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Decreased phosphate reabsorption by volume expansion in the dog

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Decreased phosphate reabsorption by volume expansion in the dog. The effect of volume expansion on tubular phosphate reabsorption (TRP) was studied in intact and acutely thyroparathyroidectomized (TPTX) dogs infused with a neutral phosphate solution. The infusion of a Ca^{++}-containing balanced electrolyte solution increased $C_{Na} \times 100/GFR$ from 0.23 to 6.87% and reduced $TRP \times 100/GFR$ from 6.2 to 3.6 mg/min in the intact dogs; in TPTX dogs these values changed from 0.35 to 7.02% and from 6.7 to 4.6 mg/min, respectively. Ultrafilterable Ca^{++} did not fall in either group. When Ca^{++} was omitted from the loading electrolyte solution ultrafilterable Ca^{++} fell significantly in both groups. In the intact dogs $C_{Na} \times 100/GFR$ increased from 0.48 to 6.26% and $TRP \times 100/GFR$ fell from 4.5 to 2.8 mg/min; in TPTX dogs these values changed from 0.48 to 8.26% and from 6.5 to 4.1 mg/min. Thus volume loading appears to inhibit TRP regardless of the presence or absence of parathyroid hormone, and whether dilutional hypocalcemia was prevented or not. It is concluded that the previously reported blunting of the phosphaturic effect of volume expansion by acute parathyroidectomy or calcium infusion may have been due to a low serum phosphorus or filtered phosphate load relative to an increased threshold or tubular reabsorptive maximum or decreased splay.

Diminution de la réabsorption tubulaire des phosphates par l'expansion chez le chien. L'effet de l'expansion sur la réabsorption tubulaire des phosphates (TRP) a été étudié chez des chiens intacts et thyroparathyroidectomisés (TPTX) perfusés avec une solution de phosphate neutre. La perfusion d'une solution équilibrée en Ca^{++} a augmenté $C_{Na} \times 100/GFR$ de 0,23 à 6,87% et diminué $TRP \times 100/GFR$ de 6,2 à 3,6 mg/min chez les chiens intacts. Chez les chiens TPTX ces valeurs passent de 0,35 à 7,02% et de 6,7 à 4,6 mg/min respectivement. Le calcium ultrafiltrable n'a diminué dans aucun des deux groupes. Quand la solution électrolytique perfusée ne contenait pas de Ca^{++} le calcium ultrafiltrable diminuait dans les deux groupes. Chez les chiens intacts $C_{Na} \times 100/GFR$ augmentait de 0,48 à 6,26% et $TRP \times 100/GFR$ diminuait de 4,5 à 2,8/100 ml. Chez les chiens TPTX ces valeurs évoluaient de 0,48 à 8,26% et de 6,5 à 4,1 mg/100 ml. Il apparaît, par conséquent, que l'expansion inhibe TRP indépendamment de la présence ou de l'absence de parathormone et indifféremment à la présence ou l'absence d'une hypocalcémie de dilution. Il est conclu que l'effacement, précédemment rapporté, de l'effet phosphaturique de l'expansion par la parathyroidectomie ou la perfusion de calcium peut avoir été lié à un abaissement du phosphore plasmatique ou du débit de phosphate filtré par rapport à un seuil ou une capacité de réabsorption maximale augmentés.

The administration of salt loads increases the excretion of phosphate in the intact rat [1, 2], dog [3] and man [4]. This effect in the dog is thought to be the specific consequence of expansion of extracellular fluid volume since it persists despite reduction of the filtered phosphate load [3, 5] but is abolished by constriction of the thoracic inferior vena cava [5]. The observations that salt loading increased phosphate excretion in thyroparathyroidectomized dogs [3, 5] and that thoracic inferior vena cava constriction abolished this effect [5], were interpreted to mean that release of parathyroid hormone (PTH) or other alterations in blood composition could not account for the phosphaturia. In the rat, however, acute suppression of PTH activity by cautery of the parathyroid glands [6, 7] or by infusion of calcium [7] prevented the rise in phosphate excretion induced by saline infusion. Qualitatively similar results in the dog were recently described in a preliminary report [8]. The reasons for the discrepancy in the effects of suppression of PTH activity on the increase in phosphate excretion induced by volume expansion are not immediately apparent. One important difference between these two groups of studies, however, is the interval between PTH suppression and the performance of the experiments. In the experiments in which phosphate excretion increased, thyroparathyroidectomy was performed two to three days earlier [3, 5]. In contrast, in those experiments where salt loading failed to increase phosphate excretion, PTH was acutely suppressed either by parathyroidectomy immedi-

