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Changes in Renal Blood Flow and Possibly the Intrarenal Distribution of Blood during the Natriuresis Accompanying Saline Loading in the Dog *

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Several recent studies have provided evidence that the increased excretion of sodium associated with expansion of the extracellular volume may result in part from factors other than an increase in the filtered load of sodium. In the dog receiving a mineralocorticoid, the infusion of isotonic saline may be accompanied by increased excretion of sodium without a spontaneous increase in the filtered load of sodium (1, 2). During saline loading glomerular filtration rate (and filtered sodium) may be reduced experimentally without abolishing the saline-induced natriuresis (1, 3–6). Thus, a large body of evidence is consistent with the concept that expansion of the extracellular volume in the dog results in a net decrease in the tubular reabsorption of sodium, independent of changes in the tubular effects of aldosterone. In a recent study from this laboratory it was demonstrated that this decreased net tubular reabsorption of sodium that accompanies saline loading may be associated with a decrease in urinary osmolality that is not accounted for by changes in either antidiuretic hormone activity or solute excretion (6). On the basis of this latter observation it was suggested that saline loading in the dog may result in an increased renal medullary blood flow which decreases medullary interstitial hypertonicity, and that decreased medullary interstitial hypertonicity may decrease net sodium reabsorption secondarily by diminishing the passive reabsorption of water from the descending limb of Henle's loop, resulting in the delivery of a larger volume of fluid of lower sodium concentration to the transport sites of the ascending limb of the loop. The present studies were undertaken to determine if a relationship could be demonstrated between changes in the tubular reabsorption of sodium and changes in renal blood flow. It was observed that the increased excretion of sodium during isotonic expansion of the extracellular volume was uniformly associated with increased renal blood flow, independent of spontaneous changes in glomerular filtration rate. Furthermore, changes in the net tubular reabsorption of sodium, which were demonstrated both spontaneously during the course of saline loading and during controlled unilateral reductions of renal blood flow, were associated with inverse changes in that portion of renal plasma flow from which *p*-aminohippurate (PAH) is not extracted.

Methods

Twenty-eight mongrel dogs of either sex, ranging in weight from 13.2 to 21.3 kg, were deprived of food and water for 20 hours before experiments. Approximately 4 hours before experiments the animals received by intramuscular injection 5 U of Pitressin Tannate in oil and 5 mg of DOCA (desoxycorticosterone acetate) in oil. Under light pentobarbital anesthesia the right ureter was exposed through a flank incision and cannulated with polyethylene tubing. The left kidney and ureter were exposed through a subcostal incison, and the left ureter was simlarly cannulated. With minimal dissection the left spermatic or ovarian vein was exposed at its entry into the renal vein. An 18-gauge needle containing a plastic catheter (2 mm o.d.) was inserted into the ovarian or spermatic vein and directed toward the kidney. The plastic catheter was then inserted 2 to 3 cm along the renal vein in the direction of the kidney, the needle was removed, and the catheter was tied tightly in place at its entry into the spermatic or ovarian vein. The position of the catheter in the direction of the kidney was always

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TABLE I

*Renal hemodynamic changes during saline loading**

	GFR	C_{PAH}	E_{PAH}†	RBF	NCPF	$U_{Na}V$
	ml/min	*ml/min*		*ml/min*	*ml/min*	*μEq/min*
Control	40 ± 14	126 ± 49	0.786 ± 0.072	261 ± 76	32 ± 10	97 ± 83
Saline load	49 ± 15	195 ± 70	0.635 ± 0.149	425 ± 120	116 ± 54	1,075 ± 538

* Values are the means and standard deviations for the left kidney from 28 experiments. Abbreviations: GFR = glomerular filtration rate, C_{PAH} = clearance of *p*-aminohippurate, E_{PAH} = extraction ratio for *p*-aminohippurate, RBF = total renal blood flow, NCPF = "noncortical plasma flow" (renal plasma flow − C_{PAH}), and $U_{Na}V$ = rate of sodium excretion.

† Includes two experiments with Diodrast-I^{131} instead of *p*-aminohippurate.

made certain by observing the movement of minute injected air bubbles along the renal vein. The venous catheter was kept patent by the infusion of 0.4% saline at 0.2 to 0.3 ml per minute. In 16 experiments, either tape or a Blalock clamp was placed around the aorta between the renal arteries and carried out of the body wall. This allowed reversible constriction of the aorta above the left renal artery. After closure of the surgical wounds, 60 to 90 minutes was allowed before beginning experimental measurements. A plastic catheter inserted into the lower aorta through a femoral artery was used to collect arterial blood samples and to measure arterial pressure.

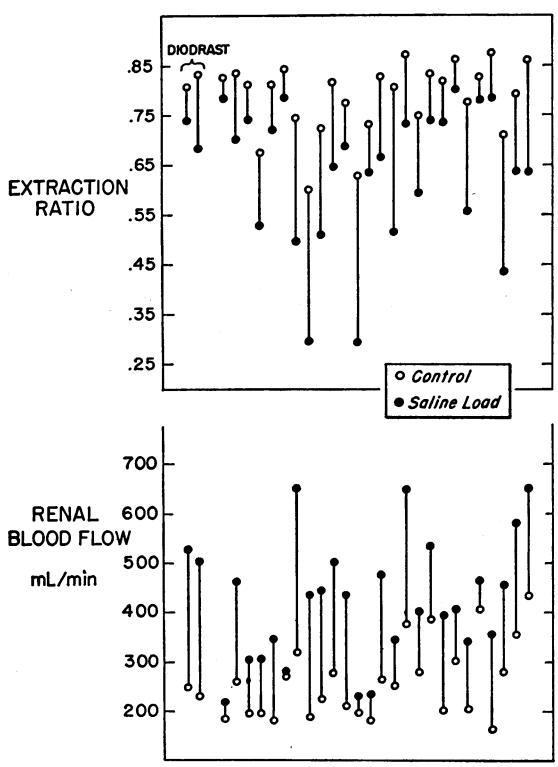

FIG. 1. CHANGES IN RBF AND EPAH OR EDIODRAST DURING SALINE LOADING. Points represent the means of three or more consecutive and uniform collection periods from the left kidney only. The first two experiments on the left were performed with Diodrast-I^{131} in the absence of PAH. All other extraction ratios are for PAH. During the control measurements sodium excretion averaged 97 μEq per minute per kidney and during saline loading increased to an average of 1,075 μEq per minute per kidney (see text).

