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THE EFFECT OF PARATHYROID EXTRACT ON RENAL TUBULAR CALCIUM REABSORPTION IN THE DOG *

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Several studies have suggested that parathyroid hormone augments renal tubular calcium reabsorption. In 1929 Albright and Ellsworth (1) studied the effect of parathyroid extract on calcium balance in a boy with idiopathic hypoparathyroidism. Calcium excretion during parathyroid administration remained below control values although plasma calcium increased by about 30 per cent. From a consideration of this experiment, Talbot, Sobel, McArthur, and Crawford (2) first suggested that parathyroid secretion might influence tubular reabsorption of calcium. Talmage and Krintz (3) observed that calcium excretion in the rat increased within several hours after parathyroidectomy despite falling plasma calcium values. More recently, Kleeman and associates (4) have investigated the effect of parathyroid on renal calcium excretion with clearance techniques in man and dog. From a variety of studies, they concluded that parathyroid secretion decreased the renal clearance of calcium.

In these previous experiments, nonparathyroid factors that affect renal calcium excretion were not fully controlled. Calcium excretion is known to vary directly with filtered calcium; under most circumstances, excreted calcium is a small fraction of the filtered load (4, 5). Therefore, to demonstrate a tubular action of parathyroid it is necessary to show rigorously that changes in urinary calcium do not reflect small changes in filtered calcium. In addition, Walser (6) has recently shown that calcium clearance is a direct

function of sodium clearance, a phenomenon that had not fully been appreciated in previous studies.

The present experiments were undertaken to investigate in the dog the possible effect of parathyroid extract (PTE) on tubular calcium reabsorption under conditions in which filtered calcium and sodium excretion could be adequately controlled. Our data demonstrate unequivocally a tubular action of PTE on calcium reabsorption. Stop-flow studies, performed in an attempt to define the locus of this action, indicate that it is exerted, at least in part, at a distal site.

METHODS

Female mongrel dogs weighing from 15 to 25 kg were used in all studies. Each dog was thyroparathyroidectomized before study. Postoperatively, the dogs were given 30 mg thyroid daily and fed a high calcium diet. Calcium gluconate was administered parenterally when signs of tetany were present. No experiment was performed before the fourth postoperative day.

One group of dogs was studied with standard clearance techniques. Infusions of saline and calcium chloride were maintained in order to produce suitable rates of sodium and calcium excretion. When excretion was stable, samples from three to five control clearance periods were obtained. Thereafter, a priming dose of 100 U of Lilly PTE was given, and an infusion of 60 U per hour was begun. Within the next 5 hours, the rates of the sodium and calcium infusions were changed, if necessary, to ensure stabilization of sodium excretion and of plasma calcium at about 10 per cent above control values. Samples from three to five experimental periods were then obtained. The same protocol was used in several experiments in which either purified bovine parathyroid hormone or formalin-inactivated Lilly PTE was administered.

A second group of dogs was studied with a stop-flow technique slightly modified from the one described by Jaenike and Berliner (7). This modification consisted of catheterizing the ureter of the experimental kidney with both PE 50 and PE 240 polyethylene tubing (Intramedic); thus, puncture of the renal parenchyma was avoided. The opposite ureter was ligated in some cases in an attempt to obtain a greater urine flow from the experimental kidney. Infusions of creatinine, sodium chlo-

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ride, and calcium chloride were maintained throughout the study. Stop-flow experiments were not performed until urine flow from the experimental kidney was at least 4 ml per min and urinary calcium at least 4.5 mEq per L. Inulin, used as a marker for the arrival of post-occlusive glomerular filtrate, was injected 1 minute before the termination of stop-flow. Stop-flow samples of 0.25 to 0.50 ml were collected after a 4-minute period of ureteral occlusion. After the control experiment was performed, a priming dose of 100 U PTE was given and a constant infusion of 60 U per hour was begun. Within the next 3 hours, the rate of the calcium infusion was changed, as necessary, to ensure stabilization of urinary calcium at about 10 per cent above the free-flow concentration in the control experiment. The stop-flow experiment was then repeated. In both experiments in any one dog, sample size was approximately uniform.