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ately prior to study [6, 7] or by the addition of calcium in a concentration of 10 mEq/liter to the saline infused throughout the experiment [7]. In rat [1] and dog [9] phosphate is reabsorbed by a saturable process; therefore, it is possible that acute parathyroidectomy, by raising the threshold or tubular maximum for phosphate reabsorption [10], or by reducing the splay at a time when serum phosphorus and the filtered load of phosphate had not yet risen, may have obscured a depressive effect of volume loading on phosphate reabsorption[1].

To test this hypothesis, studies were performed on intact and acutely thyroparathyroidectomized dogs given phosphate loads and expanded with a balanced electrolyte solution. To examine the role of changes in serum calcium, calcium chloride was added to the electrolyte solution in some experiments in a concentration designed to prevent a reduction in serum ultrafilterable calcium.

Methods

Mongrel dogs of either sex, weighing between 11 and 24 kg were studied. The animals were anesthetized with intravenous sodium pentobarbital in an initial dose of 30 mg/kg body wt; subsequent doses adequate to maintain anesthesia were given as needed at intervals thereafter. Following induction of anesthesia, the trachea was intubated and connected to a Harvard large animal respirator adjusted to maintain normal blood pH and P_{CO_2}.

Bilateral femoral arterial and venous polyethylene catheters were inserted through inguinal incisions. Both ureters were cannulated with PE 100 catheters through a midline suprapubic incision. In two groups of animals, immediately following intubation, thyroparathyroidectomy (TPTX) was performed as previously described [5]. The animals were allowed to stabilize for two to two and one-half hours before collection periods were begun.

In all animals, a loading dose of inulin, 50 mg/kg body wt, was given followed by a continuous infusion of 50 mg/kg/hr for the duration of the experiment. Systemic infusion of an isotonic buffered phosphate solution [Na_2HPO_4–NaH_2PO_4 in a molar ratio of 4:1] was then begun at rates designed to deliver between 0.035 to 0.07 mmoles/min (3 μmoles/kg/min) and continued throughout the experiment. Following adequate equilibration time (65 to 80 min), three to four control periods of 10 to 15 min each were collected. When the control collections had been obtained, systemic infusion of an electrolyte solution buffered to pH 7.4 containing 140 mEq/liter Na^+, 25 mEq/liter HCO_3^-, 3 mEq/liter K^+ and 1.5 mg/100 ml Mg^{++} was begun. Rate of administration was varied from 10 to 22 ml/min to allow collection of urine samples at increasing flow rates. In one group of intact and one group of TPTX animals, Ca^{++} (in the form of the chloride) was added to the electrolyte solution in a concentration of nine mg/100 ml in order to prevent a significant drop in ultrafilterable calcium ($UF_{Ca^{++}}$).

Glomerular filtration rate (GFR) was determined by the clearance of inulin as measured on the Technicon Auto-Analyzer in zinc sulfate-sodium hydroxide filtrates of urine and plasma. Calcium and magnesium determinations were done on the Instrumentation Laboratory (IL) atomic absorption spectrophotometer using lanthanum chloride diluent. Ultrafiltrates of plasma for the determination of calcium were prepared anaerobically in the Centriflow Ultrafiltration Apparatus. Plasma and urine phosphorus determinations were done by the stannous chloride-hydrazine colorimetric method, utilizing the Technicon Auto-Analyzer. Sodium and potassium determinations in plasma and urine were done on the IL flame photometer. Statistical analysis was performed by the paired t-test.

