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Effects of metabolic acidosis and alkalosis on sodium and calcium transport in the dog kidney

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Effects of metabolic acidosis and alkalosis on sodium and calcium transport in the dog kidney. Clearance and micropuncture studies have been performed in dogs to examine the effects of acute and chronic metabolic acidosis and acute alkalosis on tubular sodium and calcium transport. Acute metabolic acidosis, induced by the infusion of hydrochloric acid, decreased proximal fluid reabsorption and increased the fractional delivery of sodium and calcium to the distal tubule, but not to the final urine. In comparison with normal dogs, dogs with chronic metabolic acidosis (induced by feeding ammonium chloride) showed an increase in proximal fluid reabsorption and a dissociation of calcium from sodium reabsorption more distally, leading to an increased delivery of calcium relative to sodium at the distal tubule and in the final urine. The infusion of sodium bicarbonate to correct chronic metabolic acidosis, both in intact and thyroparathyroidectomized (TPTX) dogs, reduced proximal fluid reabsorption and caused a selective enhancement of calcium reabsorption relative to sodium in the more distal nephron, resulting in a reversal of the dissociation observed in acidosis, both at the distal tubule and in the final urine. By contrast, infusion of sodium chloride in parathyroid-intact acidotic dogs did not reduce proximal fluid reabsorption or enhance tubular calcium reabsorption. In nonacidotic dogs, both intact and TPTX, infusion of sodium bicarbonate to induce acute alkalosis resulted in selective enhancement of calcium over sodium reabsorption in the distal nephron segments. These data demonstrate the presence of a component of tubular calcium reabsorption situated beyond the proximal tubule, which is inhibited by chronic (but not acute) metabolic acidosis and enhanced by metabolic alkalosis (or bicarbonate infusion) independently of parathyroid hormone.

Effets de l'acidose et de l'alcalose métaboliques sur le transport de sodium et de calcium par le rein de chien. Des expériences de clearances et de microponctions ont été réalisées chez des chiens pour étudier les effets de l'acidose et de l'alcalose métaboliques aiguës et chroniques sur les transports tubulaires du sodium et du calcium. L'acidose métabolique aiguë, déterminée par la perfusion d'acide chlorhydrique, diminue la réabsorption proximale et augmente les débits fractionnels de sodium et de calcium au tube distal, mais non dans l'urine définitive. Par comparaison avec des contrôles, les chiens en acidose métabolique chronique, déterminée par l'administration orale de ammonium chloride, ont une augmentation de la réabsorption proximale et une dissociation, en aval, des réabsorptions de calcium et de sodium, avec pour conséquence un débit fractionnel de calcium proportionnellement plus grand que celui de sodium au tube distal et dans l'urine définitive. La perfusion de sodium bicarbonate, en vue de la correction de l'acidose métabolique, chez le chien intact et thyroparathyroïdectomisé (TPTX), diminue la réabsorption proximale et détermine une augmentation sélective de la réabsorption de calcium par rapport à celle du sodium, dans le néphron d'aval, ce qui a pour conséquence une reversion de la dissociation observée dans l'acidose dans le tube distal et l'urine définitive. Au contraire, la perfusion de sodium chloride à des animaux en acidose, avec des parathyroïdes intactes, ne modifie pas la réabsorption proximale et n'augmente pas la réabsorption tubulaire de calcium. Chez les animaux sans acidose, intacts ou TPTX, la perfusion de sodium bicarbonate, afin de déterminer une alcalose aiguë, a pour conséquence une augmentation sélective de la réabsorption du calcium, par rapport à celle du sodium, dans les segments plus distaux des néphrons. Ces résultats démontrent la présence d'un composant de la réabsorption tubulaire du calcium, situé au delà du tube proximal, qui est inhibé par l'acidose métabolique chronique, mais non l'acidose métabolique aiguë, et augmenté par l'alcalose métabolique (ou la perfusion de bicarbonate) indépendamment de l'hormone parathyroïdienne.

Hypercalciuria has been shown to accompany metabolic acidosis from a variety of causes, including diabetic ketoacidosis [1], acidosis induced by diet [2, 3] and by ammonium chloride feeding [4], and postprandial acidosis related to salivation in the sheep [5]. Williamson and Freeman [6] observed hypercalciuria with acute ammonium chloride-induced acidosis in dogs, which they attributed to increased glomerular filtration of calcium. Lemann, Litzow, and Lennon [7], however, showed in man that hypercalciuria accompanied acidosis due to ammonium chloride or acetazolamide administration, despite a fall in filtered load of calcium. Furthermore, this hypercalciuria was not dependent on the presence of parathyroid or thyroid hormones. These authors considered that hypercalciuria resulted from a direct effect of acidosis on renal tu-

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bule cell metabolism. Similarly, Stacy and Wilson [5] showed that the hypercalciuria which accompanies hydrochloric acid infusion in the sheep occurred despite a fall in filtered calcium.

Metabolic alkalosis was noted by earlier workers to have variable effects upon calcium excretion [2, 8]. More recently, however, a reduction in calcium excretion has been reported after sodium bicarbonate ingestion [9, 10]. Transbol, Hahnemann, and Hornum [11] reported two patients with hypercalcemia and metabolic alkalosis in whom hypocalciuria apparently resulted from enhanced tubular reabsorption of calcium.

In view of this evidence that both metabolic acidosis and alkalosis may influence tubular reabsorption of calcium, we have performed micropuncture experiments in the dog to examine the segmental handling of sodium and calcium by the nephron in acute and chronic acidosis and acute metabolic alkalosis, and we have observed the effect of correcting chronic acidosis with sodium bicarbonate infusion on calcium reabsorption in both intact and thyroparathyroidectomized (TPTX) dogs. Sodium and calcium are normally handled similarly along the nephron [12, 13]. Furthermore, under conditions of diuresis, the excretion of calcium normally parallels that of sodium [14]. In our experiments involving the infusion of sodium bicarbonate to correct acidosis or induce alkalosis, we have produced reciprocal changes in sodium and calcium excretion; the individual changes, however, are frequently not statistically significant. We have therefore examined the effects of each maneuver on the relationship of calcium to sodium delivery at each nephron site to detect significant dissociations in the tubular handling of these ions. Our studies suggest that chronic metabolic acidosis selectively impairs the tubular reabsorption of calcium whereas bicarbonate administration selectively enhances calcium reabsorption at these sites, both in the presence and absence of parathyroid hormone.

Methods

Experimental groups. Six groups of two-phase micropuncture experiments were performed in mongrel dogs. Each dog weighed 11 to 16 kg.

Group I: Acute acidosis. Intact dogs were studied during a first phase which followed a volume expansion of 3% of the animal's body weight induced by an intravenous infusion of a Ringer's solution containing 3 mEq/liter calcium (calcium-Ringer's solution). During a second phase, an acute metabolic acidosis was induced with an infusion of 10 to 12 mEq/kg of hydrochloric acid given at a rate of 12 ml/min for 1 hour.

Group II: Chronic acidosis corrected with sodium bicarbonate. Intact dogs were made acidotic by feeding them ammonium chloride (10 g daily) for 3 days prior to the experiment. The first experimental phase followed a volume expansion of 3% of body weight induced by the infusion of the calcium-Ringer's solution. The second phase followed the correction of the acidosis with an intravenous infusion of a 0.5 M sodium bicarbonate solution administered at a rate of 3 ml/min for 1 hour.

Group III: Bicarbonate correction of chronic acidosis in TPTX dogs. The protocol was identical to that of group II except that the dogs were acutely thyroparathyroidectomized on the morning of the experimental day.

Group IV: Chronic acidosis and hypertonic saline. The protocol was identical to that of group II except that a 0.5 M sodium chloride solution was administered at a rate of 3 ml/min for 1 hour, instead of the 0.5 M sodium bicarbonate infusion given prior to the second phase. These animals were therefore still acidotic in the second phase.

Group V: Acute alkalosis. Intact dogs were studied during a first phase following a volume expansion of 3% of their body weight induced with an infusion of the calcium-Ringer's solution, and then during an acute metabolic alkalosis induced with the infusion of a 0.5 M sodium bicarbonate solution, given at a rate of 3 ml/min for 1 hour.

Group VI: Acute alkalosis in TPTX dogs. Dogs were acutely TPTX on the day of experiment. A volume expansion of 3% of their body weight was induced with the infusion of a 2.5% sodium chloride solution containing 3 mEq/liter of calcium administered before the control phase. This was followed by an intravenous infusion (3% body weight) of a 0.25 M sodium bicarbonate solution to induce a metabolic alkalosis prior to the second phase. The substantial volume expansion in the first phase in these experiments was introduced in an attempt to minimize further increases in sodium excretion during the second phase.