Two paired studies were performed in which no extract was administered. The repeat stop-flow experiment was performed 2 hours after the control experiment.

Sodium was measured by flame photometry with lithium as an internal standard. Inulin was estimated by method of Walser, Davidson, and Orloff (8). Creatinine was determined either by the method of Kennedy, Hilton, and Berliner (9), or by a modification of the method of Folin and Wu (10) designed for the Auto-Analyzer. Phosphate was determined by the method of Fiske and Subbarow (11). Calcium was measured by direct titration of alkalized whole plasma, plasma ultrafiltrate, or urine with EDTA, by use of an indicator (12). Ultrafiltration of plasma was carried out by the method of Toribara, Terepka, and Dewey (13).

RESULTS

Effect of PTE on calcium reabsorption. Nine clearance experiments were performed on six dogs. Excreted calcium during PTE infusion decreased significantly from control values in every case except one, despite the fact that filtered calcium and sodium excretion were increased or unchanged. A representative experiment is shown in Table I. Calcium excretion during the control periods averaged 97.4 μ Eq per minute. Collection of the experimental periods was begun about 2 hours after the PTE infusion was started. In this experiment it was not necessary to change the rates of the calcium and sodium infusions during this interval to obtain suitable stable levels of plasma calcium and sodium excretion. Calcium excretion during PTE infusion averaged 82.6 μ Eq per minute, a significant decrease from the control value. Filtered calcium was markedly increased and sodium excretion slightly increased in the experimental periods. The increase in filtered calcium in this experiment was due entirely to a

TABLE I
The effect of parathyroid extract on calcium excretion in a representative experiment *

Time minutes	V ml/min	GFR ml/min	P ^T Ca μ Eq/ml	P ^{UF} Ca μ Eq/ml	Filtered Ca μ Eq/min	U _{Ca} μ Eq/ml	UV _{Ca} μ Eq/min	UV _{Na} μ Eq/min	PP μ moles/ml	UV _P μ moles/min	Filtered phosphate μ moles/min	Reabsorbed phosphate μ moles/min
0	Infusion I started: 1 mg/ml creatinine in 0.9% NaCl, at 12 ml/min.											
5	Infusion II started: 0.88% CaCl ₂ in 1.35% NaCl, at 3.6 ml/min.											
85	Infusion II slowed to 2.2 ml/min.											
86-92	7.73	97	6.12	4.30	417	12.9	99.7	1530	2.00	4.3	194	190
92-98	7.90	98	6.05	4.25 †	417	12.3	96.4	1580	2.01 †	5.1	197	192
98-104	8.50	99	6.05	4.20	416	11.3	96.0	1590	2.01	6.2	199	193
104-111	8.77	98	6.05	4.33	424	11.1	97.3	1640	2.05	6.9	201	194
112	100 U PTE intravenously.											
242-250	9.67	118	5.92	4.36	514	8.48	82.0	1670	1.56	51.4	184	133
250-259	9.73	115	6.05	4.32 †	497	8.85	86.2	1660	1.56 †	50.4	179	129
259-266	9.70	112	6.05	4.28	480	8.48	82.3	1720	1.55	49.4	174	125
266-274	8.70	114	6.05	4.60	524	9.18	79.9	1560	1.52	47.0	173	126

* Abbreviations: V, urine flow; P^TCa, plasma total calcium; P^{UF}Ca, plasma ultrafiltrable calcium; U_{Ca}, urinary calcium concentration; UV_{Ca}, calcium excretion; UV_{Na}, sodium excretion; P_P, plasma phosphate; UV_P, phosphate excretion; P^TE, parathyroid extract.

† Interpolated value.

