directly on the kidney.

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