Micropuncture and analytical methods. These were described previously by this laboratory [15]. Dogs were anesthetized with sodium pentobarbital and ventilated through an endotracheal tube with a Harvard respiratory pump. Intravenous fluids were administered through a polyethylene catheter inserted into the jugular vein. Blood pressure was monitored via a femoral arterial catheter, and blood samples were taken via a femoral venous catheter.

Both ureters were cannulated via a suprapubic incision. The left kidney was prepared for micropuncture as previously described. Late proximal and random distal tubules were identified by FD&C green dye injected into the renal artery. Following surgery, a priming dose (0.4% body weight) and a sustaining infusion of inulin in saline solution were given to establish a plasma inulin concentration between 70 and 100 mg/100 ml. In experimental groups I to V, phase 1 was conducted in the volume-expanded animal following intravenous administration of Ringer's solution (3% body weight) containing 3 mEq/liter calcium to minimize changes in plasma ionized calcium concentration. The volume expansion prior to phase 1 was undertaken to minimize further changes in sodium excretion following sodium bicarbonate infusion. In group VI, 2.5% sodium chloride containing 3 mEq/liter calcium was used for the initial volume expansion. Volume expansion was maintained by quantitatively replacing the urinary fluid losses with the Ringer's solution. Following the collection of proximal and distal micropuncture samples and clearance samples, the intravenous fluid was changed, as described above, to hydrochloric acid (group I), sodium bicarbonate (groups II, III, V, and VI), or sodium chloride (group IV). One hour later, tubule fluid samples were recollected, and further clearance samples were obtained. In both phases, 15-min urine samples were collected from each kidney during the period of micropuncture, and blood samples were taken at the midpoint of each urine collection. The clearance results were similar for the two kidneys; only those from the left (micropunctured) kidney are reported.

The plasma protein concentration and the hematocrit were determined: plasma ultrafiltrates (UF) were prepared using Amicon Centriflo ultrafiltration cones. Plasma and urine samples were analyzed for inulin by the Anthrone method and for sodium and potassium by flame photometry. Plasma, ultrafiltrate, and urine were analyzed for calcium by atomic absorption spectrophotometry. Plasma pH and bicarbonate were determined with a pH-blood gas analyzer (Instrumentation Laboratory Inc., Boston, Massachusetts). The tubule fluid samples were analyzed for inulin with the fluorometric method of Vurek and Pegram [16] and for sodium and calcium by the helium glow photometer (Montreal Polycrafters, Montreal, Quebec) as previously described [15].

Analysis of data. Standard statistical methods were used, Student's t test being used to determine the significance of differences between phases.

Standard formulas were used to calculate the fractional delivery of filtered sodium and calcium to the puncture sites at the proximal and distal tubule and to the final urine. To demonstrate significant changes in the relationship between tubular sodium and calcium reabsorption along successive nephron segments, we have chosen to relate the fractional (percentage) delivery of calcium to that of sodium at the proximal tubule, distal tubule, and final urine before and after each experimental maneuver. For this regression analysis, data have been logarithmically transformed to make distributions approximate more closely to normal. The corresponding regressions have been determined and statistically compared (*a*) in the control phase of normal (groups I and V) and acidotic (groups II and IV) parathyroid-intact dogs, and (*b*) before and after the infusion of hydrochloric acid, sodium bicarbonate, or sodium chloride in groups I to VI. This statistical analysis was performed at the University of British Columbia computing center with the advice of Dr. M. Schulzer. The analysis was designed to take account of the nature of the comparison in each instance, whether between the same or different dogs, and in the case of the micropuncture data to make appropriate allowance for the varying numbers of tubules sampled in each dog. Probability values are provided for the comparison of slopes and intercepts in each instance. A change in the relationship of calcium to sodium delivery between successive nephron sites could result from changes in sodium reabsorption, in calcium reabsorption, or both, in the intervening segment. We have therefore calculated from the data provided in Tables 1 through 4 the mean fractional reabsorption of the delivered loads of sodium and calcium to each successive nephron segment, defined as "proximal tubule" (prior to the late proximal puncture site), "loop" (between proximal and distal puncture sites), and "terminal segment" (between the distal puncture site and the final urine). These mean data cannot be statistically analyzed, but since they provide information concerning the individual directional changes in the reabsorptive capacities for sodium and calcium in each nephron segment, the data are provided for several of the experimental groups.

Results

The plasma and clearance data for experimental groups I through VI are shown in Tables 1 and 2. The proximal and distal micropuncture data are summarized in Tables 3 and 4.

Comparison of normal and acidotic dogs. To ex-

Table 1. Blood and clearance data for each experimental group[a]

Group	N	V *ml/min*	C_{In} *ml/min*	Hct %	Protein *g/100 ml*	Blood pH	FE_{H_2O} %	P_{HCO_3} *mEq/liter*	FE_{HCO_3} %
I	7								
Control		1.4 ± 0.3	23.2 ± 1.5	35 ± 1.7	4.5 ± 0.2	7.29 ± 0.03	6.2 ± 0.5	20.4 ± 1.4	8.5 ± 2.5
Acute acidosis		1.5 ± 0.2	21.2 ± 0.8	33 ± 1.9	3.9 ± 0.1[d]	7.13 ± 0.03[b]	7.1 ± 1.0	14.5 ± 0.7[b]	2.7 ± 0.6[d]
II	9								
Acidosis		1.4 ± 0.4	23.3 ± 0.8	35 ± 1.5	4.7 ± 0.2	7.16 ± 0.01	6.2 ± 1.6	14.8 ± 0.5	0.6 ± 0.2
$NaHCO_3$ infusion		2.1 ± 0.5[d]	19.5 ± 1.1	33 ± 1.4[c]	4.3 ± 0.2[d]	7.39 ± 0.03[b]	10.1 ± 2.1[c]	27.0 ± 1.5[b]	9.6 ± 2.2[b]
III	7								
Acidosis, TPTX		1.1 ± 0.3	19.2 ± 2.2	39 ± 1.4	5.1 ± 0.3	7.22 ± 0.03	5.0 ± 1.0	13.8 ± 0.7	1.0 ± 0.4
$NaHCO_3$ infusion		1.4 ± 0.4	17.4 ± 1.8	35 ± 1.5[c]	4.5 ± 0.3[c]	7.45 ± 0.03[b]	7.4 ± 1.8	25.1 ± 1.9[b]	8.0 ± 2.6[d]
IV	8								
Acidosis		0.5 ± 0.1	17.7 ± 2.4	39 ± 2.9	3.9 ± 0.1	7.23 ± 0.03	3.2 ± 0.9	14.9 ± 0.9	0.9 ± 0.4
NaCl infusion		1.3 ± 0.4[d]	17.1 ± 2.2	36 ± 2.3[d]	3.3 ± 0.2[c]	7.20 ± 0.04	7.7 ± 2.3[d]	13.4 ± 0.9	2.2 ± 0.8[d]
V	8								
Control		0.8 ± 0.3	26.2 ± 2.8	36 ± 0.9	4.3 ± 0.2	7.35 ± 0.02	2.6 ± 0.6	19.2 ± 0.5	3.1 ± 0.7
$NaHCO_3$ infusion		1.0 ± 0.2	25.1 ± 5.4	33 ± 1.7	3.8 ± 0.3[c]	7.51 ± 0.02[b]	4.4 ± 0.9	32.0 ± 2.2[b]	14.0 ± 3.0[d]
VI	7								
Control, TPTX		2.8 ± 0.5	28.1 ± 2.3	35 ± 1.5	4.1 ± 0.2	7.39 ± 0.02	9.8 ± 1.7	13.6 ± 1.7	4.3 ± 1.0
$NaHCO_3$ infusion		3.4 ± 0.9	23.7 ± 2.5[c]	36 ± 1.9	4.0 ± 0.2	7.53 ± 0.03[d]	14.2 ± 3.4	21.4 ± 1.9[b]	24.9 ± 4.4[b]

[a] Abbreviations are defined as V, volume; C_{In}, inulin clearance; TPTX, thyroparathyroidectomized; N, number of experiments; P_{HCO_3}, plasma concentration of bicarbonate; FE_{H_2O}, FE_{HCO_3}, fraction of filtered load of water, and bicarbonate, excreted in urine. Values represent the means ± SEM.