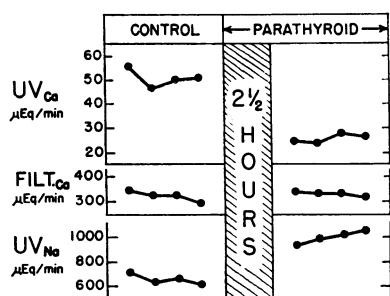


FIG. 1. EFFECT OF PARATHYROID EXTRACT ON CALCIUM EXCRETION: A REPRESENTATIVE EXPERIMENT. Each point represents the value from a single clearance period approximately 10 minutes long. UV, urinary excretion; FILT.Ca, filtered calcium.

rise in glomerular filtration rate (GFR); plasma calcium was essentially constant.

Figure 1 shows a similar experiment in a different dog. Calcium excretion averaged about 50 μ Eq per minute during the control periods. During the experimental periods, calcium excretion had decreased strikingly from the control values to a mean value of about 25 μ Eq per minute. Filtered calcium was essentially the same in the control and experimental periods. Sodium excretion was greatly increased in the experimental periods.

A summary of the data obtained in these experiments is presented by the closed circles and solid lines in Figure 2. Calcium excretion fell during PTE infusion in each experiment. This decrease was statistically significant— $p < 0.01$ by Fisher's t test—in each case except one (Experiment 6).¹ Except for a slight fall in sodium excretion on one occasion (Experiment 5), sodium excretion and filtered calcium increased or were stable in all studies. Increased filtered calcium resulted from an increased plasma calcium in three experiments, from an increased GFR in four experiments, and from a combination of both in two experiments. The effect of PTE on calcium excretion was evident throughout the wide ranges of calcium excretion and filtered calcium and sodium in these experiments.

¹ The way Figure 2 is plotted tends to minimize the significance of the decrease in calcium excretion in Experiments 1 and 7, in which the control rate of calcium excretion was very low. While the decrease in the rate of calcium excretion was smaller in these experiments than in the others, the changes in urinary calcium concentrations were striking. In Experiment 1, calcium concentration fell from 17.6 μ Eq per ml to 2.6; in Experiment 7, from 6.3 to 1.8 μ Eq per ml.

Effect of purified bovine parathyroid hormone and of "inactivated" PTE. Two experiments were performed in which purified parathyroid hormone² was infused instead of Lilly PTE. After samples from the control periods were obtained, a priming dose of 100 U of hormone was given and a constant infusion of 60 U per hour started. The results of these studies are shown in Figure 3. Calcium excretion in Experiment d rose during hormone administration from a mean control value of 32 μ Eq per minute to a mean value of 43 μ Eq per minute. During the experimental periods, both filtered calcium and sodium excretion were higher than control values. The same dog was used in Experiment 9, in which Lilly PTE was infused. Mean calcium excretion decreased significantly from 32 μ Eq per minute in the control periods to 23 μ Eq per minute in the experimental periods. Increases in filtered calcium and sodium excretion in this experiment were comparable to those seen with hormone infusion. Purified hormone was infused into a different dog in Experiment c. Calcium excretion rose slightly during the experimental periods without increases in

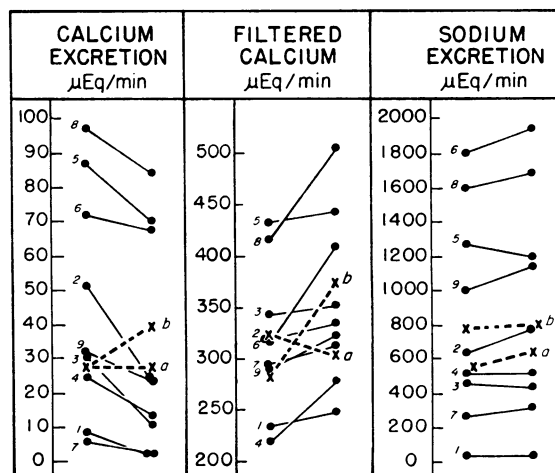


FIG. 2. EFFECT OF PARATHYROID EXTRACT ON CALCIUM EXCRETION: DATA FROM ALL EXPERIMENTS. Each point represents the mean value from three to five clearance periods. In each column, the point on the left represents the control periods, the point on the right the experimental periods. In the experiments represented by broken lines (a and b) formalin-inactivated parathyroid extract was administered.