Eighty to 100 minutes before experimental measurements, an infusion of isotonic saline was begun at a fixed rate between 0.25 and 0.30 ml per minute. (In eight experiments with aortic constriction this maintenance infusion was delivered at 1.5 ml per minute.) This infusion delivered PAH at 2.5 to 3.5 mg per minute, creatinine or inulin at approximately 12 or 10 mg per minute respectively, vasopressin at 40 to 60 mU per kg per hour, and desoxycorticosterone at 25 μg per minute. The solution was acidified to pH 5.0 to 5.5 with acetic acid. In five experiments the maintenance infusion contained either Diodrast-I^{131} or Hippuran-I^{131} [1] in tracer amounts to deliver 0.25 to 0.50 μc per minute. In two experiments the maintenance solution contained Diodrast-I^{131} but no PAH.

At the mid-point of each urine collection, arterial and renal venous blood samples were collected simultaneously into heparinzed syringes and transferred immediately to ice-packed tubes. The blood samples were centrifuged immediately at 4 to 5° C for exactly 5 minutes. The total elapsed time from beginning blood sampling to the separation of plasma was uniform in all experiments and did not exceed 10 minutes.

After three or four control collections each animal received a modified Ringer's solution (Na 145, K 3.5, Cl 128.5, HCO_3 20 mEq per L; hereafter referred to as saline) at a rate of 50 ml per minute, until a total of 1,250 to 1,750 ml (80 to 120 ml per kg) was infused. This loading infusion was then continued at a rate approximately the same as the rate of urine flow. Three to five collections were made during the saline diuresis. Five of the experiments were concluded at this point. In seven experiments the infusion of saline was then discontinued, and when the rate of urine flow had decreased to approximately 1 ml per minute, three or four additional collections were made.

In 16 experiments after collections during the maintained diuresis, the aorta was constricted between the renal arteries to reduce the flow of urine from the left kidney. In seven experiments the aortic constriction was performed in two stages. Urine flow was first reduced to 40 to 60% of the diuretic rates (aortic pressure, 70 to

[1] Abbott Laboratories, Oak Ridge, Tenn.

85 mm Hg). After collecting three to five periods, additional constriction was applied to reduce urine flow to rates 0.5 to 2.0 ml per minute greater than the presaline infusion control values (aortic pressure, 40 to 60 mm Hg). After collecting three to six periods the aortic constriction was released, and collections were continued. In nine experiments, only the more extensive aortic constriction was applied. In eight of the experiments employing aortic constriction the animals received 200 or 300 ml of isotonic saline 3 hours before beginning experimental collections. In these eight experiments the maintenance infusion (creatinine, PAH, and so forth in isotonic saline) was delivered at 1.5 ml per minute instead of 0.25 to 0.30 ml per minute.[2] In 12 of these experiments arterial pressure was recorded from the aorta, below the renal arteries, with a Sanborn pressure transducer and model 964 recorder.

Clearance calculations were not made from transitional periods during saline loading, during the subsiding diuresis following saline loading, or immediately following constriction or release of the aorta. Creatinine was determined by the Jaffe reaction as described by Kennedy, Hilton, and Berliner (7), or as modified for the Technicon autoanalyzer (8); inulin by the method of Walser, Davidson, and Orloff (9); PAH by a modification of the method of Smith and his associates (10), or as modified for the Technicon autoanalyzer (8); sodium by internal standard flame photometry; and hematocrits by centrifugation in standard Wintrobe tubes. Diodrast-I^{131} and Hippuran-I^{131} radioactivty were measured in a well type scintillation counter.[3]

The renal extraction ratios (E) of PAH, Diodrast, and Hippuran were calculated from the formula, $E = (A-R)/A$, where A is the arterial and R the renal venous concentrations of the extracted substance. Total renal plasma flow (RPF) was calculated as C_{PAH}/E_{PAH}, or (in experiments with extraction ratios less than .5) from the formula of Wolf (11). $RPF = [V(U-R)]/[A-R]$, where V = rate of urine flow and U = the urinary, R = the renal venous, and A = the arterial concentrations of the extracted substance. Total renal blood flow (RBF) was calculated from RPF and the hematocrit (Hct): $RBF = RPF/(1-.95\ Hct)$.

In the present calculations of E and RPF no corrections have been made for the estimated diffusion of the extracted substance from red blood cells (12). With C_{PAH} assumed to approximate renal cortical plasma flow, "noncortical plasma flow" (NCPF) was calculated as $RPF - C_{PAH}$.

[2] This preloading with a relatively small volume of saline and the higher rate of maintenance infusion did not impair the large hemodynamic and natriuretic responses to the experimental saline load. However, this procedure resulted in higher control rates of glomerular filtration rate (GFR) and clearance of PAH (C_{PAH}) and somewhat smaller increases in these measurements during the saline load.

[3] Nuclear-Chicago, Des Plaines, Ill.

TABLE II

*The effects of transient saline loading on renal hemodynamics and sodium excretion**

	V		GFR		C_{PAH}		Extraction ratio	RBF†		$U_{Na}V$		F_{Na}		P_{Na}	Hematocrit
	R	L	R	L	R	L		R	L	R	L	R	L		
	ml/min		*ml/min*		*ml/min*			*ml/min*		*μEq/min*		*μEq/min*		*mEq/L*	
1. Control	0.17	0.17	36	38	114‡	119‡	.831‡	219	228	36	35	5,005	5,290	139	40
Saline loading	6.60	2.82	51	47	254‡	258‡	.680‡	494	501	1,082	476	7,100	6,545	139	26
Postload	1.41	0.97	51	52	119‡	118‡	.785‡	241	239	273	190	6,990	7,120	137	38
2. Control	0.42	0.47	37	37	94	96	.810	199	197	79	100	5,165	5,165	140	42
Saline loading	3.98	5.46	47	49	163	166	.741	298	304	720	946	6,620	6,905	141	28
Postload	1.16	1.50	50	54	139	145	.805	278	285	269	349	6,800	7,350	136	39
3. Control	0.23	0.24	37	43	103	116	.835	232	260	59	58	5,360	6,240	145	50
Saline loading	6.18	5.80	49	52	192	211	.701	419	460	1,107	1,062	6,955	7,390	142	36
Postload	0.74	0.81	46	52	88	100	.843	180	205	187	198	6,160	6,970	134	44
4. Control	0.17	0.25	34	36	85	93	.825	171	187	40	43	5,065	5,412	149	42
Saline loading	4.74	6.98	42	47	116	130	.786	176	217	910	1,263	6,050	6,770	144	25
Postload	1.56	1.78	39	44	96	105	.840	164	180	384	409	5,695	6,420	146	32
5. Control	0.21	0.19	46	42	169	146	.826	305	268	34	32	6,660	6,095	145	35
Saline loading	4.32	4.65		60	250	246	.669	478	471	817	869	9,150	8,575	143	23
Postload	1.80	1.70	62	57	171	156	.830	297	269	415	388	8,560	7,870	138	31
6. Control		0.13		23		74	.683		181		23		3,405	148	42
Saline loading	9.85	8.37	38	35	105	108	.637	224	231	1,320	1,101	5,620	5,180	148	28
Postload	1.22	0.87	30	31	63	71	.756	133	152	233	157	4,410	4,560	147	39
7. Control	0.63	0.41	32	32	80	82	.673	196	195	107	74	4,390	4,390	137	40
Saline loading	3.46	4.76	33	38	115	126	.529	278	303	491	619	4,555	5,250	138	23
Postload	1.21	1.33	29	31	73	75	.696	170	175	178	202	3,945	4,215	136	40

* Values for the left kidney are the means of usually three uniform consecutive collection periods; those for the right kidney are usually a single collection over the same period of time. Control observations ranged from 30 to 80 minutes; saline loading observations were made during 30 to 90 minutes immediately after completing a 1,500- to 1,750-ml infusion; postload observations were made over a period of 30 to 60 minutes beginning 45 to 90 minutes after discontinuing the infusion of saline. Additional abbreviations: V = rate of urine flow, F_{Na} = filtered sodium, and P_{Na} = plasma sodium concentration.

