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Research Article

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Effects of Potassium Deficiency on Renal Function in the Dog

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ABSTRACT Serial determinations of the renal clearance for inulin and *para*-aminohippuric acid (PAH), maximum renal tubular reabsorptive rate for glucose, maximum urinary concentrating ability, total exchangeable potassium, extracellular volume, and plasma sodium and potassium concentrations were done in seven dogs before and after dietary potassium depletion. The same measurements were also made in two of the dogs during potassium repletion.

Inulin and PAH clearances and transport maxima for glucose decreased progressively during depletion. These changes correlated well with both the duration of depletion and the extent of depletion as measured by total exchangeable potassium. Decreases in inulin and PAH clearance closely paralleled each other, suggesting that there might be a renal hemodynamic basis for both effects. The decreases in transport maxima for glucose were greater than those for inulin or PAH clearance, indicating the presence of a defect in the cellular transport mechanism for glucose. In the dogs that were repleted, renal function gradually returned to the predepletion state.

No significant changes were found in extracellular volume or plasma sodium concentration during depletion. Renal concentrating ability decreased only moderately during depletion, with the decrease correlating better with plasma potassium concentration than with total exchangeable potassium. This finding contrasts with the marked decrease in concentrating ability and the severe polydipsia and polyuria found in animals depleted of potassium with the aid of corticosteroids. The results of the present study emphasize the importance of considering species differences and the method of producing depletion in interpreting studies of the effects of hypokalemia on renal function.

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INTRODUCTION

Chronic potassium deficiency characteristically results in a decrease in urinary concentrating ability (1–3). The effects of potassium deficiency on other aspects of renal function are less clearly defined. Glomerular filtration rate has been reported to decrease in some studies (1, 2), but others have found no consistent change (4). *Para*-aminohippuric acid (PAH) clearance is often decreased in potassium-depleted patients (2). This finding may be due to a defect in the tubular extraction or secretion of PAH rather than a decrease in effective renal plasma flow rate (5). Only limited data are available concerning the effect of potassium deficiency on the maximum renal reabsorptive rate for glucose (1, 4).

Interpretation of previous studies is complicated by possible differences between species and by the fact that in many cases potassium deficiency was produced with steroid hormones which may themselves affect renal function. Also, very few data are available on serial measurements of renal function during potassium depletion. The objective of the present study was to define the time course of changes in renal concentrating ability, renal clearances of inulin and PAH, maximum reabsorptive rate for glucose, and total exchangeable body potassium in dogs that were depleted with only a potassium-deficient diet. Such data are needed for a more comprehensive understanding of the effects of potassium deficiency on renal function.

METHODS

Experiments were done on seven mongrel female dogs weighing 10–26 kg. In each dog plastic catheters were chronically implanted in a jugular vein and a carotid artery to facilitate intravenous infusions and to obtain arterial blood samples. An episiotomy was done to permit easy catheterization of the urinary bladder. Sterile precautions were taken in handling the vascular catheters and in performing bladder catheterizations. During a control period of at least 3 wk the animals were fed 20 g/kg body weight per day of a potassium-

deficient diet (General Biochemicals, Chagrin Falls, Ohio, Hartroft formulation) which was supplemented with 40 mEq/day of potassium chloride. The weight of all of the animals became essentially constant during the control period.

Inulin clearance, PAH clearance, maximum tubular reabsorptive capacity for glucose (Tm_g), maximum urine osmolality, and total exchangeable body potassium (K_e) were determined weekly, and the averages of these measurements taken as the control values. There was no significant variation in the measured values from week to week in a given dog during the control period. As a further test of whether the presence of the catheters or of the diet with supplemental potassium affected renal function, a control period of 6 wk duration was done in one animal, with no significant changes in renal function being detected. Histological examinations of all kidneys were made after death of the animals to check for possible emboli from the vascular catheters. The supplemental potassium was deleted from the diet immediately after the last control studies were obtained. The measurements listed above were then repeated at approximately weekly intervals. More frequent determinations were made of plasma potassium concentration. Serial measurements of renal function and total exchangeable potassium were also done in two of the dogs during potassium repletion with 40 mEq/day of potassium chloride added to the diet.