² Bovine parathyroid hormone with a potency of 2,000 U per mg was prepared and assayed by Dr. Howard Rasmussen.

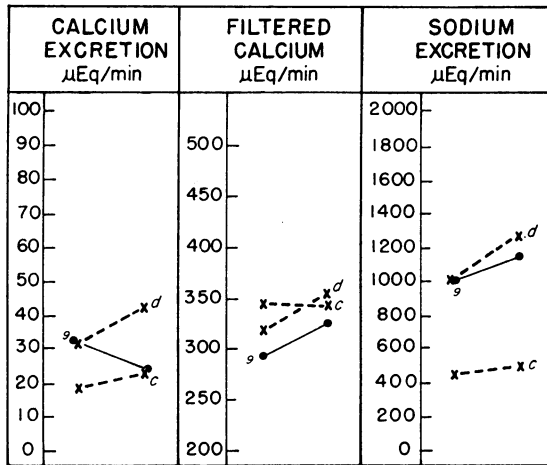


FIG. 3. FAILURE OF PURIFIED PARATHYROID HORMONE TO INFLUENCE CALCIUM EXCRETION. Data are plotted as in Figure 2. Experiments in which hormone was infused are shown by broken lines. An experiment with parathyroid extract is shown by the solid lines.

filtered calcium or sodium excretion. Phosphate excretion data from the experiments in which hormone was infused are summarized at the bottom of Table II. In each of the two experiments, hormone infusion was accompanied by decreased tubular reabsorption of phosphate. A sample of the lot of hormone used in these studies was subsequently reassayed in Dr. Rasmussen's laboratory and was found to cause increases in plasma calcium in parathyroidectomized rats (14).

Two experiments were performed with parathyroid extract "inactivated" with formalin by the method of Stewart and Bowen (15). These experiments are shown by broken lines in Figure 2. In neither study did calcium excretion fall after the administration of formalin-inactivated PTE.

Effect of PTE on phosphate reabsorption. The effect of PTE on phosphate reabsorption was determined in all clearance experiments. Data from one experiment with PTE are given in Table I and the data from all the studies with PTE are summarized in the first two sections of Table II. Tubular reabsorption of phosphate was decreased during PTE infusion in every case except one (Experiment 3). Phosphate excretion increased during the administration of extract in every case. In Experiments 1, 5, 6, 8, and 9, this increase occurred despite a fall in the filtered load. In Experiments 2, 3, 4, and 7, filtered phosphate was unchanged or increased during PTE infusion. In each case (except Experiment 3), however, the increase in excretion exceeded the increase in filtered load.

Stop-flow experiments. Stop-flow experiments were performed on six dogs in an attempt to determine the locus of action of PTE on the renal tubule. The stop-flow patterns were similar in all. One such experiment is shown in Figure 4. In the absence of parathyroid, no distinct minimal

TABLE II
The effect of parathyroid extract on phosphate excretion

Experiment	Phosphate, in μ moles per minute					
	Control			Experimental		
	Filtered	Excreted	Reabsorbed	Filtered	Excreted	Reabsorbed
1	81.0	0.6	80.4	66.4	13.7	52.7
5	178	9.1	169	145	37.0	108
6	188	43.8	144	161	57.5	105
8	197	5.6	191	177	48.5	128
9	372	14.4	357	353	57.6	294
2	152	9.0	143	168	55.6	112
3	123	0	123	162	39.0	123
4	146	0	146	168	57.1	111
7	114	0.8	113	126	53.4	73.0
a	124	12.3	112	124	48.5	75.5
b	167	26.2	141	167	42.8	124
c	265	10.9	254	203	42.2	161
d	318	19.9	298	296	49.2	247

