Effects of Volume Expansion, Purified Parathyroid Extract, and Calcium on Renal Bicarbonate Absorption in the Dog

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ABSTRACT The role of parathyroid hormone (PTH) and of Ca^{++} in the regulation of bicarbonate absorption (R_{HCO_3}) and its response to extracellular volume expansion (VE) was studied in HCO_3^--loaded dogs.

VE lowered R_{HCO_3} in both intact (from 24.8 to 22.0 mmol/liter GFR, $P < 0.01$) and thyroparathyroidectomized (TPTX) (from 24.5 to 18.0 mmol/liter GFR, $P < 0.001$) dogs; glomerular filtration rate (GFR) and filtered HCO_3^- did not change. Both groups showed a significant increase in the fractional excretion of sodium ($C_{Na} \times 100/GFR$), calcium ($C_{Ca} \times 100/GFR$), and chloride ($C_{Cl} \times 100/GFR$) and a decrease in phosphorus reabsorption. Fractional clearance of phosphate ($C_P \times 100/GFR$) rose in both groups but did not achieve significance.

Infusion of purified parathyroid extract (PTE) decreased R_{HCO_3} in intact dogs (from 24.6 to 22.5 mmol/liter GFR, $P < 0.025$) and in TPTX dogs (from 26.9 to 22.6 mmol/liter GFR, $P < 0.05$). No change was noted in GFR, renal blood flow (RBF), filtered HCO_3^-, or fractional excretion of sodium, calcium, or chloride in either group. There was a significant increase in fractional phosphorus clearance and a decrease in phosphorus reabsorption in each group.

Infusion of Ca^{++} raised ultrafilterable Ca^{++} from 5.7 to 7.9 mg/100 ml in intact and from 4.9 to 7.2 mg/100 ml in TPTX dogs; R_{HCO_3} increased in intact (from 22.9 to 26.9 mmol/liter GFR, $P < 0.025$) and in TPTX dogs (from 26.6 to 28.6 mmol/liter GFR, $P < 0.05$). The GFR, RBF, and the fractional excretion of sodium, chloride, and calcium did not change in either group. The reabsorbed phosphate increased in both groups, and fractional phosphorus clearance fell in the intact group but did not change significantly in the TPTX group.

Superimposition of PTE on hypercalcemia in TPTX dogs resulted in a decrease in R_{HCO_3} (from 27.3 to 23.9 mmol/liter GFR, $P < 0.001$), which was accompanied by an increase in the fractional excretion of phosphate and a decrease in the reabsorbed phosphate. In this group of TPTX dogs hypercalcemia caused a drop in RBF from 135.6 to 105.8 ml/min with no change in GFR. The RBF returned to control value with PTE infusion.

It is concluded that: (*a*) the lowering of R_{HCO_3} by VE is not dependent solely on stimulation of PTH by the lowered Ca^{++}, (*b*) PTE acts directly on the renal tubules to lower R_{HCO_3}, (*c*) Ca^{++} enhances R_{HCO_3} and this effect is exerted in the absence of PTH and calcitonin, (*d*) neither the effects of Ca^{++} nor of PTH appear to be mediated by altered hemodynamics, although this cannot be excluded in Ca^{++}-infused TPTX dogs, (*e*) Ca^{++} enhanced phosphate reabsorption in the absence of PTH; this may be a specific effect of hypercalcemia on phosphate reabsorption or the nonspecific consequence of the rise in serum phosphorus.

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INTRODUCTION

Most of the hydrogen ion secreted by the kidney goes towards reabsorption of the filtered bicarbonate. This

process of bicarbonate reclamation depends on carbonic anhydrase (1) and varies directly with the level of blood P_{CO_2} (2) and inversely with intracellular potassium (3) and the serum chloride (4) or the volume of the extracellular fluid (5). Bicarbonate reabsorption (R_{HCO_3}) [1] has also been shown to vary inversely with renal blood flow (RBF) (6).

In past studies it had been shown that the infusion of parathyroid extract (PTE) results in increased bicarbonate excretion (7–10). Conversely, the infusion of calcium was shown to increase hydrogen ion secretion and the excretion of ammonia (11). These observations, coupled with the clinical association of metabolic acidosis with primary (12, 13) and secondary (14–16) hyperparathyroidism and metabolic alkalosis with hypoparathyroidism (17) have led to the suggestion that parathyroid hormone (PTH) may exert a regulatory role in acid-base balance (16).

