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RENAL POTASSIUM-WASTING INDUCED BY VITAMIN D*†

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Inappropriate renal losses of potassium and impaired ability to excrete acid characterize certain patients with nephrocalcinosis (1). It has been suggested that renal tubular acidosis with potassium wasting may be acquired as a result of transient episodes of hypercalcemia (2, 3). The early lesion produced in the rat by intoxication with vitamin D seemed an appropriate one to test this hypothesis, since it is easy to induce and its morphological and functional consequences have been extensively studied (4–6).

The present experiments were therefore designed to study the effect of hypercalcemia and nephrocalcinosis induced by vitamin D upon renal excretion of potassium and acid. The results indicate that renal conservation of potassium is impaired by hypercalcemic nephropathy. The ability of the kidneys to form ammonium and excrete acid is likewise deranged, although this is apparent in the rat only after large loads of acid are administered.

METHODS

Male Sprague-Dawley rats weighing between 250 and 400 g were used in all the experiments. Animals were kept in individual metabolic cages which permitted the collection of urine without contamination by feces. Urine was collected under mineral oil, with thymol used as a preservative. The animals were rendered hypercalcemic by the intraperitoneal injection of 200,000 U of vitamin D_2 (calciferol) dissolved in 0.5 ml of peanut oil daily for 4 consecutive days. Control animals received equal quantities of peanut oil without added vitamin D. At the completion of the experiment the rats were anesthetized with pentobarbital and killed by aortic exsanguination.

Sodium and potassium in serum and urine were determined with an internal standard flame photometer, urea nitrogen and ammonia by the Conway microdiffusion method, urinary nitrogen by semimicro-Kjeldahl digestion and distillation, chloride by amperometric titration, serum CO_2 content by the method of Van Slyke and Neill, urinary phosphorus by the method of Fiske and Subbarow (7), serum calcium by the photometric method of Kingsley and Robnett (8), and serum magnesium by a Titan yellow method (9).

Experiment I. Effect of vitamin D on renal conservation of potassium. Twenty-two rats were placed on a diet containing 133 mEq of Na^+ per kg but no potassium (10) for 7 days. At the end of this time, when the urinary excretion of potassium had declined to very low levels, half of the animals were given vitamin D for 4 days. Each rat was individually pair-fed with a control animal which did not receive vitamin D. Daily urine collections were made and 5 days after the last injection of vitamin D the animals were killed and serum analyzed for sodium, potassium, CO_2, urea, and calcium. In 6 experimental and 6 control rats, the urinary excretion of potassium only was measured; in the remaining 5 of each group the urine was also analyzed for sodium, pH, titratable acid, ammonium, phosphorus, chloride, and nitrogen.

In a similar experiment, 18 rats, divided into two pair-fed groups, were fed a diet free of potassium for 22 days. After 10 days, one group was given 200,000 U of vitamin D daily for 4 days. Eight days after the last injection of vitamin D, the potassium content of muscle was measured (10), as well as serum levels of calcium, potassium, and magnesium.

Experiment II. Effect of increased excretion of phosphate on renal conservation of potassium. Five animals were fed the low potassium diet for 7 days. Sodium phosphate (200 mg of Na_2HPO_4 and 50 mg of NaH_2PO_4 per 100 g of diet) was then added to the diet used in experiment I. Rats were fed 7 g of diet daily and all animals ate their entire daily quota. Daily urines were analyzed for sodium, potassium, chloride, and phosphorus. After 10 days on the high phosphate diet the animals were sacrificed.

