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Observations on the Mechanism of Decreased Tubular Reabsorption of Sodium and Water during Saline Loading *

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It has been demonstrated by several recent studies that the regulation of sodium excretion involves factors other than the total filtered load of sodium and the renal tubular effects of mineralocorticoids. Contrary to earlier suggestions that an increase in the filtered load of sodium may be sufficient to account for the natriuresis of saline loading in the dog, de Wardener, Mills, Chapman, and Hayter (1) reported that the administration of saline to dogs receiving an exogenous mineralocorticoid results in an increased excretion of sodium that is not necessarily accompanied by an increased glomerular filtration rate. On the basis of this and other considerations, these authors suggested that natriuresis resulting from saline loading may be due largely to some unidentified circulating factor that affects tubular reabsorption. Similar observations that saline loading may result in natriuresis without a spontaneous increase in the filtered load of sodium have been made in this laboratory (2). Levinsky and Lalone (3), Blythe and Welt (4), and Rector, Van Giesen, Kiil, and Seldin (5) have demonstrated that hemodynamically induced reductions in the filtered load of sodium do not abolish the natriuresis of isotonic (3, 5) or hypertonic (4) saline loading. Thus, several recent investigations are consistent with the view that the excretion of sodium may be regulated in part by yet unidentified factors that alter net tubular reabsorption.

It was the purpose of the present studies to determine if specific changes in urinary composition may be associated with saline loading, under conditions of controlled urine flow. When the diuretic response to saline loading was prevented in one kidney by ureteral or aortic constriction, a clear effect of the saline load was evident, despite no change in the rate of urine flow. In hydropenic animals receiving vasopressin, saline loading with a constant urine flow was associated with decreased urinary osmolality, and urinary electrolyte concentrations (when initially low) were increased. These changes occurred as glomerular filtration rate decreased. The present results are consistent with the concept that saline loading in the dog results in decreased tubular reabsorption of electrolyte through a mechanism that also affects the urinary concentrating capacity.

Methods

Mongrel dogs, ranging in weight from 12.5 to 15.5 kg, received no food for 24 hours and no water for 48 hours before study. Twelve to 16 hours before experiment, the animals received by intramuscular injection 5 U of vasopressin [1] and 10 mg of desoxycorticosterone acetate (DOCA).[2] In four experiments, additional injections of vasopressin and desoxycorticosterone were administered 2 hours before experimental measurements were begun. Under pentobarbital anesthesia each ureter was exposed retroperitoneally, and a cannula was tied tightly into each renal pelvis. In three experiments umbilical tape was placed around the aorta, above the left and below the right renal artery. The ends of this tape were carried out of the incision through a plastic tube, which allowed regulated and reversible constriction of the aorta between the renal arteries. A minimum of 45 minutes was allowed before beginning experimental measurements. Two hours before collections a constant infusion of saline was begun at 0.25 to 0.60 ml per minute. This contained creatinine and *p*-aminohippurate (PAH) in amounts necessary for clearance determinations. This maintenance infusion was acidified to pH 5.5 and delivered vasopressin at a rate of 50 to 125 mU per kg per hour and desoxycorticosterone at 20 μg per minute. Blood was collected into heparinized syringes at the midpoint of urine collections.

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[1] Pitressin Tannate, Parke, Davis & Co., Detroit, Mich.

[2] Organon, Inc., West Orange, N. J.

In sixteen experiments, urine flow from one kidney during saline loading was controlled either by ureteral constriction or by constriction of the aorta between the renal arteries. In eleven experiments the effects of ureteral constriction were observed before saline loading, and in two experiments the effects of aortic constriction were observed before saline loading. To permit observations at varying rates of solute excretion and at low urinary electrolyte concentrations, a constant infusion of 15% mannitol in 50 mM sodium chloride was infused at 0.5 to 2.0 ml per minute in some experiments. These experimental designs are outlined in Table I.

