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Research Article

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The Influence of Salt Intake on the Metabolic Acidosis of Chronic Renal Failure

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ABSTRACT The influence of dietary salt on the levels of plasma bicarbonate and on the characteristics of bicarbonate reabsorption was studied in experimental chronic renal failure. Chronic renal failure was produced in rats by sequential partial nephrectomies. The control group received a diet constant in salt content throughout the progression of renal failure; the other group (PRNa), at each stage of renal failure, received salt intake reduced in direct proportion to the fall in glomerular filtration rate (GFR). In the steady state, the quantities of urinary sodium closely approximated intake in both groups of animals. The adaptive increased natriuresis per nephron exhibited by the control animals was prevented in the PRNa animals. The PRNa group had (*a*) higher plasma bicarbonate levels, (*b*) increased bicarbonate thresholds, and (*c*) increased maximal tubular reabsorptive capacity for bicarbonate.

As renal failure progresses, dietary salt can become a determining factor of the levels at which plasma bicarbonate is maintained. Proportional reduction of dietary salt results in bicarbonate conservation in rats with experimental progressive renal failure.

INTRODUCTION

Bicarbonate deficit and metabolic acidosis are common complications of chronic progressive renal failure (1, 2). Since in both normal and in uremic states, there is a direct association between sodium and bicarbonate reabsorption by the kidney (3–6), it is possible that as renal failure progresses, the quantities of dietary salt may substantially influence the mechanisms regulating bicarbonate homeostasis. This study was designed therefore to investigate the influence of dietary salt on the steady-state plasma bicarbonate concentrations and on the characteristics of bicarbonate reabsorption in experimental chronic renal failure. The experiments were performed in rats in which chronic renal failure was produced by sequential partial nephrectomies. One group received a diet constant in salt content throughout the progression of renal failure; the other group (PRNa),[1] at each stage of renal failure, received salt intake reduced in direct proportion to the fall in glomerular filtration rate (GFR) (7). Sodium balance was evaluated on the days preceding the bicarbonate infusion experiments. Bicarbonate titration experiments were performed by a standard technique that minimized extracellular fluid (ECF) volume expansion (4).

METHODS

Experimental animals. Experiments were performed on female Sprague-Dawley rats of the Holtzman strain weighing between 250 and 300 g. Chronic renal failure was produced by sequential partial nephrectomies in three stages separated by an interval of at least 2 wk. Stage IIA consisted of the removal of approximately 75% of the left kidney; stage IIB, 75% of the right kidney; and stage III, removal of remnant right kidney.

Balance studies. The animals were divided into two groups. The control group was maintained on constant dietary salt intake throughout the progression of chronic renal failure. The experimental group (PRNa) received a proportional reduction in sodium chloride intake at each fall in GFR. Dietary sodium was administered in the following doses: (*a*) Control: 2.50 meq/day (0.75 meq with each morning and evening meal and 1 meq at separate noon feedings); (*b*) PRNa: stage IIA, 2.00 meq/day; stage IIB, 1.00 meq/day; stage III, 0.25 meq/day. As in the control animals, the NaCl dose was divided into three separate feed-

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[1] *Abbreviations used in this paper:* ECF, extracellular fluid; FE_{Na}, fractional sodium excretion; GFR, glomerular filtration rate; PRNa, experimental rats, with salt intake reduced in proportion to fall in GFR; $U_{Na}V$, rate of sodium excretion.

ings and reduced within the first 24 h after the designated removal of renal mass. The animals were pair fed a synthetic sodium-free diet to which NaCl was added according to the stipulations of the protocol. The diet (ICN Nutritional Biochemicals Division, International & Nuclear Corporation, Cleveland, Ohio) has the following composition: 20% casein, 8% corn oil, 67% dextran, and 4% sodium-free salt mixture and supplementary vitamins. Each animal received a total of 16 g of this diet daily; each 8 g homogenized in 10 ml of a distilled water-sodium chloride solution given directly through a gastric tube at morning and evening. The sodium content of the diet was measured frequently. The animals were kept in metabolic cages, and urine was collected daily for volume and sodium determinations.