Experiment III. Effect of varying the intake of sodium on the renal response to vitamin D. After eating

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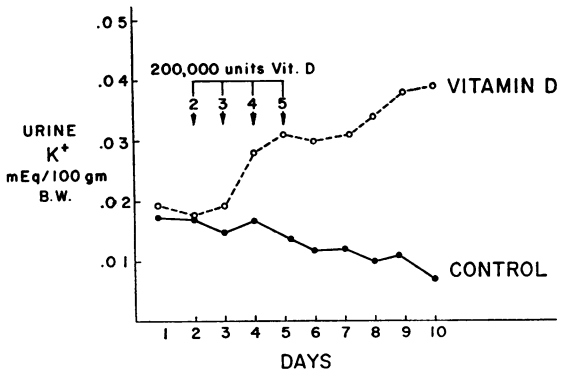

FIG. 1. POTASSIUM-WASTING INDUCED BY VITAMIN D. Urinary potassium, low as a result of dietary restriction, increased significantly in rats rendered hypercalcemic by vitamin D. Values plotted in this figure are the average results in 11 experimental rats given vitamin D and in 11 pair-fed controls.

the low potassium diet for 7 days, one group of 5 rats was fed approximately twice as much sodium chloride per day as previously. Concomitant with the high sodium diet, vitamin D was injected for 4 days, and urine collected for another 5 days before the experiment was terminated. A second group of 6 rats was placed on the low potassium diet for 7 days, after which sodium was removed from their food. After 4 more days, when urinary excretion of sodium had become negligible, vitamin D was injected in the usual manner and individual collections of urine were continued for several days.

Experiment IV. Potassium-wasting induced by vitamin D in adrenalectomized rats. Ten rats were adrenalectomized and immediately after the operation placed on the low potassium diet. After adrenalectomy, 0.032 mg of deoxycorticosterone acetate in oil was given subcutaneously each day for maintenance. On the seventh day of low potassium intake the animals were divided into two groups and placed in individual metabolic cages. Vitamin D was given for 4 days to the rats in one group; the other animals served as controls. Daily urines were collected and the experiment was terminated 2 days after the last injection of vitamin D.

Experiment V. The ability of hypercalcemic animals to excrete an acid load. Experimental animals were made hypercalcemic by four daily injections of 200,000 U of vitamin D. Two days after the last dose of vitamin D the rats were placed in metabolic cages and a measured amount of NH_4Cl was given by stomach tube as a solution containing 0.5 mmole per ml. The daily dose of NH_4Cl was divided into two equal doses, given in the morning and afternoon. Ammonium chloride was given for 3 consecutive days, during which time urine was collected under oil and analyzed for pH, NH_4, and titratable acid. Throughout the experiment the animals were allowed free access to water and Purina chow. No attempt was made to pair-feed the animals.

It was necessary to discard occasional urine samples in this study because of fecal contamination, which was clearly evident to inspection and caused elevation of the urinary pH above 8.

At the completion of the study the animals were sac-

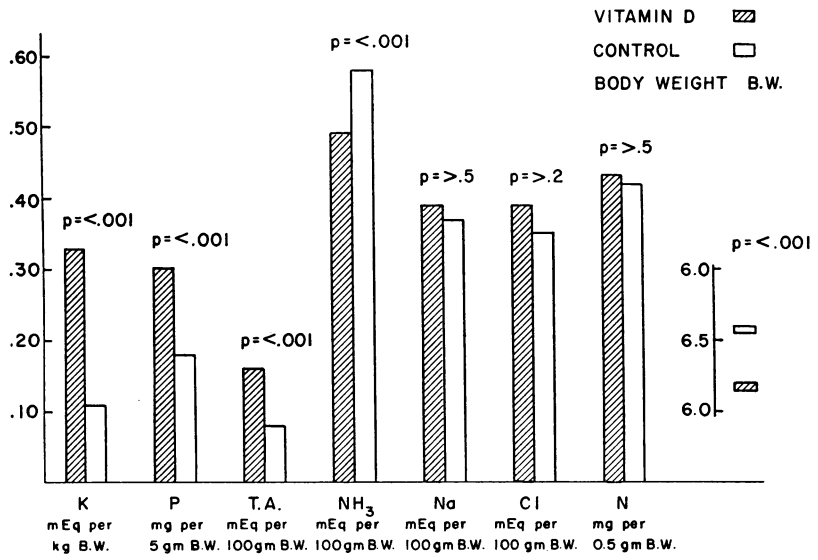

FIG. 2. URINARY CONSTITUENTS OF FIVE HYPERCALCEMIC AND FIVE CONTROL RATS ON A LOW POTASSIUM DIET. The columns indicate the mean daily excretion over 5 days, starting after the last dose of vitamin D. Average urinary pH is shown on the right. Note that the scale for potassium excretion is 10 times that for other electrolytes.