[b] Significant at $P < 0.001$

[c] Significant at $P < 0.01$

[d] Significant at $P < 0.05$

Table 2. Plasma and clearance data for sodium and calcium for each experimental group[a]

Group	N	P_{Na} *mEq/liter*	$U_{Na}V$ *μEq/min*	FE_{Na} %	P_{Ca} *mEq/liter*	UF_{Ca} *mEq/liter*	$U_{Ca}V$ *μEq/min*	FE_{Ca} %
I	7							
Control		149 ± 0.9	189 ± 44	5.2 ± 0.9	4.5 ± 0.1	2.9 ± 0.1	3.0 ± 0.7	4.2 ± 0.8
Acute acidosis		149 ± 1.1	161 ± 35	5.1 ± 1.1	4.4 ± 0.1	3.2 ± 0.2[c]	2.8 ± 0.7	4.3 ± 0.9
II	9							
Acidosis		153 ± 1.3	129 ± 28	3.0 ± 0.5	4.7 ± 0.1	3.1 ± 0.1	3.7 ± 0.6	5.5 ± 0.9
$NaHCO_3$ infusion		169 ± 2.9[b]	197 ± 35	6.1 ± 1.0[c]	4.4 ± 0.1	2.9 ± 0.1[c]	2.4 ± 0.4	4.2 ± 0.8
III	7							
Acidosis, TPTX		152 ± 1.9	85 ± 20	2.6 ± 0.5	4.6 ± 0.3	2.9 ± 0.1	3.2 ± 0.7	5.2 ± 1.0
$NaHCO_3$ infusion		164 ± 1.8[b]	123 ± 30[d]	4.0 ± 0.9[d]	4.0 ± 0.3[b]	2.6 ± 0.1[d]	1.7 ± 0.5[b]	2.9 ± 0.7[c]
IV	8							
Acidosis		152 ± 1.8	38 ± 8	2.2 ± 0.8	4.7 ± 0.1	3.1 ± 0.1	1.5 ± 0.2	3.0 ± 0.5
NaCl infusion		165 ± 0.9[b]	140 ± 41[d]	5.2 ± 1.4[d]	4.3 ± 0.1[c]	3.1 ± 0.1	2.6 ± 0.7	5.2 ± 1.4
V	8							
Control		152 ± 1.7	95 ± 43	1.9 ± 0.5	4.9 ± 0.1	3.2 ± 0.1	2.6 ± 1.5	2.4 ± 0.7
$NaHCO_3$ infusion		162 ± 2.2[b]	139 ± 28	3.6 ± 0.7	4.5 ± 0.1[b]	3.0 ± 0.1[c]	1.4 ± 0.6	1.5 ± 0.4
VI	7							
Control, TPTX		163 ± 3.6	441 ± 89	9.5 ± 1.8	4.1 ± 0.7	2.7 ± 0.1	7.0 ± 1.8	8.8 ± 2.0
$NaHCO_3$ infusion		175 ± 4.5[b]	437 ± 133	10.4 ± 2.9	3.6 ± 0.6	2.6 ± 0.1[b]	4.0 ± 2.1	6.5 ± 3.4

[a] Abbreviations are defined in Table 1 and as P_{Na}, P_{Ca}, plasma concentration of sodium or calcium; UF_{Ca}, calcium concentration in plasma ultrafiltrate; FE_{Na}, FE_{Ca}, fraction of filtered load of sodium or calcium excreted in urine.

[b] Significant at $P < 0.001$.

[c] Significant at $P < 0.01$.

[d] Significant at $P < 0.05$.

amine differences in the tubular handling of sodium and calcium between acidotic (ammonium-chloride-fed) and control dogs, we have made a comparison (see Table 5) between the pooled control-phase data from dogs in groups I and V (nonacidotic, parathyroid intact) and the pooled control phase data from groups II and IV (acidotic, parathyroid intact). In the final urine, the mean fractional excretions of sodium (FE_{Na}) and calcium (FE_{Ca}) were 3.4 and 3.2%, respectively, in the 15 nonacidotic dogs and 2.6 and 4.3%, respectively, in the 17 acidotic dogs. Although these differences between normal and acidotic dogs are not significant, the acidotic dogs had a higher mean calcium excretion despite a

Table 3. Micropuncture data for proximal tubule[a]

Group	*N*	TF/P_{In}	TF/P_{Na}	TF/UF_{Ca}	RF_{Na}, %	RF_{Ca}, %
I	7					
Control		1.60 ± 0.09	0.98 ± 0.02	1.25 ± 0.03	65.7 ± 3.3	81.4 ± 4.4
HCl infusion		1.44 ± 0.06[c]	1.02 ± 0.01[c]	1.25 ± 0.03	72.4 ± 2.6[c]	87.6 ± 4.7
II	9					
Control acidosis		1.69 ± 0.07	1.02 ± 0.01	1.10 ± 0.04	54.0 ± 5.4	65.3 ± 5.8
$NaHCO_3$ infusion		1.49 ± 0.05[c]	0.99 ± 0.01	1.02 ± 0.04	70.0 ± 3.4[c]	73.2 ± 6.2
III	7					
Acidosis TPTX		1.81 ± 0.10	1.02 ± 0.02	1.20 ± 0.08	60.2 ± 4.4	69.7 ± 4.3
$NaHCO_3$ infusion		1.56 ± 0.04[c]	1.01 ± 0.01	1.14 ± 0.07	66.6 ± 1.9	74.8 ± 5.4
IV	8					
Acidosis		1.73 ± 0.16	0.98 ± 0.02	1.11 ± 0.03	57.7 ± 4.1	65.1 ± 4.7
NaCl infusion		1.75 ± 0.08	1.02 ± 0.02	1.07 ± 0.06	55.9 ± 2.2	58.2 ± 3.4
V	8					
Control		1.56 ± 0.05	0.97 ± 0.01	1.18 ± 0.04	63.3 ± 2.6	77.2 ± 4.0
$NaHCO_3$ infusion		1.51 ± 0.07	0.97 ± 0.01	1.18 ± 0.03	66.6 ± 3.4	78.1 ± 5.3
VI	7					
Control TPTX		1.90 ± 0.18	1.00 ± 0.02	1.03 ± 0.04	55.4 ± 4.7	59.9 ± 6.0
$NaHCO_3$ infusion		1.71 ± 0.19	0.95 ± 0.20[c]	0.89 ± 0.05[b]	62.1 ± 5.8	56.9 ± 4.0

[a] Abbreviations are defined as TF/P_{In}, TF/P_{Na}, tubule fluid to plasma concentration ratio for inulin and sodium; TF/UF_{Ca}, tubule fluid to plasma ultrafiltrate concentration ratio for calcium; RF_{Na}, RF_{Ca}, fraction of filtered load of sodium and calcium rejected from proximal puncture site. Values represent the means ± SEM.
[b] Significant at $P < 0.001$
[c] Significant at $P < 0.05$

Table 4. Micropuncture data for distal tubule[a]

Group	*N*	TF/P_{In}	TF/P_{Na}	TF/UF_{Ca}	RF_{Na}, %	RF_{Ca}, %
I	7					
Control		4.34 ± 0.33	0.30 ± 0.03	0.32 ± 0.05	7.6 ± 1.3	7.3 ± 1.0
HCl infusion		3.31 ± 0.25[c]	0.38 ± 0.04[d]	0.41 ± 0.06	12.0 ± 1.3[c]	12.2 ± 1.8[b]
II	9					
Control acidosis		5.82 ± 0.44	0.30 ± 0.02	0.44 ± 0.02	5.5 ± 0.4	8.0 ± 0.5
$NaHCO_3$ infusion		4.62 ± 0.29[c]	0.47 ± 0.04[b]	0.33 ± 0.03[c]	10.6 ± 0.9[b]	7.8 ± 0.8
III	7					
Acidosis TPTX		4.19 ± 0.26	0.31 ± 0.03	0.56 ± 0.04	7.5 ± 0.8	13.6 ± 0.9
$NaHCO_3$ infusion		3.46 ± 0.26[c]	0.40 ± 0.02[d]	0.42 ± 0.04[c]	11.7 ± 0.9[c]	12.5 ± 1.4
IV	8					
Acidosis		5.25 ± 0.39	0.21 ± 0.02	0.30 ± 0.03	4.0 ± 0.7	6.0 ± 0.9
NaCl infusion		4.57 ± 0.37[d]	0.33 ± 0.03[b]	0.35 ± 0.03	8.9 ± 1.2[b]	9.6 ± 1.6[d]
V	8					
Control		6.68 ± 0.33	0.30 ± 0.03	0.28 ± 0.03	5.3 ± 0.6	4.8 ± 0.8
$NaHCO_3$ infusion		6.23 ± 0.42	0.38 ± 0.03[d]	0.14 ± 0.01[b]	6.9 ± 0.6[d]	2.7 ± 0.3[c]
VI	7					
Control TPTX		4.92 ± 0.31	0.41 ± 0.03	0.35 ± 0.04	8.9 ± 1.1	14.6 ± 5.6
$NaHCO_3$ infusion		4.13 ± 0.32	0.48 ± 0.06	0.29 ± 0.06	13.5 ± 4.5	14.8 ± 7.3

[a] Abbreviations are defined in Table 3 and as RF_{Na}, RF_{Ca}, fraction of filtered sodium and calcium rejected from distal puncture site.
[b] Significant at $P < 0.001$
[c] Significant at $P < 0.01$
[d] Significant at $P < 0.05$

lower sodium excretion. Furthermore, in Fig. 1 FE_{Ca} is plotted against FE_{Na} for these acidotic and nonacidotic dogs, and it is clear that at each level of sodium excretion the acidotic dogs have a significantly higher calcium excretion than do the normal dogs (comparison of intercepts, $P < 0.001$; comparison of slopes, $P > 0.1$).