urinary calcium concentration was seen. When PTE was infused, however, a definite calcium pattern emerged. There was a progressive decline in urinary calcium until the twelfth sample was reached. In this case the minimal value was 1.7 μ Eq per ml. Subsequently, calcium concentration increased until the nineteenth sample was reached and thereafter was relatively stable. With PTE, calcium concentrations in the later, proximal samples never reached the values seen in the comparable control samples. The patterns of urinary sodium concentrations in both parts of the study are similar to that reported by Jaenike and Berliner (7). In this study, free-flow and stop-flow urinary sodium concentrations were higher during PTE infusion than in the control experiment. The minimal sodium concentration during PTE infusion was seen in the ninth sample. During PTE infusion, the calcium minimum was just proximal to the sodium minimum. Urine to plasma creatinine concentration (U/P creatinine) ratios were used to measure water reabsorption. The ratios in the samples with the minimal calcium concentrations were essentially the same in the absence and in the presence of PTE.

The data from all six studies are summarized in the upper part of Table III. In each control experiment, the minimal stop-flow calcium concentration was somewhat less than the free-flow value. The difference, however, was never more than 30 per cent of the free-flow value. In contrast, the minimal stop-flow concentration was always strikingly less than the free-flow value when

PTE was infused. Minimal stop-flow calcium concentrations with PTE varied from 1.7 to 2.6 μ Eq per ml, representing a fall of at least 60 per cent from corresponding free-flow values.

The U/P creatinine ratios of the samples with the minimal stop-flow calcium concentrations are shown in the fourth and eighth columns of Table III. These ratios ranged from 7.7 to 24.8 in the control experiments and from 4.6 to 16.4 in the experiments in which PTE was infused. The ratios were roughly comparable in the control and PTE experiments of the first three studies. In the remaining studies, the ratio was larger in the control experiment.

Corrections for differences in water reabsorption in each experiment were made by division of the minimum stop-flow calcium concentration by the U/P creatinine ratio of the same sample. The results of these calculations are shown in the fifth and ninth columns of Table III. In five of six cases, the corrected minimum calcium concentration in the control experiments was greater than the corresponding figure in the PTE experiment.

Repetition of stop-flow in the absence of PTE. To eliminate the possibility that simple repetition of stop-flow accounts for the differences between the control and PTE experiments, two additional paired studies were performed in dogs in which no PTE was administered. In neither dog was the second pattern of urinary calcium different from the first. Data from these experiments are summarized at the bottom of Table III.

TABLE III
Summary of data from stop-flow experiments*

Study	Control						Experimental						
	Free-flow U_{Ca}	Stop-flow U_{Ca}	P_{Ca}	U/P creat †	U_{Ca} U/P creat		Free-flow U_{Ca}	Stop-flow U_{Ca}	P_{Ca}	U/P creat †	U_{Ca} U/P creat		$U_{Na}\dagger$
	μ Eq/ml	μ Eq/ml	μ Eq/ml		μ Eq/ml	μ Eq/ml	μ Eq/ml	μ Eq/ml	μ Eq/ml		μ Eq/ml	μ Eq/ml	
1	4.8	3.9	5.8	16.2	0.241	63	5.1	1.7	7.1	16.4	0.104	112	
2	5.0	4.7	4.7	16.7	0.281	93	6.8	2.6	5.1	13.5	0.193	107	
3	6.0	4.2	6.4	8.6	0.488	54	7.6	2.1	7.8	8.2	0.256	108	
4	5.1	4.9	5.2	24.8	0.198	83	5.2	2.0	6.4	12.7	0.158	90	
5	4.7	4.6	5.9	13.9	0.346	49	6.1	2.3	8.3	5.9	0.390	75	
6	5.2	3.7	7.2	7.7	0.480	96	7.1	2.0	8.6	4.6	0.435	166	
a	5.2	3.7	7.7	12.3	0.301	36	6.2	5.2	8.5	4.9	1.06	85	
b	5.0	3.9		11.5	0.339	58	5.7	4.7		9.5	0.495	99	

* Abbreviations as in Table I, and U/P creat = urine to plasma creatinine concentration ratio.
† Value in sample with minimal U_{Ca} .