It is not clear from published reports whether the effect of PTE is specifically that of PTH or is a nonspecific consequence of the renal hemodynamic effects of a nonhormonal protein present in PTE. Also, it is not clear whether calcium specifically enhances hydroen ion secretion or if it simply suppresses PTH secretion thereby eliminating the wasting of bicarbonate caused by it. Furthermore, whether PTH acts on the threshold or on the capacity for bicarbonate reabsorption has not been elucidated. Finally, if indeed PTH depresses bicarbonate reabsorptive capacity it is possible that it may play a role in bringing about the depression of bicarbonate reabsorption observed during expansion with saline or with bicarbonate solution (5). Alkalosis (18) and volume expansion (19) both lower the ionized calcium and may stimulate PTH secretion (20). The reported depression of bicarbonate reabsorption by volume expansion, therefore, may have been the nonspecific consequence of stimulation of PTH secretion.

To investigate these possibilities the effects of bicarbonate and of balanced salt solution and also of calcium and PTH on bicarbonate absorption were studied in bicarbonate-loaded intact and thyroparathyroidectomized (TPTX) dogs.

METHODS

Studies were performed on 49 mongrel dogs of either sex weighing 9–28 kg. Anesthesia was induced with sodium pentobarbital, 32 mg/kg body wt i.v., and additional doses given as needed. All animals were intubated with an endotracheal tube and their respiration supported by a Harvard large-animal respirator (Harvard Apparatus Co., Inc., Millis, Mass.). The P_{CO_2} was maintained between 35 and 45 mm Hg by varying the frequency of respiration.

The femoral arteries and veins were cannulated through bilateral femoral incisions. Blood pressure was monitored with a Statham pressure transducer (Statham Instruments, Inc., Oxnard, Calif.) from one arterial line. The other artery was used to obtain blood samples anaerobically for the measurement of the pH and P_{CO_2}. The ureters were cannulated with polyethylene catheters through a small midline suprapubic incision for the collection of urine under oil. The left renal vein was catheterized through the spermatic or ovarian vein using a left subcostal incision. A minimum of 1 h was allowed for recovery before starting each experiment.

In all experiments, a loading dose of inulin, 50 mg/kg body wt, was given followed by a continuous infusion of 50 mg/kg/h for the duration of the experiment. An infusion of 0.7 M $NaHCO_3$ was used to raise the serum bicarbonate above threshold and to maintain the serum bicarbonate between 30 and 36 mmol/liter.

The renal plasma flow (RPF) was calculated from the extraction of inulin by using Wolf's formula (21), and the RBF was calculated from the relation: RBF = RPF/1 − hematocrit.

Glomerular filtration rate (GFR) was determined by inulin clearance. Determinations of Na^+, K^+, inulin, Ca^{++}, and phosphorus in the plasma and urine were made as described by Hebert, Rouse, Eknoyan, Martinez-Maldonado, and Suki (22). Chloride was determined in a Cotlove Chloridometer (Buchler Instruments Div., Nuclear-Chicago Corp., Fort Lee, N. J.).

Plasma and urine bicarbonate were calculated from the pH and P_{CO_2} by using the Henderson-Hasselbach equation as previously published (6, 23). Numerous determinations of HCO_3^- in this manner did not differ significantly from HCO_3^- values determined simultaneously by the manometric method using the Natelson microgasometer (Scientific Industries, Inc., Springfield, Mass.). Statistical analysis was performed by the paired *t* test where only one experimental condition was induced, and by analysis of variance with one degree of freedom where two experimental conditions were induced.

Eight groups of animals were studied:

Group I. Five dogs were studied to determine the effects of continued HCO_3^- infusion. The serum bicarbonate level was raised above 30 mmol/liter and a steady state was maintained with 0.7 M sodium bicarbonate solution. The infusion of sodium bicarbonate will be referred to as "bicarbonate loading." After a steady state was reached, blood and urine samples were collected every 10–20 min depending on the urine flow rate, and continued for a 3-h period. The first 3–4 collections were used as the control period and the remainder of the collections were considered as the experimental period.

Group II. Seven intact animals were bicarbonate loaded and the first four collections were used as control. The animals were then volume expanded with isotonic saline containing 13 meq KCl/liter given at 2 ml/kg/min for 30 min then at 1 ml/kg/min for the remainder of the experiment. Blood and urine samples were collected every 10–20 min for approximately 2 h.