Figure 2 shows the individual proximal micropuncture data for these same acidotic and nonacidotic dogs, with the fractional delivery of calcium plotted against fractional delivery of sodium. It is apparent that at the proximal micropuncture site, for any given level of sodium delivery, the calcium delivery is significantly lower in the acidotic than it is in the control dogs (comparison of intercepts, $P < 0.001$; comparison of slopes, $P > 0.1$).

Figure 3 shows the corresponding distal data. Here, as in the final urine, calcium delivery is greater at any given level of sodium delivery in the acidotic than it is in the control dogs (comparison of intercepts, $P < 0.001$; comparison of slopes, $P < 0.01$).

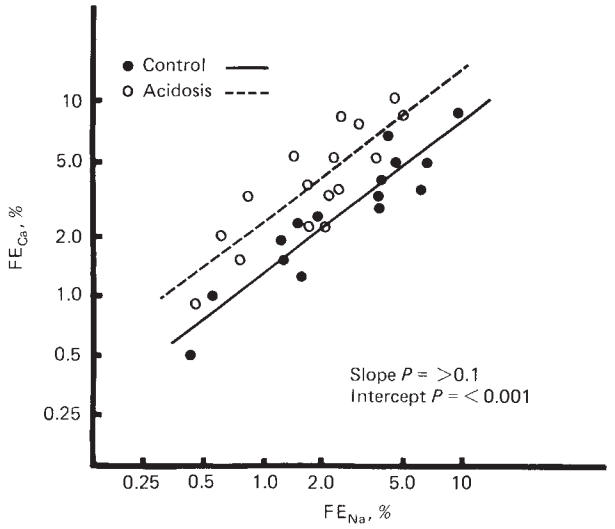


Fig. 1. *Relationship of fractional urinary excretion of calcium (FE_{Ca}) to that of sodium (FE_{Na}) in parathyroid intact control dogs* (closed circles, *groups I and V*) *and chronically acidotic dogs* (open circles, *groups II and IV*).

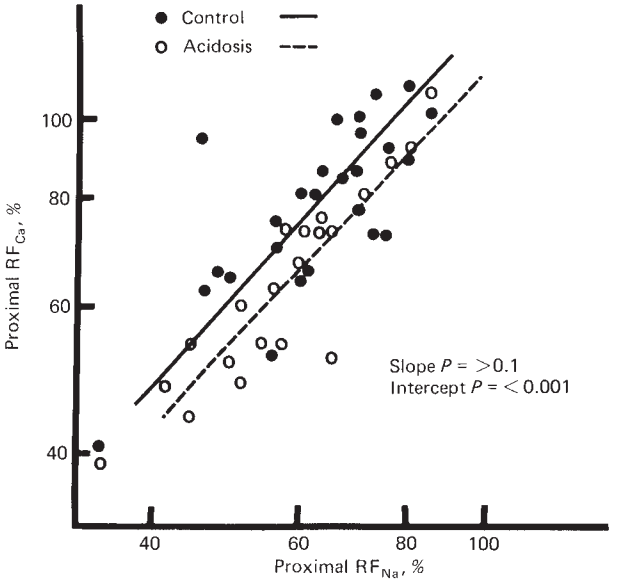


Fig. 2. *Relationship of proximal rejected fraction of calcium (RF_{Ca}) to that of sodium (RF_{Na}) in control* (closed circles, *groups I and V*) *and acidotic* (open circles, *groups II and IV*) *dogs*. Each point represents a single proximal tubule sample.

These data indicate that the dissociation of calcium from sodium excretion seen in the chronically ammonium chloride-fed dog resulted from an impairment of calcium reabsorption in the renal tubule relative to sodium, which occurs beyond the late proximal tubule but is apparent at the distal puncture site. Indeed, in acidotic dogs calcium delivery at the proximal tubule is actually lower relative to sodium than it is in the control dogs.

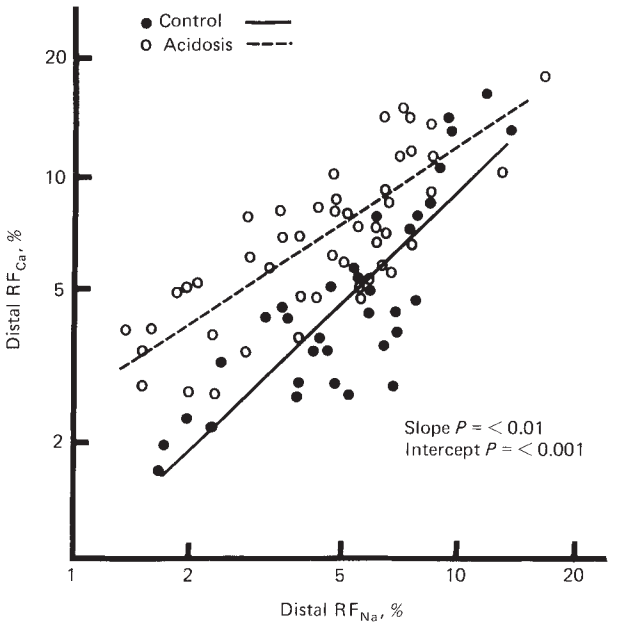


Fig. 3. *Relationship of distal rejected fraction of calcium (RF_{Ca}) to that of sodium (RF_{Na}) in control* (closed circles, *groups I and V*) *and acidotic* (open circles, *groups II and IV*) *dogs*. Each point represents a single distal tubule sample.

Table 5, calculated from the data in Tables 1 to 4, shows that fractional proximal reabsorption of both sodium and calcium is greater in chronic acidosis than it is in control. In the loop and terminal segments, however, fractional reabsorption of delivered calcium loads is lower in acidosis than it is in controls, despite similar or lower delivered loads. These data indicate that the dissociation of calcium from sodium delivery at the distal tubule and final urine in chronic acidosis results in part from decreases in the reabsorptive capacities of both loop and terminal segments for calcium.

Acute acidosis (group I). The infusion of hydrochloric acid (blood pH, 7.29 to 7.13; $P < 0.001$) did not significantly change either FE_{Ca} or FE_{Na}. GFR was unchanged. At the late proximal tubule, the tubular fluid to plasma (TF/P) inulin concentration fell (1.60 to 1.44, $P < 0.05$), indicating a significant inhibition of fluid reabsorption in acute acidosis. The marked increases in fractional sodium and calcium delivery to the distal puncture site in acute acidosis (7.6 to 12.0%, $P < 0.01$; and 7.3 to 12.2%, $P < 0.001$; respectively) coupled with the lack of change in fractional urinary excretions of these ions, indicate that the reabsorption of both ions increased in the terminal segment in this condition. Calculation from the data in Tables 1 to 4 shows that in the terminal segment the mean fractional reabsorption of delivered sodium and calcium in-

Table 5. Segmental analysis of calcium and sodium handling in normal controls (groups I and V) and chronic acidosis (groups II and IV)

	Calcium		Sodium	
	Normal	Chronic acidosis	Normal	Chronic acidosis
Filtered load, *μEq/min*	76.1	64.1	3737	3153
"Proximal" reabsorption, *% delivered load*	20.8	34.8	35.6	44.3
"Loop" delivery, *μEq/min*	60.1	41.7	2404	1749
"Loop" reabsorption, *% delivered load*	92.4	89.3	90.1	91.4
"Terminal" delivery, *μEq/min*	4.4	4.6	235	155
"Terminal" reabsorption, *% delivered load*	46.5	39.6	49.0	45.1
Fractional excretion, %	3.2	4.3	3.4	2.6

creased from 43 to 65% and 32 to 58%, respectively, despite increases in the absolute deliveries of both ions to this segment.

