Depression of Fractional Sodium Reabsorption by the Proximal Tubule of the Dog Without Sodium Diuresis

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ABSTRACT The effect of infusions of hyperoncotic solutions on fractional sodium reabsorption by the proximal tubule of the dog was studied by the recollection micropuncture method. Tubule fluid to plasma inulin concentration ratios were measured for identified proximal tubule segments before and after infusion of 25% albumin or dextran solutions. Results were compared with changes in fractional reabsorption during saline diuresis. Plasma volume increased 66% ± SE 5.8 after infusion of albumin solution and 94% ± SE 8.2 after infusion of dextran solution. Fractional sodium reabosorption by the proximal tubule was depressed after infusion of both of these hyperoncotic solutions. Nevertheless, changes in sodium excretion after infusion of albumin and dextran were small. In contrast, after infusions of isotonic sodium chloride solution, which increased plasma volume 61% ± SE 5.8, a decrease in fractional reabsorption of 50.7% ± SE 7.2 was associated with large changes in sodium excretion.

INTRODUCTION

The studies of DeWardener, Mills, Clapham, and Hayter (1) and Levinsky and Lalone (2) demonstrated that infusion of isotonic saline in the dog results in an increase in sodium excretion despite a reduction in glomerular filtration rate. Thus, a depression of sodium reabsorption contributes to the natriuresis after saline administration. Subsequent micropuncture studies in the dog (3) and rat (4) have revealed depressed fractional sodium reabsorption in the proximal tubule after infusion of isotonic saline. Depression of fractional sodium reabsorption by the proximal tubule has been thought responsible for the large increase in sodium excretion after infusion of saline.

The present studies were designed to determine the effect on fractional reabsorption of sodium by the proximal tubule of expansion of the vascular volume at the expense of the interstitial volume. Since expansion of the vascular volume with hyperoncotic salt-poor albumin does not cause a natriuresis (5–7), we anticipated that sodium reabsorption by the proximal tubule would either remain at levels observed in hydropenia or would increase. Infusion of either hyperoncotic albumin or dextran solutions into dogs had little or no effect on sodium excretion; however, it did result in a large depression of sodium reabsorption by the proximal tubule.

METHODS

Two types of experiments were performed with mongrel dogs: (*I*) Recollection micropuncture experiments in which samples from proximal tubules were obtained during hydropenia and again from the same tubules after infusion of a test solution; and (*II*) Experiments in which a water diuresis was established and the change in

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free water clearance after infusion of hyperoncotic albumin or dextran solution was measured.

Recollection micropuncture experiments. Dogs were anesthetized with pentobarbital (30 mg/kg). A tracheotomy was performed. Cannulae were inserted into both external jugular veins for intravenous infusions and into the right femoral vein for blood sampling. The right ureter was catheterized through a suprapubic incision. The left kidney was exposed through a subcostal incision, and prepared for micropuncture as previously described (3).

A priming dose of 240 mg/kg of inulin was followed by a constant inulin infusion at 4.8 mg/kg per min in 1.0 ml/min of saline. Samples were obtained by micropuncture from proximal tubules on the surface of the kidney and urine was collected in 15-min periods during continued hydropenia. Urine was collected from both experimental and control kidneys. Blood samples were drawn at the mid-point of urine collection periods.

After the collections of urine, blood, and proximal tubule fluid during hydropenia, one of the four infusions was given: (*1*) Albumin solution, 25% human albumin solution (salt-poor human albumin)[1] found to contain 127 mEq/liter of Na^+ was infused at 0.32 ml/kg per min for 20 min in seven dogs. When urine flow and hematocrit had stabilized, 30 min after completion of the albumin infusion, second samples were collected from the previously punctured tubules at the original puncture sites. Proximal tubule fluid, urine, and blood samples were obtained, as in the protocol, Table I. (*2*) Dextran solution, 25% dextran solution (Dextran 110)[2] in 127 mEq/liter of

[1] Courtland Laboratories, Los Angeles, Calif.

[2] Pharmacia, Uppsala, Sweden.

TABLE I

Protocol: Infusion of Hyperoncotic Albumin Solution, Expt. 3 a, 15.4 kg Dog

Elapsed time	Urine flow		Sodium excretion		Inulin clearance		Plasma inulin	Hct	Tubule fluid sample	T.F.‡ inulin	Fractional sodium reabsorption proximal tubule§	Change in fractional reabsorption
	E*	C*	E	C	E	C						
min	*ml/min*		*μEq/min*		*ml/min*		*mg/100 ml*	%		*mg/100 ml*		
8							90	56	1 a‖	195	54	
11									2 a	164	44	
15	0.06	0.09	2.9	2.6	20.5	28.9						
18									3 a	174	46	
22							96	56	4 a	157	39	
29									5 a	129	28	
30	0.07	0.09	2.3	0.6	21.4	29.2						
34									6 a	278	67	
36							92	55	7 a	232	60	
42									8 a	210	57	
45	0.08	0.11	1.2	0.7	23.4	33.0			9 a	194	54	
											Mean 49.9	
48–68	100 ml of 25% human albumin, intravenous infusion											
99								42				
105							81	41	1 b	127	36	−33
108									3 b	122	33	−25
112									2 b	113	28	−39
115	0.17	0.23	14.9	33.4	27.3	35.4			4 b	104	21	−46
118									5 b	102	21	−25
121							80	41	6 b	125	36	−47
124									7 b	174	53	−12
127									8 b	127	38	−33
130	0.18	0.23	16.1	32.1	30.9	37.1			9 b	132	40	−26
138							77	42				
145	0.17	0.21	14.3	27.8	29.9	38.6						
											Mean 34.0	−32

* E, C, experimental and control kidney, respectively.