DISCUSSION

The present experiments were designed to study the effect of PTE on tubular calcium reabsorption under conditions in which filtered calcium and sodium excretion were adequately controlled. Calcium excretion decreased significantly during PTE infusion in eight of nine experiments. Except for a slight fall in sodium excretion on one occasion, sodium excretion and filtered calcium were increased or unchanged. Both increases in filtered calcium (4, 5) and increases in sodium excretion (6) are known to result in increased calcium excretion. Therefore the decrease in calcium excretion during PTE infusion despite increases in filtered calcium and in sodium excretion must be a parathyroid effect. The decrease in excreted calcium was evident whether the increase in filtered load resulted from increased plasma calcium, increased GFR, or from a combination of both. This effect of PTE was demonstrated over wide ranges of control calcium excretion, of filtered calcium, and of sodium excretion. Calcium excretion did not fall in the four experiments in which formalin-inactivated PTE or purified parathyroid hormone was infused. These data show that there is no regular tendency for calcium excretion to fall spontaneously with time during prolonged experiments. Thus, our data demonstrate clearly that in the dog PTE directly enhances renal tubular calcium reabsorption. In addition, the data on phosphate excretion indicate that PTE decreases tubular reabsorption of phosphate, as has been reported by others³ (16, 17).

An analysis of the relation between calcium excretion and sodium excretion was made using data from all clearance experiments. As Walser (6) has reported, a strongly positive correlation was found. The present studies, however, do not dissociate the effect of sodium excretion from that of

³ In the two experiments in which formalin-inactivated PTE was infused, an increase in phosphate excretion was observed, as reported by Stewart and Bowen (15). They concluded that this phosphaturic effect was due to an artefact because the formalin-treated extract failed to raise plasma calcium in parathyroidectomized dogs. In the two present experiments, however, phosphate excretion increased significantly despite unchanged filtered loads of phosphate, demonstrating decreased tubular reabsorption. Since reabsorption is similarly decreased by PTE and by "inactivated" extract, the phosphaturic effect of the latter is not necessarily an artefact.

urine flow. Since saline was infused in all experiments, urine flow and sodium excretion were also highly correlated.

Calcium excretion did not decrease in the two experiments in which bovine parathyroid hormone was infused. Owing to the limited supply of available hormone, more data could not be obtained. The striking contrast, however, between the effects of purified hormone and Lilly PTE on calcium excretion seem to justify presentation of the limited data. The contrast between the effects of the hormone and the extract is shown particularly well in Experiments 9 and d in Figure 3. These experiments were performed on the same dog, and comparable changes in filtered calcium and sodium excretion between control and experimental periods were obtained in both studies. Calcium excretion, however, increased when purified hormone was infused and decreased, as expected, when extract was given. In each case, decreased tubular phosphate reabsorptive capacity was observed (Table II). Furthermore, a sample of this lot of hormone was subsequently found to cause increases in plasma calcium in parathyroidectomized rats.

There are several possible explanations of the different effect of hormone and extract on calcium excretion. First, the action of Lilly PTE on tubular calcium reabsorption may be an artefact due to impurities present in the extract. This explanation appears unlikely, since the experiments of Talmage and Krintz (3) and some of those of Kleeman and associates (4) suggest decreases in tubular calcium reabsorption after parathyroidectomy alone. Second, the ability to raise plasma calcium and to decrease urinary calcium may be present in different proportions in the hormone and extract. The hormone and extract units used in these experiments are defined in terms of ability to increase plasma calcium. Therefore, the dose of hormone, although equal in units to the dose of extract, may still have been insufficient to decrease urinary calcium. The data do not permit evaluation of this possibility. Finally, it is possible that PTE contains several physiologically active parathyroid hormones. Copp and associates (18) have recently demonstrated in the dog the presence of a humoral agent of parathyroid origin that causes an immediate decrease in plasma calcium.