† RBF for each kidney calculated from extractions measured from left kidney.

‡ Clearance and extraction ratio for Diodrast-I^{131}; all other clearances and extraction ratios are for PAH.

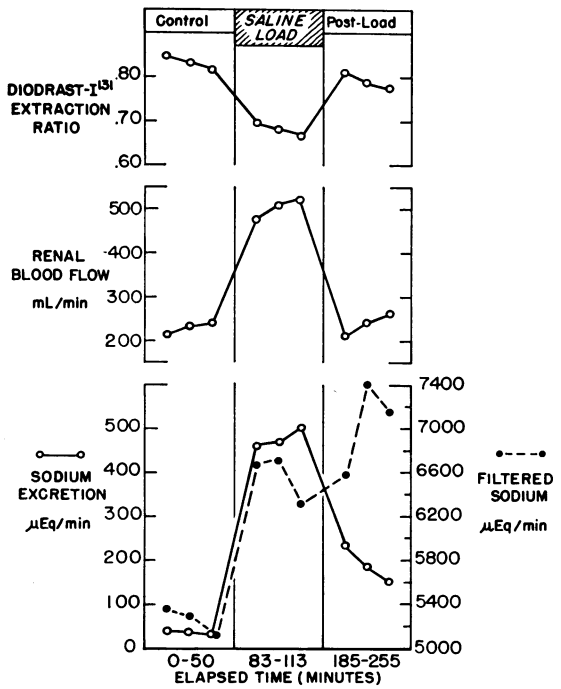

FIG. 2. CHANGES IN SODIUM EXCRETION, FILTERED SODIUM, RBF, AND $E_{Diodrast}$ DURING THE TRANSIENT COURSE OF NATRIURESIS ACCOMPANYING SALINE LOADING. Consecutive collection periods from the left kidney are shown. The periods during rapid saline loading and immediately after discontinuing the infusion of saline are not included. Elapsed time is from the beginning of the first control collection. In this experiment GFR and filtered sodium continued to increase as sodium excretion diminished during the postloading period. PAH was not infused in this experiment. Changes in sodium excretion correlated closely with changes in RBF and $E_{Diodrast}$. The scale for filtered sodium is four times that for sodium excretion.

Results

The effects of saline loading on renal blood flow and extractions of PAH, Diodrast, and Hippuran. In a total of 28 experiments extraction ratios were measured and renal blood flow was calculated from collections before saline loading and during the diuresis accompanying a maintained saline load. These results are summarized in Table I and Figure 1. The renal extraction of PAH, Diodrast, or Hippuran decreased in every experiment, with an average absolute fall of 15.1% (range, 3.9 to 33.7%). In the 28 experiments, E_{PAH} (or $E_{Diodrast}$) before saline loading averaged 0.786 ± .072 (SD) and during saline loading averaged 0.635 ±.149. RBF increased from a mean of 261 ± 76 ml per minute per kidney to a mean of 425 ± 120 ml per minute per kidney. Even though minimal increases in RBF occurred in some experiments, E_{PAH} was always decreased during saline loading (Figure 1). RPF increased by a mean of 153 ml per minute with an increase in noncortical plasma flow (see Methods) of 84 ml per minute. The excretion of sodium in these experiments increased from a control mean of 97 μEq per minute per (left) kidney (range, 6 to 238) to a mean of 1,075 μEq per minute per kidney (range, 313 to 2,412) during the maintained saline load (Table I).

Relationship between sodium excretion and RBF, E_{PAH}, and filtered sodium. In seven experiments measurements were made before, during, and after saline loading (Table II). In all seven of these experiments GFR and filtered sodium increased during saline loading, as RBF increased

TABLE III

Effects of saline loading on renal hemodynamics and sodium excretion in the absence of spontaneous increases in filtered sodium

	V		GFR		C_{PAH}			RBF		$U_{Na}V$		F_{Na}			Hematocrit
	R	L	R	L	R	L	E_{PAH}	R*	L	R	L	R	L	P_{Na}	
	ml/min		*ml/min*		*ml/min*			*ml/min*		*μEq/min*		*μEq/min*		*mEq/L*	
8. Control	0.11	0.17	19†	23†	49	62	.620	136	197	4	6	2,678	3,360	146	44
Saline loading	3.54	4.40	19†	20†	51	53	.291	216	230	529	560	2,579	2,810	141	20
9. Control	0.49	0.32	38	36	120	117	.810	250	253	128	87	5,548	5,183	146	43
Saline loading	6.60	6.17	37	33	134	137	.531	335	344	898	755	5,402	4,838	146	26
10. Control	0.98	1.05	47	47	110	113	.774	201	162	217	233	6,746	6,746	143	31
Saline loading	8.25	8.05	49	48	153	150	.556	348	355	1,273	1,180	6,958	6,804	143	22
11. Control	0.85	0.95	37	50	99	124	.710	224	281	139	199	5,365	7,155	145	40
Saline loading	5.34	7.19	32	45	108	145	.434	339	454	847	1,110	5,616	6,493	145	28
12. Control	0.97	0.65	66	63	229	240	.825	394	407	188	161	9,438	8,937	143	31
Saline loading	5.32	2.97	64	61	286	285	.780	469	468	798	613	9,088	8,590	142	23

* Blood flow calculated from extractions measured from left kidney.
† Clearance of inulin; all other measurements of GFR are clearances of exogenous creatinine.

