Phosphaturic Effect of Cortisone in Normal and Parathyroidectomized Rats.* (23566)

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(Introduced by J. Aub)
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In intact humans and dogs cortisone has been found to increase urinary phosphate excretion by depressing its renal tubular reabsorption(1,2). Since parathyroid hormone causes phosphaturia by a similar mechanism (3), the possibility that cortisone exerts its influence through the parathyroid glands must be considered. In favor of this possibility is the reported failure of urinary phosphorus excretion to increase in a cortisone treated patient with hypoparathyroidism and Addison's disease(4).

The investigation to be reported was designed to establish whether the phosphaturic effect of cortisone is mediated by the parathyroid glands.

Material and methods. Albino male rats weighing 150 to 200 g were used. Parathyroidectomy was performed surgically under ether anesthesia. Seven days postoperatively an elevation of serum inorganic phosphorus concentration to or above 11.5 mg % on a dietary intake which preoperatively had yielded mean levels of 8.7 $\pm$ 0.6 mg %, was taken as an indication of successful parathyroid removal. The experimental period was 3 days. The rats were kept in individual metabolic cages and, except as noted below, fed a known amount of ground, commercial rat chow.† Distilled water was given *ad libitum*. Ten mg of cortisone‡ was injected in one ml of saline intraperitoneally every day during the experimental period. In certain groups, phosphorus as a neutral Na_2HPO_4 and KH_2PO_4 solution was added to the food in an amount of 32 mg of phosphorus/rat/day. Urine of each individual rat was collected under thymol and pooled for the 3 day period. Blood was drawn by cardiac puncture under ether anesthesia at the end of each experiment. Serum and urinary phosphorus was determined by the method of Fiske and Subbarow(5). The urinary phosphate values are expressed as mg of inorganic phosphorus/100 g of mean body weight/24 hours. Mean body weight was determined by halving the sum of the weights at the start and end of the experiment. The parathyroidectomized animals were investigated by the cross-over experimental design. Thus some groups acted as controls and then received cortisone, others received cortisone first and were studied without treatment later. There was an interval of at least three days between periods of study.

Results are shown in Table I. In Section A it is evident that in intact animals serum inorganic phosphorus concentration is not significantly influenced by cortisone administration. Urinary phosphate excretion values, however, are about 60% greater in the presence of cortisone. In Section B the influence of parathyroidectomy as reflected in the higher serum inorganic phosphorus concentration is seen. Here as with the intact animals it is evident that cortisone promotes phosphaturia without significant effect on serum inorganic phosphorus concentration.

To test whether phosphate loading influences the cortisone effect, the data shown in the lower part of Section B, Table I were obtained. Phosphate loading in the parathyroidectomized rats was productive of great variability in the serum and urinary phosphorus values, which may have been due to irregular and incomplete intake of the load. In spite of this it is evident as in non-loaded

* This work was supported in part by grant from Commonwealth Fund of New York and Research Grant MOF-2 of the Amer. Cancer Soc.

† Purina Rat Chow, Ralston Purina Co., Chicago, Ill.

‡ Cortone Acetate, Sharp and Dohme.

TABLE I. The Effect of Cortisone upon Serum and Urinary Phosphorus in Intact and Parathyroidectomized Rats.

Section A: Intact rats

Untreated			Cortisone treated			
SIP	UVP	C_p	SIP	UVP	C_p	Statistical evaluation*
1	2	3	4	5	6	
8.08	12.3	153	7.64	21.0	276	1 *vs* 4: $t = .67$ $p < .5$
9.68	9.47	98	8.09	24.6	304	
8.48	13.4	158	7.44	17.9	242	2 *vs* 5: $t = 4.12$ $p < .01$
7.72	8.13	105	7.16	16.7	234	
8.80	18.0	204	8.45	16.6	197	3 *vs* 6: $t = 4.96$ $p < .001$
8.45	12.0	145	8.65	22.5	260	
8.5 ± .67‡	12.2 ± 3.13	143.8 ± 38.7	7.9 ± .59	19.9 ± 3.3	252 ± 36.8	

Section B: Parathyroidectomized rats

SIP	UVP	C_p	Study sequence	SIP	UVP	C_p	
7	8	9		10	11	12	
12.2	4.07	33.4	——→	13.6	11.1	81.6	7 *vs* 10: $\bar{m}\Delta = .99 \pm .5$ †
13.6	5.83	49.9	——→	13.7	9.4	68.6	$t = 1.93$ $p = < .1$
12.4	4.50	36.3	——→	12.5	7.6	60.7	8 *vs* 11: $\bar{m}\Delta = 4.6 \pm 1.65$
12.4	6.77	54.0	←——	15.6	14.0	90.0	$t = 2.78$ $p = < .05$
12.2	6.17	50.4	←——	13.2	9.5	72.0	9 *vs* 12: $\bar{m}\Delta = 28.5 \pm 4.77$
12.8	6.85	53.5	←——	12.8	9.7	75.9	$t = 5.98$ $p = < .01$
		Phosphate loaded					
13	14	15		16	17	18	
12.3	20.2	149	- - —→	11.7	23.2	199	13 *vs* 16: $\bar{m}\Delta = .15 \pm 1.1$
14.6	26.5	163	- - —→	16.2	21.9	135	$t = 0.136$ $p = < .9$
18.7	37.2	178	- - - →	13.6	26.0	191	14 *vs* 17: $\bar{m}\Delta = 9.62 \pm 6.65$
11.7	15.7	135	←— - -	14.3	39.5	276	$t = 1.45$ $p = < .1$
11.2	15.2	135	←— - -	11.9	44.3	372	15 *vs* 18: $\bar{m}\Delta = 91.8 \pm 12.65$
12.9	17.8	138	←——	12.8	35.5	277	$t = 7.25$ $p = < .001$