Saline loading was accomplished by infusion of 1,000 to 1,750 ml of a modified Ringer's solution (Na, 140 or 145; K, 3.5; Cl, 128.5; and HCO_3, 15 or 20 mEq per L). After loading was complete, this infusion was continued at 10 to 15 ml per minute. This solution contained creatinine, PAH, and (in experiments employing mannitol) mannitol in amounts estimated to be the plasma concentrations of these substances. At the same moment the loading infusion was begun, adjustment of the ureteral or aortic constriction was initiated and continued during a 15- to 20-minute period so as never to stop the flow

TABLE I

Experimental designs utilized in study of effects of saline loading during controlled urine flow

Control of urine flow		
Ureteral constriction	Aortic constriction	15% mannitol infusion
		ml/min
Exp'ts 1–9		0.5–2.0
Exp'ts 10–13		None
	Exp'ts 14–16	0.5

TABLE II

*Effects of saline loading on urinary composition during controlled urine flow**

								Urine								Plasma	
		V		GFR		C_{PAH}		Osmolality		Urea		Sodium		Chloride			
Exp't	Time	R	L	R	L	R	L	R	L	R	L	R	L	R	L	Osmolality	Sodium
	min	*ml/min*		*ml/min*		*ml/min*		*mOsm/kg*		*mmoles/L*		*mEq/L*		*mEq/L*		*mOsm/kg*	*mEq/L*
13.	40–60	0.42	0.43	40	39	114	110	1,091	1,091	300	304	299	288	230	235		
	60–80	0.42	0.42	37	36	103	100	1,092	1,088	288	286	294	294	230	237	292	147
	1,000 ml saline, 80–100 minutes, then 10 ml per minute; adjust left ureteral constriction, 80–90 minutes																
	80–105	2.5	0.31	44	26	122	83	538	1,020			213	295	202	241	290	149
	105–125	4.9	0.40	40	30	122	137	418	805	28	182	178	246	174	222	289	146
	125–145	6.6	0.42	47	23	143	116	394	753	24	143	171	200	168	195	286	145
	145–165	6.0	0.41	47	27	123	127	388	753	11	153	170	183	166	178	284	147
	165–185	4.5	0.40	43	24	115	103	411	695	29	145	175	186	174	170	280	145
	Release left ureteral constriction, 185 minutes																
	185–195	5.0	2.3	43	47	112	154	404	434	22	38	177	148	170	140	281	145
	195–205	4.5	2.7	45	40	116	125	432	437	32	28	186	130	178	118	279	146
7.†	105–115	2.2	2.8	22	24	63	65	532	520	29	23	14	23	16	23	340	140
	115–120	2.4	2.7	22	24	64	65	523	515	20	27	15	25	16	23		138
	1,000 ml saline, 120–140 minutes, then 15 ml per minute; adjust left ureteral constriction, 120–135 minutes																
	120–140	5.6	3.0	27	19	112	88	378	448			76	50	74	48	339	140
	140–150	9.2	2.8	31	22	119	88	342	466	10	22	92	46	86	44	341	143
	150–160	10.3	2.8	31	22	114	89	331	475	9	21	67	42	87	40	337	141
	160–170	10.2	2.9	34	22	111	83	336	436	9	16	81	36	83	33	336	140
	Release left ureteral constriction, 170 minutes																
	170–185	7.7	6.1	29	28	103	113	330	339	10	9	74	59	71	60	340	143
	185–195	8.4	7.4	30	29	104	106	326	310	7	6	70	60	77	63	338	144
	195–205	9.8	8.8	30	28	100	102	328	318	7	8	76	64	80	70	343	144
14.‡	66–76	0.62	0.76	28	30	94	117	743	727	128	92	31	62			311	147
	76–86	0.62	0.76	29	31	95	102	737	711		95	31	58		54	312	148
	1,000 ml saline, 86–106 minutes, then 12 ml per minute; adjust inter-renal aortic constriction, 86–96 minutes																
	86–111	4.0	0.31	29	9	121	42	392	597			126	74			310	146
	111–121	7.3	0.37	30	11	123	67	334	560	8	53	126	57			310	146
	121–140	10.4	0.56	35	12	126	88	324	547	7	41	126	85			313	149
	Partially release aortic constriction, 140 minutes																
	140–148	10.8	0.71	34	13	122	68	320	525			125	74			313	148
	148–162	9.8	0.75	33	12	120	74	322	480	7	36	124	75		73	313	146
	162–167	9.5	0.98	34	15	129	81	323	451	8	36	121	68			314	147
	Release aortic constriction, 167 minutes																
	167–179	7.7	3.3	33	26	130	120	330	371			122	104			314	148
	179–194	7.7	4.5	33	27	128	112	327	337	9	12	121	111			315	147
	194–209	9.6	6.5	37	29	125	102	321	318	8	10	121	114		115	314	148

* V = urine flow; GFR = glomerular filtration rate; C_{PAH} = para-aminohippurate clearance; R = right; L = left.
† 15% mannitol in 50 mM sodium chloride infused at 2.0 ml per minute throughout this experiment.
‡ 15% mannitol in 50 mM sodium chloride infused at 0.5 ml per minute throughout this experiment.