All clearance measurements were made on conscious animals after a 12 hr fast. After a suitable priming dose, inulin, PAH, and glucose were infused intravenously to produce steady-state plasma concentrations of about 20 mg/100 ml, 1 mg/100 ml, and 400 mg/100 ml, respectively. Because of the possibility of glucose and PAH reacting in the infusion mixture (6), two separate infusions were given, one consisting of PAH in 0.45% NaCl solution and the other of glucose and inulin in distilled water. Both solutions were infused at a rate of 2 ml/min, with the two infusion streams being combined in a T-fitting just before entering the venous catheter. 30 min after the infusions were started, four successive 10 min urine collections were made. Urine was collected through an indwelling catheter, and the bladder flushed with 30 ml of distilled water at the end of each collection. Plasma samples were obtained at the midpoint of each clearance. Values for the four clearance periods were averaged. Inulin was determined by the method of Schreiner (7), PAH by the method of Smith et al. (8), and glucose by an enzymatic method using Glucostat reagent obtained from Worthington Biochemical Corporation, Freehold, N. J. (9).

To determine maximum urinary concentrating ability, the dog was deprived of water for 20 hr. The bladder was emptied by catheterization after 18 hr dehydration and again at 20 hr. The osmolality of the second urine sample was measured with an Advanced Instruments osmometer.

Plasma potassium concentration was measured by flame photometry. Total exchangeable body potassium was determined with the method of 42K dilution (10). 500 μc of 42K in the form of potassium carbonate, supplied by the University of Michigan Ford Nuclear Reactor, were injected intravenously. The dog was placed in a metabolism cage and all urine that was voided during the next 20 hr was collected. Urine samples were obtained by an indwelling catheter at 20, 22, 24, and 26 hr after injection of the tracer. Urine specific activity was determined with a deep-well gamma radiation counter and flame photometry. Total exchangeable potassium was determined from the last three urine samples, using the relationship

$$K_e = (cpm_{injected} - cpm_{excreted})/(\text{urine specific activity})$$

with suitable corrections for radioactive decay. The results for the three samples were averaged.

To study changes in extracellular volume during depletion, serial measurements of inulin distribution space were done in two dogs. Plasma inulin concentration was measured at the end of the clearance experiments, at which time inulin concentration had reached a steady-state value. Total body inulin content at that time was taken equal to the amount of inulin excreted in the urine during the next 24 hr. The 24-hr urine sample was collected in an iced container with the dog in a metabolism cage.

Studies in dogs 1–5 were continued until the onset of muscular weakness. This occurred when K_e had decreased to 30–40 mEq/kg body weight, and usually appeared several hr after the infusion of glucose for Tm measurement.

RESULTS

The initial and final values for inulin and PAH clearances, glucose Tm, total exchangeable potassium, and weight during potassium depletion for the five dogs which were not repleted are given in Table I, and the complete data obtained during depletion and repletion for dogs 6 and 7 are shown in Table II. In order to compare the data obtained from different dogs, C_{in}, C_{PAH}, Tm_g, and K_e were expressed as fractions of their predepletion controls. Values obtained after various durations of depletion, averaged for all seven dogs, are presented in Table III. In all of the animals the clearances

TABLE I

Initial and Final Values for Weight, Inulin Clearance, PAH Clearance, Tm Glucose, and Total Exchangeable Potassium for the Five Dogs That Were Not Repleted

Dog	Days of depletion	Weight		C_{in}		C_{PAH}		Tm_g		K_e	
		Initial	Final	Initial	Final	Initial	Final	Initial	Final	Initial	Final
		kg	*kg*	*ml/min*	*ml/min*	*ml/min*	*ml/min*	*mg/min*	*mg/min*	*mEq*	*mEq*
1	60	26.6	24.4	106	78.6	333	230	280	186	1322	940
2	51	14.4	14.0	59.7	43.7	185	135	205	143	880	590
3	87	12.4	12.5	47.4	32.9	182	127	137	89.5	543	396
4	53	10.9	11.2	37.2	26.4	128	85	122	76.4	473	363
5	46	10.5	10.3	59.0	40.1	184	135	145	95.0	462	348