Results

The results of all experiments are summarized in Tables 1 to 4. In Table 1 are tabulated the results of studies on acutely thyroparathyroidectomized animals in which Ca^{++} was added to the electrolyte solution. Volume expansion did not change the GFR, plasma phosphorus (Pp) or $UF_{Ca^{++}}$ significantly. Tubular reabsorption of phosphate (TRP) decreased from 2.9 to 2.4 mg/min but this change failed to achieve statistical significance ($P<0.1>0.05$). When corrected for changes in the GFR, however, TRP fell significantly from 6.7 to 4.6 mg/min ($P<0.001$) as fractional sodium excretion ($FE_{Na} = C_{Na} \times 100/GFR$) increased from 0.35 to 7.02%. Phosphate excretion (UpV) increased from 1.0 to 1.6 mg/min ($P<0.05$).

In Table 2, the results of experiments performed on eight acutely thyroparathyroidectomezed animals in which $CaCl_2$ was omitted from the electrolyte solution are summarized. The GFR and Pp did not change significantly; $UF_{Ca^{++}}$, however fell from 5.92 to 4.75 mg/100 ml ($P<0.001$). As FE_{Na} increased from 0.48 to 8.26% ($P<0.001$), TRP fell from 2.5 to 1.5 mg/min ($P<0.05$) and TRP/GFR diminished from 6.5 to 4.1 mg/min ($P<0.001$); UpV increased from 1.1 to 1.9 mg/min ($P<0.001$).

Table 3 summarizes the results of experiments performed on seven intact animals expanded with electrolyte solution containing Ca^{++}. The GFR, $UF_{Ca^{++}}$ and Pp did not change significantly. TRP fell from 2.4 to 1.8 mg/min but failed to attain statistical significance ($P>0.05$). When corrected for the GFR, however, TRP fell from 6.2 to

[1] For the purposes of this report threshold is defined as the filtered load (or plasma concentration) at which significant amounts of increased phosphate begin to appear in the urine, splay as the area where reabsorbed phosphate is less than filtered phosphate but is still increasing, and tubular maximum (Tm) as the value for phosphate reabsorption when it had become constant. It is probable that no true threshold exists for phosphate since it is present in urine even at very low filtered loads. The authors are cognizant of the possibility that a Tm for phosphate may be an artifact of the experimental model that is brought about by the expansion of extracellular fluid volume.

Table 1. Studies in acutely thyroparathyroidectomized dogs expanded with Ca^{++}-containing electrolyte solution

Experiment No.	GFR		TRP		$\frac{TRP \times 100}{GFR}$		$\frac{C_{Na} \times 100}{GFR}$		$UF_{Ca^{++}}$		P_p	
	ml/min		*mg/min*		*mg/min*		%		*mg/100 ml*		*mg/100 ml*	
	C	E	C	E	C	E	C	E	C	E	C	E
1	60	64	3.6	3.6	6.5	5.6	0.94	4.52	5.20	4.90	9.3	7.8
2	54	65	5.1	4.3	9.4	6.6	0.09	4.38	5.63	6.20	10.6	10.0
3	26	28	1.2	0.5	4.6	1.6	0.07	10.09	6.06	5.73	7.4	8.8
4	44	50	2.1	1.3	4.7	2.7	0.43	5.07	5.17	5.13	7.6	7.1
5	26	40	2.2	2.5	8.6	6.2	0.21	6.93	5.60	5.90	10.9	9.1
6	36	26	2.4	1.2	6.8	3.9	0.53	12.35	5.90	5.80	10.5	7.8
7	57	69	3.6	3.5	6.4	5.2	0.21	5.82	6.30	6.05	7.3	7.5
Mean	43	49	2.9	2.4	6.7	4.6	0.35	7.02	5.69	5.67	9.1	8.3
SD	5.4	6.7	0.5	0.6	0.7	0.7	0.12	1.16	0.16	0.18	0.6	0.4
P	>0.1		>0.05		<0.001		<0.005		>0.8		>0.1	

Control (C) and experimental (E) values represent the means of values in periods in which fractional sodium excretion ($C_{Na} \times 100/GFR$) was less than 1% and greater than 3% respectively. GFR = glomerular filtration rate, TRP = tubular reabsorption of phosphate, $TRP \times 100/GFR$ = TRP corrected to 100 ml/min of GFR, $UF_{Ca^{++}}$ = ultrafilterable calcium, and P_p = plasma phosphorus.