TABLE 1

Effect of vitamin D on urine and serum in rats on a low potassium diet

Daily excretion	Day 1 n=5 Exp.	Day 1 n=5 Cont.	Day 2* Exp.	Day 2* Cont.	Day 3* Exp.	Day 3* Cont.	Day 4* Exp.	Day 4* Cont.	Day 5* Exp.	Day 5* Cont.	Day 6 Exp.	Day 6 Cont.
K *mEq/100 g*	0.022 ±0.006	0.017 ±0.006	0.0196 ±0.005	0.014 ±0.006	0.024 ±0.007	0.017 ±0.004	0.017 ±0.01	0.016 ±0.004	0.027 ±0.01	0.015 ±0.004	0.032 ±0.012	0.014 ±0.006
Na *mEq/100 g*	0.47 ±0.08	0.30 ±0.12	0.33 ±0.079	0.25 ±0.103	0.39 ±0.09	0.37 ±0.13	0.42 ±0.07	0.44 ±0.11	0.39 ±0.09	0.40 ±0.05	0.44 ±0.06	0.43 ±0.06
Cl *mEq/100 g*	0.49 ±0.06	0.37 ±0.08	0.34 ±0.05	0.28 ±0.078	0.39 ±0.07	0.34 ±0.11	0.45 ±0.11	0.40 ±0.09	0.41 ±0.08	0.36 ±0.03	0.48 ±0.10	0.40 ±0.08
P *mg/100 g*	5.55 ±1.20	3.78 ±0.60	4.16 ±0.78	2.95 ±0.93	3.63 ±0.72	3.26 ±0.76	4.57 ±1.08	3.49 ±0.85	4.84 ±1.17	3.82 ±1.20	5.77 ±1.09	3.53 ±0.52
Titratable acidity *mEq/100 g*	0.12 ±0.038	0.08 ±0.023	0.096 ±0.017	0.09 ±0.03	0.13 ±0.01	0.09 ±0.06	0.094 ±0.04	0.076 ±0.026	0.12 ±0.05	0.072 ±0.024	0.16 ±0.038	0.085 ±0.045
NH_4^+ *mEq/100 g*	0.59 ±0.158	0.55 ±0.125	0.55 ±0.08	0.77 ±0.15	0.63 ±0.18	0.70 ±0.31	0.64 ±0.08	0.58 ±0.12	0.56 ±0.12	0.54 ±0.06	0.56 ±0.09	0.55 ±0.09
Urinary pH	6.24 ±0.29	6.36 ±0.18	6.5 ±0.14	6.54 ±0.31	6.54 ±0.18	6.67 ±0.15	6.46 ±0.30	6.57 ±0.16	6.34 ±0.20	6.45 ±0.15	6.09 ±0.11	6.5 ±0.26

Daily excretion	Day 7 Exp.	Day 7 Cont.	Day 8 Exp.	Day 8 Cont.	Day 9 Exp.	Day 9 Cont.	Day 10 Exp.	Day 10 Cont.
K *mEq/100 g*	0.034 ±0.014	0.015 ±0.008	0.034 ±0.009	0.010 ±0.004	0.035 ±0.014	0.009 ±0.003	0.032 ±0.016	0.008 ±0.003
Na *mEq/100 g*	0.41 ±0.04	0.38 ±0.08	0.38 ±0.06	0.40 ±0.06	0.36 ±0.09	0.35 ±0.03	0.38 ±0.05	0.29 ±0.12
Cl *mEq/100 g*	0.40 ±0.02	0.38 ±0.09	0.35 ±0.04	0.36 ±0.09	0.37 ±0.10	0.34 0.04	0.36 ±0.05	0.29 ±0.07
P *mg/100 g*	5.56 ±1.13	3.12 ±0.83	6.12 ±1.99	3.79 ±1.36	6.50 ±2.14	3.68 ±0.78	6.39 ±1.01	3.66 ±1.38
Titratable acidity *mEq/100 g*	0.18 ±0.04	0.06 ±0.05	0.19 ±0.06	0.09 ±0.04	0.17 ±0.09	0.08 ±0.04	0.16 ±0.04	0.08 ±0.03
NH_4^+ *mEq/100 g*	0.47 ±0.05	0.60 ±0.07	0.43 ±0.08	0.60 ±0.10	0.47 ±0.07	0.56 ±0.07	0.51 ±0.11	0.59 ±0.09
Urinary pH	6.16 ±0.09	6.44 ±0.31	6.10 ±0.14	6.47 ±0.29	6.24 ±0.22	6.51 ±0.31	6.26 ±0.06	6.79 ±0.44