SIP = Serum inorganic phosphorus; expressed as mg/100 ml. UVP = Urine phosphate; expressed as mg/100 g wt/24 hr. C_p = Phosphate clearance; expressed as ml/100 g wt/24 hr.

* Note that in Section A the comparison was made between 2 separate groups of 6 animals each. In Section B the comparison was made between values obtained on 2 occasions in the same animal; thus the degrees of freedom in computing probability in Section A were 10, in Section B, 5.

† ± stand. error. ‡ Mean ± stand. dev.

animals that the phosphaturia was augmented by cortisone. Statistically the increase of phosphaturia falls short of significance. However, if these data are viewed in terms of clearance which takes into account the large variability of serum inorganic phosphorus, the cortisone effect becomes significant.

One circumstance was encountered, that of starvation, in which the phosphaturic effect of cortisone was absent. This is evident in the data of Table II for cortisone treated and control parathyroidectomized rats given no food but allowed free access to water over the three day period of study. The large weight losses consequent to the starvation are indicated. Here it may be noted for comparison that the fed rats of Table I showed a mean weight gain, expressed as percent of starting body weight, of 1.6% ± 6.55 when no cortisone was given and a mean weight loss of 2.0% ± 6.7 during periods of cortisone treatment. Other measurements of urinary phosphate output not included in Table II corroborate the finding that in starvation cortisone fails to augment phosphaturia. It is of interest to compare phosphate excretion rates of starved animals of Table II with those of the fed but non-loaded parathyroidectomized animals of Section B of Table I. The phosphate excretion values of the starving animals are similar to those of fed animals treated with cortisone but are appreciably higher than those of fed, non-cortisone treated controls.

Discussion. It is evident from the data

TABLE II. Effect of Cortisone on Serum and Urinary Phosphorus in Starved Parathyroidectomized Rats.

Untreated				Cortisone treated			
		Urine PO_4				Urine PO_4	
Wt loss, %	Serum PO_4, mg %	mg/100 g wt/24 hr	clearance, ml/100 g wt/24 hr	Wt loss, %	Serum PO_4, mg %	mg/100 g wt/24 hr	clearance, ml/100 g wt/24 hr
16.8	15.1	12	79.6	21.8	15.6	16.3	104.5
23.8	13.0	15.6	120.0	20.6	13.8	13.6	98.5
28.8	13.5	16.7	123.7	15.2	13.7	14.7	107.2

presented that cortisone increases urinary phosphate excretion in both intact and parathyroidectomized rats. The phosphaturic action is thus clearly not mediated by the parathyroid glands. Inasmuch as the phosphaturia due to the hormone is unaccompanied by elevation of serum inorganic phosphorus concentration and cortisone is known to have but little influence on the glomerular filtration rate of the rat(6,7), it seems fair to surmise that, as in dog and man(1,2), the increased excretion reflects inhibition of renal tubular phosphate reabsorption.

The renal effect of the steroid occurring in the absence of a reduction in serum inorganic phosphorus concentration suggests that the hormone has other influences which prevent depletion of the extracellular inorganic phosphate pool. In this regard it is known that cortisone increases gastrointestinal phosphate absorption in the rat.§ It may also act both to divert phosphate from incorporation in new protoplasm as well as to effect its release from organic tissue complexes(8).

A relatively high rate of phosphate excretion refractory to administered cortisone was observed in the acutely starved, parathyroidectomized rats. It appears that starvation may elicit endogenous release of renally maximally effective amounts of glucocorticosteroid. This interpretation is supported by the hypertrophy of the adrenal zona fasciculata in the acutely starved guinea pig(9) as well as by the increased 11-oxycorticoid excretion of fasted human subjects(10).

§ Unpublished data.

Summary. 1) The effect of cortisone on serum inorganic phosphorus concentration and urinary phosphorus excretion has been investigated in normal and parathyroidectomized rats. 2) It has been found that cortisone exerts a phosphaturic action which is not dependent upon the presence of the parathyroid glands nor accompanied by elevation of serum phosphorus concentration.

The authors are indebted to Dr. Hedda Acs and Mr. James Fortunato for their assistance.

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Received August 15, 1957. P.S.E.B.M., 1957, v96.