Control and bicarbonate titration studies. All studies were performed on the unanesthetized animal at the final stage (III) of reduction of renal mass. The preparation of the animals for these procedures has been described by others previously (8). The rat was lightly anesthetized with ether to allow for insertion of arterial, venous, and bladder catheters. After the animal was placed on the plastic restraining device, a period of 90–120 min was allowed for complete recovery from the anesthesia. Thereafter, an [^{14}C]inulin priming dose and sustaining infusion was begun, and after a period of 60 min for equilibration, observations were made during three successive control periods, each lasting 30 min. Bicarbonate titration experiments were performed utilizing a standard technique in which ECF volume expansion was minimized (4). Observations were made over a range of plasma bicarbonate concentrations extending from values as low as 5 μeq/ml to values as high as 50 μeq/ml. The sustaining infusions contained a sodium concentration of 140 μeq/ml. The rate of bicarbonate administration was adjusted by increasing the bicarbonate concentration of the infusate progressively from 0 to 120 μeq/ml. The concentration of chloride, the only other anion, was changed reciprocally. 15 to 20 clearance periods, each 30 min in duration, were obtained. As many as three clearance periods were obtained at each level of bicarbonate infusion. The sustaining solutions containing sodium bicarbonate, sodium chloride, and inulin were infused at a rate of 0.028 ml/min. Before each increment of bicarbonate infusion, a single injection of 0.45 meq of bicarbonate was infused in a volume of 0.3 ml. An equilibration period of at least 15 min was allowed after initiation of each new sustaining solution. All urine samples were collected under oil, and blood samples were obtained directly from the indwelling femoral arterial cannula. The pH and P_{CO_2} determinations were made immediately after collection of blood and urine with an Instrumentation Laboratory Microgas Analyzer (Radiometer Model BMS3; Instrumentation Laboratory, Inc., Lexington, Mass.). Bicarbonate concentrations in urine and plasma were calculated with the Henderson-Hasselbalch equation with a pK′ value of 6.1 and an α value of 0.0301 for plasma. An α value of 0.0309 was used for urine, and pK′ values were calculated for each urine sample by the formula $pK' = 6.33 - 0.5 \times \sqrt{B}$, where B represents the total cation concentration estimated as the sum of sodium concentration plus potassium concentration. Bicarbonate reabsorption was calculated as the difference between the amount filtered and the amount excreted. A Donnan factor of 1.05 was employed for estimating the concentration of bicarbonate in the ultrafiltrate. GFR was measured with [*carboxyl*-^{14}C]inulin. A priming dose of 1 μCi of [^{14}C]inulin was followed by a sustaining solution to provide counting rates at least 10 times greater than background in a 10-μl sample of plasma. [*carboxyl*-^{14}C]inulin was counted in a Packard Tri-Carb liquid scintillation counter (Packard Instrument Co., Inc., Downers Grove, Ill.). Sodium was measured with a flame photometer. The sodium content of the diet was determined in nitric acid extracts.

Statistical significance was determined by the Student's t test.

RESULTS

Table I presents the details of a bicarbonate titration study performed in a control animal maintained on a constant dietary salt intake throughout the progression of renal failure. During the control periods, the GFR averaged 0.29 ml/min, the rate of sodium excretion ($U_{Na}V$), 2.47 μeq/min, with a corresponding fractional excretion of sodium (FE_{Na}), 6.48. Plasma bicarbonate averaged 11.3 μeq/ml, and the rate of bicarbonate excretion ($U_{HCO_3}V$) was less than 0.01 μeq/min. During the bicarbonate infusion, the plasma bicarbonate rose from 13.0 to 42.0 μeq/ml. The arterial P_{CO_2} oscillated between 24 and 28 mm Hg. Bicarbonate reabsorption increased from 12.5 to 27.0 μeq/ml GFR, and the $U_{HCO_3}V$ increased from 0.02 to 5.82 μeq/min. Increase in $U_{HCO_3}V$ was observed immediately after the infusion of bicarbonate was begun. These losses occurred at plasma bicarbonate levels below the normal range, continued, and became more accentuated as the levels were raised progressively. The $U_{Na}V$ increased from 2.30 to 7.80 μeq/min, with a corresponding change in FE_{Na} from 8.85 to 20.53. Hence, there was a parallel increase in the rates of bicarbonate and sodium excretion.