Serum	Exp.	Cont.
Na *mEq/L*	142.8 ± 2.8	140.2 ± 4.3
K *mEq/L*	3.4 ± 0.9	4.1 ± 1.29
CO_2 *mEq/L*	27.1 ± 2.9	26.1 ± 0.46
Urea N *mg/100 ml*	21.5 ± 5.3	20.4 ± 3.3
Ca *mg/100 ml*	12.2 ± 1.43	9.1 ± 1.5

* 200,000 U of vitamin D was given intraperitoneally to each animal in the "experimental" group on days 2, 3, 4, and 5.

rificed and serum was analyzed for urea, CO_2, and calcium.

Three doses of ammonium chloride were used: In *Experiment Va,* 7 experimental and 7 control animals received 1 mmole of NH_4Cl per 100 g of body weight daily. In *Experiment Vb,* 6 experimental and 6 control rats received 1.75 mmoles per 100 g body weight daily. In *Experiment Vc,* 6 experimental and 6 control animals received 2.5 mmoles per 100 g body weight daily.

RESULTS

Effect of vitamin D on renal conservation of potassium (Figures 1 and 2, Table I). In normal rats deprived of potassium for 1 week, renal conservation of potassium was rapidly evident, as urinary losses steadily declined to 0.01 mEq per 100 g of body weight per day. After the administration of vitamin D, however, renal excretion of potassium mounted. One week after the last injection, the average daily loss of potassium into the urine was four times that of control rats (range, 0.025 to 0.060 mEq per 100 g). Vitamin D produced moderate hypercalcemia (serum calcium of 12 to 14 mg per 100 ml), but no change in the concentration of sodium, potassium, CO_2, or urea nitrogen in serum.

The excretion of phosphate also increased in the rats receiving vitamin D, presumably as a result of dissolution of bone mineral. Perhaps as a consequence (11), urinary pH was slightly lower than in control animals. Total hydrogen ion excretion in the two groups was equal since, although the excretion of titratable acid was somewhat increased, the excretion of ammonium decreased by an equivalent amount in rats receiving vitamin D,

TABLE II

Muscle potassium and serum magnesium, calcium, and potassium in rats treated with vitamin D *

	Muscle K	Serum K	Serum Ca	Serum Mg
	mEq/100 g FFDS†	*mEq/L*	*mg/100 ml*	
Control n=8	40.3±2.8	2.9±0.3	8.9±0.96	1.89±0.11
Vit. D n=9	35.4±3.5	3.0±0.6	15.0±1.2	1.85±0.44
p	<0.01	0.4	<0.01	0.5

* Rats were killed 12 days after the first injection of vitamin D, having been on a low K diet for 22 days.
† Fat-free dry solids. Values in each column are mean±standard deviation.

as compared to controls. Urinary excretion of sodium, chloride, and nitrogen of hypercalcemic rats was not significantly different from that of their pair-fed controls.

When hypercalcemia was sustained for 12 days in animals on a low potassium diet, muscle stores of potassium were significantly depleted when compared to pair-fed control rats (Table II).

Vitamin D intoxication has been reported to reduce serum magnesium (12). Magnesium depletion may in itself induce renal potassium-losing and depletion of muscle potassium (13). In the present experiments, however, the serum magnesium of hypercalcemic rats was unaltered. Changes in magnesium metabolism do not appear to be responsible for the renal potassium-wasting caused by vitamin D (Table II).