‡ T. F., tubule fluid.

§ $\left[1 - \frac{(P)}{(TF)_{In}} \times 100\right]$.

‖ a,b, first and second collection of tubule fluid from the same tubule.

NaCl was infused in the same manner as the albumin solution and recollection samples of tubule fluid were obtained from 19 dogs at varying intervals from 30 to 180 min after the infusion had been completed. In three of these animals tubule fluid samples were recollected 30 min after the completion of the dextran infusion and again from the same tubules 60–85 min later. The dextran used had an average molecular weight of 101,000 with 95% of the preparation having a molecular weight between 45,000 and 160,000. To test whether a significant amount of the dextran was filtered by the kidney, a normal hydropenic dog was given the standard dextran infusion without having been given inulin. The anthrone method of Führ, Kaczmarczyk, and Kruttgen, (8), found to be 50 times less sensitive for dextran than for inulin, was used to estimate dextran concentration in plasma and urine. Clearance of dextran in this dog was 0.6 ml/min and compared with the normal inulin clearance under these conditions of approximately 60 ml/min indicates that less than 1% of the circulating dextran was filtered. This value agrees with the observation of Wallenius that no dextran of molecular weight exceeding 55,000 appears in the urine (9). (*3*) Control solution: To evaluate the effect of the salt and fluid volume associated with the albumin and dextran solutions, a 127 mEq/liter of NaCl solution was infused in the same manner as the albumin and dextran solutions and recollection samples were obtained from five dogs. (*4*) Saline solution: Isotonic saline was infused at 1 ml/kg per min for 20 min and thereafter at 0.5 ml/kg per min until the end of the experiment. Recollection samples were obtained 1 hr after the start of the saline infusion. Data and details of five of the six saline experiments have been previously reported (10). The total volume of infusion given in the albumin, dextran, and control studies was 6.5 ml/kg and in the saline experiments was 62.5 ml/kg.

In all experiments, except those involving dextran infusion, inulin in plasma and urine was determined by the anthrone method of Führ et al. (8). In all experiments the concentration of inulin was determined in 10 nl aliquots of tubule fluid by the microfluometric method of Vurek and Pegram, however cuvettes were incubated for 10 min in boiling water rather than 5 min as originally described (11). This method was found to be approximately 140 times more sensitive to inulin than to dextran. In an experiment in which no inulin was infused and the dextran protocol was otherwise followed, no fluorescence attributable to dextran could be detected in fluid from eight tubules. Sodium concentration in urine and plasma was determined by flame photometry.

Because dextran was found to interfere with the anthrone method for inulin, the inulin concentration in the urine and plasma in the experiments involving dextran was determined by both the anthrone method and by analysis for inulin carboxyl ^{14}C [3] by liquid scintillation counting. The mean specific activity of inulin in the three plasma samples obtained before infusion of the dextran solution was used to estimate the concentration of inulin from the ^{14}C counts in the later samples of plasma that also contained dextran. In the absence of dextran, the inulin clearance for the left kidney of 19 dogs determined by the radioisotope method was 0.88 ml/min ± SD 1.83 greater than that found by the anthrone method. Each liter of scintillation solution contained 200 ml of Triton X 100,[4] 800 ml of toluene,[5] 5.5 g of 2,5-diphenyloxazole (PPO)[6] and 150 mg of 1,4-bis[2-(5-phenyloxazolyl)]benzene (POPOP).[6] Since standard solutions, plasma and urine samples with and without dextran, had similar quenching properties, as determined with a radium external standard, no corrections for quenching were made.

Data from the three clearance periods before and after the infusions have been averaged and are totals for both kidneys. Changes in plasma volume were calculated from changes in hematocrit. In two experiments plasma volumes were calculated both from hematocrits and from distribution of ^{131}I albumin (RISA-131).[7] In a dog given only the standard infusion of inulin at a rate of 1.0 ml/min, the albumin space measured by ^{131}I albumin increased 6% in 1 hr and the change in plasma volume calculated from the hematocrit was + 4%. In a dog given an infusion of 25% dextran solution the increases in plasma volume were 57% measured by ^{131}I albumin and 58% calculated from the hematocrit. Changes in fractional sodium reabsorption by the proximal tubule were calculated by the formula:

$$(R \text{ infusion} - R \text{ hydropenia}) / (R \text{ hydropenia}) \times 100.$$

Where $R = [1 - (P/TF)_{in}]$ is the fraction of glomerular filtrate reabsorbed up to the site of micropuncture of the proximal tubule and $(P/TF)_{in}$ is the measured (plasma/tubule fluid) inulin concentration ratio. For statistical analysis, the mean control values for glomerular filtration rate, sodium excretion, plasma volume, and proximal tubule sodium reabsorption in each dog were treated as single observations and compared with the mean values during the experimental periods. The significance of these mean differences was determined by Student's *t* test.

Free water clearance experiments. Four dogs were anesthetized with thiopental (25 mg/kg). A tracheotomy was performed and cannulae were inserted into both external jugular veins for intravenous infusions and into the right femoral vein for blood sampling. Both ureters were catheterized through a suprapubic incision.