Group III. Thyroparathyroidectomy was performed on five dogs after the endotracheal tube was in place by using a technique previously described (24). 1½ h was allowed before starting the experiment to permit circulating PTH

[1] *Abbreviations used in this paper:* GFR, glomerular filtration rate; PTE, parathyroid extract; PTH, parathyroid hormone; RBF, renal blood flow; R_{HCO_3}, bicarbonate reabsorption; R_{HCO_3}/GFR, R_{HCO_3}, corrected to GFR; RPF, renal plasma flow; TPTX, thyroparathyroidectomized; UfCa, ultrafilterable calcium.

levels to decline. The remainder of the experiment was the same as described for group II.

Group IV. Six intact animals were bicarbonate loaded and the first four periods were used as control. The animals were then given 100 U PTE (purified parathyroid extract lot no. 153727, Wilson Laboratories, Chicago, Ill.) intravenously over 3 min and 5 U/min was infused for the remainder of the collection periods in the manner described by Hellman, Au, and Bartter (10).

Group V. Six animals underwent thyroparathyroidectomy, and after the previously designated time lapase, the experiment was performed in a manner identical to group IV.

Group VI. A routine control period was collected in six intact dogs. The animals were then infused with calcium chloride, 0.75 mg/kg/min (25), until the serum calcium rose above 10.6 mg/100 ml (required 75±25 min). The serum calcium was determined every 20 min thereafter, and the rate of calcium infusion was adjusted to maintain serum calcium between 10.6 and 13.6 mg/100 ml. Urine and blood samples were collected for approximately 2 h.

Group VII. Eight animals underwent thyroparathyroidectomy and were then bicarbonate loaded. The dogs were then infused with calcium in a manner identical to group VI.

Group VIII. Six TPTX animals were loaded with bicarbonate. After the control period, the dogs were made acutely hypercalcemic in the manner described for group VI and three collections made. PTE was then infused as for group IV while maintaining the serum calcium in a steady state.

RESULTS

The results of studies performed on intact animals receiving a sustained infusion of 0.7 M $NaHCO_3$ are summarized in Table I. The hematocrit before the infusion of $NaHCO_3$ was 36.0±3.4 and fell to 32.8±2.7 in the control period; it remained stable thereafter and was 32.6±2.3 in the experimental period. From Table I it is apparent that there were no significant changes between the control period and the experimental period, with the exception of a slight rise in the filtered bicarbonate. Specifically there was no significant fall in R_{HCO_3} corrected to GFR (R_{HCO_3}/GFR) or in the hematocrit, nor rise in the fractional clearances of sodium, chloride, calcium, or phosphate. Thus the continued administration of bicarbonate for a duration comparable to that in the other experiments performed does not in itself alter renal bicarbonate absorption or further expand extracellular volume.

The effects of volume expansion with isotonic saline in bicarbonate-loaded intact dogs (group II) and TPTX dogs (group III) are shown in Table II. Volume expansion resulted in a drop in the R_{HCO_3}/GFR from 24.8 to 22.0 mmol/liter, $P < 0.01$, in intact animals and in a similar but more marked decrease in the R_{HCO_3}/GFR from 24.5 to 18 mmol/liter, $P < 0.001$, in the TPTX animals. The serum potassium concentration did not change significantly; ultrafilterable calcium (UfCa) dropped from 5.2 to 4.2 mg/100 ml, $P < 0.001$, in intact dogs, and from 5.1 to 4.2 mg/100 ml, $P < 0.025$, in TPTX dogs, and the fractional clearances of sodium, chloride, and calcium rose significantly in both groups. The hematocrit fell significantly in both groups. Fractional clearance of phosphate rose in both groups but did not attain significance; reabsorbed phosphate corrected to the GFR, however, fell significantly in both groups. The more profound depression of R_{HCO_3} in the TPTX group is probably related to the greater increase in the clearances of sodium and of chloride effected in this group.