Table II presents a typical bicarbonate titration study in a PRNa animal, in which increased natriuresis was prevented by reducing dietary salt intake in direct proportion to the fall in GFR. The average GFR for the control periods was 0.20 ml/min. The $U_{Na}V$, 0.16 μeq/min, and the corresponding FE_{Na}, 0.60, were substantially lower than the values of the control animal. In addition, at a plasma bicarbonate of 17 μeq/ml, no bicarbonate appeared in the urine. When bicarbonate was infused, the plasma concentration increased from 17.5 to 43.0 μeq/ml. The arterial P_{CO_2} oscillated between 28 and 36 mm Hg. The bicarbonate reabsorption increased from 17.5 to 40.0 μeq/ml GFR. A slow progression of bicarbonate excretion began at a plasma bicarbonate of 19.0 μeq/ml; however, excretion only became substantial at plasma levels above 24.5 μeq/ml, at which level the rate of sodium excretion had increased to 0.95 μeq/min, with a corresponding FE_{Na} of 2.71. Thus, the increase in bicarbonate excretion began at higher plasma bicarbonate levels than in the control animal and became substantial only when the $U_{Na}V$ had increased significantly from the control periods.

TABLE I

A Bicarbonate Titration Study in a Control Animal

Clearance period	Time	GFR	Plasma			Urine			HCO_3 reabsorption		HCO_3 excretion		$U_{Na}V$	FE_{Na}
			pH	P_{CO_2}	HCO_3	pH	P_{CO_2}	HCO_3						
	min	*ml/min*		*mm Hg*	*μeq/ml*		*mm Hg*	*μeq/ml*	*μeq/min*	*μeq/ml GFR*	*μeq/min*	*μeq/ml GFR*	*μeq/min*	%
1	0–30	0.29	7.31	19.0	10.0	5.80	10.0	0.13	2.90	10.0	0.00	0.00	2.50	6.63
2	30–90	0.29	7.35	20.0	12.0	6.00	12.0	0.26	3.48	12.0	0.01	0.03	2.47	6.55
3	90–120	0.30	7.36	21.0	12.0	6.20	10.0	0.34	3.60	12.0	0.01	0.03	2.44	6.26
120–40 min: prime 0.3 ml, 1.5 M $NaHCO_3$ (0.45 meq HCO_3^-), sustaining solution containing $NaHCO_3$ 45 meq/liter at 0.028 ml/min.														
4	140–170	0.20	7.36	24.0	13.0	6.28	11.0	0.41	2.50	12.5	0.02	0.10	2.30	8.85
5	170–200	0.28	7.37	25.0	14.0	6.51	18.0	1.13	3.64	13.0	0.07	0.25	2.60	7.14
6	200–230	0.32	7.35	27.0	14.5	6.66	14.0	1.28	7.48	14.0	0.09	0.28	3.40	3.65
230–250 min: prime 0.3 ml, 1.5 M $NaHCO_3$ (0.45 meq HCO_3^-), sustaining solution containing $NaHCO_3$ 45 meq/liter at 0.028 ml/min.														
7	250–280	0.40	7.44	28.0	17.0	6.68	16.0	1.53	6.40	16.0	0.12	0.38	3.55	6.34
8	280–310	0.25	7.44	28.0	18.5	6.70	18.0	1.82	4.25	17.0	0.08	0.32	3.71	10.60
9	310–340	0.28	7.59	23.0	21.5	7.01	19.0	4.10	5.32	19.0	0.20	0.71	3.71	9.45
340–360 min: prime 0.3 ml, 1.5 M $NaHCO_3$ (0.45 meq HCO_3^-), sustaining solution containing $NaHCO_3$ 60 meq/liter at 0.028 ml/min.														
10	360–390	0.36	7.67	20.0	23.0	7.40	19.0	10.33	7.49	20.8	0.48	1.33	3.70	7.34
11	390–420	0.30	7.60	25.0	24.0	7.44	19.0	11.46	6.42	21.4	0.69	2.30	3.80	9.05
12	420–450	0.30	7.73	19.0	25.0	7.55	20.0	15.66	6.60	22.0	0.78	2.60	3.90	9.29
450–470 min: prime 0.3 ml, 1.5 M $NaHCO_3$ (0.45 meq HCO_3^-), sustaining solution containing $NaHCO_3$ 60 meq/liter at 0.028 ml/min.														
13	470–500	0.29	7.71	22.0	28.0	7.68	17.0	17.87	6.96	24.0	0.97	3.34	4.00	9.85
14	500–530	0.28	7.74	22.0	30.0	7.70	22.0	24.52	7.00	25.0	1.23	4.39	4.20	10.71
15	530–560	0.27	7.75	23.0	32.0	7.75	20.0	25.39	6.89	25.5	1.52	5.63	4.50	11.90
560–580 min: prime 0.3 ml 1.5 M $NaHCO_3$ (0.45 meq HCO_3^-), sustaining solution containing $NaHCO_3$ 120 meq/liter at 0.028 ml/min.														
16	580–610	0.25	7.77	24.0	35.0	7.81	21.0	30.51	6.60	26.4	2.10	8.40	5.60	14.60
17	610–640	0.20	7.85	22.0	39.0	8.10	24.0	69.22	5.40	27.0	3.46	17.30	6.00	18.70
18	640–670	0.24	7.92	20.0	42.0	8.20	26.0	97.07	6.48	27.0	5.82	24.25	7.80	20.53