Effect of increased excretion of phosphate on renal conservation of potassium (Figure 3). It seemed possible that the renal losses of potassium observed in rats given vitamin D were a consequence of increased delivery of phosphate and perhaps of sodium to the distal tubular site of potassium secretion. Accordingly, rats deprived of potassium were fed sodium phosphate in amounts exceeding the average urinary increment of phosphate observed in rats which were made hypercalcemic. (The amount of phosphate added to the diet was far less than that necessary to cause nephrocalcinosis in rats.) Such loads of sodium phosphate did not result in increased urinary losses of potassium. It seems unlikely, therefore, that renal potassium-wasting induced by vitamin D is primarily a result of an increase in urinary excretion of phosphate and of sodium.

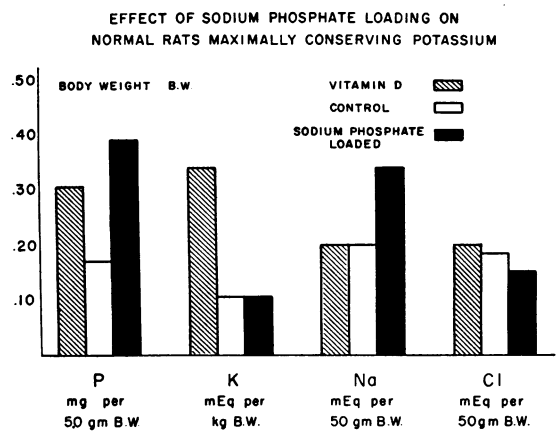

FIG. 3. EFFECT OF LOADING WITH SODIUM PHOSPHATE ON RENAL CONSERVATION OF POTASSIUM. In contrast to the effect of vitamin D on urinary potassium, renal excretion of potassium was not increased by augmenting the intake and excretion of phosphate and of sodium. The figure indicates average daily excretion during the 5 days corresponding to those charted in Figure 2.

Effect of altered sodium intake upon the renal response to vitamin D (Table III). Renal excretion of potassium was increased by vitamin D in rats fed a diet high or low in sodium. Unlike the increase in potassium excretion stimulated by deoxycorticosterone (14), urinary losses of potassium induced by vitamin D were not diminished by prefeeding a diet low in sodium. As reported previously (5), however, an increase in urinary sodium was produced by vitamin D in every animal on the low sodium diet.

Effect of prior adrenalectomy upon the renal response to vitamin D (Figure 4). Adrenalectomy did not prevent the renal losses of potassium associated with hypercalcemia.

Effect of hypercalcemia upon the ability of rats to excrete an acid load (Table IV, Figure 5).

TABLE III

Effect of varying sodium intake upon the potassium-losing induced by vitamin D

	K*	Na
	mEq/100 g/day	*mEq/100 g/day*
Low-Na (n = 5)	0.056 ± 0.073	0.03 ± 0.04
Normal diet (n = 5)	0.034 ± 0.013	0.37 ± 0.06
High-Na (n = 5)	0.039 ± 0.008	0.67 ± 0.03

* Mean daily urinary excretion (± standard deviation) during the 5 days after the last injection of vitamin D.

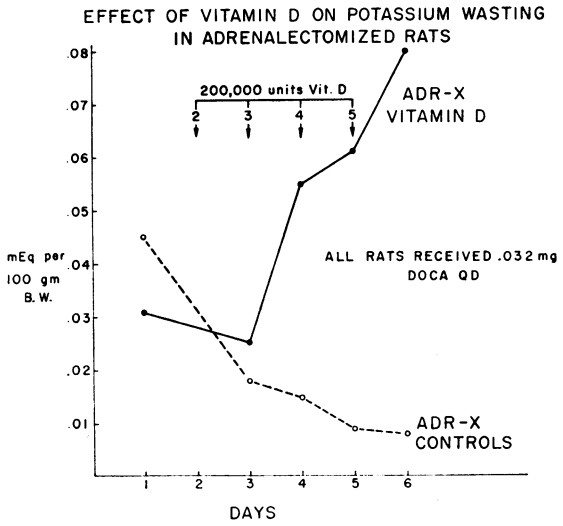

FIG. 4. EFFECT OF ADRENALECTOMY UPON POTASSIUM-LOSING INDUCED BY VITAMIN D. Potassium-wasting was not prevented by removing both adrenals before giving vitamin D. Average serum calcium in adrenalectomized rats receiving vitamin D was 14.3 mg per 100 ml.