Since our data demonstrated a tubular action of PTE, stop-flow studies were performed in an attempt to define the locus of this action on the renal tubule. In the absence of PTE, no distinct minimal calcium concentration was seen. When, however, PTE was infused into the same dog, there was an unequivocal minimal concentration, as shown in Figure 4. In every case, the calcium minimum coincided with or was slightly proximal to the sodium minimum. The latter is usually considered to represent a distal site. The stop-flow patterns during PTE infusions are similar to those observed by Howard, Wilde, and Malvin (19) in the normal dog. Thus, roughly comparable patterns are seen in the normal dog and in the parathyroidectomized dog receiving PTE. As shown in Table III, the calcium minimum in each control experiment was only slightly less than the free-flow value. In contrast, the calcium minimum when PTE was given was always strikingly less than the free-flow value. In each study, the control calcium minimum was higher than the experimental calcium minimum. Thus, the present stop-flow studies demonstrate that PTE exerts an effect on tubular calcium reabsorption at a distal site.

This difference between control and experimental calcium minima cannot be explained by comparable differences in plasma calcium levels.

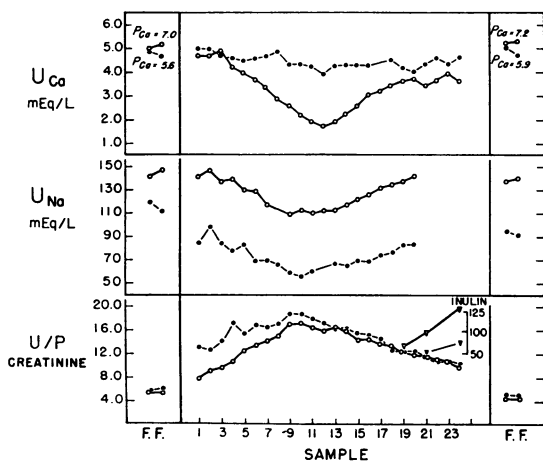


FIG. 4. EFFECT OF PARATHYROID EXTRACT ON STOP-FLOW PATTERNS. Closed circles represent values from the control experiment, open circles those from the experiment in which parathyroid extract was infused in the same dog. Free-flow values (F.F.) are shown flanking the stop-flow values of urinary concentrations and urine to plasma concentration ratio.

On the contrary, plasma calcium in each experiment in which PTE was infused was greater than the control value, so that differences in U/P calcium were even more striking than the differences in calcium minima. Similarly, these results cannot be due to simple repetition of stop-flow, as shown by the two paired studies in which no PTE was infused. In both studies the second pattern of urinary calcium was similar to the first.

These studies also eliminate the possibility that the differences in urinary calcium in studies with PTE are due to the differences observed in urinary sodium. Although urinary sodium was higher in the second part of each study, the difference was at least as great in the two paired control studies as in the six studies with PTE. If the data of Walser (6), derived from clearance experiments, can be extrapolated to stop-flow studies, the observed increase in sodium concentration would be expected to result in an increase, not a decrease, in urinary calcium. We are unable to give a definite explanation of the increase in urinary sodium, but the two control studies show that it is probably not due to PTE.