Rat wt, 290 g. At −160 min, the rat was put under light ether anesthesia to insert the jugular vein and femoral artery cannulas and bladder catheter and to position the animal in the holder. This lasted 30 min. At −60 min, a priming solution of 1 μCi [^{14}C]inulin in 0.5 ml normal saline and a sustaining solution containing 0.75 μCi [^{14}C]inulin/ml normal saline at 0.28 ml/min were given.

Fig. 1 depicts the characteristics of bicarbonate reabsorption for all animals. The control group presented a restriction in bicarbonate reabsorption beginning at plasma bicarbonate levels as low as 8 μeq/ml, with subsequent stabilization of the maximal capacity between 16 and 34 μeq/ml. The PRNa group, in contrast, followed closely the line of 100% reabsorption with slight restriction beginning only at 26 μeq/ml.

Fig. 2 depicts the quantities of bicarbonate appearing in the urine with increasing concentrations of plasma bicarbonate for both groups of animals. In addition to the difference observed between the bicarbonate thresholds, at each level of plasma bicarbonate the excretion rates were greater in the control group of animals than in the PRNa group.

Table III presents comparative data for both groups of animals for plasma pH, P_{CO_2}, and characteristics of bicarbonate and sodium excretion during the control periods and during periods of bicarbonate diuresis. There was no significant difference in GFR between the two groups of animals during the control periods. A significant difference, however, was observed in the levels of plasma bicarbonate, with an average for the controls of 10.1±1.2, as compared with the PRNa's, averaging 14.3±0.6 μeq/ml ($P < 0.01$). Bicarbonate losses were not observed in either group. The control animals had a P_{CO_2} of 20.0, and the PRNa animals, 27.1 mm Hg. These changes in P_{CO_2} represent appropriate respiratory compensation for the degree of metabolic acidosis. Similarly, the rate and fractional excretion