Water diuresis was established by intravenous infusion of 50 ml/kg of 2.5% dextrose in water at 1 ml/kg per min followed by infusion at a rate equal to the urine flow rate. A priming dose of 60 mg/kg of inulin was followed by a constant inulin infusion of 1.2 mg/kg per min in 1.0 ml/min of saline.

When urine osmolalities were less than 100 mOsm/kg and the urine flow rate was stable, clearances were measured during three periods. Hyperoncotic albumin or dex-

[3] New England Nuclear Corp., Boston, Mass.

[4] Packard Instrument Company, Downers Grove, Ill.

[5] J. T. Baker Chemical Company, Phillipsburg, N. J.

[6] Nuclear-Chicago Corp., Des Plaines, Ill.

[7] Abbott Laboratories, North Chicago, Ill.

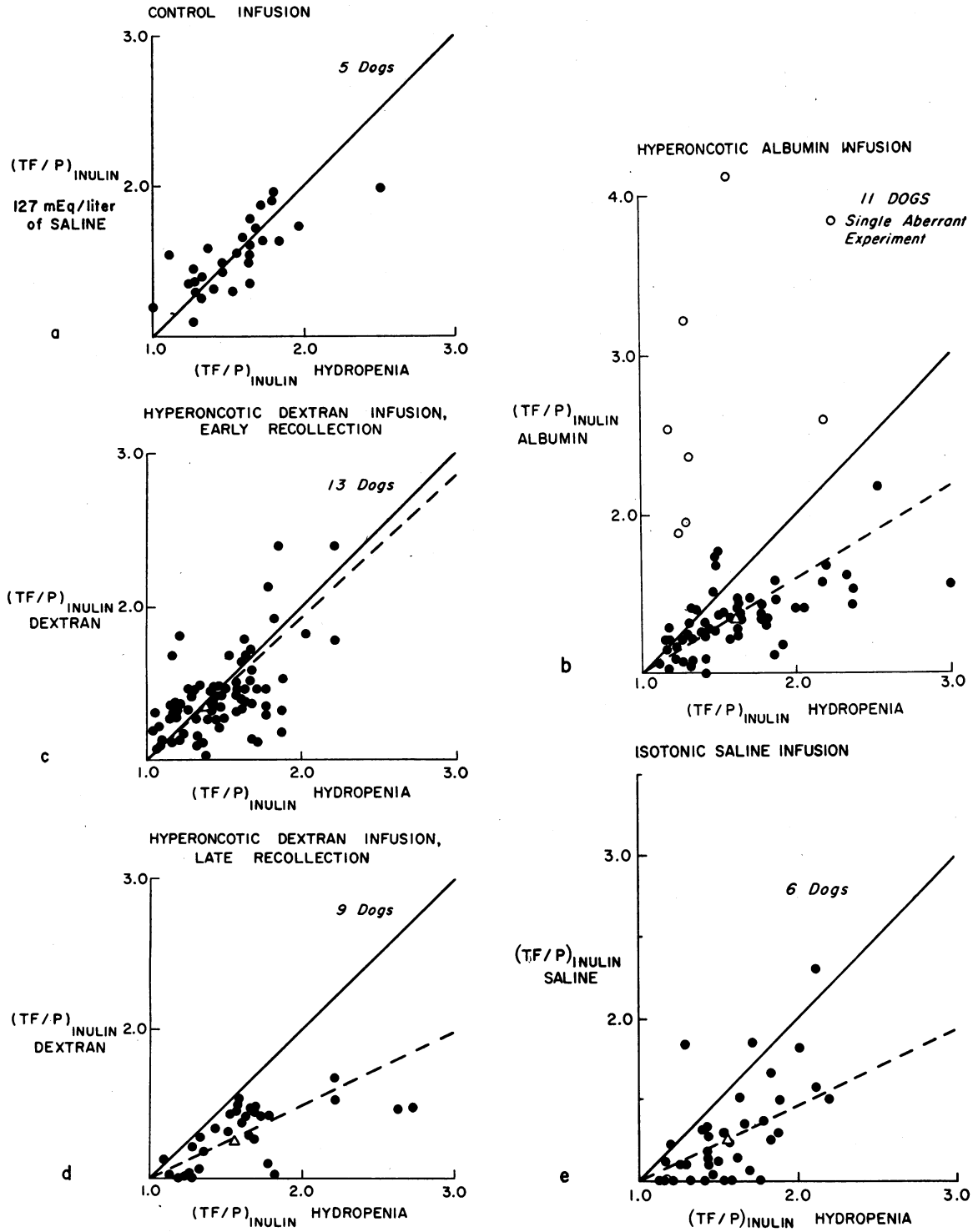

FIGURE 1 Changes in (TF/P) inulin concentration ratios. Points represent paired collections of proximal tubule fluid with value of (TF/P) inulin during hydropenia plotted against the value after infusion. The solid line indicates no change; the broken line indicates the mean change from control to experimental collections. *A*, effect of infusion of 6.5 ml/kg of 127 mEq/liter of sodium chloride solution, 29 paired collections, in five dogs. *B*, effect of infusion of 6.5 ml/kg of hyperoncotic albumin solution, 65 paired collections, in 11 dogs. *C*, effect (from 30 to 90 min) of infusion of 6.5 ml/kg of hyperoncotic dextran solution, 72 paired collections, in 13 dogs. *D*, effect (from 90 to 180 min) of infusion of 6.5 ml/kg of hyperoncotic dextran solution, 32 paired collections in nine dogs. *E*, effect of infusion of 62.5 ml/kg of isotonic sodium chloride solution, 33 paired collections, in six dogs.

tran solution was then infused in the same manner as in the micropuncture experiments. Approximately 30 min after the completion of the infusion of the albumin or dextran solution, three more clearance measurements were obtained (see protocol, Table IV). Urine and plasma osmolalities were determined with a Bowman osmometer.