Figure 4 shows the effects of acute hydrochloric acid infusion on the relationship between sodium and calcium delivery to the proximal and distal tubule and in the final urine. No significant change in this relationship was observed at the proximal tubule or in the final urine. At the distal tubule, a slight change in this relationship is seen with a relative decrease in calcium delivery after hydrochloric acid infusion (comparison of slopes, $P < 0.05$; comparison of intercepts, $P > 0.1$).

Chronic acidosis: Correction with sodium bicarbonate (group II, intact dogs; group III, TPTX dogs). In both intact and TPTX dogs, the infusion of hypertonic sodium bicarbonate corrected the acidosis (blood pH, 7.16 to 7.39, $P < 0.001$; and 7.22 to 7.45, $P < 0.001$; respectively) and was associated with a significant increase in plasma sodium (P_{Na}) and a decrease in plasma ultrafilterable calcium (UF_{Ca}) concentration. FE_{Na} increased from 3.0 to 6.1% in group II ($P < 0.01$) and from 2.6 to 4.0% in group III ($P < 0.05$), and FE_{Ca} decreased from 5.5 to 4.2% in group II ($P > 0.05$) and from 5.2 to 2.9% in group III ($P < 0.01$).

Fractional fluid reabsorption fell in the proximal tubule following sodium bicarbonate infusion in both groups as indicated by significant declines in TF/P inulin. TF/P_{Na} and TF/UF_{Ca} were unchanged at the proximal tubule, but at the distal tubule TF/P_{Na} increased and TF/UF_{Ca} decreased (Fig. 5). Calculation from Tables 1 to 4 of the mean fractional reabsorption of delivered calcium to successive nephron segments indicates that in both groups, calcium reabsorption fell in the proximal tubule, but increased both in the loop (88 to 89% and 81 to 83% in groups II and III, respectively) and the terminal segment (31 to 46% and 62 to 77%, respectively). These increases in fractional reabsorption were, however, associated with decreases in absolute calcium deliveries to loop and terminal segments.

Figure 6 shows the relationship between sodium and calcium deliveries at the proximal and distal tubule and in the final urine in the group-III TPTX dogs before and after sodium bicarbonate infusion. At the proximal tubule, correction of the chronic metabolic acidosis in these TPTX dogs did not alter the relationship between sodium and calcium deliveries (comparison of slopes, $P > 0.1$; comparison of intercepts, $P > 0.1$). At the distal tubule, at a given sodium delivery it is apparent that calcium delivery is higher in the acidotic (control-phase) dogs, and decreases after sodium bicarbonate (comparison of slopes, $P > 0.1$; comparison of intercepts, $P < 0.005$). In the final urine this effect of sodium bicarbonate infusion is again apparent (comparison of slopes, $P > 0.1$; comparison of intercepts, $P < 0.001$). A similar analysis of the data from group II (parathyroid intact) yielded very similar results (not illustrated), with no change in the sodium-calcium relationship at the proximal tubule, but with a highly significant change in the relationship of calcium to sodium delivery at the distal tubule and in the final urine (comparison of intercepts at distal tubule, $P < 0.001$, and at final urine, $P < 0.001$).

Chronic acidosis: Infusion of hypertonic sodium chloride (group IV). Sodium chloride infusion in these parathyroid-intact dogs did not change blood pH (7.23 to 7.20) and resulted in a rise in P_{Na} and no change in UF_{Ca}. In contrast to the infusion of sodium bicarbonate (group II), the infusion of sodium chloride did not decrease proximal fluid reabsorption (TF/P inulin, 1.73 to 1.75). Proximal rejected fractions of sodium and calcium were unchanged. At the distal tubule, rejected fractions of both sodium and calcium increased significantly (4.0 to 8.9% and 6.0 to 9.6%, respectively). FE_{Na} increased

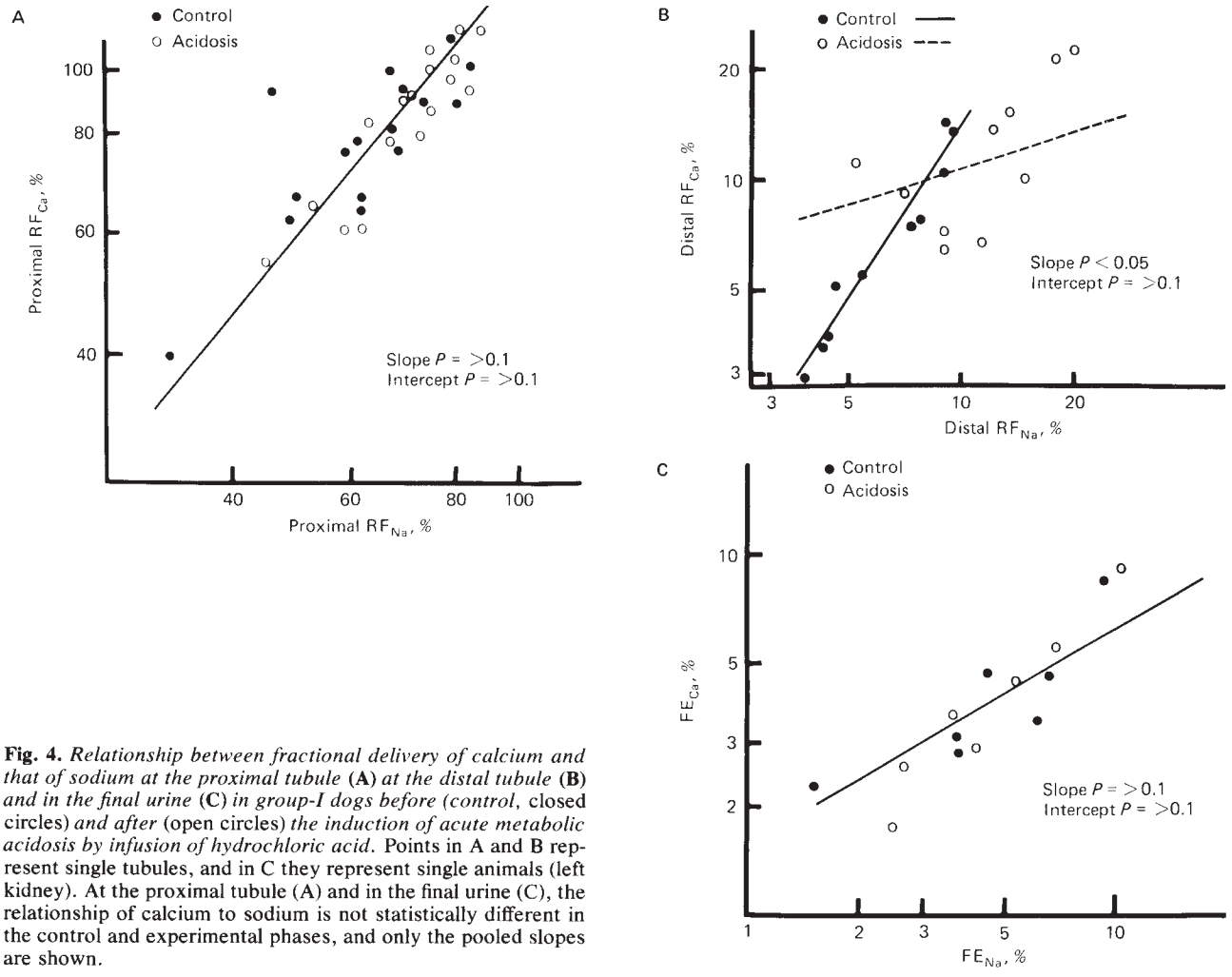


Fig. 4. *Relationship between fractional delivery of calcium and that of sodium at the proximal tubule* (**A**) *at the distal tubule* (**B**) *and in the final urine* (**C**) *in group-I dogs before (control,* closed circles) *and after* (open circles) *the induction of acute metabolic acidosis by infusion of hydrochloric acid.* Points in A and B represent single tubules, and in C they represent single animals (left kidney). At the proximal tubule (A) and in the final urine (C), the relationship of calcium to sodium is not statistically different in the control and experimental phases, and only the pooled slopes are shown.