TABLE II

A Bicarbonate Titration Study in an Experimental (PRNa) Animal

Clearance period	Time	GFR	Plasma			Urine			HCO_3 reabsorption		HCO_3 excretion		$U_{Na}V$	FE_{Na}
			pH	P_{CO_2}	HCO_3	pH	P_{CO_2}	HCO_3						
	min	*ml/min*		*mm Hg*	*μeq/ml*		*mm Hg*	*μeq/ml*	*μeq/min*	*μeq/ml GFR*	*μeq/min*	*μeq/ml GFR*	*μeq/min*	%
1	0–30	0.19	7.35	28.0	14.5	5.30	10.0	0.04	2.76	14.5	0.00	0.00	0.14	0.57
2	30–90	0.22	7.38	30.0	17.0	5.39	11.0	0.05	3.74	17.0	0.00	0.00	0.16	0.50
3	90–120	0.19	7.35	30.0	16.0	5.42	8.0	0.04	3.04	16.0	0.00	0.00	0.18	0.73
120–140 min, prime 0.3 ml 1.5 M $NaHCO_3$ (0.45 meq HCO_3^-), sustaining solution containing $NaHCO_3$ 45 meq/liter at 0.028 ml/min.														
4	140–170	0.21	7.36	32.0	17.5	5.10	15.0	0.03	3.66	17.5	0.00	0.00	0.26	0.88
5	170–200	0.19	7.36	35.0	19.0	5.53	14.0	0.09	3.61	19.0	0.01	0.05	0.32	1.20
6	200–230	0.25	7.40	35.0	21.0	5.50	15.0	0.09	5.25	21.0	0.01	0.04	0.34	0.97
230–250 min, prime 0.3 ml 1.5 M $NaHCO_3$ (0.45 meq HCO_3^-), sustaining solution containing $NaHCO_3$ 45 meq/liter at 0.028 ml/min.														
7	250–280	0.30	7.49	29.0	21.5	5.93	12.0	0.19	6.45	21.5	0.01	0.03	0.45	1.07
8	280–310	0.25	7.49	33.0	24.5	6.05	14.0	0.30	6.13	24.5	0.03	0.12	0.95	2.71
9	310–340	0.18	7.53	31.0	25.5	6.09	12.0	0.28	4.50	25.0	0.03	0.17	1.10	4.40
340–360 min, prime 0.3 ml 1.5 M $NaHCO_3$ (0.45 meq HCO_3^-), sustaining solution containing $NaHCO_3$ 60 meq/liter at 0.028 ml/min.														
10	360–390	0.15	7.52	35.0	28.0	6.25	17.0	0.63	4.19	27.0	0.04	0.27	1.30	6.19
11	390–420	0.20	7.59	32.0	30.0	6.25	24.0	0.80	5.90	29.0	0.05	0.25	1.20	4.14
12	420–450	0.30	7.65	28.0	30.5	6.45	27.0	1.19	9.00	30.0	0.13	0.43	1.65	3.92
450–470 min, prime 0.3 ml 1.5 M $NaHCO_3$ (0.45 meq HCO_3^-), sustaining solution containing $NaHCO_3$ 60 meq/liter at 0.028 ml/min.														
13	470–500	0.25	7.65	30.0	33.0	6.50	28.0	1.87	8.00	32.0	0.10	0.40	1.50	4.29
14	500–530	0.22	7.63	36.0	36.0	6.91	38.0	7.09	7.48	33.0	0.61	2.77	1.80	5.14
15	530–560	0.19	7.70	32.0	40.0	7.55	27.0	22.54	7.22	38.0	1.10	5.79	2.00	6.66
560–580 min, prime 0.3 ml 1.5 M $NaHCO_3$ (0.45 meq HCO_3^-), sustaining solution containing $NaHCO_3$ 120 meq/liter at 0.028 ml/min.														
16	580–610	0.18	7.75	31.0	43.0	7.81	21.0	30.51	7.20	40.0	1.90	10.55	2.10	7.24

Rat wt, 300 g. At −170 min, the rat was put under light ether anesthesia for 35 min to insert the jugular vein and femoral artery cannulas and the bladder catheter, and to position the animal in a holder. At −60 min, a priming, solution of 1 μCi [^{14}C]inulin in 0.5 ml normal saline and a sustaining solution containing 0.75 μCi [^{14}C]inulin/ml normal saline at 0.028 ml/min were given.

of sodium were significantly different: $U_{Na}V$, 2.06 and 0.20 μeq/min; FE_{Na}, 6.33 and 0.66 for controls and PRNa's, respectively ($P < 0.01$). During the bicarbonate diuresis, the levels of bicarbonate reabsorption were compared at plasma concentrations between 35 and 40 μeq/ml. For approximately the same levels of plasma bicarbonate, the controls excreted 16.4±3.4; whereas the PRNa's excreted 3.36±1.25 μeq/ml GFR of bicarbonate.