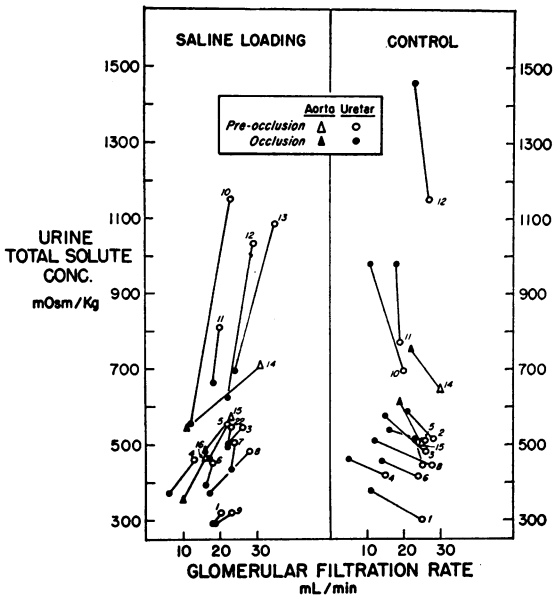

FIG. 1. RELATIONSHIP BETWEEN URINARY TOTAL SOLUTE CONCENTRATION AND GLOMERULAR FILTRATION RATE DURING CONTROLLED URINE FLOW BY URETERAL OR AORTIC CONSTRICTION. Open symbols represent the last collection period before constriction of the aorta or one ureter, and closed symbols represent the last of three or four collection periods during a constant degree of constriction. On the left are represented experiments in which constriction and saline loading were initiated simultaneously to maintain a constant rate of urine flow. On the right are represented those control experiments in the same animals in which constriction of the aorta or the opposite ureter was carried out before saline loading. Numbers refer to individual experiments and are the same as used in Tables I and II. In experiment 9, ureteral constriction was initiated after a stable diuretic response to loading was present. All other experiments were performed as described in the Methods.

of urine and at the same time prevent an increase in the rate of urine flow. This resulted in a flow of urine less than the preconstriction value, which slowly increased to equal, or in some experiments, slightly exceeded the preconstriction rate. After collecting a minimum of four periods (total volume, 23 to 201 ml) during a period of 38 to 105 minutes of controlled urine flow, the ureteral or aortic constriction was usually completely released, and collections were continued. Before complete release, the ureteral constriction was released in stepwise fashion in three experiments, and in two experiments increased constriction was applied before complete release.

In three experiments the effects of ureteral constriction were observed during increasing mannitol diuresis. Urine was collected at frequent intervals during the infusion of 15% mannitol in 50 mM sodium chloride. One ureter was then constricted to produce a urine flow equal to some lower value observed during the increasing diuresis. This allowed comparison of the urinary composition at similar rates of urine flow, with and without ureteral constriction, and in the absence of saline loading.

Glomerular filtration rate was measured by the clearance of exogenous creatinine (6), and PAH was measured by a modification of the method of Smith, Finkelstein, Aliminosa, Crawford, and Graber (7). Sodium and potassium were measured by internal standard flame photometry, chloride by amperometric titration (8), urea by a modification of the method of Fawcett and Scott (9), and osmolality by the freezing point depression.

Results

In sixteen experiments urine flow was kept at or near control rates by ureteral or aortic constriction during saline loading. The results of representative experiments are given in Table II. While urine flow was nearly constant in one kidney, the contralateral kidney underwent a diuretic response to the infusion of saline (Table II). In the experimental kidney, saline loading was associated with a fall in urine osmolality [3] in every experiment, despite little or no change in urine flow (Figure 1). This was true both in experiments with relatively high control rates of solute (mannitol) excretion (experiments 1 through 9) and in those with relatively low control rates of solute excretion (experiments 10 through 16). Although the decreases in osmolality were associated with decreases in the concentration of urea, the major decrease was in the concentration of nonurea solute (Table II). Glomerular filtration was reduced 5 to 62% (average, 27%) during saline loading, when the flow of urine was little changed from control (Figure 1). At the same time glomerular filtration in the contralateral kidneys undergoing diuresis increased by an average of 13%. In four experiments in which the urinary concentrations of electrolytes were high during the preloading control periods (experiment 13, Table II), the concentrations of sodium and chloride in the