Table 2. Studies in acutely thyroparathyroidectomized dogs expanded with Ca^{++}-free electrolyte solution

Experiment No.	GFR		TRP		$\frac{TRP \times 100}{GFR}$		$\frac{C_{Na} \times 100}{GFR}$		$UF_{Ca^{++}}$		P_p	
	ml/min		*mg/min*		*mg/min*		%		*mg/100 ml*		*mg/100 ml*	
	C	E	C	E	C	E	C	E	C	E	C	E
1	45	41	3.1	1.7	6.9	4.1	0.31	6.43	6.20	4.80	9.3	7.8
2	32	29	2.1	1.0	5.9	3.4	0.71	11.62	6.80	5.40	9.7	9.5
3	49	38	3.3	1.6	6.7	4.3	0.12	5.48	6.10	4.88	9.5	9.0
4	26	29	2.4	2.5	7.4	6.3	0.19	11.01	5.70	4.20	9.0	8.8
5	33	39	1.7	1.4	5.8	4.6	0.89	11.91	5.60	4.20	9.5	9.0
6	26	28	1.6	0.9	6.2	3.1	0.76	12.02	5.30	4.78	10.2	10.1
7	61	50	4.3	1.3	7.0	2.5	0.22	4.55	5.80	4.85	10.2	9.1
8	26	42	1.5	1.7	5.7	4.1	0.61	3.09	5.87	4.90	11.4	9.8
Mean	37	37	2.5	1.5	6.5	4.1	0.48	8.26	5.92	4.75	9.9	9.1
SD	4.6	2.8	0.4	0.2	0.2	0.4	0.11	1.32	0.16	0.14	0.3	0.2
P	>0.8		<0.05		<0.001		<0.001		<0.001		<0.02	

For explanation see Table 1.

Table 3. Studies in intact dogs expanded with Ca^{++}-containing electrolyte solution

Experiment No.	GFR		TRP		$\frac{TRP \times 100}{GFR}$		$\frac{C_{Na} \times 100}{GFR}$		$UF_{Ca^{++}}$		P_p	
	ml/min		*mg/min*		*mg/min*		%		*mg/100 ml*		*mg/100 ml*	
	C	E	C	E	C	E	C	E	C	E	C	E
1	28	37	1.5	0.9	5.5	2.3	0.07	5.97	6.56	6.43	8.9	8.8
2	41	47	2.5	0.3	6.0	0.7	0.14	6.67	6.20	6.30	8.4	7.8
3	35	40	2.4	1.0	6.7	3.2	0.09	11.28	5.80	6.00	7.9	8.1
4	63	67	2.6	2.2	4.2	3.3	0.05	8.05	6.40	6.80	6.6	6.1
5	49	49	2.6	2.4	5.3	4.9	0.10	6.48	6.30	6.70	7.7	7.4
6	24	50	2.0	2.6	9.3	5.2	0.26	4.58	6.60	6.50	9.9	8.4
7	54	55	3.4	3.2	6.7	5.7	0.89	5.04	6.20	6.20	12.4	12.3
Mean	42	49	2.4	1.8	6.2	3.6	0.23	6.87	6.29	6.42	8.8	8.4
SD	5.4	3.7	0.2	0.4	0.6	0.7	0.11	0.85	0.10	0.11	0.7	0.7
P	>0.05		>0.05		<0.02		<0.001		>0.1		>0.05	

For explanation see Table 1.