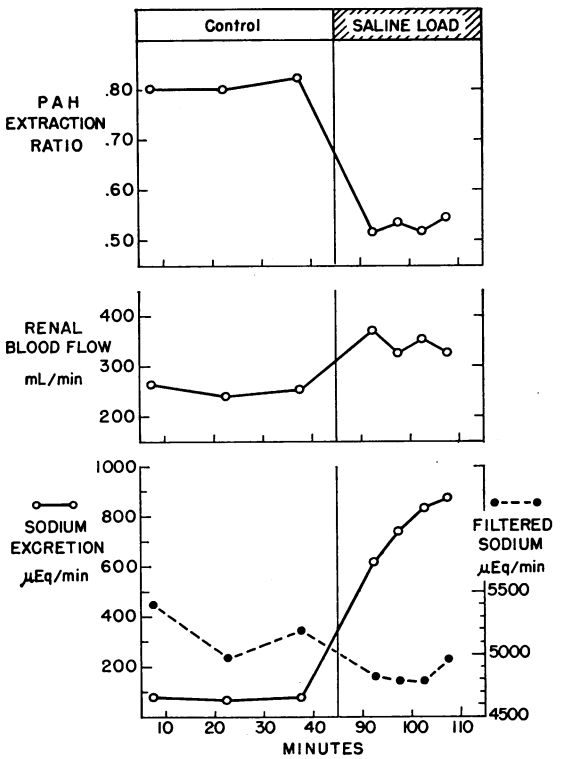

FIG. 3. RENAL HEMODYNAMICS DURING SALINE LOADING WITHOUT A SPONTANEOUS RISE IN FILTERED SODIUM. Consecutive collections from left kidney are shown, except that the transition period during inital saline loading is not included. Sodium excretion increased strikingly during saline loading despite decreases in the filtered load of sodium. Accompanying this increased excretion of sodium was a rise in renal blood flow and a fall in the extraction of PAH.

and E_{PAH} decreased. However, after the infusion of saline had been discontinued and the diuresis allowed to subside, changes in GFR and filtered sodium were unpredictable. In five of the seven studies the decrease in filtered sodium was insufficient to account for the fall in excreted sodium following the saline load. In three studies GFR either remained maximal or continued to increase at a time when the saline-induced natriuresis had largely subsided (first three experiments, Table II). However, in every study the increased RBF and decreased E_{PAH} (accompanying the saline load) returned to or toward the preloading control values as the natriuresis subsided. These results are summarized in Table II, and consecutive collection periods from a representative experiment are shown in Figure 2.

In five experiments GFR and filtered sodium were unchanged or decreased during saline loading, despite striking increases in the excretion of sodium (Table III). In these experiments E_{PAH} was reduced and RBF increased during saline loading, as in all other experiments. Also, in these five experiments C_{PAH} during saline loading was either not increased or increased less than the average increase for all experiments. Thus, in these five experiments no increase in filtered sodium accompanied the natriuretic response to saline loading, yet the usual decrease in E_{PAH} and increase in RBF were present during saline loading. Consecutive collection periods from one of these experiments are shown in Figure 3.

Therefore, in the 12 studies summarized in Tables II and III, changes in sodium excretion (related to saline loading) correlated directly with changes in RBF and inversely with changes in E_{PAH}, but did not correlate directly with the spontaneous changes in GFR and filtered sodium.

Effects of reduced blood flow on renal hemodynamics and sodium excretion. In a total of 16 experiments blood flow to the left kidney was re-

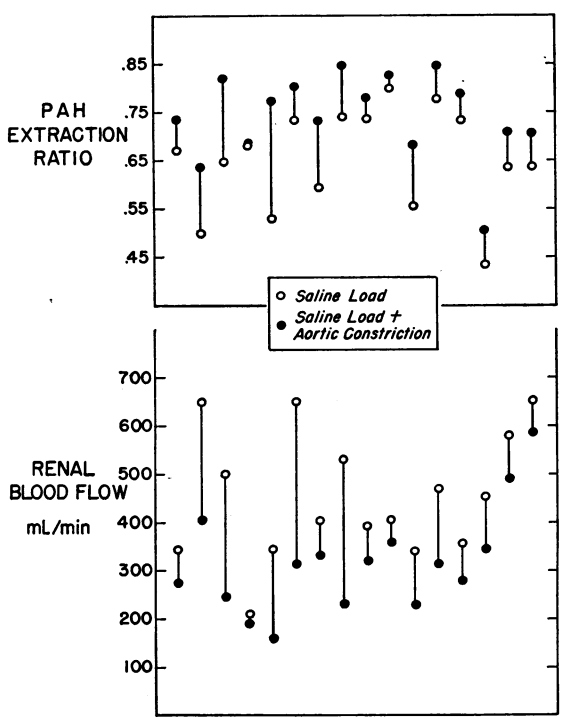

FIG. 4. THE EFFECTS OF AORTIC CONSTRICTION ON RBF AND E_{PAH} DURING MAINTAINED SALINE LOAD. Points shown are the means of three or more consecutive and uniform collections from the left kidney. Values for E_{PAH} were reduced below inital controls during saline loading (open circles). During aortic constriction these reduced values increased (solid circles) as RBF decreased.

TABLE IV

The relationships between renal hemodynamics and changes in the net reabsorption of sodium during saline loading, demonstrated by unilateral reductions of renal blood flow