[3] The urinary osmolalities observed in these animals before saline loading and during mannitol infusion were in most instances distinctly lower than those expected in the normal unanesthetized hydropenic dog. The influence of anesthesia and the surgical procedures on these control values cannot be assessed. However, maximal effects of hydropenia and vasopressin must have been present, and the conclusions based on the qualitative changes observed in these experiments would be independent of the exact degree of urinary hypertonicity as long as a maximal and constant permeability of the collecting duct is assumed.

urine decreased as urinary osmolality fell during saline loading. In experiments in which urinary electrolyte comprised a smaller fraction of the total urinary solute, electrolyte concentrations were usually increased during saline loading, despite decreases in urinary osmolality and little or no change in urine flow (Table II, Figure 2).

In order to determine whether the kidney was able to reduce the urinary concentration of electrolyte to minimal values during saline loading, additional ureteral constriction was applied in two experiments to reduce urine flow approximately 50%. The concentration of sodium promptly fell to 3 and 4 mEq per L in the two experiments, and this fall in the concentration of sodium was accompanied by a fall in the concentrations of chloride and potassium. Thus, the presence of saline loading did not prevent the attainment of minimal urinary electrolyte concentrations when the flow of urine was slowed sufficiently.

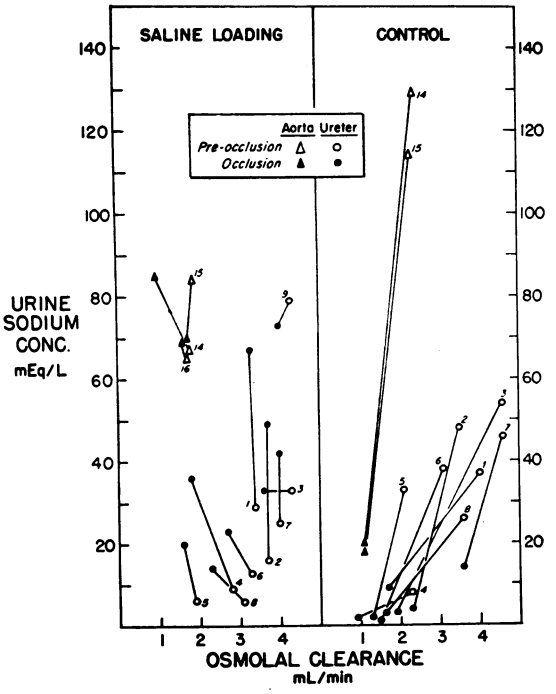

FIG. 2. RELATIONSHIP BETWEEN URINARY SODIUM CONCENTRATION AND OSMOLAL CLEARANCE DURING CONTROLLED URINE FLOW IN EXPERIMENTS EMPLOYING A CONSTANT MANNITOL INFUSION. Collection periods shown for these experiments are the same as in Figure 1. During maintenance of a relatively constant rate of urine flow by ureteral or aortic constriction during saline loading, urinary sodium concentration usually increased despite decreased osmolal clearance. In contrast, urinary sodium concentration was decreased strikingly as osmolal clearance decreased during ureteral or aortic constriction during control constrictions without saline loading.