Table 4. Studies in intact dogs expanded with Ca^{++}-free electrolyte solution

Experiment No.	GFR		TRP		$\frac{TRP \times 100}{GFR}$		$\frac{C_{Na} \times 100}{GFR}$		$UF_{Ca^{++}}$		P_p	
	ml/min		*mg/min*		*mg/min*		%		*mg/100 ml*		*mg/100 ml*	
	C	E	C	E	C	E	C	E	C	E	C	E
1	57	53	1.9	0.9	3.4	1.6	0.57	6.08	5.80	4.80	7.5	6.1
2	53	51	2.0	1.1	3.7	2.1	0.61	4.36	4.70	4.10	6.9	8.5
3	33	37	0.8	0.5	2.6	1.3	0.29	7.45	5.60	4.50	6.0	5.6
4	47	49	2.1	0.9	3.7	1.7	0.90	7.77	5.70	4.80	9.2	7.5
5	45	46	3.2	3.1	7.1	6.7	0.45	7.90	5.60	4.86	9.5	9.5
6	72	59	4.9	1.9	6.8	3.1	0.08	3.98	4.60	3.90	7.7	6.0
Mean	51	59	2.5	1.4	4.5	2.8	0.48	6.26	5.33	4.49	7.8	7.2
SD	5.4	3.1	0.6	0.4	0.8	0.8	0.12	0.71	0.22	0.17	0.6	0.6
P	>0.4		<0.05		<0.02		<0.001		<0.001		>0.3	

For explanation see Table 1.

3.6 mg/min ($P<0.02$) as FE_{Na} rose from 0.23 to 6.87%; UpV increased from 1.2 to 2.3 mg/min ($P<0.02$).

Table 4 summarizes the results of experiments on six intact animals expanded with calcium-free electrolyte solution. GFR and Pp did not change significantly; $UF_{Ca^{++}}$, however, fell from 5.33 to 4.49 mg/100 ml ($P<0.001$). TRP fell from 2.5 to 1.4 mg/min ($P<0.05$) and TRP corrected to GFR fell from 4.5 to 2.8 mg/min ($P<0.02$) as FE_{Na} rose from 0.48 to 6.26% ($P<0.001$); UpV increased from 1.6 to 2.1 mg/min ($P<0.05$).

Discussion

The present studies were designed to examine the effects of acute ablation of the parathyroid glands and lowering of the serum calcium on the increased phosphaturia induced by volume expansion in the dog. Previous studies in the rat [6, 7] and preliminary studies in the dog [8] have suggested that acute parathyroidectomy or calcium infusion abolish this increased phosphaturia. Since the serum phosphorus does not rise immediately after suppression of PTH secretion, it was possible that an inhibitory effect of volume expansion on tubular reabsorption of phosphorus may have been obscured by an increase in the threshold or capacity for its reabsorption [10]. To obviate this difficulty dogs in the present study were infused with a buffered phosphate solution to increase the serum phosphorus to levels well above the threshold. In hydrated dogs, Pitts and Alexander [9] showed that phosphate reabsorption increased only slightly after plasma phosphorus levels of six mg/100 ml had been reached and that there was no further increase at plasma concentrations above eight mg/100 ml. Consequently, in almost all the present experiments, plasma phosphorus concentrations were raised to above six mg/100 ml. The results demonstrate that with the attainment of a sodium diuresis, on the average in excess of six percent of the filtered load, tubular reabsorption of phosphate is uniformly depressed in both intact (Table 4) and thyroparathyroidectomized (Table 2) dogs. Thus, acute ablation of the parathyroid glands does not abolish the inhibitory effect of volume expansion on tubular phosphate reabsorption when the filtered load of phosphate is increased by phosphate infusion.

Changes in the level of serum calcium have been shown to alter the tubular reabsorption of phosphate. The infusion of calcium into normal subjects decreases the renal excretion of phosphate [11]. This is thought to be due to suppression of parathyroid hormone since in parathyroidectomized man calcium infusion increases the renal excretion of phosphate [11, 12]. On the basis of these studies the suggestion was made that the increased phosphaturia of volume expansion was the consequence of reduction of the serum calcium by dilution [7]. To examine the role of changes in serum calcium, a drop in serum ultrafilterable calcium was prevented in intact (Table 3) and thyroparathyroidectomized (Table 1) dogs by the addition of calcium to the electrolyte solution. Volume expansion still resulted in a reduction in the tubular reabsorption of phosphate. This change, however, was of only borderline statistical significance. When corrected to 100 ml/min GFR, the change in tubular phosphate reabsorption became highly significant and of a magnitude comparable to that observed in thyroparathyroidectomized dogs expanded with clacium-free electrolyte solution. The importance of relating tubular phosphate reabsorption to GFR has already been pointed out by Hellman, Baird and Bartter [13]. It appears from the above, therefore, that a reduction in serum calcium is not necessary for increased phosphaturia to develop following volume expansion.