	Time*	V		GFR		C_{PAH}		E_{PAH}	RBF†		NCPF	$U_{Na}V$		F_{Na}		P_{Na}	Aortic pressure‡
		R	L	R	L	R	L		R	L	L	R	L	R	L		
	min	*ml/min*		*ml/min*		*ml/min*			*ml/min*		*ml/min*	*μEq/min*		*μEq/min*		*mEq/L*	*mm Hg*
13.	−190	300 ml Ringer's solution at 50 ml per minute; PAH, 3.5 mg per minute; creatinine, 10.8 mg per minute; vasopressin, 15 mU per minute; desoxycorticosterone, 25 μg per minute in 0.9% saline at 1.5 ml per minute															
	0– 22		0.97		57		151	0.852		289	26		261		8,436	148	105
	22– 32		0.85		57		160	0.861		305	26		224		8,322	146	105
	32– 42		0.85		57		162	0.890		298	20		218		8,322	146	103
	42– 52	1.21	0.86	50	57	141	166	0.857	264	318	28	255	212	7,300	8,379	147	103
		1,500 ml Ringer's solution, 52 to 85 minutes, then 25 ml per minute															
	52– 95	8.72	5.97									1,395	1,006				117
	95–101		8.80		64		248	0.806		403	58		1,417		9,344	146	107
	101–107		9.50		59		220	0.790		389	58		1,511		8,673	147	106
	107–113		9.17		66		252	0.795		443	65		1,458		9,636	146	108
	113–118	12.00	9.40	60	63	227	224	0.814	397	385	51	1,824	1,532	8,760	9,261	147	107
		Adjust inter-renal aortic constriction, 118 to 126 minutes															
	118–133		6.20										1,160				
	133–140		5.80		65		218	0.856		357	37		1,079		9,425	145	88
	140–146		5.47		67		216	0.862		351	35		1,017		9,782	146	86
	146–152	11.85	5.02	66	66	228	217	0.828		366	45	1,849	939	9,636	9,570	146	80
		Increase inter-renal aortic constriction, 152 to 167 minutes; decrease Ringer's solution to 18 ml per minute															
	152–183		1.32										275				
	183–188		2.08		54		212	0.834		355	42		333		7,938	147	57
	188–192		2.49		56		235	0.800		411	59		374		8,064	144	57
	192–197		2.60		54		242	0.808		418	55		367		7,830	145	
	197–202	9.45	2.68	65	52	249	232	0.808		401	55	1,474	362	9,425	7,488	144	65
		Release inter-renal aortic constriction, 202 minutes															
	202–210		6.06										709				100
	210–215		7.80		64		262	0.803		456	64		913		9,280	145	100
	215–220		8.66		64		285	0.781		510	80		1,013		9,152	143	100
	220–225	12.12	9.56	67	63	258	243	0.805	455	421	58	1,733	1,119	9,648	9,072	144	105
14.	−132	300 ml Ringer's solution at 50 ml per minute; PAH, 3.5 mg per minute; creatinine, 10.8 mg per minute; vasopressin, 15 mU per minute; desoxycorticosterone, 25 μg per minute in 0.9% saline at 1.5 ml per minute															
	0– 15		1.12		42		83	0.862		158	14		258		6,006	143	103
	15– 22		0.94		42		88	0.877		166	13		243		6,006	143	99
	22– 30	1.04	0.88	42	41	88	89	0.878	165	167	13	256	230	6,006	5,822	142	97
		1,500 ml Ringer's solution, 30 to 55 minutes, then 25 ml per minute															
	30– 65	6.15	6.86									1,027	1,118				
	65– 73		9.73		46		179	0.734		328	64		1,430		6,578	143	98
	73– 79		9.83		49		198	0.721		371	77		1,425		7,007	143	99
	79– 85		10.17		51		207	0.725		385	78		1,464		7,344	144	98
	85 91	8.59	10.55	47	50	191	188	0.756	351	335	60	1,263	1,498	6,721	7,150	143	99
		Adjust inter-renal aortic constriction, 91 to 96 minutes															
	91–105		4.64										728				
	105–110		5.46		42		154	0.810		253	36		846		5,964	142	60
	110–115		5.68		43		175	0.758		308	56		886		6,106	142	
	115–120		6.20		44		170	0.779		291	48		942		6,248	142	67
	120–125	10.56	6.02	48	44	204	156	0.795		261	40	1,468	915	6,816	6,248	142	65

TABLE IV—*Continued*

	Time*	V R	V L	GFR R	GFR L	C_{PAH} R	C_{PAH} L	E_{PAH}	RBF† R	RBF† L	NCPF L	$U_{Na}V$ R	$U_{Na}V$ L	F_{Na} R	F_{Na} L	P_{Na}	Aortic pressure‡
	min	*ml/min*		*ml/min*		*ml/min*			*ml/min*		*ml/min*	*μEq/min*		*μEq/min*		*mEq/L*	*mm Hg*
		Increase inter-renal aortic constriction, 125 to 140 minutes; decrease Ringer's solution to 15 ml per minute															
	125–154		2.18				136	0.781		235	38		392		5,396	142	49
	154–159		2.60		38		136	0.793		231	35		452		5,254	142	50
	159–164		2.62		37		127	0.788		218	34		453		4,970	143	48
	164–169		2.24		35								394				
	169–181	11.77	2.17	50	38	195	131	0.813		218	30	1,565	395	7,100	5,396	142	42
		Release inter-renal aortic constriction, 181 minutes															
	181–190		8.28										1,167				
	190–195		9.02		47		162	0.786		286	44		1,272		6,674	142	93
	195–200		8.98		47		163	0.780		290	46		1,203		6,721	143	93
	200–205	11.82	9.00	48	47	178	166	0.785	334	293	46	1,537	1,188	6,864	6,768	144	105
15.	−135	300 ml Ringer's solution at 50 ml per minute; PAH, 3.5 mg per minute; creatinine, 10.8 mg per minute; vasopressin, 15 mU per minute; desoxycorticosterone, 25 μg per minute in 0.9% saline at 1.5 ml per minute															
	0–9		1.06		45		100	0.784		184	27		236		6,435	144	103
	9–15		1.08		45		108	0.784		200	30		243		6,435	144	102
	15–21		1.06		46		118	0.765		223	33		234		6,578	145	95
	21–27	0.98	1.01	45	44	110	108	0.783	199	200	30	217	220	6,480	6,292	143	96
		1,500 ml Ringer's solution, 27 to 54 minutes, then 15 ml per minute															
	27–65	4.45	4.71									721	782				
	65–71		7.47		45		144	0.553		330	117		1,098		6.435	143	113
	71–77		7.97		49		163	0.533		384	140		1,156		7,056	144	113
	77–85		8.40		48		144	0.574		316	106		1,243		6,864	143	113
	85–91	8.25	8.37	48	48	153	147	0.565	360	329	113	1,246	1,222	6,864	6,864	143	113
		Adjust inter-renal aortic constriction, 91 to 99 minutes															
	91–106		5.34										828				
	106–111		5.00		44		119	0.688		227	54		815		6,248	142	80
	111–116		4.90		43		117	0.676		227	56		813		6,106	142	75
	116–121		5.06		46		127	0.669		248	62		835		6,578	143	
	121–126	8.60	4.81	47	44	133	113	0.686		216	52	1,273	794	6,674	6,248	142	80
		Increase inter-renal aortic constriction, 126 to 158 minutes															
	127–175		1.81										340				
	175–181		2.40		41		88	0.710		156	35		439		5,781	141	70
	181–186		2.10		39		82	0.734		142	40		361		5,499	141	55
	186–202		1.20		37		85	0.740		146	36		224		5,217	141	
	202–213		0.90		44		103	0.721		181	40		176		6,160	140	52
	213–218		1.87		43		96	0.708		181	40		348		6,063	141	
	218–232	9.49	1.64	48	38	121	82	0.727		140	31	1,395	286	6,768	6,282	139	63
		Release inter-renal aortic constriction, 232 minutes															
	232–240		3.50										588				
	240–247		3.07		42		98	0.690		192	44		525		5,922	141	
	247–252	7.70	2.78	46	40	114	89	0.710	220	169	36	1,155	478	6,394	5,560	139	110

* Collections from right kidney were consecutive and extended throughout the period of multiple collection periods from the left kidney. Clearances from the right kidney calculated from mean plasma values during the period of collection.

† Blood flow for right kidney calculated from average E_{PAH} from left kidney during period of collection from the right. Blood flow not calculated for right kidney during periods of inter-renal aortic constriction.