Table IV presents the sodium balance data of the five consecutive days before the bicarbonate titration experiments. The quantities of urinary sodium were close to dietary sodium in both groups of animals at the three stages of decrease in renal mass. Equally, body weights and rate of body weight gain were comparable for all animals.

DISCUSSION

The present study demonstrates, first, that constant dietary salt administered throughout the progression of experimental chronic renal failure is associated with a marked bicarbonate deficit; and second, that gradual reduction of dietary salt in direct proportion to the fall in GFR leads to (*a*) partial correction of the bicarbonate deficit, (*b*) increase in the threshold at which bicarbonate appears in the urine, and (*c*) increase in the maximal tubular reabsorptive capacity for bicarbonate.

The difference in the levels of plasma bicarbonate between the two groups of animals suggests that, as renal failure progresses, dietary salt becomes an important determinant of the levels at which plasma bicarbonate is maintained. Other factors that influence bicarbonate homeostasis were excluded in these experi-

TABLE III

Sodium and Bicarbonate Excretion

	GFR	Plasma pH	Plasma P_{CO_2}	Plasma HCO_3	Urine pH	Urine P_{CO_2}	Urine HCO_3 excretion		$U_{Na}V$	FE_{Na}
	ml/min		*mm Hg*	*μeq/ml*		*mm Hg*	*μeq/min*	*μeq/ml GFR*	*μeq/min*	%
					Control periods					
Control (8)	0.26	7.33	20.0	10.1	5.96	10.3	0.00	0.00	2.06	6.33
±SEM	0.02	0.01	2.4	1.2	0.09	1.7	0.00	0.00	0.17	0.52
PRNa (9)	0.23	7.34	27.1	14.3	5.73	8.3	0.00	0.00	0.20	0.66
±SEM	0.01	0.01	1.5	0.6	0.06	1.0	0.00	0.00	0.02	0.05
P value	NS	NS	0.05	0.01	0.05	NS	NS	NS	0.01	0.01
					Bicarbonate diuresis					
Control (6)	0.24	7.77	25.7	37.6	7.59	26.5	3.74	16.4	8.43	28.89
±SEM	0.02	0.04	2.2	0.4	0.15	1.9	0.83	3.4	1.28	5.24
PRNa (7)	0.31	7.66	33.7	36.6	6.98	22.6	0.67	3.36	3.03	11.71
±SEM	0.07	0.02	1.5	0.5	0.20	5.7	0.15	1.25	0.81	5.01
P value	NS	0.05	0.01	NS	0.05	NS	0.01	0.01	0.01	0.05

Values are means ± 1 SEM. Number of animals are in parentheses.

ments by keeping both groups of animals on the same diet, except for salt, on the same metabolic demands, and by allowing the same interval of time for adaptation to each stage of reduction of renal mass. The difference in the levels of plasma bicarbonate between the two groups of animals might be explained by the difference in the characteristics of bicarbonate reabsorption. In the animals that received a proportional reduction of salt, when plasma bicarbonate was progressively increased, a progressive increase in tubular bicarbonate reabsorption occurred throughout the normal range of plasma levels. In contrast, in the animals on a constant salt intake, despite initial lower plasma bicarbonate levels, bicarbonate reabsorption was depressed, beginning at plasma levels below the normal range. Thus, conservation of bicarbonate might account for the initial higher plasma bicarbonate concentrations in the PRNa group.