Normal rats given 1.0 mmole of NH_4Cl per 100 g of body weight for 3 days were able to excrete the entire daily increment of H^+ from the very first day, so that serum bicarbonate remained normal. About 25 per cent of the load of H^+ was excreted as titratable acid, the remainder as NH_4^+. With increasing loads of NH_4Cl (1.75 and 2.5 mmoles per 100 g of body weight), renal excretion of H^+ on the first day fell short of complete compensation, but rose to equal or surpass the administered

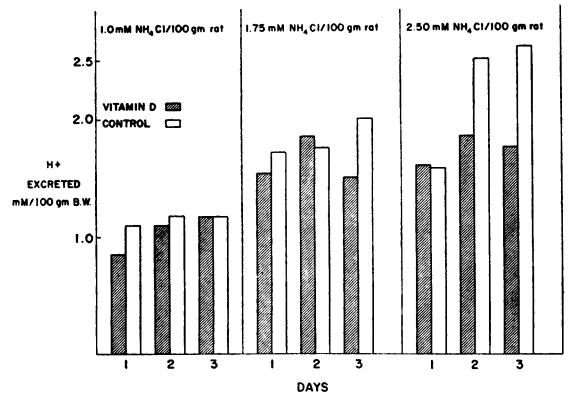

FIG. 5. EFFECT OF HYPERCALCEMIC NEPHROPATHY ON RENAL CAPACITY TO EXCRETE ACID. Deficient hydrogen ion excretion, owing entirely to diminished formation of ammonium, was evident in hypercalcemic rats at the largest acid load.

load of H^+ on the second and third days. This was accomplished entirely by increasing the excretion of NH_4^+; urinary pH and titratable acid remained the same as at the lowest dose of NH_4Cl. After 3 days of the highest dose of acid, normal rats were moderately acidotic (average serum CO_2, 14.5 mEq per L).

In rats treated with vitamin D, renal excretion of acid was unimpaired when tested with the *lowest* dose of NH_4Cl (1.0 mmole per 100 g). Restriction of the ability of the kidneys to excrete acid, because of impaired formation of ammonium, was apparent on the third day of treatment with the *intermediate* dose of NH_4Cl (1.75 mmole) and was clearly evident when the *largest* daily load of acid (2.5 mmoles per 100 g) was administered. After 3 days of 2.5 mmoles of NH_4Cl per 100 g of body weight, the hypercalcemic animals were markedly acidotic (average serum CO_2, 10.8 mEq per L) and their average blood urea nitrogen was slightly elevated (33.5 mg per 100 ml).

DISCUSSION

Nephrocalcinosis induced in rats by the administration of vitamin D results in a distinctive pattern of morphological and functional impairment. Cellular disruption and calcification is most marked in the ascending limb of Henle's loop, the distal convolution, and the collecting ducts (4). Concentrating ability is greatly diminished at a time when blood urea nitrogen, urea clearance, and phenolsulfonphthalein excretion are still normal (4). This is associated with a decreased concentration of sodium in the tissues of the medulla and papilla (5). Although salt-wasting is not a prominent feature of the experimental disease, difficulty in conserving sodium is apparent when a low sodium diet is fed (5).