‡ Mean aortic pressure recorded below point of aortic constriction.

duced during saline loading by constriction of the aorta between the renal arteries. In each experiment E_{PAH} (which was reduced during saline loading) was increased as total blood flow decreased (Figure 4). However, E_{PAH} was usually not increased to the higher values present before saline loading, even when total renal blood flow was reduced to values equal to or less than the presaline loading control rates (second constriction, experiment 15, Table IV). During mild aortic constriction the calculated noncortical fraction of renal plasma flow was reduced proportionately more than C_{PAH}, but with increased aortic constriction E_{PAH} did not continue to increase strikingly as RBF decreased.

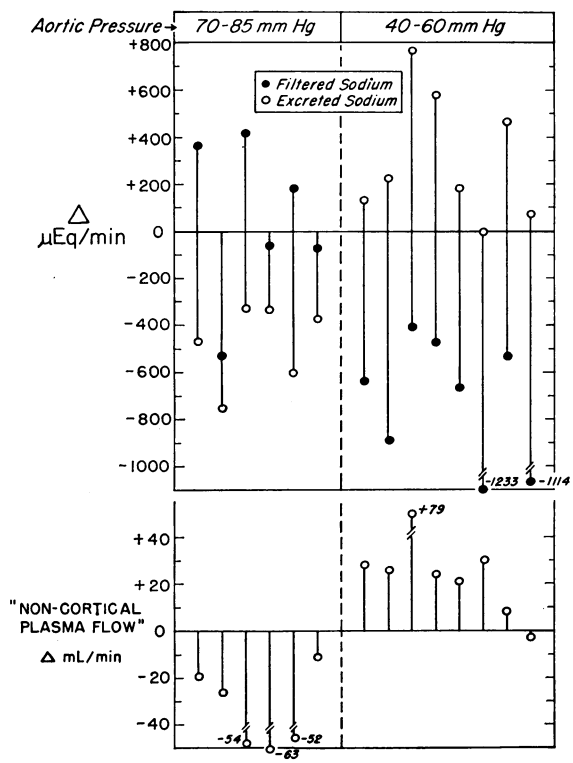

FIG. 5. CHANGES IN THE NET TUBULAR REABSORPTION OF SODIUM DEMONSTRATED BY AORTIC CONSTRICTION DURING SALINE LOADING. Values are the means of three or more consecutive collections from the left kidney. Shown on the left are demonstrations of increased tubular reabsorption of sodium during mild aortic constriction during the maintained saline load. Sodium excretion decreased without an equivalent decrease in filtered sodium as noncortical plasma flow (see text) decreased. Changes on the left are from mean values during the saline load and before aortic constriction. Shown on the right are demonstrations of decreased tubular reabsorption during saline loading demonstrated by more marked aortic constriction. These changes in filtered and excreted sodium and noncortical plasma flow are from mean values before saline loading. In all but one experiment in which excreted sodium was increased in the presence of reduced filtered sodium, noncortical plasma flow was increased (see text).

In 5 of these 16 experiments the relationships between filtered and excreted sodium necessary to demonstrate changes in tubular reabsorption were not achieved during aortic constriction. In the remaining 11 experiments changes in the net tubular reabsorption of sodium were demonstrated. The association between these changes in tubular reabsorption and changes in noncortical plasma flow is summarized in Figure 5. Details of three representative experiments are given in Table IV.

In seven experiments mild aortic constriction (aortic pressure, 70 to 85 mm Hg) was employed during saline loading, and measurements of hemodynamics and sodium excretion were compared to those present during the stable natriuresis immediately preceding the reduction of blood flow. In six of these experiments the reduction in sodium excretion was not accompanied by an equivalent reduction in filtered sodium. Therefore, in these six studies increased net tubular reabsorption of sodium occurred in the presence of mild aortic constriction during saline loading. This increased reabsorption of sodium was associated with increased E_{PAH} and decreased noncortical plasma flow (first constriction, experiment 13, Table IV; left side of Figure 5). GFR, C_{PAH}, and sodium excretion in the contralateral kidneys were unchanged during the periods of inter-renal aortic constriction.

In eight experiments additional aortic constriction (aortic pressure, 40 to 60 mm Hg) during saline loading reduced filtered sodium to rates clearly below the presaline loading control values at a time when excreted sodium was equal to or greater than the preloading values. Thus, in these eight experiments it was demonstrated that net tubular reabsorption of sodium was decreased below that present before saline loading. In all eight of these experiments (during increased aortic constriction) E_{PAH} remained lower than the presaline loading control values, and noncortical plasma flow remained greater than control in all but one experiment. In this single experiment (last experiment, right side of Figure 5) sodium excretion was reduced to rates only slightly different from the preloading control, and although noncortical plasma flow did not remain increased,

E_{PAH} remained less than control (.773 compared to .814). These results are summarized in the right-hand portion of Figure 5, and details of three experiments are given in Table IV (second constriction, experiments 13 and 14, and experiment 15).

Control observations. To establish that the changing extractions of PAH were not related to some unrecognized systematic error in the measurement of PAH, extraction ratios of PAH and Diodrast I^{131} or Hippuran I^{131} were measured simultaneously in five experiments. These results are summarized in Table V. Both the extraction and clearance of Hippuran I^{131} were 5 to 12% less than simultaneous determinations of PAH. However, the changes in extraction and clearance during saline loading were parallel for the two substances. $E_{Diodrast}$ was 1 to 9% greater than simultaneously measured E_{PAH}, but parallel changes in the extraction of these two substances also occurred during saline loading.

TABLE V

*Simultaneous measurements of extraction ratio and renal blood flow using PAH and I^{131} Diodrast or Hippuran**

	Extraction ratio		$E_{I^{131}}$	RPF		RPF (I^{131})
	PAH	I^{131}	E_{PAH}	PAH	I^{131}	RPF (PAH)
				ml/min		
Control	0.620	0.628†	1.01	100	100†	1.00
Saline loading	0.291	0.319	1.09	186	195	1.05
Control	0.765	0.805†	1.05	180	174†	0.97
Saline loading	0.677	0.741	1.09	429	404	0.94
Control	0.825	0.777‡	0.94	113	106‡	0.94
Saline loading	0.786	0.747	0.95	165	159	0.96
Postload	0.840	0.777	0.93	125	120	0.96
Control	0.826	0.726‡	0.88	177	164‡	0.93
Saline loading	0.669	0.627	0.94	368	368	1.00
Postload	0.830	0.732	0.88	188	178	0.95
Control	0.810	0.735‡	0.91	109	§	
Saline loading	0.741	0.657	0.89	224		
Postload	0.805	0.714	0.89	180		

* Each value is the mean of three or four consecutive collection periods from the left kidney only. Additional abbreviation: RPF = total renal plasma flow.
† Diodrast–I^{131}.
‡ Hippuran–I^{131}.
§ Radioactivity in urine samples not measured.