The effects of infusion of PTE in intact (group IV) and TPTX (group V) dogs are shown in Table III. Infusion of PTE caused a significant fall in the R_{HCO_3}/GFR from 24.6 to 22.5 mmol/liter, $P < 0.025$, in intact dogs and a similar but more pronounced fall in TPTX dogs (from 26.9 to 22.6 mmol/liter, $P < 0.05$). The clearance of sodium rose significantly in TPTX dogs;

TABLE I

Effects of Sustained Bicarbonate Infusion (Group I)

	GFR	RBF	B_{HCO_3}	F_{HCO_3}	R_{HCO_3}/GFR	UfCa	P_P	P_K	Hct	$C_{Na} \times 100$/GFR	$C_{Cl} \times 100$/GFR	$C_{Ca} \times 100$/GFR	$C_P \times 100$/GFR	R_P/GFR
	ml/min		*mmol/liter*	*μmol/min*	*mmol/liter*	*mg/100 ml*		*meq/liter*	%	%		%		*mg/liter*
Control	31.0	162.7	31.9	1002	24.5	5.5	4.60	3.20	32.8	6.20	0.92	3.60	22.6	33.0
SEM	7.1	30.2	0.5	246	1.0	0.2	0.58	0.16	2.7	1.00	0.36	0.94	6.6	5.0
Experimental	32.8	132.2	32.6	1062	24.1	5.5	4.50	3.20	32.6	6.30	0.68	3.25	30.2	30.0
SEM	7.6	31.2	0.4	263	1.3	0.2	0.40	0.15	2.3	0.93	0.22	0.96	2.3	4.0
P	>0.05	>0.2	>0.2	<0.05	>0.3		>0.5	>0.6	>0.7	>0.8	>0.5	>0.6	>0.1	>0.2

B_{HCO_3}, blood bicarbonate; F_{HCO_3}, filtered bicarbonate; P_P, plasma phosphorus; P_K, plasma potassium; Hct, hematocrit; $C_{Na} \times 100$/GFR, fractional clearance of soidum; $C_{Cl} \times 100$/GFR, fractional clearance of chloride; $C_{Ca} \times 100$/GFR, fractional clearance of calcium; $C_P \times 100$/GFR, fractional clearance of phosphorus, R_P/GFR, reabsorbed phosphorus corrected to 1,000 ml GFR. The values listed are the means of all collections in a respective period.

TABLE II

Effects of Volume Expansion (VE) in Intact (Group II) and TPTX (Group III) Dogs

	GFR	B_{HCO_3}	F_{HCO_3}	R_{HCO_3}/GFR	UfCa	P_P	P_K	Hct	$C_{Na} \times 100$/GFR	$C_{Cl} \times 100$/GFR	$C_{Ca} \times 100$/GFR	$C_P \times 100$/GFR	R_P/GFR
	ml/min	*mmol/liter*	*μmol/min*	*mmol/liter*	*mg/100 ml*		*meq/liter*	%	%		%		*mg/liter*
Group II													
Control	47.2	34.4	1605	24.8	5.2	5.2	2.6	30	7.9	2.3	6.0	34.3	35.3
SEM	10.1	1.1	336	1.6	0.3	0.55	0.11	1.49	2.0	1.5	2.5	3.9	5.7
VE	51.1	33.8	1711	22.0	4.2	4.1	2.7	25	15.7	10.9	16.6	45.5	22.3
SEM	10.7	1.0	349	1.5	0.3	0.39	0.17	2.37	3.8	3.9	5.4	5.1	3.4
P	>0.05	>0.7	>0.2	<0.01	<0.001	<0.025	>0.3	<0.01	<0.02	<0.02	<0.025	>0.05	<0.05
Group III													
Control	38.7	32.1	1237	24.5	5.10	4.20	3.00	33.0	6.8	2.5	5.7	15.0	36.0
SEM	9.5	0.5	304	1.1	0.16	0.38	0.36	1.6	1.3	1.0	1.4	7.3	5.0
VE	36.0	31.5	1126	18.0	4.20	3.60	3.20	27.0	20.2	15.2	16.9	27.0	28.0
SEM	6.7	0.3	210	1.4	0.16	0.38	0.70	1.3	4.2	4.2	4.1	11.5	6.0
P	>0.3	>0.3	>0.3	<0.001	<0.025	>0.1	>0.2	<0.01	<0.02	<0.05	<0.025	>0.05	<0.05

For explanation see Table I.

the clearance of chloride and the hematocrit did not change significantly in either group. The clearance of calcium was also unchanged in the two groups but the clearance of phosphate rose and phosphate reabsorption fell significantly in both groups.