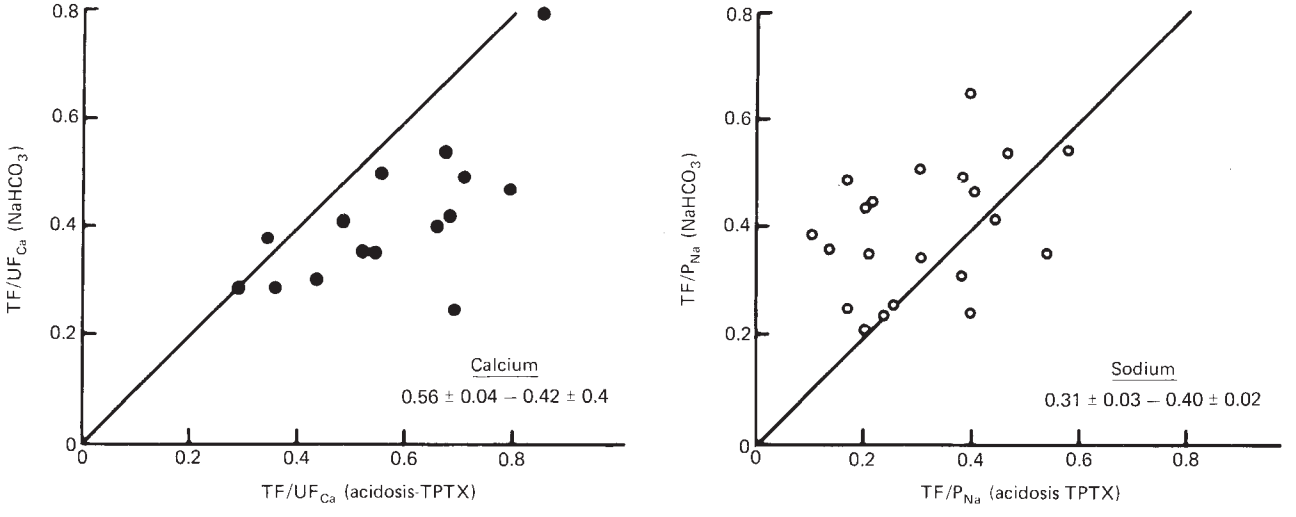


Fig. 5. *Individual distal calcium and sodium micropuncture data (TF/UF_{Ca} and TF/P_{Na}) from group-III dogs in chronic acidosis and after correction with sodium bicarbonate ($NaHCO_3$).*

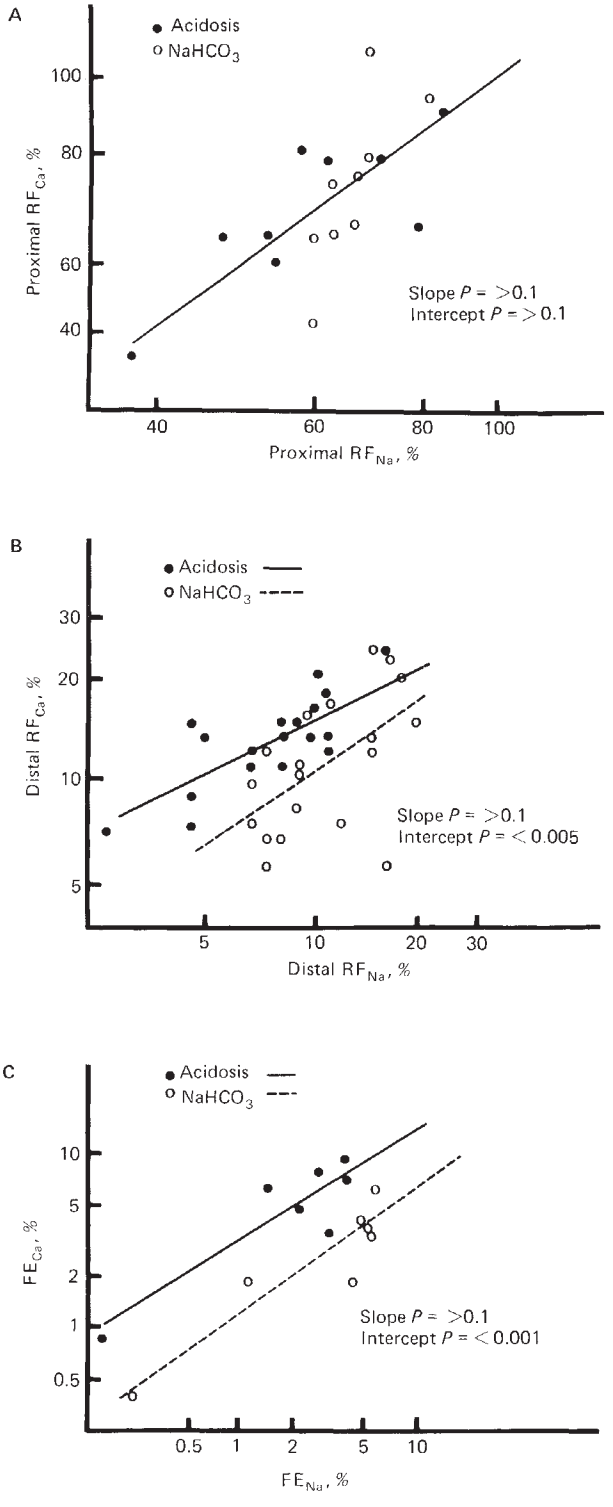


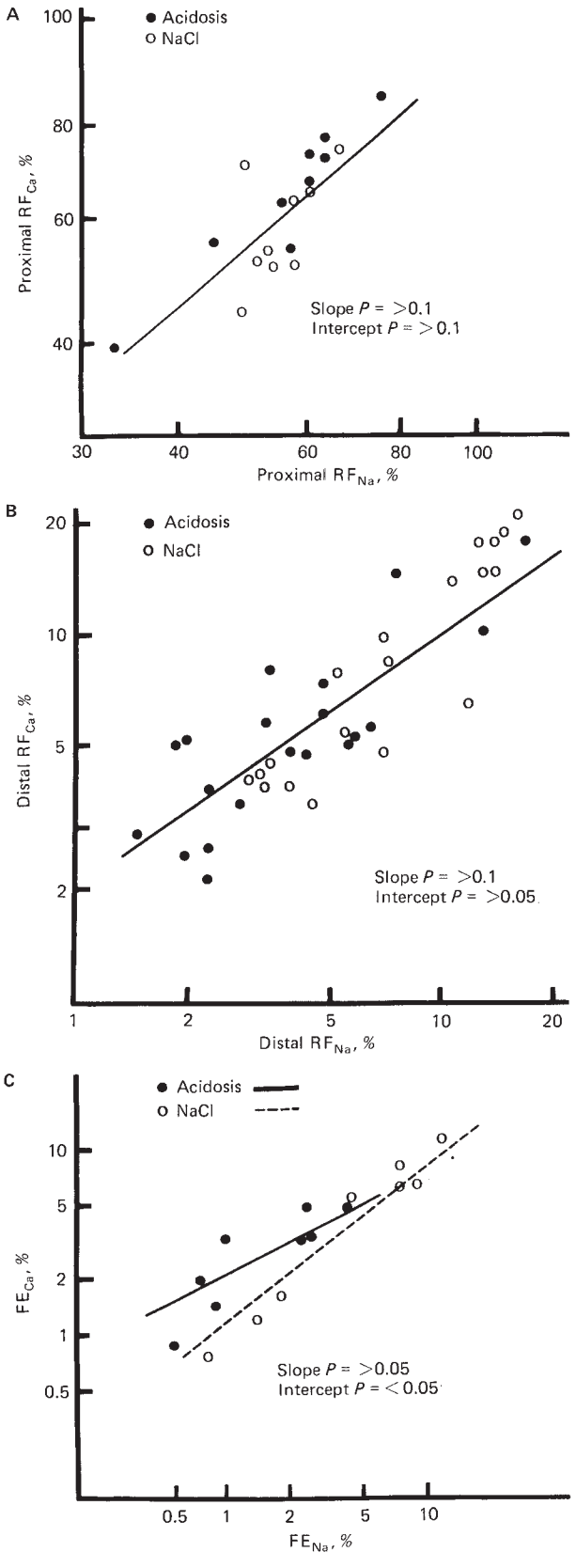
Fig. 6. *Relationship between calcium and sodium delivery to the proximal tubule* **(A)**, *the distal tubule* **(B)**, *and in the final urine* **(C)** *in the group-III dogs (TPTX) before (acidosis*, closed circles) *and after* (open circles) *the infusion of sodium bicarbonate to correct the chronic metabolic acidosis.* In A and B the points represent single tubules as in Fig. 4.

from 2.2 to 5.2% ($P < 0.05$), and FE_{Ca} increased nonsignificantly from 3.0 to 5.3%. Calculation from the data in Tables 1 to 4 showed that in both loop and terminal segments, mean fractional reabsorptions of delivered calcium decreased (from 91 to 84% and 50 to 46%, respectively). In the loop segment, this decrease occurred despite a fall in absolute calcium delivery, indicating a decrease in the reabsorptive capacity for calcium in this segment in response to sodium chloride infusion.