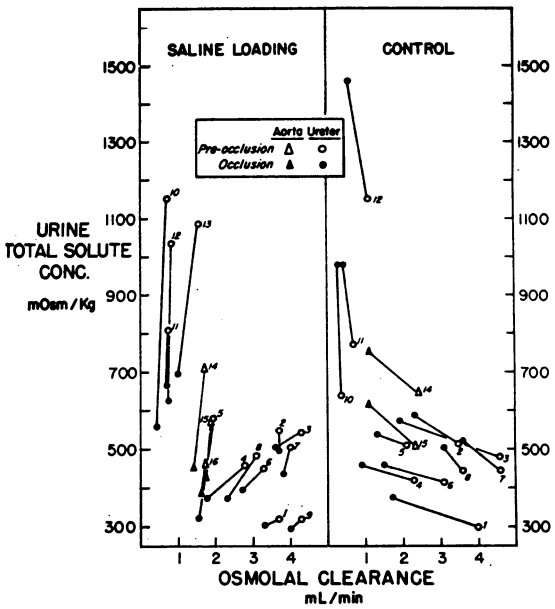

FIG. 3. RELATIONSHIP BETWEEN URINARY TOTAL SOLUTE CONCENTRATION AND OSMOLAL CLEARANCE. The collection periods shown are the same as in Figure 1. The decreases in urinary osmolality during saline loading occurred despite decreases in osmolal clearance, in contrast to increases in osmolality during constrictions before saline loading.

Since it was not possible to control the flow of urine at precisely the control rates in all of the above experiments, the changes in urinary sodium concentration and osmolality have been compared to the changes in total solute excretion (osmolal clearance) in Figures 2 and 3. In the control experiments in which urine flow was reduced by ureteral or aortic constriction, before saline loading, urinary osmolality increased, and urinary sodium concentration decreased, as osmolal clearance was decreased. In contrast, similar decreases in osmolal clearance during saline loading were associated with decreases in urinary osmolality in all experiments, and in most experiments (in the presence of mannitol) urinary sodium concentration increased (Figure 2).

When the ureteral or aortic constriction was released during saline loading, the excretion of sodium and water and the glomerular filtration rate increased immediately to values approaching those of the contralateral kidney undergoing diure-

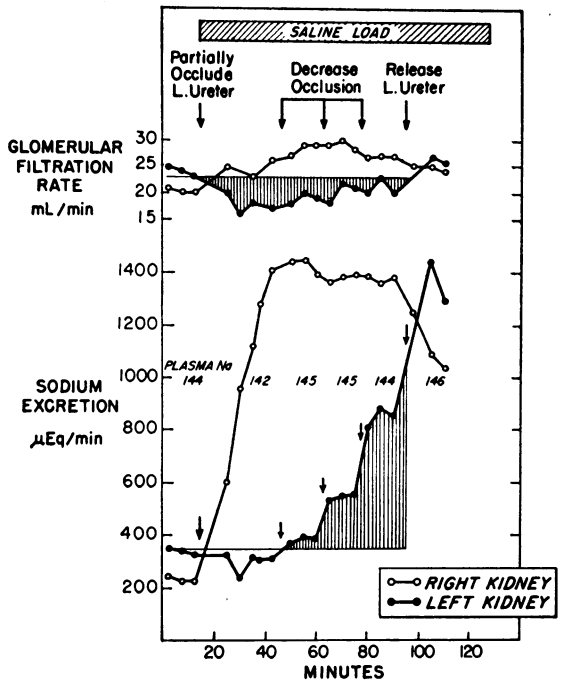

FIG. 4. EFFECT OF SALINE LOADING ON SODIUM EXCRETION DURING CONTROL OF GLOMERULAR FILTRATION RATE BY URETERAL CONSTRICTION. Saline loading and constriction of the left ureter were initiated simultaneously. The ureteral constriction was then partially released in three steps, with collection periods being made at each stage of partial release, before being completely released. The shaded areas represent the extent to which glomerular filtration rate of the left kidney was decreased below the lowest preloading control value and the extent to which sodium excretion by the left kidney was increased above the highest preloading control value. The effects of the maintained saline load on glomerular filtration rate and sodium excretion by the control right kidney are shown.

sis (Table II). In two experiments the ureteral constriction was released in a stepwise fashion during saline loading. In these experiments frank diuresis occurred in the experimental kidney, with the excretion of sodium approaching 50% of that of the control kidney undergoing diuresis, at a time when the glomerular filtration rate was maintained distinctly below the preloading control value (Figure 4), Since diuresis never occurred during or after ureteral constriction in the absence of saline loading, this natriuresis during partial release of the ureteral constriction clearly related to the saline infusion.

The above described changes in urinary osmolality and electrolyte concentrations, during saline loading with constant urine flow, occurred with little or no changes in plasma osmolality and sodium concentration (Table II, Figure 4).