Hypercalcemia induced acutely in intact dogs (group VI) was followed by a rise in R_{HCO_3}/GFR from 22.9 to 26.9 mmol/liter, $P < 0.025$, (Table IV). This does not appear to be due to suppression of PTH since R_{HCO_3}/GFR in TPTX dogs (group VII, Table IV) also rose from 26.6 to 28.6 mmol/liter, $P < 0.05$. The clearances of sodium, chloride, and calcium did not change significantly. The hematocrit was unchanged in group IV, but fell significantly in group VII. The clearance of phosphate fell significantly in the intact group but not in the TPTX group. Phosphorus reab-

TABLE III

Effects of PTE in Intact (Group IV) and TPTX (Group V) Dogs

	GFR	RBF	B_{HCO_3}	F_{HCO_3}	R_{HCO_3}/GFR	UfCa	P_P	P_K	Hct	$C_{Na} \times 100$/GFR	$C_{Cl} \times 100$/GFR	$C_{Ca} \times 100$/GFR	$C_P \times 100$/GFR	R_P/GFR
	ml/min		*mmol/liter*	*μmol/min*	*mmol/liter*	*mg/100 ml*	*mg/100 ml*	*meq/liter*	%	%		%		*mg/liter*
Group IV														
Control	26.2	140.2	31.9	840	24.6	6.00	5.10	2.90	35.0	6.46	2.7	4.4	30.0	37.0
SEM	4.9	26.0	0.2	153	1.2	0.22	0.61	0.08	1.5	1.50	1.3	1.3	5.4	7.0
PTE	26.6	136.0	31.9	855	22.5	5.80	4.90	2.80	33.0	7.11	1.6	4.1	39.8	32.0
SEM	4.2	10.4	0.4	139	1.1	0.26	0.69	0.07	2.2	0.82	0.7	0.7	2.4	6.0
P	>0.80	>0.80		>0.10	<0.025	<0.05	>0.4	>0.3	>0.1	>0.40	>0.10	>0.60	<0.05	<0.05
Group V														
Control	28.8	167.2	32.5	928	26.9	5.00	4.60	3.10	29.0	3.67	0.40	1.37	9.7	42.0
SEM	5.2	49.3	0.5	156	0.9	0.22	0.27	0.13	4.0	0.53	0.07	0.38	4.8	1.0
PTE	27.6	166.6	32.5	889	22.6	4.90	4.20	2.80	29.0	6.73	0.60	2.03	26.7	34.0
SEM	4.9	43.8	0.5	147	0.9	0.22	0.33	0.12	3.3	0.81	0.25	0.35	4.9	2.0
P	>0.5	>0.975		>0.6	<0.05	>0.7	>0.3	<0.02		<0.02	>0.30	>0.10	<0.001	<0.005

For explanation see Table I.

TABLE IV

Effects of Acute Hypercalcemia in Intact (Group VI) and TPTX (Group VII) Dogs

	GFR	RBF	B_{HCO_3}	F_{HCO_3}	R_{HCO_3}/GFR	UfCa	P_P	P_K	Hct	C_{Na} × 100/GFR	C_{Cl} × 100/GFR	C_{Ca} × 100/GFR	C_P × 100/GFR	R_P/GFR
	ml/min		*mmol/liter*	*μmol/min*	*mmol/liter*	*mg/100 ml*		*meq/liter*	%	%		%		*mg/liter*
Group VI														
Control	23.9	121.9	33.6	810	22.9	5.70	4.50	2.90	32.0	8.30	1.72	4.6	37.8	28.0
SEM	4.3	26.5	1.0	159	0.7	0.15	0.48	0.16	2.3	2.39	0.72	1.5	4.0	4.0
Hypercalcemia	22.4	100.9	33.6	779	26.9	7.90	5.20	2.90	32.0	5.40	1.74	4.4	21.9	41.0
SEM	3.8	16.6	1.0	150	0.8	0.29	0.35	0.12	2.2	0.57	0.43	0.7	5.2	3.0
P	>0.3	>0.2		>0.4	<0.025	<0.001	<0.05	>0.8		>0.05	>0.95	>0.8	<0.05	<0.005
Group VII														
Control	28.1	118.6	33.3	922	26.6	4.9	4.80	3.10	29.3	4.4	0.70	2.90	8.6	43.0
SEM	5.7	25.0	0.6	182	0.7	0.20	0.28	0.10	1.9	0.46	0.09	0.46	3.1	2.0
Hypercalcemia	25.5	103.0	34.1	859	28.6	7.2	6.10	3.10	26.8	4.2	1.10	4.30	14.4	53.0
SEM	5.6	23.4	1.1	176	0.8	0.31	0.18	0.12	1.8	0.92	0.33	1.30	3.5	2.0
P	>0.1	>0.2	>0.2	>0.2	<0.05	<0.001	<0.005	>0.8	<0.05	>0.8	>0.2	>0.3	>0.1	<0.05