Figure 7 shows the relationship between sodium and calcium delivery at proximal and distal tubules and in the final urine before and after sodium chloride infusion. At both proximal and distal tubules, this relationship was not significantly changed following sodium chloride infusion; in the final urine there was a slight fall in calcium excretion relative to sodium (comparison of slopes, $P > 0.05$; comparison of intercepts, $P < 0.05$).

Acute alkalosis: Infusion of sodium bicarbonate (group V, intact dogs; group VI, TPTX dogs). In group V, volume-expanded with isotonic Ringer's solution in the control phase, the infusion of hypertonic sodium bicarbonate (0.5 M) resulted in a rise in blood pH from 7.35 to 7.51 ($P < 0.001$), a rise in P_{Na}, and a fall in UF_{Ca}. At the proximal tubule, a nonsignificant fall in TF/P inulin occurred, and rejected fractions of sodium and calcium were not significantly changed. At the distal tubule, rejected fraction of sodium increased (5.3 to 6.9%, $P < 0.05$) and that of calcium decreased (4.8 to 2.7%, $P < 0.01$). In the final urine, neither the increase in FE_{Na} (1.9 to 3.5%) nor the fall in FE_{Ca} (2.4 to 1.5%) was statistically significant. Calculation of the mean segmental reabsorption of delivered calcium load from the data in Tables 1 to 4 showed an increase in calcium reabsorption from 94 to 97% in the loop and a slight fall in the terminal segment from 50 to 45%, which was, however, associated with a major reduction in delivered load of calcium to this segment. Comparison of the relationship between delivery of sodium and calcium to proximal and distal tubule and final urine (not illustrated) showed no significant change following sodium bicarbonate infusion at the proximal tubule, but there was a significant decrease in calcium delivery relative to sodium at the distal tubule (comparison of slope, $P > 0.1$; comparison of intercept, $P < 0.001$) and in the final urine (comparison of slope, $P > 0.1$; comparison of intercept, $P < 0.05$).

The group-VI TPTX dogs were given hypertonic (2.5%) sodium chloride (3% body weight) in the



control phase, resulting in a dilutional acidosis (plasma bicarbonate, 13.6 mEq/liter), which was compensated by hyperventilation (P_{CO_2}, 23 mm Hg), so that pH was 7.39. The subsequent infusion of 0.25 M sodium bicarbonate increased the plasma bicarbonate to 21.4 ($P < 0.001$) and the pH to 7.53 ($P < 0.05$). The P_{CO_2} was unchanged at 26 mm Hg. GFR fell significantly, P_{Na} increased, and UF_{Ca} fell. At the proximal tubule, both TF/P sodium and TF/UF calcium fell significantly (1.00 to 0.95, $P < 0.05$; and 1.03 to 0.89, $P < 0.001$); this was the only group of experiments using sodium bicarbonate infusion in which these proximal concentration ratios changed ratios significantly. At the distal tubule, fractional deliveries of both sodium and calcium increased, but not significantly, and in the final urine FE_{Na} increased and FE_{Ca} decreased, again nonsignificantly. Calculation from Tables 1 to 4 of mean fractional reabsorption of delivered calcium load to the loop and terminal segments showed a decrease in the loop segment (76 to 74%) associated with a decrease in loop calcium delivery, and an increase in the terminal segment (40 to 56%) associated with a small decrease in delivered calcium load. Although the fractional reabsorption of delivered calcium decreased in the loop, a larger decrease occurred in the mean fractional reabsorption of delivered sodium (84 to 78%), so that calcium delivery to the distal tubule decreased relative to that of sodium.

Figure 8 shows the relationship between calcium and sodium delivery to proximal and distal tubules and in the final urine before and after bicarbonate infusion in these TPTX dogs. There was no change in this relationship at the proximal tubule. At the distal tubule, calcium delivery decreased relative to sodium (comparison of slopes, $P > 0.1$; comparison of intercepts, $P < 0.05$), whereas in the final urine the changes were more significant (comparison of slopes, $P < 0.01$; comparison of intercepts, $P < 0.001$).

Discussion

The relationship between renal sodium and calcium clearance has received considerable study since the observation of Walser [14] that the clearance of ultrafilterable calcium approximately

Fig. 7. *Relationship between calcium and sodium delivery to the proximal tubule* (**A**), *the distal tubule* (**B**), *and in the final urine* (**C**) *in the group-IV dogs before (acidosis*, closed circles) *and after* (open circles) *the infusion of sodium chloride*. In A and B the points represent individual tubules as in Fig. 4.

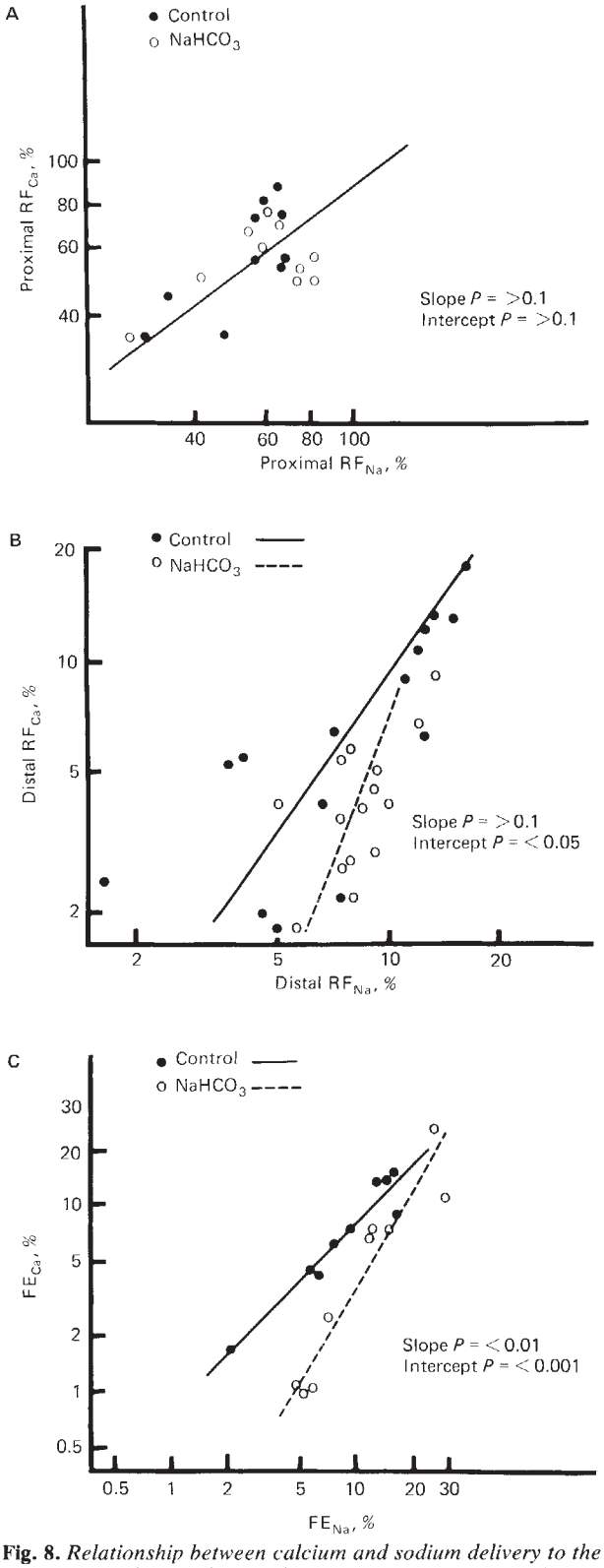


Fig. 8. *Relationship between calcium and sodium delivery to the proximal tubule* **(A)**, *the distal tubule* **(B)**, *and in the final urine* **(C)** *in the group-VI (TPTX) dogs before (control,* closed circles) *and after* (open circles) *the infusion of sodium bicarbonate.* In A and B the points represent individual tubules as in Fig. 4.

equaled that of sodium under a variety of diuretic conditions. The clearance data in the present study show that the relationship between sodium and calcium clearance may be markedly altered both by metabolic acidosis and alkalosis. Lemann, Litzow, and Lennon [7] showed that the hypercalciuria produced by ammonium-chloride-feeding in man resulted from reduced tubular calcium reabsorption and that it occurred even in the absence of parathyroid hormone, suggesting a direct effect of metabolic acidosis on the renal tubule cell. Stacy and Wilson [5] showed that the infusion of hydrochloric acid in the sheep increased urinary calcium excretion despite a falling filtered calcium load, again indicating an inhibition of tubular calcium reabsorption in acidosis.