RESULTS

Recollection micropuncture experiments

Infusion of control solution. Infusion of 6.5 ml/kg of 127 mEq/liter of saline solution resulted in a + 2% ± SE 7.2 change in plasma volume and

TABLE II

Summary of Clearance and Micropuncture Data

Dog	Wt	No. of tubules	Urine flow		Inulin clearance		Sodium Excretion		Fractional sodium reabsorption proximal tubule‡		Change in fractional reabsorption
			H*	I*	H	I	H	I	H	I	
	kg		*ml/min*		*ml/min*		*μEq/min*		%		%
Control: *127 mEq/liter of NaCl solution, 6.5 ml/kg*											
1 c	13.4	7	0.57	0.59	55.9	67.1	80.8	61.0	24.9	25.9	+4
2 c	12.2	6	0.30	0.97	49.2	45.7	21.7	92.4	28.8	30.3	+5
3 c	11.5	5	1.21	0.98	35.2	31.9	12.8	37.8	26.4	27.8	+5
4 c	14.2	6	0.23	0.42	70.3	66.2	23.2	45.8	41.7	42.0	+1
5 c	12.0	5	0.55	0.45	50.1	55.5	89.3	83.7	41.8	38.8	−7
Mean			0.57	0.68	42.1	53.1	45.6	64.1	32.7	33.0	+1.6
SE			0.17	0.12	5.7	6.6	16.4	10.6	3.7	3.1	2.3
Albumin: 25% human albumin solution, *6.5 ml/kg*											
1 a	14.0	5	0.13	0.44	61.8	64.4	9.6	72.3	35.8	15.6	−56
2 a	18.3	8	0.21	0.55	52.3	68.7	35.5	111.7	18.5	11.8	−36
3 a	16.0	7	0.16	0.37	58.1	78.5	2.2	48.5	36.7	34.6	−6
4 a	15.4	9	0.17	0.40	52.2	66.4	3.5	46.2	50.1	33.8	−33
5 a	16.0	5	0.18	0.39	57.3	62.8	5.1	97.5	39.0	18.0	−54
6 a	13.2	7	0.98	0.92	54.6	47.5	16.5	5.7	31.0	24.7	−20
7 a	13.2	2	0.13	0.29	73.1	64.2	3.8	42.7	48.5	32.5	−33
8 a	12.0	4	0.32	0.53	52.0	55.7	35.5	83.2	28.5	25.6	−9
9 a	17.2	6	0.23	0.66	73.5	63.4	13.3	97.7	42.4	28.4	−33
10 a	13.9	5	0.16	0.68	66.0	77.7	4.2	112.9	28.4	16.4	−47
11 a§	14.6	7	0.32	0.88	65.8	74.1	—	156.3	28.1	60.1	+112
Mean			0.27	0.52	60.0	64.9	12.9	71.8	35.9	24.1	−32.3
SE			0.08	0.05	2.6	2.9	4.2	11.4	3.1	2.6	5.3
Dextran: 25% dextran solution, *6.5 ml/kg*, less than 90 min after infusion											
1 d	14.8	6	0.16	0.34	48.3	58.2	5.9	7.5	30	32	+7
2 d	12.1	4	0.11	0.15	42.3	32.5	5.3	3.6	42	27	−36
3 d	14.5	6	0.44	1.84	58.1	68.4	74.3	192.9	33	35	+6
4 d	16.0	7	0.18‖	0.32	40.3	58.4	17.4	18.3	23	22	−4
5 d	14.5	6	0.35	0.70	61.9	68.8	27.7	75.6	31	33	+6
6 d	15.1	8	0.15	0.26	61.2	67.3	17.2	44.7	40	34	−15
7 d	16.1	6	0.16	0.29	49.9	59.0	4.8	35.9	20	23	+15
8 d	16.0	8	0.12	0.34	62.9	66.7	3.7	41.6	35	16	−54
9 d	18.2	6	0.19	0.30	62.4	68.5	2.7	6.0	30	25	−17
10 d	14.1	3	0.75	1.52	36.0	49.4	44.7	64.3	10	16	+60
17 d	16.5	5	0.16	0.28	48.2	53.2	1.5	1.0	42	42	0
18 d	15.2	3	0.12	0.27	45.7	63.5	4.1	3.9	23	25	+9
19 b	13.0	4	0.12	0.21	43.8	59.1	1.4	3.4	9	10	+53
Mean			0.23	0.53	50.85	59.79	16.25	38.36	28.4	26.2	+2.3
SE			0.05	0.15	2.60	2.53	6.28	15.20	2.99	2.46	8.4

TABLE II—(*Concluded*)