During the periods of control ureteral or aortic constriction (before saline loading) shown in Figures 1, 2, and 3, urine flow was reduced to values ranging from 35 to 56% of preconstriction values, whereas with similar constriction during saline loading urine flow was intentionally kept near the preconstriction value. Although under the two conditions the changes in urinary osmolality and sodium concentration were qualitatively opposite with similar decreases in glomerular filtration and osmolal clearance (Figures 1 and 2), it appeared necessary to establish whether ureteral constriction in the absence of saline loading, and without a reduction in urine flow, also would be associated with changes in osmolality and electrolyte concentration opposite to those observed during saline loading, and without a reduction in urine flow. In three experiments frequent collection periods were made during increasing hypertonic mannitol diuresis. The flow of urine was then reduced by ureteral constriction to some lower value observed during the increasing diuresis. This allowed comparison of glomerular filtration and urinary composition at equal rates of urine flow, with and without ureteral constriction. In the presence of ureteral constriction glomerular filtration was reduced 20, 31, and 36% (reductions entirely comparable to those observed during saline loading with controlled urine flow). At the same time urinary sodium and chloride concentrations were strikingly reduced, and urinary osmolality (and urine/plasma osmolality) was increased to the same values observed at the lower urine flow during the increasing diuresis before ureteral constriction. Details of one of these control experiments are given in Table III. Thus, reductions in glomerular filtration by ureteral constriction in the absence of saline loading produced changes in osmolality and electrolyte concentrations qualitatively opposite to those observed during saline loading, even when the same rates of urine flow are compared in both situations.

Discussion

The observations that glomerular filtration may not spontaneously increase during saline diuresis

(1, 2), and that hemodynamically induced reductions in glomerular filtration may not abolish the natriuresis of saline loading (3–5), provide strong evidence that saline loading in the normal dog is associated with a decrease in the net tubular reabsorption of sodium, which is not prevented by the administration of mineralocorticoids (1–3, 5). The present studies provide additional evidence that expansion of the extracellular volume by saline infusion decreases tubular reabsorption, since in the present experiments sodium excretion increased during saline loading as urinary sodium concentrations increased in the presence of a reduced glomerular filtration rate and unchanged flow. In addition, striking natriuresis occurred without an increased filtered load of sodium as ureteral constrictions were partially released during saline loading. The present studies also demonstrate that a decrease in the reabsorption of water accompanies the decreased reabsorption of sodium, since urine volumes were kept constant as the total filtered volume was decreased. The most consistent change produced by saline loading (as urine flow was kept constant) was a decrease in urinary osmolality. Regardless of the control osmolality, the concentration of total solute, as well as nonurea solute, decreased during saline loading, despite no increase in urine volume or total solute excretion. When urinary sodium concentrations were initially high, saline loading with constant urine flow was associated with a fall in sodium concentration (and sodium excretion) as osmolality decreased. When electrolyte comprised a smaller fraction of urinary solute (during mannitol diuresis), the fall in urinary osmolality was accompanied by an increased concentration of sodium and an increased excretion of sodium when urine flow was constant during saline loading. These changes occurred despite pretreatment with, and the constant infusion of, vasopressin and desoxycorticosterone. Reduction of glomerular filtration rate by ureteral or aortic constriction in the absence of saline loading was always associated with increased urinary osmolality and decreased urinary electrolyte concentrations, as others have previously reported (10–13). Even when reductions in glomerular filtration were produced by ureteral constriction during increasing mannitol diuresis, electrolyte concentrations were reduced and osmolality was not decreased when comparison was made with similar rates of urine flow before ureteral constriction.

On the basis of the present observations it may be suggested that the decreased net tubular reab-

TABLE III

*Effects of ureteral constriction during mannitol diuresis on urinary composition**

Time	V	GFR	Urine				Plasma	
			Osmolality	Urea	Sodium	Chloride	Osmolality	Sodium
min	*ml/min*	*ml/min*	*mOsm/kg*	*mmoles/L*	*mEq/L*	*mEq/L*	*mOsm/kg*	*mEq/L*
−70	15% mannitol in 50 mM sodium chloride, 1 ml per minute							
0	Mannitol infusion increased to 2 ml per minute							
0–10	1.58	30	633	56	34	34	331	149
10–20	1.90	28	600	48	35	35	334	147
20	Mannitol infusion increased to 3 ml per minute							
20–30	2.2	28	579	40	35	37	339	144
30–40	2.4	27	573	35	35	33	340	143
84–94	3.3	27	555	25	39	41	357	148
94	Adjust ureteral constriction							
94–108	2.9	24	564	28	28	30	357	149
108–120	3.0	25	588	30	17	19	357	146
120	Increase ureteral constriction							
120–130	2.2	19	600	29	9	11	359	143
130–140	2.0	18	606	28	7	10	360	144