The present experiments demonstrate that inability to conserve potassium and restriction of ammonia formation are also features of the experimental nephropathy produced by vitamin D. Urinary losses of potassium observed in potassium-depleted rats after hypercalcemia was induced, were roughly equivalent to 30 mEq of potassium per 24 hours in an adult man weighing 70 kg. This increased excretion of potassium was not secondary to urinary losses of sodium or of phosphate, since it was not simulated by feeding sodium

TABLE IV

Effect of vitamin D on renal response to acid loading

	Urinary excretion								
	Day 1		Day 2		Day 3				
	n=7 Exp.	n=7 Cont.	n=7 Exp.	n=7 Cont.	n=7 Exp.	n=7 Cont.		Serum values	
								Exp.	Cont.
	1 mmole NH_4Cl/100 g rat								
pH	5.9 ±0.14	6.06 ±0.22	6.2 ±0.35	6.1 ±0.22	6.25 ±0.44	6.2 ±0.25	CO_2 *mEq/L*	27.0 ± 3.7	27.7 ± 1.0
Titratable acidity *mEq/100 g*	0.24 ±0.03	0.23 ±0.07	0.17 ±0.02	0.25 ±0.04	0.19 ±0.12	0.25 ±0.02	Urea N *mg%*	20.9 ± 1.79	19.7 ± 1.14
NH_4^+ *mEq/100 g*	0.62 ±0.17	0.89 ±0.17	0.95 +0.25	0.93 ±0.11	0.99 ±0.11	0.93 ±0.12	Ca *mg%*	11.8 ±0.93	10.5 ±0.63
	1.75 mmoles NH_4Cl/100 g rat								
	Day 1		Day 2		Day 3				
	n=6 Exp.	n=6 Cont.	n=6 Exp.	n=6 Cont.	n=6 Exp.	n=6 Cont.		Exp.	Cont.
pH	5.9 ±0.14	6.19 ±0.17	5.99 ±0.30	6.36 ±0.12	6.1 ±0.31	6.19 ±0.2	CO_2 *mEq/L*	20.9 ± 8.0	27.7 ± 2.3
Titratable acidity *mEq/100 g*	0.50 ±0.14	0.31 ±0.02	0.43 ±0.19	0.23 ±0.03	0.30 ±0.11	0.24 ±0.04	Urea N *mg%*	29.5 ±16.3	11.08 ± 2.88
NH_4^+ *mEq/100 g*	1.04 ±0.22	1.39 ±0.03	1.44 ±0.21	1.52 ±0.2	1.21 ±0.03	1.72 ±0.2	Ca *mg%*	14.3 ± 1.28	9.99 ±0.17
	2.5 mmoles NH_4Cl/100 g rat								
	Day 1		Day 2		Day 3				
	n=6 Exp.	n=6 Cont.	n=6 Exp.	n=6 Cont.	n=6 Exp.	n=6 Cont.		Exp.	Cont.
pH	6.3 ±0.14	6.0 ±0.14	5.9 ±0.022	6.33 ±0.14	6.33 ±0.16	6.4 ±0.25	CO_2 *mEq/L*	10.9 ± 7.15	15.9 ± 7.48
Titratable acidity *mEq/100 g*	0.19 ±0.17	0.25 ±0.020	0.4 ±0.14	0.24 ±0.025	0.24 ±0.00	0.19 ±0.021	Urea N *mg%*	33.5 ±13.3	24.2 ± 5.0
NH_4^+ *mEq/100 g*	1.4 ±0.28	1.24 ±0.28	1.65 ±0.39	2.24 ±0.25	1.51 ±0.34	2.41 ±0.2	Ca *mg%*	14.33 ± 1.3	9.23 ± 0.73

phosphate; nor could it be ascribed to increased secretion of adrenal cortical hormones, since potassium-wasting was as marked in adrenalectomized rats given vitamin D as in intact animals. The loss of potassium was not accompanied by excessive losses of nitrogen in the urine, and it eventually produced significant depletion of muscle potassium.

Whether hypercalcemia promoted the *secretion* or diminished the *reabsorption* of potassium by renal tubules is not resolved by these experiments. It is pertinent to note, however, that the magnitude of the urinary increment of potassium was approximately the same at three different levels of sodium intake and that potassium-wasting was not eliminated by prefeeding a diet free of sodium. It seems unlikely, therefore, that renal losses of potassium induced by hypercalcemia were limited by the availability in distal tubular urine of sodium for exchange with secreted potassium.