Dog	Wt	No. of tubules	Urine flow H*	Urine flow I*	Inulin clearance H	Inulin clearance I	Sodium Excretion H	Sodium Excretion I	Fractional sodium reabsorption proximal tubule‡ H	Fractional sodium reabsorption proximal tubule‡ I	Change in fractional reabsorption
	kg		*ml/min*		*ml/min*		*μEq/min*		%		%
Dextran: 25% dextran solution, *6.5 ml/kg*, more than 90 min after infusion											
11 d	18.2	3	0.17	0.46	57.5	71.2	4.4	8.9	51	36	−29
12 d	16.3	3	0.34	0.33	70.4	69.6	23.9	28.3	35	25	−29
13 d	15.3	3	0.19	0.36	61.8	67.8	28.0	63.2	48	21	−35
14 d	16.9	3	0.20	0.66	96.9	102.1	10.4	63.4	25	11	−56
15 d	13.7	3	0.32	0.34	60.9	51.6	37.2	14.3	28	25	−11
16 d	12.6	5	0.42	0.68	50.2	59.1	40.4	124.9	38	30	−21
17 d	16.5	5	0.16	0.23	48.2	55.7	1.5	1.5	42	30	−29
18 d	15.2	3	0.12	0.26	45.7	60.0	4.1	20.0	23	3	−87
19 d	13.0	4	0.12	0.22	43.8	58.6	1.4	17.6	17	5	−71
Mean			0.23	0.39	59.49	66.19	17.30	39.57	34.1	20.8	−40.0
SE			0.03	0.06	5.5	5.0	5.1	12.8	3.2	3.9	8.6
Saline: saline solution, *62.5 ml/kg*											
1 s	12.2	7	0.26	2.62	44.3	46.6	9.4	323.5	23.0	10.3	−55
2 s	14.5	8	0.19	1.15	59.4	71.6	8.5	220.6	32.1	7.8	−75
3 s	14.5	6	0.22	1.01	78.3	91.5	2.4	132.2	44.8	28.0	−37
4 s	17.7	6	0.24	3.17	57.6	80.7	9.6	372.0	34.5	21.2	−38
5 s	18.1	4	0.21	1.08	57.9	68.0	12.4	268.7	24.0	9.0	−63
6 s	12.7	7	0.11	2.09	78.0	79.8	2.3	505.4	41.1	26.3	−36
Mean			0.21	1.99	62.6	73.0	7.4	303.7	33.3	17.1	−50.7
SE			0.07	0.41	5.4	6.3	1.7	39.0	3.9	4.1	7.2

* H, I, Hydropenia periods and postinfusion periods.
‡ Fractional reabsorption of glomerular filtrate by the proximal tubule at the point of micropuncture. Value is the mean for the number of tubules indicated for each experiment.
§ Aberrant experiment, not included in means.
‖ Values for one kidney × 2.

a + 1.6% ± SE 2.3 change in fractional sodium reabsorption by the proximal tubule in five dogs in which 29 pairs of tubule fluid samples were collected (Fig. 1 *a* and Table II). Neither the increase in sodium excretion of 18.6 μEq/min ± SE 15.5 nor the increase in glomerular filtration rate of 1.1 ml/min ± SE 3.1 was statistically significant (Table II).

Infusion of hyperoncotic albumin solution. Plasma volume increased 66% ± SE 5.8 after infusion of hyperoncotic albumin solution. In Fig. 1 *b* the (TF/P) inulin concentration ratios after infusion of albumin solution are plotted against the (TF/P) inulin concentration ratios in hydropenia. Fractional sodium reabsorption by the proximal tubule decreased 32.3% ± SE 5.3 ($P < 0.001$) in 10 dogs in which 58 pairs of tubule fluid samples were analyzed. In one aberrant experiment, the calculated fractional reabsorption increased 112%. This unexplained result is not included in the means, since this experiment is clearly different from the other 10 experiments.

Sodium excretion increased from 12.9 to 71.8 μEq/min after the infusion of albumin solution. The mean increase of 58.9 μEq/min ± SE 10.7 was statistically significant ($P < 0.001$). The mean increase in glomerular filtration rate of 4.8 ml/min ± SE 3.5 was not statistically significant (Table II).

Infusion of hyperoncotic dextran solution. Recollection samples of tubule fluid were obtained in 13 dogs from 30 to 90 min after infusion of dex-

TABLE III

Protocol: Infusion of Hyperoncotic Dextran Solution, Double Recollection, Expt. 17 d, 16.5 kg Dog

Elapsed time	Urine flow E*	Urine flow C*	Sodium excretion E	Sodium excretion C	Inulin clearance E	Inulin clearance C	Plasma inulin	Hct	Tubule fluid sample	T.F.‡ inulin	Fractional sodium reabsorption proximal tubule§	Change in fractional reabsorption
min	*ml/min*		*μEq/min*		*ml/min*		*mg/100 ml*	%		*mg/100 ml*		
3									1 a‖	215	44	
8							120	59				
15	0.095	0.093	0.52	1.86	24.4	25.9						
19									2 a	189	37	
28							120	59				
30	0.095	0.080	0.47	0.96	24.9	26.3						
34									3 a	173	31	
39									4 a	270	55	
42							121	59				
45	0.101	0.067	0.51	0.80	27.1	—						
50									5 a	205	41	
53							121	59				
											Mean 42	
62–82	dextran, intravenous infusion, *107 ml 25%*											
109									1 b	258	53	+20
116							121	42	2 b	182	33	−11
120									3 b	168	28	−10
123	0.137	0.080	0.41	1.60	31.8	21.2						
131							122	42				
137	0.126	0.100	0.44	1.90	27.6	25.2			5 b	193	37	−10
141									4 b	290	58	+5
145							120	42				
154	0.127	—	0.44	—	27.2	—						
											Mean 42	−1
187									1 c	170	30	−32
201							119	43				
207									2 c	181	33	−11
210	0.153	—	0.77	—	27.5	—			3 c	158	26	−16
215							115	45	4 c	198	41	−25
219									5 c	145	21	−49
224	0.153	—	0.77	—	28.2	—						
											Mean 30	−27

* E, C, Experimental and control kidney respectively.