Two associated mechanisms, both related to sodium balance and maintenance of ECF volume, could explain

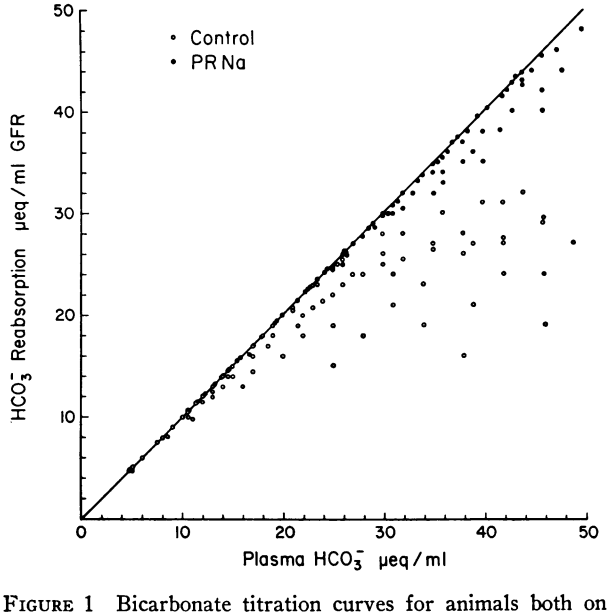

FIGURE 1 Bicarbonate titration curves for animals both on a constant (control) and proportional reduction of sodium intake (PRNa) at the final stage of progressive chronic renal failure.

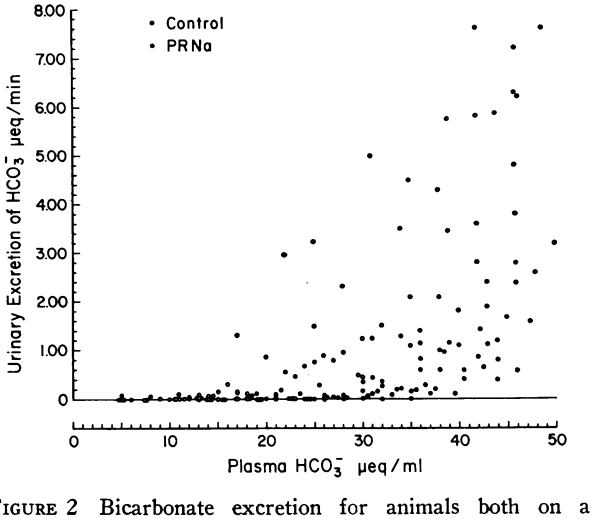

FIGURE 2 Bicarbonate excretion for animals both on a constant (control) and proportional reduction of sodium intake (PRNa) at the final stage of progressive chronic renal failure.

the differences in the levels of bicarbonate threshold. First, the animals on a constant salt intake might have retained sodium, with associated ECF volume expansion, before they entered the steady state conditions of sodium balance. This is suggested by the observation that in these animals during the bicarbonate diuresis there was a higher rise in the absolute and proportional rate of sodium excretion. The FE_{Na} rose from 6.33 to 28.89 in the constant salt intake group and from 0.66 to 11.71 in the PRNa group. Since ECF volume expansion restricts bicarbonate reabsorption (3–6), it is possible that constant salt produces relative ECF volume expansion and that, conversely, the proportional reduction of salt intake prevents the associated restriction of bicarbonate reabsorption. The second possibility arises from the observation that, in the steady-state conditions, the quantities of daily urinary sodium closely approximated the dietary intake in both groups of animals. Thus, the animals on constant salt presented the characteristic increased natriuresis per unit nephron of chronic renal failure. Since there is a direct association between the patterns of sodium and bicarbonate reabsorption (4–6), it is possible that the same mechanisms that result in an increased natriuresis per unit nephron also result in insidious urinary bicarbonate losses (9, 10). It is also possible that a combination of these two mechanisms could explain the difference in plasma levels and in the characteristics of bicarbonate reabsorption.

The response to the high bicarbonate doses necessary to elevate plasma levels above threshold further emphasizes the influence of salt intake on the characteristics of bicarbonate reabsorption in chronic renal failure. The PRNa animals exhibited a pattern similar to that described in normal rats in that they follow closely the line of 100% reabsorption (4). In contrast, the animals on a constant salt intake exhibited a reabsorptive maximum capacity similar to that described in chronically uremic rats (9).