For explanation see Table I.

sorption, however, increased with calcium infusion in both intact and TPTX dogs. This may represent either a direct effect of calcium to enhance phosphorus absorption not mediated by suppression of PTH, or a passive consequence of the rise in plasma phosphorus.

To investigate the interaction between calcium and PTE and to further ascertain that the drop in R_{HCO_3}/GFR induced by PTE was not simply due to sustained bicarbonate infusion, TPTX dogs were first made hypercalcemic and then PTE was given (Table V). Hypercalcemia caused a rise in R_{HCO_3}/GFR from 25.3 to 27.3 mmol/liter, $P < 0.005$, a change that is similar to that seen in group VII dogs (Table IV). The superimposition of PTE infusion in the face of sustained hypercalcemia caused a drop in R_{HCO_3}/GFR from 27.3 to 23.9 mmol/liter, which is significantly lower than the value during hypercalcemia ($P < 0.001$) and even lower than the control period ($P < 0.05$). The induction of hypercalcemia in this group was associated with a significant drop in RBF from 135.6 to 105.8 ml/min even though the rise in UfCa (5.6 to 7.4 mg/100 ml) was comparable to that seen in groups VI and VII. The RBF returned to near the control level (141.3 ml/min) with the infusion of PTE without a change in the ultrafilterable calcium. The clearance of phosphate did not change with hypercalcemia and rose

TABLE V

Effects of Acute Hypercalcemia and of Superimposed PTE Infusion in TPTX Dogs (Group VIII)

	GFR	RBF	B_{HCO_3}	F_{HCO_3}	R_{HCO_3}/GFR	UfCa	P_P	P_K	Hct	C_{Na} × 100/GFR	C_{Cl} × 100/GFR	C_{Ca} × 100/GFR	C_P × 100/GFR	R_P/GFR
	ml/min		*mmol/liter*	*μmol/min*	*mmol/liter*	*mg/100 ml*		*meq/liter*	%	%		%		*mg/liter*
Control	28.5	135.6	32.1	913	25.3	5.60	5.30	3.10	31.0	5.30	0.82	2.20	10.3	47.0
SEM	4.0	19.0	0.6	131	0.5	0.15	0.36	0.15	0.9	0.57	0.28	0.49	2.7	2.0
Hypercalcemia	26.4	105.8	32.0	840	27.3	7.40	6.60	3.20	30.0	4.80	1.50	2.90	10.9	60.0
SEM	3.7	18.9	0.4	107	0.7	0.14	0.29	0.08	1.3	0.68	0.59	0.58	1.4	3.0
PTE	28.2	141.3	31.7	894	23.9	7.20	5.90	3.10	31.0	7.10	1.40	4.20	34.1	41.0
SEM	3.6	16.7	0.3	114	0.3	0.10	0.32	0.13	0.8	0.43	0.31	0.55	2.4	3.0
P (control vs. hypercalcemia)	>0.05	<0.05	>0.05	>0.05	<0.005	<0.005	<0.005	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	<0.005
P (control vs. PTE)	>0.05	>0.05	>0.05	>0.05	<0.05	<0.005	<0.05	>0.05	>0.05	<0.05	>0.05	<0.005	<0.005	<0.05
P (hypercalcemia vs. PTE)	>0.05	<0.05	>0.05	>0.05	<0.001	>0.05	<0.025	>0.05	>0.05	<0.05	>0.05	>0.05	<0.001	<0.001

For explanation see Table I.

after PTE. However, there was a rise in the reabsorbed phosphorus during hypercalcemia and a fall to below control after the infusion of PTE. The clearances of both sodium and calcium increased with the infusion of PTE but did not change with hypercalcemia alone. The hematocrit remained relatively constant throughout the experiment.