‡ T. F., Tubule fluid.

§ $\left[1 - \frac{(P)}{(TF)_{in}}\right] \times 100.$

‖ a, b, c first, second and third collection of tubule fluid from the same tubule.

tran. In six additional dogs samples were taken after 90 min and in three dogs samples were taken during both the early and late time periods. The protocol of one of these experiments is presented in Table III.

During the period from 30 to 90 min after dextran infusion, plasma volume increased 96% ± SE 4.9. The mean change in fractional sodium reabsorption in the proximal tubule of + 2.3% ± SE 8.4 was not significant. Data for these 72 pairs of tubule fluid samples from 13 dogs are shown in Figure 1 *c* and Table II. Sodium excretion increased from 16.3 to 38.4 μEq/min. The mean increase of 22.2 μEq/min ± SE 9.3 was statistically

TABLE IV

Protol: Infusion of Hyperoncotic Albumin Solution, Expt. 2 w, 19.3 kg Dog, Water Diuresis Previously Established by Infusion of 2.4% Dextrose in Water Solution

Elapsed time	Urine flow	Urine sodium	Sodium excretion	Urine osmolality	Plasma osmolality	Free water clearance	Inulin clearance
min	*ml/min*	*mEq/liter*	*μEq/min*	*mOsm/kg of H_2O*	*mOsm/kg of H_2O*	*ml/min*	*ml/min*
7					251		
15	6.05	1.1	6.1	68		4.3	72
22					256		
30	5.47	1.2	6.6	85		3.7	78
37					254		
45	7.06	1.1	7.8	70		5.1	77
45–65	Intravenous infusion of 25% human albumin solution, *100 ml*						
99					251		
106	10.3	2.7	27.9	55		8.1	85
114					254		
121	14.0	2.7	37.8	48		11.4	89
129					253		
136	13.9	2.2	30.5	38		11.8	80

significant ($P < 0.05$). The mean increase in glomerular filtration rate of 8.6 ml/min ± SE 2.0 was also significant ($P < 0.005$).

Measurements made from 90 to 180 min after the infusion of hyperoncotic dextran showed an increase in plasma volume of 94.0% ± SE 8.2. Fractional sodium reabsorption by the proximal tubule decreased 40.0% ± SE 8.6 ($P < 0.001$). This depression of fractional sodium reabsorption is not different from that after infusion of isotonic saline or hyperoncotic albumin. Data for these 32 pairs of samples from nine dogs are shown in Fig. 1 *d* and Table II. Sodium excretion changed from the hydropenic level of 17.3 to 39.6 μEq/min. The mean increase of 21.2 μEq/min ± SE 10.7 was not statistically significant. The mean increase in glomerular filtration rate of 6.7 ml/min ± SE 2.6 was significant ($P < 0.05$).

Infusion of saline solution. Plasma volume increased 61% ± SE 5.8 and fractional reabsorption by the proximal tubule decreased 50.7% ± SE 7.2 ($P < 0.001$) after infusion of 62.5 ml/kg of saline solution in six dogs in which 38 pairs of tubule fluid samples were collected (Fig. 1 *e* and Table II). Sodium excretion increased from 7.4 to 303.7 μEq/min. The mean increase of 296.9 μEq/min ± SE 34.9 was highly significant ($P < 0.001$) and much greater than the increase after the infusion of hyperoncotic albumin ($P < 0.001$) or dextran solutions ($P < 0.001$). The mean increase in glomerular filtration rate of 10.4 ml/min SE 3.3 was also statistically significant ($P < 0.025$).

TABLE V

Summary of the Effect of Infusion of Hyperoncotic Albumin during Water Diuresis

	Urine flow		Sodium excretion		Urine osmolality		Free water clearance		Inulin clearance	
Dog	W*	A*	W	A	W	A	W	A	W	A
	ml/min		*μEq/min*		*mOsm/kg H_2O*		*ml/min*		*ml/min*	
1 w	3.67	9.18	6.2	73.8	54	42	2.90	7.67	56.3	65.4
2 w	6.19	12.73	6.8	32.1	74	47	4.36	10.40	75.5	84.8
3 w	5.09	11.67	74.0	209.0	105	63	3.09	8.93	77.9	78.5
Mean	4.98	11.19	29.0	105.0	78	51	3.45	9.00	69.9	76.2
P	< 0.01						< 0.01			

* W, A, means for three periods during water diuresis and for three periods after infusion of albumin solution, respectively.

Free water clearance experiments

The infusion of hyperoncotic albumin solution during water diuresis resulted in a significant increase in urine flow, from a mean of 4.98 to 11.19 ml/min ($P < 0.01$) and in free water clearance, from a mean of 3.45 to 9.00 ml/min ($P < 0.01$). Urine osmolality averaged 78 mOsm/kg of water during water diuresis and 51 mOsm/kg of water after infusion of albumin solution. Inulin clearance increased in two dogs and was unchanged in one dog after infusion of albumin solution (Table V).

In one dog given hyperoncotic dextran solution during water diuresis, urine flow increased from 4.85 to 8.70 ml/min and free water clearance increased from 3.50 to 7.14 ml/min. Inulin clearance was 70.2 ml/min in water diuresis and 68.1 after infusion of dextran solution.