TABLE II

Renal Function Studies in Dogs 6 and 7 during Potassium Depletion and Repletion

Dog No. and wt	Days of depletion or repletion	C_{in}	C_{PAH}	Tm_g	Maximum urine osmolality*	K_e/kg*	Plasma potassium concentration
		ml/min	*ml/min*	*mg/min*	*mOsm/kg H_2O*	*mEq/kg*	*mEq/liter*
6–16.8 kg	Control	71.9	228	224	1767	39.8	4.4
	Depletion						
	2	73.6	226	228		37.1	4.2
	10	65.0	217	198	1111		2.7
	16	60.6	198	196		33.4	2.5
	23	59.6	204	186	1311		2.5
	30	63.1	185	168	1160	31.8	2.3
	37	55.5	183	162		30.4	2.6
	42	53.3	179	148	1146		2.7
	Repletion						
	1	57.1	188	142	1178		3.0
	8	63.7	196	174	1347	38.3	4.1
	22	69.0	215	167	1575	37.2	4.4
	29	66.1	209	195	1698	38.8	4.6
	36	70.5	218	218	1793		4.6
7–16.2 kg	Control	63.0	198	195	1796	48.1	4.2
	Depletion						
	2	61.5	183	193	1742	46.3	3.8
	8	63.7	185	175			2.3
	15	56.8	173	162	1523	42.7	2.2
	22	52.0	179	157			2.3
	29	52.2	155	139	1175	41.7	2.3
	36	47.0	156	121	1421	41.3	2.6
	43	48.3	151	140	1352		2.4
	49	44.2	142	115			2.4
	Repletion						
	6	50.5	171	139	1485		4.2
	13	56.3	184	161		47.7	4.0
	21	56.2	198	162	1822	46.6	4.1
	30	59.6	197	186	1788	47.2	4.0

* Maximum urine osmolalities and total exchangeable potassium measurements were done 1 or 2 days before or after the clearance determinations. To conserve space here, values for urine osmolality and K_e are shown with the data for the nearest clearance

for inulin and PAH, Tm_g, and K_e decreased in what appeared to be an exponential manner following institution of the potassium-deficient diet. An equation of the form $\ln Y = -bt$, where Y is the fraction of the predepletion control value, t is duration of depletion, and b is a constant, was fitted to the data for each variable for each dog, using the method of least squares. The resulting regression lines for dog 1 are shown in Fig. 1, and the slopes of the regression lines for the data obtained during depletion of all seven dogs (the constant $-b$) are given in Table IV. The slopes of the regression lines for Tm_g were greater than those for either inulin clearance or PAH clearance in all animals. In four of the dogs the slopes of the regression lines for PAH clearance were greater than those for inulin, whereas in three dogs the inulin clearance regression lines had higher slopes than those for PAH. Differences in the slopes of the regression lines for C_{in}, C_{PAH}, and Tm_g for the seven dogs taken as a group were compared using the t test for paired samples (11). The resulting P values are given in Table V. There was no significant difference ($P = 0.8$) between the slopes of the regression lines for C_{in} and C_{PAH}. The slopes of the regression lines for Tm_g were significantly greater ($P < 0.05$) than those for C_{in} or C_{PAH}. Thus the decreases in filtration rate and renal plasma flow rate during depletion paralleled each

TABLE III

*Average Values Obtained for Seven Dogs of C_{in}, C_{PAH}, Tm_g, and K_e after Various Durations of Potassium Depletion**

Days of depletion	C_{in}	C_{PAH}	Tm_g	K_e
2	0.99	0.98	1.00	0.97
9	0.94	0.95	0.91	0.93
16	0.87	0.90	0.86	0.89
23	0.84	0.85	0.83	0.86
30	0.82	0.81	0.77	0.83
37	0.79	0.79	0.74	0.79
44	0.76	0.74	0.70	0.77
51	0.74	0.72	0.68	0.76

* All values are expressed as a fraction of the corresponding predepletion control value. For cases in which values for an individual dog were measured at a time other than that shown, interpolated values were used to obtain the average.

other, whereas Tm_g decreased at a faster rate than either filtration rate or renal plasma flow rate.