* Values shown are those from the left kidney only.

sorption of sodium, chloride, and water which accompanies extracellular volume expansion in the dog occurs through a mechanism that also decreases the ability to concentrate the urine. Under the conditions of the present experiments, the decreases in urinary osmolality cannot be attributed to either a decreased availability of vasopression or to an increased total solute excretion. It also appears unlikely that the availability of sodium reaching the transport site of the ascending limb of Henle's loop limited the concentrating capacity in the present studies, since urinary sodium concentration and sodium excretion were usually increased during saline loading. However, the possibility cannot be excluded that the reduction in glomerular filtration (during controlled urine flow) limited the delivery of sodium to the ascending limb to such an extent that the concentrating capacity was diminished. This would require, however, that sufficient sodium and chloride still escaped reabsorption in Henle's loop, only to be rejected from reabsorption at some more distal site, in order that sodium excretion could still be increased. Likewise, the possibility cannot be excluded that saline loading through some unidentified pathway directly affects the transport system of the ascending limb. If sodium reabsorption at this site were slowed, then urinary osmolality should decrease as the excretion of sodium increased. Since less water would be reabsorbed by the collecting duct, it would be possible to have a reduced glomerular filtration rate without a reduction in urine flow under these circumstances. However, Rector and associates (5) have reported that during water diuresis urinary dilution may increase with saline loading and reduced glomerular filtration, and on the basis of this observation these authors have suggested that the decreased tubular reabsorption occurs at some site proximal to the ascending limb of Henle's loop.

An additional factor that may influence urinary osmolality is the rate of medullary blood flow, since an inverse relationship must exist between medullary blood flow and the degree of medullary hypertonicity (14–16). This factor could be of importance in producing the decreased urinary osmolality observed in the present studies, and it is entirely possible that changes in medullary blood flow may indirectly influence sodium reabsorption and sodium excretion. Under conditions of antidiuresis the isotonic tubular fluid entering Henle's loop is progressively concentrated during passage through the descending limb (17). This increased concentration very likely occurs as the result of a passive loss of tubular water to the hypertonic medullary interstitium and perhaps to a lesser extent as the result of a gain in solute. Therefore, the concentration of sodium (chloride) in the fluid reaching the ascending limb is increased above isotonicity. Probably the same qualitative situation obtains during water diuresis, since medullary interstitial (nonurea) hypertonicity may persist to some degree during water diuresis (18–20). If medullary blood flow is increased, the degree of medullary hypertonicity will decrease, and secondarily the volume of water lost from the descending limb would be diminished. Therefore, the rate of flow through the ascending limb would be increased, and the concentration of sodium in the fluid reaching this latter segment would be decreased. It is entirely possible that the net transport of sodium by the ascending limb would be diminished under such conditions. Even if this transport site could achieve the same minimal concentration of sodium in the tubular fluid, net reabsorption would be decreased as an increased rate of flow of less concentrated fluid entered the ascending limb. Little direct information is available that bears on the relationships between substrate (sodium) concentration and rate of flow, and net reabsorption by the ascending limb of Henle's loop. However, Lassiter, Mylle, and Gottschalk (21) and Giebisch, Klose, and Windhager (22) have reported that during saline loading in the rat, fractional reabsorption by the proximal tubule is unchanged, whereas the tubular fluid to plasma inulin ratio in the early part of the distal convolution of cortical nephrons may be decreased (21). This latter observation is consistent with the view that volume reabsorption within Henle's loop is diminished during saline loading, and unless the concentration of sodium in the fluid leaving the ascending limb is decreased (in comparison with antidiuresis) then less sodium must be reabsorbed within the loop. Such changes could be even more marked in juxtamedullary nephrons with long loops of Henle.