DISCUSSION

The demonstration by Dirks, Cirksema, and Berliner (3) that fractional sodium reabsorption in the proximal tubule of the dog is depressed by infusion of isotonic saline solution and the subsequent similar finding in the rat by Cortney, Mylle, and Gottschalk (4) led to the conclusion that the natriuresis seen after infusion of saline is secondary to the observed depression of sodium reabsorption in the proximal tubule. A corollary of this thesis is that depression of sodium reabsorption in the proximal tubule should be accompanied by a natriuresis. Thus the finding in the present micropuncture experiments that infusion of solutions of hyperoncotic albumin and dextran results in a significant depression of sodium reabsorption by the proximal tubule without correspondingly large increases in sodium excretion was unexpected.

To test the inference of depression of sodium reabsorption in the proximal tubule without natriuresis, the free water clearance experiments were performed. The interpretation of the free water clearance experiments is based on the postulate that, in the absence of antidiuretic hormone, the clearance of free water is determined primarily by the volume of fluid that reaches the diluting segment of the nephron and this volume, in turn, by the glomerular filtration rate and fractional reabsorption by the proximal tubule. In the present experiments, the delivery of tubule fluid from the proximal tubule during water diuresis probably approximates that during hydropenia since fractional sodium reabsorption by the proximal tubule of the dog is not affected by infusion of 50 ml/kg of 2.5% dextrose in water (12). Infusion of hyperoncotic albumin solution resulted in a significant increase in free water clearance, from a mean of 4.93 to 11.82 ml/100 ml GFR/min ($P < 0.01$). The large percentage increase in free water clearance after infusion of albumin or dextran solutions indicates a significant depression of fractional sodium reabsorption in the proximal tubule. Furthermore, the increase in free water clearance makes it unlikely that the decreased fractional reabsorption measured in the micropuncture experiments was a local change confined to the surface nephrons. The increase in free water clearance, which cannot be accounted for by changes in glomerular filtration rate, indicates that there is a decrease in absolute as well as fractional reabsorption by the proximal tubule after the infusion of hyperoncotic solutions. Thus, while an increase in filtration rate is excluded as the cause of the decrease in fractional reabsorption, nevertheless, the nature of the intrarenal mechanism of the change in absolute sodium reabsorption is not apparent from our data. Results from micropuncture and water diuresis experiments therefore show that infusion of hyperoncotic solutions results in decreased fractional and absolute sodium reabsorption by the proximal tubule.

Infusion of isotonic saline also resulted in a depression of sodium reabsorption in the proximal tubule. However, in contrast to the small changes in sodium excretion after infusion of hyperoncotic solutions, infusion of isotonic saline resulted in an average increase in sodium excretion of 296 μEq/min (Fig. 2). The mean increase in sodium delivery distal to the point of micropuncture calculated from the mean changes in inulin clearance and proximal tubule sodium reabsorption was greater after saline infusion than after infusion of hyperoncotic solutions. However, as can be seen from Fig. 3, in both the albumin and late dextran groups there were six dogs which had increases of 30–70% in sodium delivery distal to the site of micropuncture that were similar to the elevations seen in the six animals in the saline group. (Five of the seven dogs in the two hyperoncotic groups, which did not have increases in de-

livery comparable with those in the saline group actually had decreases in the glomerular filtration rate during the experimental period.) Nevertheless, the increases in sodium excretion in the six dogs which received hyperoncotic albumin (71.5 μEq/min SE 10.6) and the six animals infused with hyperoncotic dextran (26.2 μEq/min SE 12.8) were both significantly less than the increase of 296.9 μEq/min in the six dogs which received saline ($P < 0.005$, $P < 0.001$). These large differences in sodium excretion in dogs with similar delivery of sodium distal to the point of micropuncture indicate that changes in distal delivery of sodium cannot account for the observed differences in final sodium excretion. Therefore, in this situation, factors different from those which control proximal sodium reabsorption must operate distally to govern the reabsorption of sodium in the distal nephron and consequently

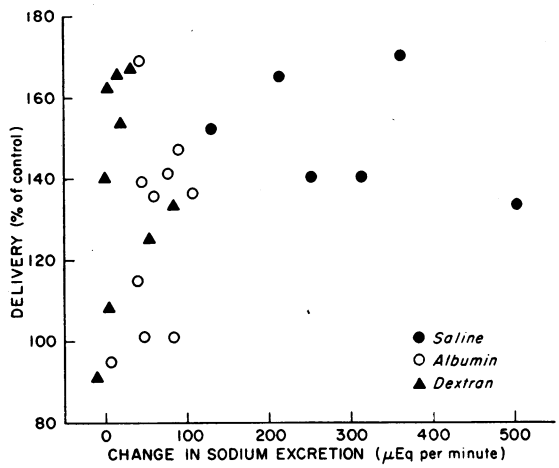

FIGURE 3 Increase in sodium excretion after infusion of experimental solution plotted against an index of delivery distal to point of micropuncture after infusion. Delivery calculated from data in Table II from the formula: Delivery (per cent of control) = [(Experimental/Control) clearance of inulin][(Experimental/Control) fraction of sodium not reabsorbed].