In most experiments, urinary wasting of potassium could not be ascribed to concomitant decreases in hydrogen ion excretion. The urine of rats treated with vitamin D was no less acid than that of normal animals, and total acid excretion, measured as the sum of urinary ammonium plus titratable acidity, was not diminished except when ammonium chloride was given.

It is improbable that these results can be explained simply as a consequence of reduction in effective renal mass, i.e., in the number of functioning nephrons. Blood urea nitrogen and urea clearance are little affected by the dose of calciferol used in these experiments (4). Furthermore, removal of an entire kidney from rats on a low potassium diet did not increase the urinary excretion of potas-

sium, which had previously declined to negligible levels (15). Subtotally nephrectomized rats with five-sixths of the renal mass removed are reported to reduce their urinary loss of potassium in much the same fashion as do normal animals (16).

There is considerable evidence that hypercalcemia or hypercalciuria, or both, influence the renal handling of potassium. It has been known for many years that infusions of calcium salts in dogs increase urinary potassium (17). This effect is especially striking during stop-flow experiments under mannitol diuresis (hence is probably not itself a result of solute diuresis induced by calcium) and is apparent whether the gluconate or chloride salt is infused (18). It is not clear whether the increased excretion of potassium is a result of diminished reabsorption from the glomerular filtrate or of increased tubular secretion (18, 19). Calcium infusions also stimulate the excretion of potassium in monkeys, but do so less consistently in human subjects (20). Excessive concentrations of calcium in the bathing medium have been shown to restrict the effective pore diameter available for the diffusion of water from renal tubules of Necturus (21), to depress the transfer of water out of the toad bladder in response to vasopressin (22), to alter the permeability of frog skin so as to inhibit transport of sodium and chloride (23), and to decrease the active inward transport of potassium by red blood cells (24). Reabsorption of potassium from the lumen of the renal tubule may be interfered with by hypercalcemia and nephrocalcinosis via related mechanisms.

The moderate renal wastage of potassium caused by vitamin D is most clearly appreciated when the kidneys are being maximally stimulated to retain this ion (i.e., after prior deprivation of potassium). It might be anticipated that renal losses of potassium secondary to hypercalcemia would produce potassium deficiency in patients only when food intake had been substantially reduced; in a preliminary survey this appeared to be the case (3). Nevertheless, it is noteworthy that in experiments in which potassium intake was not restricted, the potassium content of muscle was significantly lower in rats treated with vitamin D than in control animals (25).

In the relatively mild nephrocalcinosis of the present experiments, inability to excrete acid was apparent only when the capacity of the kidneys was challenged. Administration of an acid load uncovered a defect in the adaptive increase in the renal production of ammonium. Urinary pH was not raised by hypercalcemia; in this respect the clinical syndrome of renal tubular acidosis was not reproduced. It should be noted that, relative to man or the dog, rats have an enormous capacity to respond to acidosis by increasing the excretion of ammonium. The deleterious effect of hypercalcemia on acid excretion might, perhaps, be expected to be more striking in man than in the rat.

Deficiencies in acid excretion in human patients attributable to hypercalcemia have been reported by Wrong and Davis (26) and by Fourman, McConkey and Smith (27). In addition, the syndrome of potassium-wasting coupled with renal tubular acidosis has been documented in patients after hyperthyroidism (2, 28), sarcoidosis (29), hyperparathyroidism (30), and vitamin D intoxication (3). The present data support the hypothesis that under some circumstances the ability of the kidneys to conserve potassium and excrete acid may be substantially and selectively impaired by nephrocalcinosis acquired as a result of hypercalcemia and hypercalciuria.

SUMMARY

Hypercalcemic nephropathy produced in rats by vitamin D impaired renal conservation of potassium and the ability of the kidneys to excrete ammonium after acid loading. It is suggested that renal potassium-wasting and renal tubular acidosis may be acquired as a result of hypercalcemia and hypercalciuria.

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