As shown in Fig. 1 and Table III, in all of the dogs progressive decreases in renal function were accompanied by nearly proportional decreases in total exchangeable potassium during depletion. The slopes of the regression lines obtained for C_{in}, C_{PAH}, and Tm_g were compared with those obtained for K_e with the t test for paired samples. The resulting P values are given in Table V.

TABLE IV

Slopes of the Regression Lines for Inulin and PAH Clearances, Tubular Reabsorptive Maxima for Glucose, and Total Exchangeable Body Potassium

	Fractional change, ln Y/day × 10^5			
Dog	C_{in}	C_{PAH}	Tm_g	K_e
1	−561	−650	−736	−521
2	−676	−684	−776	−673
3	−440	−497	−505	−508
4	−808	−857	−895	−658
5	−766	−737	−899	−605
6	−692	−603	−928	−584
7	−702	−678	−810	−539

There were no significant differences between the rate of decrease of C_{in} or Tm_g and K_e. The difference between the rate of change of C_{PAH} and K_e was significant at the 5% level.

Exchangeable potassium per kilogram of body weight (K_e/kg) and plasma potassium concentration are shown as a function of duration of potassium depletion in Fig. 2 and Table II. Plasma potassium concentration dropped rapidly during the 1st 5–10 days of depletion, and then stabilized at between 2–3 mEq/liter. Exchangeable potassium showed a progressive decrease throughout the experiment in all of the animals. The average value of

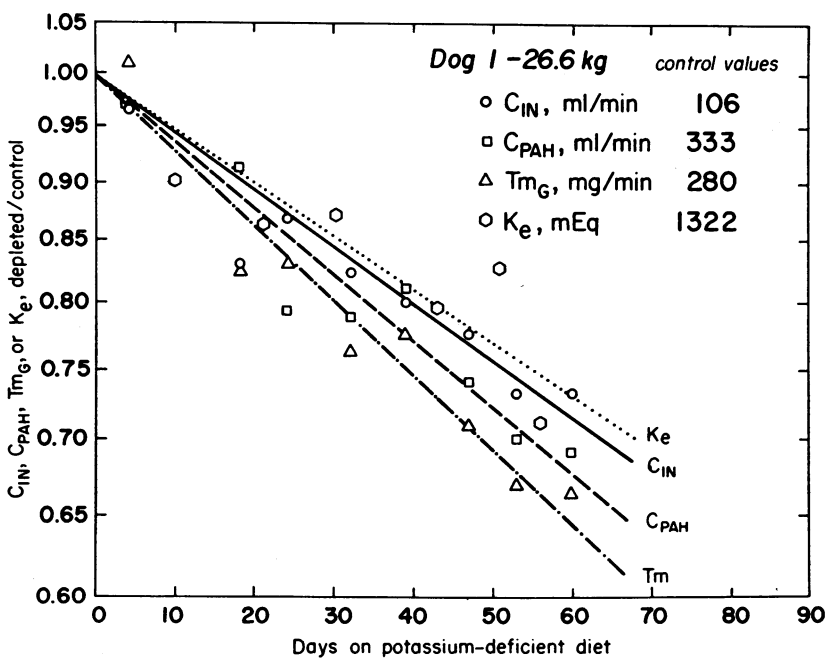

FIGURE 1 Inulin clearance, PAH clearance, Tm_g, and total exchangeable potassium data for dog 1. Variables plotted on the ordinate are expressed as the fraction of the average predepletion value.

TABLE V

Significance Levels of the Differences between the Slopes of the Regression Lines for Inulin Clearance, PAH Clearance, Tubular Reabsorptive Maximum for Glucose, and Total Exchangeable Potassium for the Group of Seven Dogs

Slopes compared	*P* value*
C_{in}–C_{PAH}	0.8
C_{in}–Tm_g	<0.01
C_{PAH}–Tm_g	<0.05
C_{in}–K_e	<0.2
C_{PAH}–K_e	<0.05
Tm_g–K_e	<0.10

* *P* value from *t* test for paired samples.