The mean values for TRP corrected for 100 ml/min GFR were similar in both groups of thyroparathyroidectomized dogs and in the intact dogs receiving calcium-containing solution. In the intact dogs receiving calcium-free infusion TRP corrected for GFR was the lowest of all four groups studied. This suggests that in this group PTH must have been stimulated by the infusion of phosphate or that it

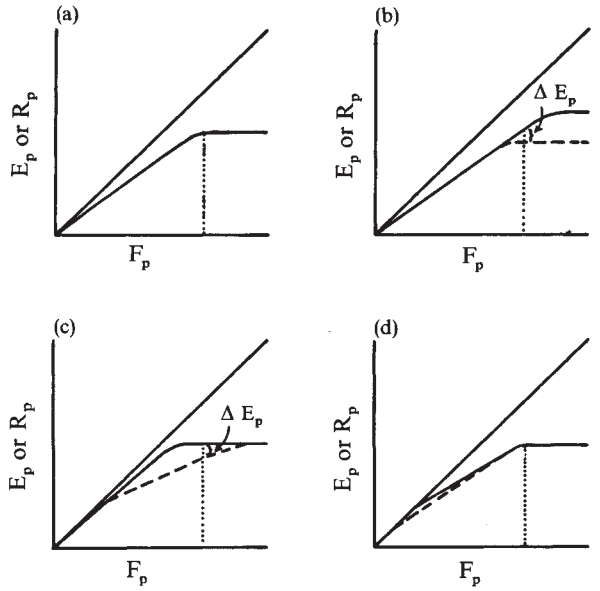

Fig. 1. *Theoretical treatment of the renal handling of phosphate in intact and hypoparathyroid states.* Filtered phosphate (F_p) is plotted on the horizontal axis. The diagonal solid line represents the line of complete phosphate reabsorption (R_p) and the solid curve represents actual R_p at varying levels of F_p; the difference represents excreted phosphate (E_p). Fig. la represents the normal titration curve, and Fig. 1b, 1c and 1d represent the three possible ways hypoparathyroidism may alter the titration curve from normal: increased tubular maximum (Fig. 1b), decreased splay (Fig. 1c) or raised threshold (Fig. 1d). The interrupted curves represent the three possible ways volume expansion may alter R_p in hypoparathyroidism. The vertical dotted line represents a high arbitrary level of F_p and the bracketed portion represents the increment in excretion to be expected following volume expansion (ΔE_p).

was suppressed in the other three groups by ablation of the parathyroids or by calcium infusion. A higher tubular maximum for phosphate reabsorption in parathyroidectomized as compared to normal dogs has been previously reported by Hogben and Bollman [10].

The present studies clearly demonstrate a uniform inhibition of tubular phosphate reabsorption by volume expansion irrespective of the level of serum calcium or PTH. Since in these studies the achieved levels of plasma phosphorus were in the general area where tubular phosphate reabsorption begins to reach a plateau, the observed decrease in TRP may represent a depression of tubular maximum (Tm_p) or an increase in splay. In discussing the renal handling of phosphate it should be pointed out that its reabsorption differs from that of other compounds transported by saturable processes. In several previous studies phosphate has been shown to be present in the urine and its excretion rate made to vary at filtered loads well below those required to saturate the tubular reabsorptive mechanism [14–16]. Thus, changes in tubular threshold or splay may play a major role in the regulation of phosphate excretion. A theoretical treatment of the changes from normal induced by hypoparathyroidism and the effects of volume expansion is illustrated in Fig. 1. Parathyroidectomy may raise the Tm_p (Fig. 1b) or the threshold (Fig. 1d) or decrease the splay (Fig. 1c). At low filtered loads of phosphate (F_p) a decrease in Tm_p or in threshold or an increase in splay induced by volume expansion may not be detected. At higher F_p, as in the studies reported herein, depression in Tm_p or an increase in splay may be easily detected. While changes in threshold may not be detectable in the present studies, such changes cannot be excluded and all three changes depicted in Fig. 1 combined may have led to the discrepancy between the effects on phosphate excretion of volume expansion in intact and chronically parathyroidectomized animals on the one hand and acutely parathyroidectomized animals on the other.

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