Even though arterial concentrations of PAH in the present studies (0.5 to 2.5 mg per 100 ml) were well below expected Tm values, the possibility was considered that during saline loading the tubular transport maximum for PAH was approached or exceeded, thereby resulting in the observed decreased extraction ratios. This possibility was examined in three different ways: *1)* Tm_{PAH} was determined before and during saline loading in two experiments under precisely the same conditions as in all other experiments. Before saline loading these values averaged 4.6 and 7.5 mg per minute (left kidney only), and during saline loading the respective values were 5.3 and 6.4 mg per minute. These values of Tm_{PAH} are well above the tubular load of PAH (usually less than 1.5 mg per minute per kidney) employed in the present studies. *2)* If the decreased extraction ratios during saline loading were due to an approach toward the transport maxima, then an increase in the tubular load of PAH during saline loading should result in a further decrease in E_{PAH}. In two experiments the rate of infusion of PAH was changed approximately twofold, both before and after saline loading. E_{PAH} decreased during saline loading, but at these low rates of infusion of PAH no relationship between tubular load and E_{PAH} was observed, either before or during the saline load. *3)* The measurement of isotopic tracer amounts of the transported substance, in the absence of significant chemical concentrations, should eliminate the influence on the extraction ratio of even large changes in transport maxima. In two experiments the extraction of tracer amounts of Diodrast-I^{131} was measured without the simultaneous infusion of PAH (first experiment, Table II, and first two experiments, Figure 1). $E_{Diodrast\text{-}I^{131}}$ was decreased during saline loading in exactly the same manner as was chemically measured PAH in all other experiments.

Another possibility considered was that during saline loading, increases in capillary and interstitial volume (and perhaps other unrecognized factors) may impose a diffusion barrier that limits the access of PAH to the cellular sites of transport. If the extraction of PAH (from renal cortical blood) is near 100% before saline loading, but becomes limited by diffusion during saline loading, then a larger (more slowly diffusing) transported molecule should be affected to a greater extent than PAH. However, this was not the case in the two experiments in which the extractions of Diodrast (mol wt, 510) and PAH (mol wt, 194) were measured simultaneously. The ratio of $E_{Diodrast}/E_{PAH}$ was not decreased during saline loading (Table V). Furthermore, E_{PAH} remained depressed during saline loading despite reductions of blood flow to values less than control (experiment 15, Table IV). This latter

observation makes it unlikely that increased blood flow per se limits the extraction of PAH.

Discussion

The present studies provide further demonstrations of the dissociation that may occur spontaneously between the filtered load of sodium and the rate of sodium excretion during saline loading in the dog (1, 2). In four of seven experiments the fall in sodium excretion after discontinuing the infusion of saline clearly exceeded the fall in filtered sodium. In five experiments of the series, no increase in GFR and filtered sodium occurred during saline loading, despite large increases in sodium excretion. Thus changes in the net tubular reabsorption of sodium during saline loading were evident spontaneously in nine of the present experiments. Also, the present studies employing aortic constriction provide additional demonstrations of decreased tubular reabsorption of sodium during saline loading, by means of controlled reductions in the filtered load of sodium (1, 3–6). The changes in tubular reabsorption of sodium observed both spontaneously and during aortic constriction were accompanied by consistent changes in E_{PAH} and renal blood flow. Decreases in tubular reabsorption of sodium were associated with decreases in E_{PAH} and, in all but one instance, increases in noncortical plasma flow. Conversely, increases in sodium reabsorption were accompanied by increased E_{PAH} and decreased noncortical plasma flow. Although increases in total renal blood flow were present during most observations of decreased tubular reabsorption of sodium, this was not true in all experiments. In some studies decreased tubular reabsorption of sodium accompanied by decreased E_{PAH} and increased noncortical plasma flow was observed in the presence of reduced C_{PAH} and total renal blood flow.

Mild unilateral reductions in renal perfusion pressure during saline loading resulted in increased E_{PAH} and reduced renal blood flow accompanied by immediate large decreases in sodium excretion without equivalent decreases in filtered sodium. Sodium excretion and reabsorption were unaffected in contralateral control kidneys. These observations provide strong evidence that diminution in renal blood flow may result in increased net tubular reabsorption of sodium through intrarenal mechanisms. During more marked aortic constriction the maintained decreases in E_{PAH} and continued increases in noncortical plasma flow in the presence of decreased tubular reabsorption of sodium (as compared to presaline loading values) also demonstrated an inverse relationship between tubular reabsorption and renal blood flow. However, the latter observations do not eliminate the possibility that the diminished tubular reabsorption of sodium resulted from extrarenal factors initiated by saline loading, and that the observed hemodynamic changes are incidental and not related causally to the diminished reabsorption of sodium.

The factors determining the renal extraction ratio for PAH are not entirely understood. It has been suggested that blood leaving juxtamedullary glomeruli and passing into the vasa recta does not perfuse sufficient cortical convolutions to allow complete extraction of Diodrast, PAH, and other derivatives of hippuric acid, and that this factor accounts in part for the failure of the kidney to completely extract these substances (13–16). The anatomy of the medullary circulation is consistent with this premise (17). However, Thurau has reported that during antidiuresis the concentration of PAH in blood collected from vasa recta by micropuncture may be 4 to 12 times as great as the concentration of PAH in arterial blood (18). Since the concentration of PAH in vasa recta blood was not found to be low (as expected in renal venous blood), these latter findings are not inconsistent with the possibility that PAH is not removed from blood perfusing the renal medulla. Such observations (18) could be explained by a "leak" of PAH from collecting duct or Henle's loop into vasa recta. However, it would not appear that such a leak of PAH from tubular lumen into capillary could explain the present changes in E_{PAH}, since E_{PAH} decreased during diuresis at a time when tubular fluid concentrations would be lower and net loss into blood should be less.

That the extraction of PAH and similarly transported organic compounds may represent in part the distribution of blood between the renal cortex and medulla remains a distinct possibility. Some support for this concept is afforded by the present observations. Thurau and Deetjen have suggested that renal medullary blood flow is not autoregulated and therefore is affected more readily than cortical blood flow by changes in perfusion pressure (19). Such a relationship between perfusion pressure and medullary blood flow could account for the increases in E_{PAH} observed during aortic constriction in the present studies. Re-

duced perfusion pressure would produce a relatively greater decrease in medullary blood flow than in cortical blood flow. If PAH is not extracted from blood perfusing the medulla (except to the extent of filtration through juxtamedullary glomeruli), then the maintenance of cortical blood flow as medullary flow decreased would result in a rise in E_{PAH} as was observed in the present experiments.