In the present study, a comparison of chronically acidotic dogs with control dogs shows that, in acidosis, at a given urinary sodium excretion, calcium excretion is significantly higher than it is in controls. A similar enhancement of calcium delivery relative to sodium is apparent at the distal micropuncture site. By contrast, in late proximal samples, for a given sodium delivery, calcium delivery is actually significantly lower in the acidotic dogs. These data indicate that the dissociation of calcium from sodium excretion in ammonium chloride-induced acidosis in the dog results from impaired calcium reabsorption relative to sodium at a site beyond the late proximal tubule.

Calculation of the mean fractional reabsorption of delivered calcium load to successive segments (Table 5) suggests that the reabsorptive capacity for calcium was decreased in both the loop and terminal nephron segments in chronic acidosis. The reason for the reduced delivery of calcium relative to sodium at the proximal tubule in the chronically acidotic dogs is not clear. Proximal fluid reabsorption was greater in chronic acidosis than it was in normal controls, and was reduced significantly by sodium bicarbonate infusion (group II) but not by sodium chloride infusion (group IV).

In contrast to chronic acidosis, the induction of acute acidosis by hydrochloric acid infusion in normal dogs (group I) caused a significant reduction in proximal fluid reabsorption, as reported by Dubb, Goldberg, and Agus in the rat [20]. The relationship of calcium to sodium delivery, however, was unchanged at the proximal tubule and in the final urine. There was no evidence in these acutely acidotic dogs of a reduction in calcium reabsorption relative to sodium in the later nephron segments. A significant increase in the delivery of both sodium

and calcium to the distal puncture site was offset by an increase in the reabsorption of these ions in the terminal nephron segment. The failure of acute acidosis to dissociate renal sodium and calcium transport in the dog has been noted previously [12]. Hypercalciuria, however, was observed in the sheep during acute hydrochloric acid infusion [5] without corresponding changes in sodium excretion.

Having demonstrated the dissociation of calcium from sodium reabsorption in chronic metabolic acidosis in the dog, we examined the effect of acute correction of the acidosis with intravenous infusions of bicarbonate. Hypertonic sodium bicarbonate was used in an attempt to minimize the accompanying volume changes. In acidotic dogs, both intact (group II) and immediately after TPTX (group III), sodium bicarbonate infusion selectively enhanced calcium reabsorption relative to sodium at sites beyond the late proximal tubule and restored the normal parallel delivery of these ions to the distal puncture site and to the final urine. In both groups, mean fractional reabsorption of delivered calcium loads increased in both the loop and terminal segment. That sodium bicarbonate corrected the impairment of calcium reabsorption of acidosis in the TPTX dog indicates that these effects of acidosis and sodium bicarbonate are independent of parathyroid hormone. The experiments in group IV were undertaken as a control to observe the effect of an infusion of sodium chloride of comparable magnitude to that of sodium bicarbonate in the previous experiments. Unlike the sodium-bicarbonate-infused dogs, the animals receiving sodium chloride showed no decrease in proximal fluid reabsorption and generally parallel changes in sodium and calcium deliveries to successive nephron segments. No significant dissociation was apparent at the proximal or distal tubule, whereas in the final urine only a modest decrease in calcium excretion relative to sodium was observed after sodium chloride infusion. Mean fractional reabsorption of delivered calcium decreased in both the loop and terminal segments. Because these dogs had intact parathyroid glands, it is possible that the sodium chloride infusion was accompanied by parathyroid hormone release, though unlike the sodium-bicarbonate-infused dogs no fall in UF_{Ca} was observed. It is thus possible that the slight dissociation of sodium and calcium excretions which was observed in this group may not have been due to the sodium chloride infusion itself, but rather to parathyroid hormone (PTH) release.

Following the demonstration that the infusion of sodium bicarbonate caused a relative enhancement of calcium reabsorption in the acidotic dog, we next sought to determine the effect of sodium bicarbonate infusions in the nonacidotic dog, both intact and TPTX. In group V (parathyroid intact), sodium bicarbonate infusion caused a marked enhancement of calcium transport relative to sodium, which occurred beyond the late proximal tubule but was evident at the distal micropuncture site and in the final urine. This effect could have been partly or entirely related to PTH release, since a fall in UF_{Ca} was documented. Group VI dogs were TPTX and received substantial volume expansion in the control phase with the objective of avoiding a further increase in volume expansion and sodium excretion after sodium bicarbonate infusion. Insofar as hematocrit and protein concentration remained unchanged, this objective was accomplished; this group of animals, however, showed a significant fall in both GFR and UF_{Ca}, so that filtered calcium load fell in association with the bicarbonate infusion. Despite the absence of PTH, a marked dissociation of calcium and sodium transport was observed, occurring beyond the late proximal tubule and evident in the distal tubule and the final urine. Although this relative enhancement of calcium reabsorption may be a direct effect of the infused bicarbonate, the possibility that it resulted from the reduction in UF_{Ca} or filtered calcium load cannot be excluded. We have previously shown that acute hypercalcemia causes relative inhibition of calcium reabsorption [18], though in those experiments, and in those of LeGrimellec, Roinel, and Morel in the rat [19] the parathyroid glands were intact and the observed changes in calcium transport could have resulted from parathyroid suppression. These experiments (group VI) were the only group in which a change was observed in the proximal TF/UF_{Ca} ratio. We have previously observed a small but significant fall in proximal TF/UF_{Ca} in other experiments using massive isotonic sodium bicarbonate infusion [21], suggesting that under some circumstances sodium bicarbonate infusion can modestly enhance proximal calcium transport relative to that of water. Nevertheless, in all of the other experimental groups, proximal TF/UF_{Ca} was unchanged despite large changes in acid-base status.

In summary, these observations in the dog suggest that chronic metabolic acidosis dissociates calcium reabsorption from sodium beyond the proximal tubule and that this effect is corrected with sodium bicarbonate infusion even in the absence of

PTH. Sodium bicarbonate infusion in the non-acidotic dog enhances the reabsorption of calcium relative to sodium both in the presence and absence of the parathyroid glands. Acute metabolic acidosis produced by hydrochloric acid infusion does not dissociate sodium and calcium transport in the dog nephron.

The mechanism of these effects of acidosis and alkalosis on calcium transport is not known. Ullrich, Rumrich, and Kloss [22] have recently shown in microperfusion experiments in the rat that an electrochemical potential difference exists for calcium in the proximal tubule (implying active transport), and is not influenced by acetazolamide or the absence of buffer in the perfusate, suggesting that active calcium transport in this segment is not influenced by changes in hydrogen ion transport or pH changes in the perfusate.

Borle [23] has recently studied the effects of acid-base changes on calcium transport in isolated kidney cells. Intracellular acidosis, due either to decreased bicarbonate or increased P_{CO_2}, decreased cellular calcium influx, total cell calcium, and both the cytosol and mitochondrial calcium pools. Calcium efflux also decreased. Intracellular alkalosis increased total cell calcium and increased the mitochondrial but not the cytosol calcium pool. These experiments provide further evidence of direct effects of acid-base disturbances on renal cell calcium transport.

It is not possible from our micropuncture experiments to localize these acid-base effects precisely within the distal nephron. Our distal tubule samples were unselected and presumably represent both early and late distal convolutions. The fact that the dissociation of calcium from sodium reabsorption which these maneuvers produced was usually present at the distal tubule and not at the late proximal tubule suggests an effect within the loop of Henle and/or the distal convoluted tubule. Further studies, with in vivo or in vitro microperfusion, will be required to obtain more precise localization.

The effects which we have shown, whereby chronic metabolic acidosis increases calcium excretion relative to sodium, while sodium bicarbonate infusion reduces calcium excretion relative to sodium, may have relevance to several clinical situations. The hypercalciuria of metabolic acidosis may be in part due to reduced tubular calcium reabsorption [7], and in renal failure acidosis may contribute to hypocalcemia by the same mechanism [24]. The relative enhancement of calcium reabsorption by alkalosis or increased bicarbonate delivery from the proximal tubule may contribute to hypercalcemia [11] in the milk alkali syndrome [25] and to the dissociation of calcium from sodium transport which is observed with parathyroid hormone [26] and acetazolamide [27] administration (both of which increase proximal bicarbonate rejection). This enhancement of calcium reabsorption also may account for the absence of hypercalciuria in proximal renal tubular acidosis [28] in contrast to its frequent occurrence in the distal variety of renal tubular acidosis.

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