The values of R_{HCO_3}/GFR in the control periods of experiments on intact dogs (groups I, II, IV, and VI) were remarkably close and averaged 24.2±0.6 mmol/liter. Parathyroidectomy raised R_{HCO_3} in groups V and VII, and to a lesser extent in group VIII; it had seemingly little effect on animals in group III. Taken together, however, R_{HCO_3} in this group averaged 25.9 ±0.4 mmol/liter, a value that is significantly higher than that of intact dogs ($P < 0.025$).

DISCUSSION

The present studies were designed to examine the specific effects of volume expansion, purified PTE, and calcium on R_{HCO_3} in the intact and the TPTX dog.

Previous studies have demonstrated that volume expansion causes a decrease in reabsorption of bicarbonate (5, 26), calcium (19), and phosphate (22, 24). Our studies in bicarbonate-loaded intact dogs confirm these findings. The concentration of ultrafilterable calcium fell, however, and this coupled with the alkalosis (20) could have stimulated PTH secretion. Since PTH has been shown to increase urinary bicarbonate excretion (7–10), it is possible that the observed decrease in bicarbonate reabsorption was the consequence of the elaboration of PTH and not of volume expansion per se. To resolve this question TPTX animals were studied. Despite hypoparathyroidism R_{HCO_3} fell significantly with volume expansion thus excluding the possibility that the effect of volume expansion is mediated entirely through PTH. In confirmation of our previous studies, volume expansion of these acutely TPTX dogs did result in a fall in phosphate reabsorption (22) even though the clearance of phosphate did not change significantly.

As early as 1935 Ellsworth and Nicholson (7) noted that the infusion of PTE was followed by a rise in urinary pH, bicarbonate, sodium, and phosphate. They postulated that PTE produced an increase in sodium excretion and secondarily increased phosphate and bicarbonate excretion. Kleeman and Cooke (8) and Nordin (9) reported similar findings but were unable to determine from their data whether the changes were the result of an increase in GFR or of a direct effect of PTE on the renal tubule. The effects of PTE have been shown to precede any rise in the GFR by Hellman et al. (10). They postulated that the PTE inhibits sodium-for-hydrogen ion exchange in the renal tubule and that the inhibition is mediated by direct interference with the ability of the kidney to maintain a hydrogen ion gradient between the renal tubular cells and tubular fluid. These findings have clinical significance since primary hyperparathyroidism (12, 13) and hyperparathyroidism secondary to intestinal malabsorption (14, 15) and to renal failure are associated with systemic acidosis. It has also been shown that the acidosis can be blunted or corrected by parathyroidectomy (16). These observations have led to the suggestion that PTH causes the systemic acidosis by depressing tubular absorption of bicarbonate. This view, however, has been challenged by a number of authors. Kurtzman, Karlinsky, and Sager (27) could not demonstrate a decrease in R_{HCO_3} when they infused 60 U PTE/h in dogs. Other investigators (28–30) have attributed the changes in bicarbonate homeostasis in hyperparathyroidism to phosphate depletion induced by PTH rather than to the direct action of the hormone on R_{HCO_3}.

To help resolve this conflict we studied the effects of a purified PTE, that is devoid of hemodynamic effects (31, 32), in intact and TPTX dogs loaded with bicarbonate. The infusion of PTE in a dose similar to that previously employed by Hellman et al. (10) led to a fall in bicarbonate absorption in both groups, but more marked in the TPTX group. The infusion of PTE produced no change in GFR or RBF. Thus, PTE appears to exert a direct effect on the renal tubules to inhibit hydrogen ion secretion and R_{HCO_3}, and this effect is not dependent on the induction of a state of phosphate depletion. Since PTE has been shown to inhibit proximal tubular sodium and water absorption (31, 32) it is possible that R_{HCO_3} in this segment of the nephron is also inhibited. It may be argued, however, that the fall in bicarbonate absorption in our experiments may have been due to the expansion of extracellular volume consequent to the continued infusion of bicarbonate solution. In experiments on dogs receiving bicarbonate solution for a total duration comparable to that of the experiments on PTE, however, R_{HCO_3} remained stable. Furthermore, the hematocrit in the experimental periods was unchanged from that in control in five of the six groups not receiving saline solution. Finally, in four of the six groups not given saline, the fraction of the filtered chloride excreted was less than 1% and does not rise significantly in any of the groups during the experimental periods. These observations militate against significant expansion by bicarbonate solution in the present experiments both in the control and experimental periods. Thus, it appears that the fall in R_{HCO_3} was not spontaneous, but rather the consequence of PTE infusion. The difference between our data and those of Kurtzman et al. (27) may be attributed to the larger dose employed in the present studies. However, since they did observe a fall in R_{HCO_3} after PTE, their conclusion differs from

ours primarily because R_{HCO_3} also fell in their control animals thereby obscuring the effects of PTE. There is no disagreement, however, with respect to the depression of R_{HCO_3} by PTE in TPTX animals.