No evidence could be obtained in the present study that the ability to transport PAH was diminished during saline loading. This is in contrast to the report of Levy and Ankeney that Tm_{PAH} decreased during hypertonic saline loading (20). On the other hand, Mudge and Taggart (21) found no decrease in Tm_{PAH} in dogs infused with isotonic saline in amounts sufficient to increase urine flow and GFR. Also, it did not appear likely in the present studies that diffusion from blood to the cellular transport sites was a limiting factor in determining E_{PAH} during saline loading. The possibility that the changes in extraction of PAH, Diodrast, and Hippuran were in some way related to the changes in the rate of urine flow that accompanied saline loading cannot be excluded, but seems unlikely. As discussed above, any leak of PAH from tubular lumen back into blood should be greater at low urine flows than at high urine flow when the tubular fluid concentration of PAH is lower. It is possible, however, that the permeability of the tubule to these substances is greater during saline loading, and the loss from tubule to blood thereby increased. It has been suggested that E_{PAH} less than 100% may be due to the perfusion of renal capsule, hilar adipose tissue, and other "nonfunctioning" renal structures (17). Although the entry of such blood into the renal vein may account in part for extraction ratios less than 100%, it appears unlikely that such blood flow could account for the striking decreases in E_{PAH} observed in the present studies. This noncortical plasma flow averaged 32 ml per minute per kidney before saline loading and increased to 116 ml per minute per kidney during saline loading. It is suggested, therefore, that the decreased E_{PAH} during saline loading may reflect in part a relative increase in medullary blood flow. Since total renal blood flow increased during saline loading in every experiment, the decreased E_{PAH} also could represent an absolute increase in medullary blood flow.

The mechanisms whereby increases in renal blood flow, and more specifically increases in noncortical plasma flow, may decrease the net tubular reabsorption of sodium are only speculative. If, as suggested above, renal plasma flow from which PAH is not extracted represents in part medullary blood flow, then the present studies provide evidence that net reabsorption of sodium may change inversely with changes in medullary blood flow. This interpretation of the present data supports the earlier suggestion that increases in medullary blood flow during saline loading may diminish sodium reabsorption. In a previous report from this laboratory (6) it was suggested that an increased medullary blood flow during saline loading may result in decreased medullary hypertonicity, a decreased passive reabsorption of water from the descending limb of Henle's loop, and consequently the delivery of a larger volume of tubular fluid with a lower sodium concentration to the ascending limb of Henle's loop. This increased rate of flow of more dilute fluid past the transport sites of the ascending limb could then result in a decreased net reabsorption of sodium at these sites. In addition, this premise requires, *1*) that the rate of transport by the ascending limb is not influenced to a great extent by the transtubular gradient of sodium concentration, but transport at this site does relate in some direct fashion to the absolute concentration of sodium in the tubular fluid, and *2*) that increases in medullary blood flow decrease medullary interstitial hypertonicity and passive water reabsorption from the descending limb of Henle's loop. The first of these requirements should obtain if the back leak of sodium into the ascending limb is negligible, and if some diffusion barrier separates the luminal sodium from the active transport site. The second requirement would appear to be on sound theoretical grounds (22–24). The large increases in sodium excretion observed in the present studies (as great as 14% of the filtered load, in the absence of increased GFR) render it likely that the reabsorption of sodium may be diminished in other portions of the nephron during saline loading. If proximal reabsorption is diminished during saline loading, an increased medullary blood flow could contribute to increased sodium excretion (through the above mechanism) by limiting reabsorption by the loops of the increased delivery of sodium from the proximal convolution.

Alternatively, the decreases in E_{PAH} occurring during saline loading may represent a relative increase in both medullary blood flow and juxtamedullary glomerular filtration. If the reabsorptive capacity for sodium of juxtamedullary nephrons is exceeded during such a redistribution of filtrate, changes in net reabsorption of the total filtered load of sodium could occur without an actual diminution of tubular reabsorptive capacity. This appears somewhat unlikely, since in some of the present studies saline loading resulted in no change in GFR, which would require that the increased filtration by some glomeruli was exactly balanced by a decreased filtration through other glomeruli. In addition, the possibility cannot be excluded that increases in renal blood flow (or an intrarenal redistribution of blood as suggested by the present observations) may affect tubular reabsorption of sodium through other unidentified intrarenal mechanisms.

These results do not provide evidence to suggest the mechanism whereby such a change in the intrarenal distribution of blood may occur during saline loading. Arterial pressure usually was not increased during saline loading, and this is consistent with previous reports that saline loading in the dog may not increase arterial blood pressure (25). However, the large increases in renal blood flow that occur (in the absence of increased perfusion pressure) would require that the resistance to blood flow through the kidney be strikingly diminished during saline loading. In the present experiments the arterial hematocrit was reduced to a mean value of 27 (control mean, 40), and this could be a factor that both decreases the resistance to blood flow (26) and affects the distribution of blood within the kidney (27). Acute reductions in the hematocrit are known to be associated with reductions in E_{PAH} (26–28), but such studies have not provided information on filtered and excreted sodium. Also, expansion of the plasma volume with albumin may decrease E_{PAH} (16, 29, 30), and Elpers and Selkurt (16) have suggested that this may represent an increase in medullary blood flow. These latter authors reported a mean decrease in excreted sodium as E_{PAH} decreased during albumin infusion; however, these latter observations were made during saline infusion, and individual details of GFR and sodium excretion were not reported.

Summary

The effects of isotonic expansion of the extracellular volume on filtered and excreted sodium, renal blood flow, and extraction ratios of *p*-aminohippurate (PAH), Diodrast, and Hippuran were studied in anesthetized dogs. During saline loading renal blood flow increased and the extraction ratio of PAH (E_{PAH}) decreased. In some experiments spontaneous changes in the net tubular reabsorption of sodium were observed during the course of saline loading. Changes in net tubular reabsorption of sodium during the natriuresis of saline loading could be demonstrated also by unilateral reduction of renal blood flow. Decreased reabsorption of sodium was always accompanied by decreased E_{PAH} and increased renal blood flow, whereas increased reabsorption was accompanied by increased E_{PAH} and decreased blood flow.

The fall in E_{PAH} during saline loading did not appear to be due to diminished ability to transport the substance, and it is suggested that the changes in the extraction ratio may relate in part to changes in noncortical plasma flow, which could include medullary blood flow. A causal relationship may exist between these hemodynamic changes and the associated changes in sodium reabsorption. These observations are consistent with the suggestion that diminished net tubular reabsorption of sodium during saline loading may relate in part to an increased medullary blood flow.

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Addendum

Dirks, Cirksena, and Berliner have recently reported that isotonic saline loading in the dog is associated with large decreases in fractional reabsorption in the proximal convolution, and that these changes persist in the presence of reduced glomerular filtration (31). If such changes in proximal reabsorption by cortical nephrons accessible to micropuncture are representative of the total nephron population, then it is unnecessary to postulate that saline loading diminishes the reabsorption of sodium in more distal portions of the nephron as discussed in the text of this report. In view of the findings of these latter authors and the present observations, more emphasis should be given to the possibility that proximal tubular reabsorption of sodium may be regulated in part by some indirect intrarenal mechanism and that a change in blood flow is a factor affecting such a regulatory system.

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