It is concluded that in experimental chronic renal failure, reduction of dietary salt in direct proportion to the fall in GFR results in conservation of bicarbonate. This partial correction of the bicarbonate deficit may have therapeutic applications in the management of metabolic acidosis of chronic renal failure.

TABLE IV

Sodium Balance in Control and PRNa Groups at the Three Stages of Decrease in Renal Mass

	GFR	Intake	Urine	P_{Na}	Body wt	Average wt gain
	ml/min	*meq/day*	*meq/day*	*μeq/ml*	*g*	*g/day*
			Stage IIA			
Control (8)	2.20	2.50	2.35	135.0	275	1.20
±SEM	0.20		0.16	1.2	10	0.05
PRNa (9)	2.30	2.00	1.85	137.0	283	1.18
±SEM	0.36		0.10	0.7	12	0.10
			Stage IIB			
Control (8)	1.10	2.50	2.40	138.0	295	0.75
±SEM	0.15		0.20	0.3	13	0.18
PRNa (9)	0.98	1.00	0.90	137.6	302	0.80
±SEM	0.15		0.10	0.8	14	0.10
			Stage III			
Control (8)	0.26	2.50	2.38	135.0	300	0.30
±SEM	0.02		0.22	1.0	20	0.09
PRNa (9)	0.23	0.25	0.20	134.0	310	0.35
±SEM	0.01		0.10	0.9	18	0.13

P_{Na} = plasma sodium concentrations. Values are means ±SEM. Number of animals are in parentheses. Body weight given is for the last day of balance studies.

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REFERENCES

1. Seldin, D. W., N. W. Carter, and F. C. Rector, Jr. 1971. Consequences of renal failure and their management. *In* Diseases of the Kidney. M. B. Strauss and L. G. Welt, editors. Little, Brown and Company, Boston, Mass. 2nd edition. 211–272.
2. Schwartz, W. B., P. W. Hall, III, R. M. Hays, and A. S. Relman. 1959. On the mechanism of acidosis in chronic renal disease. *J. Clin. Invest.* **38**: 39–52.
3. Kunau, R. T., Jr., A. Frick, F. C. Rector, Jr., and D. W. Seldin. 1966. Effect of extracellular fluid (ECF) volume expansion, K^+ deficiency and P_{CO_2} on bicarbonate reabsorption in the rat kidney. *Clin. Res.* **14**: 380. (Abstr.)
4. Purkerson, M. L., H. Lubowitz, R. W. White, and N. S. Bricker. 1969. On the influence of extracellular fluid volume expansion on bicarbonate reabsorption in the rat. *J. Clin. Invest.* **48**: 1754–1760.
5. Kurtzman, N. A. 1970. Regulation of renal bicarbonate reabsorption by extracellular volume. *J. Clin. Invest.* **49**: 586–595.
6. Slatopolsky, E., P. Hoffsten, M. L. Purkerson, and N. S. Bricker. 1970. On the influence of extracellular fluid volume expansion and of uremia on bicarbonate reabsorption in man. *J. Clin. Invest.* **49**: 988–998.
7. Espinel, C. H., and N. S. Bricker. 1973. Prevention of increased natriuresis per nephron in uremic rats. *Clin. Res.* **21**: 75. (Abstr.)
8. Shankel, S. W., A. M. Robson, and N. S. Bricker. 1967. On the mechanism of the splay in the glucose titration curve in advanced experimental renal disease in the rat. *J. Clin. Invest.* **46**: 164–172.
9. Purkerson, M. L., H. Lubowitz, and N. S. Bricker. 1967. The genesis of the bicarbonate leak in chronic renal disease. *Clin. Res.* **15**: 367. (Abstr.)
10. Lubowitz, H., M. L. Purkerson, D. B. Rolf, F. Weisser, and N. S. Bricker. 1971. Effect of nephron loss on proximal tubular bicarbonate reabsorption in the rat. *Am. J. Physiol.* **220**: 457–461.