Metabolic alkalosis has been associated with extraparathyroid hypercalcemia (33, 34). The mechanism for the alkalosis has not been elucidated, but it is possibly the consequence of suppression of PTH secretion since hypoparathyroidism has been associated with alkalosis (17), and thyroparathyroidectomy in our experiments significantly raises R_{HCO_3}. Calcium, however, has been shown to stimulate tubular secretion of hydrogen ion (11) and could conceivably enhance tubular R_{HCO_3}. Indeed, when we induced acute hypercalcemia in intact dogs R_{HCO_3} rose and a similar rise was observed in TPTX dogs. Thus, calcium appears to enhance bicarbonate absorption by a direct effect on the renal tubules not dependent on the suppression of PTH. Calcitonin also is secreted after elevation of the serum calcium, and although its effect on bicarbonate absorption is variable in different species (35, 36) it does not appear to play a role in mediating the effect of calcium on bicarbonate absorption since calcium exerted an effect in animals that were also thyroidectomized and free of the potential for secreting this hormone.

Since hypercalcemia and hyperparathyroidism frequently coexist we investigated the interrelationship of calcium and parathyroid hormone action on the renal tubule. PTE was infused into TPTX dogs made hypercalcemic. Hypercalcemia caused a rise in R_{HCO_3} and an increase in the reabsorption of phosphate as shown in a similar group of dogs discussed above. Although RBF fell somewhat in this group, GFR was not altered. The infusion of PTE returned the R_{HCO_3} to below the control value. The RBF and the reabsorbed phosphate returned to control values. Therefore, it is apparent that calcium exerts a separate action on the renal tubule and this effect can be suppressed with PTE. These studies also lend further support to the conclusion that PTE does depress tubular absorption of bicarbonate. This is the probable explanation for the observation that patients with primary hyperparathyroidism may be acidotic despite hypercalcemia.

Of interest in this group of studies is the demonstration that calcium infusion enhanced phosphate reabsorption even when the parathyroid glands had been ablated, thus supporting the view that a phosphate transport system may exist which is independent of PTH and responsive to calcium (37). Lavender and Pullman have also observed increased phosphate absorption when they infused calcium into the renal arteries of dogs (38). Wen, on the other hand, could not detect a decrease in phosphate clearance after the infusion of $CaCl_2$ into dogs (39). Also at variance with our studies are the observations of Eisenberg (40) who reported increased clearance of phosphate after infusion of calcium for 72 h in hypoparathyroid patients. His patients, however, were hypocalcemic at the outset and became normocalcemic after the calcium infusion. They were also preloaded with an acidic mixture of sodium phosphate, and they received a prolonged infusion of calcium and also received 2 liters of half-isotonic saline every 24 h. The role of each of these factors in bringing about the increased clearance and decreased absorption of phosphate remains to be elucidated. Thus, the data on the effect of Ca^{++} on phosphate reabsorption are quite conflicting. Because of the inconsistency between phosphate clearance and reabsorption in our TPTX dogs made hypercalcemic, it is possible that the apparent enhancement of phosphate reabsorption is simply a passive consequence of the rise in serum phosphorus.

In summary, the lowering of R_{HCO_3} by volume expansion does not depend solely on the stimulation of PTH secretion. PTH, however, does appear to act directly on the renal tubule to lower R_{HCO_3}. Calcium enhances R_{HCO_3} in the presence and in the absence of PTH and thyrocalcitonin. The enhanced R_{HCO_3} by calcium can be suppressed by elevated levels of PTH. The effects of volume expansion, calcium, and PTH do not appear to be mediated by changes in renal hemodynamics although, in the case of calcium infusion in TPTX dogs, this cannot be completely excluded. Calcium also appears to enhance phosphate reabsorption independent of PTH; this apparent effect, however, may have been the passive consequence of increased plasma phosphorus.

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