The possible effect of differences in water reabsorption on minimal stop-flow urinary calcium concentrations must be considered. Water reabsorption as measured by the U/P creatinine ratios (Table III) was roughly the same during the control and experimental parts of Studies 1 through 3. Therefore, differences in water reabsorption cannot account for the differences in calcium minima in these experiments. In Studies 4 through 6, however, the U/P creatinine ratios for the control experiments were much larger than the ratios for the experiments in which PTE was given. Correction for differences in water reabsorption can be made by dividing the minimal stop-flow calcium concentration by the U/P creatinine ratio of the same sample. As seen in the sixth and eleventh columns of Table III, the corrected values are nearly equal in the control and experimental parts of Studies 4 through 6. However, the use of this correction in the evaluation of these experiments is probably not valid. If differences in water reabsorption influence minimal stop-flow calcium concentrations, a direct correlation between the calcium minima and the U/P creatinine ratios ought to exist. These data for all experiments are plotted in Figure 5. It is read-

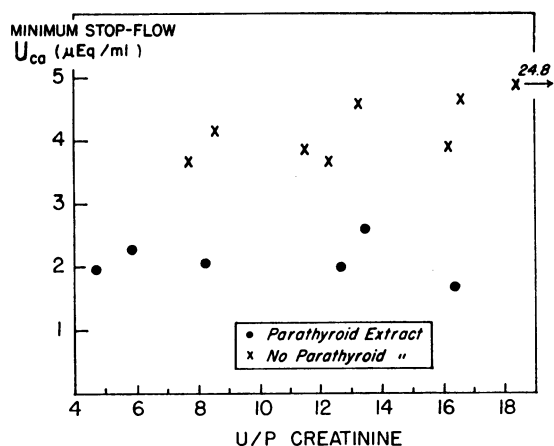


FIG. 5. LACK OF CORRELATION BETWEEN MINIMAL STOP-FLOW URINARY CALCIUM CONCENTRATIONS AND URINE TO PLASMA CREATININE CONCENTRATION RATIOS.

ily seen that there is no correlation between urinary calcium and U/P creatinine in either type of experiment. Thus, we conclude that differences in water reabsorption do not significantly affect the minimal stop-flow calcium concentrations and that the use of this correction in the evaluation of these experiments is probably misleading. The independence of the calcium minimum from water reabsorption suggests that calcium transport in the distal tubule during stop-flow proceeds until a minimal concentration is attained in the urine.

No conclusions can be drawn from our data concerning the possibility that, in addition to its distal action, PTE acts proximally to enhance calcium reabsorption. In the experiments performed during PTE infusion, calcium concentrations in the more proximal samples were consistently less than comparable control values. This difference in concentrations is consistent with a proximal action of PTE. It is equally possible, however, that the difference is due to the fact that proximal samples obtained when PTE has been infused must pass, before collection, through a distal tubule with augmented reabsorptive capacity.

The present data, and those of previous workers (1-4), indicate that PTE can promote tubular reabsorption of an amount of calcium equal to about 2 per cent of the filtered load. Variations in filtered calcium undoubtedly play a major role in determining calcium excretion. The facultative reabsorption of even a small fraction of filtered

calcium, however, can exert an important effect on the fine regulation of calcium excretion. This action of PTE on calcium excretion may be considered to be somewhat analogous to the effect of aldosterone on sodium excretion. Clinically, this renal effect of PTE presumably accounts for such observations as elevated calcium excretion in the face of low plasma calcium in some hypoparathyroid patients treated with vitamin D (4).

SUMMARY

1. The effect of parathyroid extract on renal calcium excretion in the dog was studied with clearance techniques. Filtered calcium and sodium excretion were carefully controlled. In eight of nine experiments, calcium excretion during administration of parathyroid extract decreased significantly despite increased or unchanged filtered calcium and sodium excretion. Increased filtered calcium resulted from increased plasma calcium concentration, increased glomerular filtration rate, or both. Decreased calcium excretion was observed over wide ranges of control calcium excretion, filtered calcium, and sodium excretion.

2. Stop-flow studies show that when parathyroid activity is present, there is a marked fall in urinary calcium concentration at a distal site, whereas there is little or no fall in concentration in its absence.

3. It is concluded that parathyroid extract directly enhances tubular calcium reabsorption, and that this effect is exerted, at least in part, at a distal site.

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