Likewise, there is very little direct information bearing on the factors that may influence medul-

lary blood flow. Maude and Wesson have suggested that the fall in renal concentrating capacity ($T^c_{H_2O}$) which sometimes accompanies saline loading may be due to an increased medullary blood flow (23). In this laboratory $T^c_{H_2O}$ has been found to be distinctly lower in mineralocorticoid-treated dogs during massive expansion with isotonic saline than at similar rates of solute excretion during hypertonic mannitol or hypertonic saline diuresis (24). These observations indicate that the concentrating mechanism is less efficient during expansion of the extracellular volume, and this could be due to an increased medullary blood flow. Thurau, Deetjen, and Kramer (25) have reported that the circulation time of medullary blood flow is decreased during hypotonic saline loading.

It may appear unlikely that an increased flow through Henle's loop could have occurred in the present studies at a time when glomerular filtration was reduced, unless a simultaneous decrease in proximal reabsorption occurred. However, the decreased urinary osmolality (and presumably, medullary interstitial osmolality) would be associated with decreased water reabsorption by both the descending limb and the collecting duct. This total decreased volume reabsorption could be reflected by an equivalent decrease in glomerular filtration as urine flow is kept constant. As a consequence of the diminished loss of water from the descending limb, a similar or even increased volume could still be delivered to the ascending limb and more distal parts of the nephron. The actual increases in sodium excretion observed in these studies were small and occurred only if the relative concentration of sodium in the urine was initially low. However, any influence that flow rate and substrate concentration may have on reabsorption by the ascending limb should be much greater if glomerular filtration were not depressed and the kidney allowed to undergo diuresis.

The clearance of PAH increased during saline loading as glomerular filtration was depressed by ureteral constriction, but aortic constriction was associated with a decreased clearance of PAH. This latter observation may not be inconsistent with the suggestion that medullary blood flow is increased. The studies of Thurau and Deetjen are consistent with the view that medullary and cortical blood flow may vary independently (26), and Carriere, Thorburn, O'Morchoe, and Barger, utilizing the krypton technique, have suggested that during hemorrhage medullary blood flow may not decrease despite large falls in cortical blood flow (27). In this laboratory we have found that during saline loading the extraction ratio for PAH is decreased 5 to 25% (28). This observation indicates that the clearance of PAH becomes a smaller fraction of total renal blood flow during saline loading, and furthermore, the decreased extraction ratio may indicate that a redistribution of blood away from the cortex occurs during saline loading.

The suggestion that medullary blood flow may indirectly alter sodium excretion requires the assumption that net reabsorption by the ascending limb is influenced by the rate of intratubular flow, or the concentration of substrate electrolyte, or both. Confirmation of this hypothesis will depend upon the demonstration that this transport system does indeed have such characteristics and that medullary flow is increased during saline loading. This concept is not inconsistent with the findings of others who observed that during water diuresis, saline loading and a reduction in glomerular filtration were associated with increased urinary dilution as sodium excretion increased (5). Since significant medullary hypertonicity may persist during water diuresis, water will be lost from the descending limb and a hypertonic fluid delivered to the ascending limb, even though the final urine is dilute. If this passive loss of water from the descending limb is diminished as a consequence of increased medullary blood flow during saline loading, then urinary dilution could be enhanced by the delivery of a larger volume of less concentrated fluid to the more distal "water-impermeable" segments of the nephron.

Summary

The effects of saline loading on tubular reabsorption were studied in the dog by maintaining a constant rate of urine flow by ureteral or aortic constriction during saline loading. Under these conditions of unchanged urine flow, saline loading was associated with a decreased glomerular filtration, decreased urinary osmolality (despite hydropenia and vasopressin infusion), and usually in-

creased urinary electrolyte concentrations. Similar reductions in filtration rate by ureteral or aortic constriction in the absence of saline loading were associated with increases in urinary osmolality and decreases in electrolyte concentration. Decreased tubular reabsorption during saline loading was evident by *1*) increased sodium and chloride excretion with a decreased filtered load of electrolyte and *2*) an unchanged rate of urine flow in the presence of a reduced filtration rate. This decreased tubular reabsorption was associated with decreased urinary osmolality despite a constant infusion of vasopressin, no increase in solute excretion, and maintained or increased sodium excretion. To account for this combination of changes, we suggest that saline loading may result in a primary increase in medullary blood flow. As a consequence of the decreased medullary interstitial hypertonicity, passive water reabsorption from the descending limb of Henle's loop could be decreased. The resulting increased rate of flow of fluid with a lower concentration of sodium may then lead to a decrease in the net reabsorption of sodium by the ascending limb and more distal portions of the nephron.

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