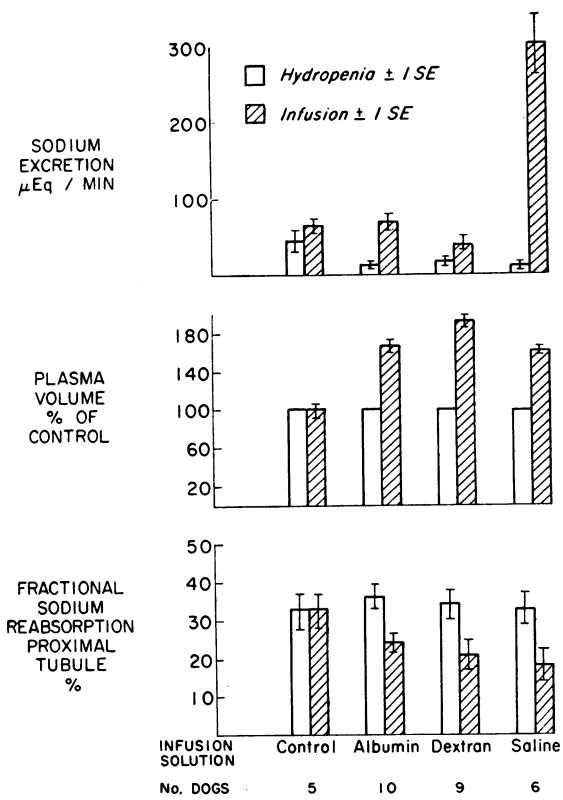

FIGURE 2 Sodium excretion, plasma volume, and fractional sodium reabsorption by the proximal tubule during hydropenia and after infusion of control, albumin, dextran, and isotonic sodium chloride solutions. Recollection samples were obtained 90–180 min after dextran infusion and 45–75 min after infusion of other solutions.

to regulate final sodium excretion. During saline diuresis the increased delivery of sodium from the proximal tubule is greater than the increase in final sodium excretion, which indicates that sodium reabsorption from distal sites must be increased (3). The increase in reabsorption of sodium from distal sites must be much greater after infusion of hyperoncotic albumin and dextran solutions, since very little of the excess sodium presented to the distal tubule appears in the urine.

Recent investigations in dogs undergoing water diuresis (13, 14) have indicated that proximal tubule reabsorption of sodium is depressed by significantly smaller infusions of hypotonic saline than are required to decrease sodium reabsorption in the diluting segment of the dog nephron. The authors of these studies also concluded that control of distal sodium reabsorption is distinct from control of proximal sodium reabsorption.

Bahlmann, McDonald, Dunningham, and de Wardener (15) have suggested that albumin may have a direct effect upon the renal tubule epithelium which causes a decrease in reabsorption. Since both albumin and dextran solutions produced similar decreases in proximal tubule sodium reabsorption, it is unlikely that the observed depressions are due to a specific effect of either the dextran or the albumin. The extrarenal mechanisms by which infusions of saline or of hyperoncotic

solutions lead to depression of sodium reabsorption in the proximal tubule are not known. Nor is it clear whether saline and hyperoncotic solutions produce this change by acting through identical pathways. The infusion of hyperoncotic solutions did not change plasma sodium concentration and contributed only a negligible addition to body sodium content. The control experiments, infusion of 6.5 ml/kg of 127 mEq/liter of NaCl solution, demonstrate that this small quantity of sodium had no effect on fractional sodium reabsorption by the proximal tubule. Thus, fractional sodium reabsorption by the proximal tubule can be depressed without significant changes in total body sodium content or plasma sodium concentration.

It is also evident that fractional sodium reabsorption by the proximal tubule is not correlated with the volume of the interstitial space, since the interstitial space is contracted by infusion of hyperoncotic dextran or albumin solutions and expanded by the infusion of saline, yet all three infusions result in depressed fractional reabsorption by the proximal tubule.

On the other hand infusions of saline, dextran, and albumin all expanded the vascular volume (Fig. 2). Although expansion of the vascular space may be a prerequisite for depression of proximal sodium reabsorption, additional factors must have operated in these experiments, since 30–90 min after infusion of hyperoncotic dextran, plasma volume is significantly expanded (+96% ± SE 4.9), whereas fractional sodium reabsorption in the proximal tubule is not depressed.[8]

The existence and location of a receptor sensitive to changes in vascular volume for regulation of reabsorption by the proximal tubule remain speculative. Stretch receptors located in the left atrium have been proposed as volume receptors for the control of sodium excretion (16). However, ablation of the afferent cardiac nerves of the dog does not affect the depression of fractional reabsorption by the proximal tubule resulting from the infusion of saline solution (10).

A humoral agent has been suggested as one of the means by which a signal from an extrarenal receptor could be conveyed to the proximal tubule. The finding of increased sodium excretion in cross circulation experiments has been offered as evidence by DeWardener et al. (1), by Lichardus and Pearce (17), and by Johnston and Davis (18) that infusion of saline results in the release of a hormone that effects a decrease in both fractional and absolute sodium reabsorption. Evidence for another humoral agent that decreases fractional and absolute sodium reabsorption in the rat proximal tubule, but does not result in a significant increase in sodium excretion, has recently been presented by Martinez-Maldonado, Kurtzman, Rector, and Seldin (19). If the effect of hyperoncotic infusions in our experiments is mediated by a hormone it would appear that this hormone is similar to the one described by Martinez-Maldonado et al., since in both instances sodium reabsorption in the proximal tubule is significantly depressed without a corresponding natriuresis.

[8] In fact, the observation that the Lissamine green dye transit time through the proximal tubule decreased significantly in the period from 90 to 180 min after the administration of hyperoncotic dextran led us to study sodium reabsorption by the proximal tubule during this later period.

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