K_e/kg for all animals before depletion was 47.1 mEq/kg, and the average value for the five nonrepleted dogs at the time of onset of paralysis was 35.3 mEq/kg.

Maximum urine osmolalities are shown in Fig. 3 and Table II. All dogs showed a significant drop in urinary concentrating ability within 5 days after institution of the potassium-deficient diet. However, after this initial decrease there was not a progressive drop in concentrating ability with time or increasing degree of potassium deficiency. For all of the animals as a group, maximum urine osmolalities after depletion averaged 76% of the control values.

Weights and plasma sodium concentrations in all dogs, and inulin distribution volume in the two dogs in whom it was measured, did not show any consistent change throughout the period of depletion. Fig. 4 illustrates this finding for dogs 3 and 4.

In serial studies during repletion in dogs 6 and 7 (Table II) total exchangeable potassium had returned to predepletion levels after 10 days of repletion. Inulin and PAH clearances and glucose transport maxima had nearly returned to predepeletion values after 30 days repletion. However, glucose Tm's returned to predepletion values more slowly than inulin or PAH clearances.

Histological studies of kidneys from the depleted dogs showed varying degrees of vacuolar change in proximal tubular epithelium. No changes were seen in the collecting ducts. There was no evidence of embolization from the sites of the vascular catheters. The kidneys from the repleted dogs were normal on histological examination.

DISCUSSION

Inulin and PAH clearances and glucose Tm dropped progressively during potassium depletion in all animals. Only limited data on serial measurements of these aspects of renal function in animals depleted with diet alone are available in the literature. In one dog that was depleted with dietary restriction only, creatinine clearance after 38 days of depletion was 77.7% of the predepletion value (1). This finding is in good agreement with an average value of 77.5% predicted from the regression curves for inulin clearance for our animals.

Our finding of reduced PAH clearance in potassium deficiency agrees with the results of studies in patients (12). Detailed serial studies of PAH clearance during depletion have apparently not been reported. In serial studies during repletion of diarrhea-induced hypokalemia in two patients, Schwartz and Relman (5) found that PAH clearance gradually returned to normal. They also found that Tm_{PAH} was decreased during depletion, and suggested that the apparent decrease in renal plasma flow rate could be due to a reduction in tubular extraction of PAH. However, it is unlikely that the reductions in C_{PAH} observed in our experiments were caused by a reduced extraction ratio, since with the very low plasma PAH concentrations that were used PAH secretion was less than 10% of the expected normal Tm_{PAH}.

Several possible reasons can be suggested for the decreases that we observed in filtration rate and renal plasma flow rate. Changes in the state of hydration affect filtration rate and renal plasma flow rate (13). Our finding of no significant change in extracellular volume, body weight, or plasma sodium concentration (Fig. 4) indicates that changes in the state of hydration were not responsible for the changes in clearances. It has been proposed that the changes in filtration rate that occur in potassium deficiency can be explained by partial obstruction of nephrons due to lesions in the collecting ducts (14). However, whereas such lesions have been described in the rat (15), they are not characteristic of the renal lesions found in hypokalemic dogs, and were not present in our animals. Reduced renal blood flow rate and glomerular filtration rate during potassium depletion may be at least partially due to a direct effect of hypokalemia on the renal vasculature. Scott et al. (16, 17) gave renal arterial infusions of KCl solution in dogs with perfused and nonperfused kidneys. They found that renal vascular resistance decreased progressively with increasing infusion rate until renal venous potassium concentration rose above 10.8 mEq/liter. In other experiments with a similar preparation, renal arterial infusion of a potassium-free solution caused an increase in renal perfusion pressure and renal vascular resistance (18). The authors concluded that renal vessels respond to local hypokalemia by constricting. This effect could result in the parallel changes in renal blood flow rate and GFR observed in our experiments. However, one must recognize that the findings in experiments on acute changes in local potassium concentration may not apply directly to chronic depletion studies.

Two previous studies on the effect of potassium de-

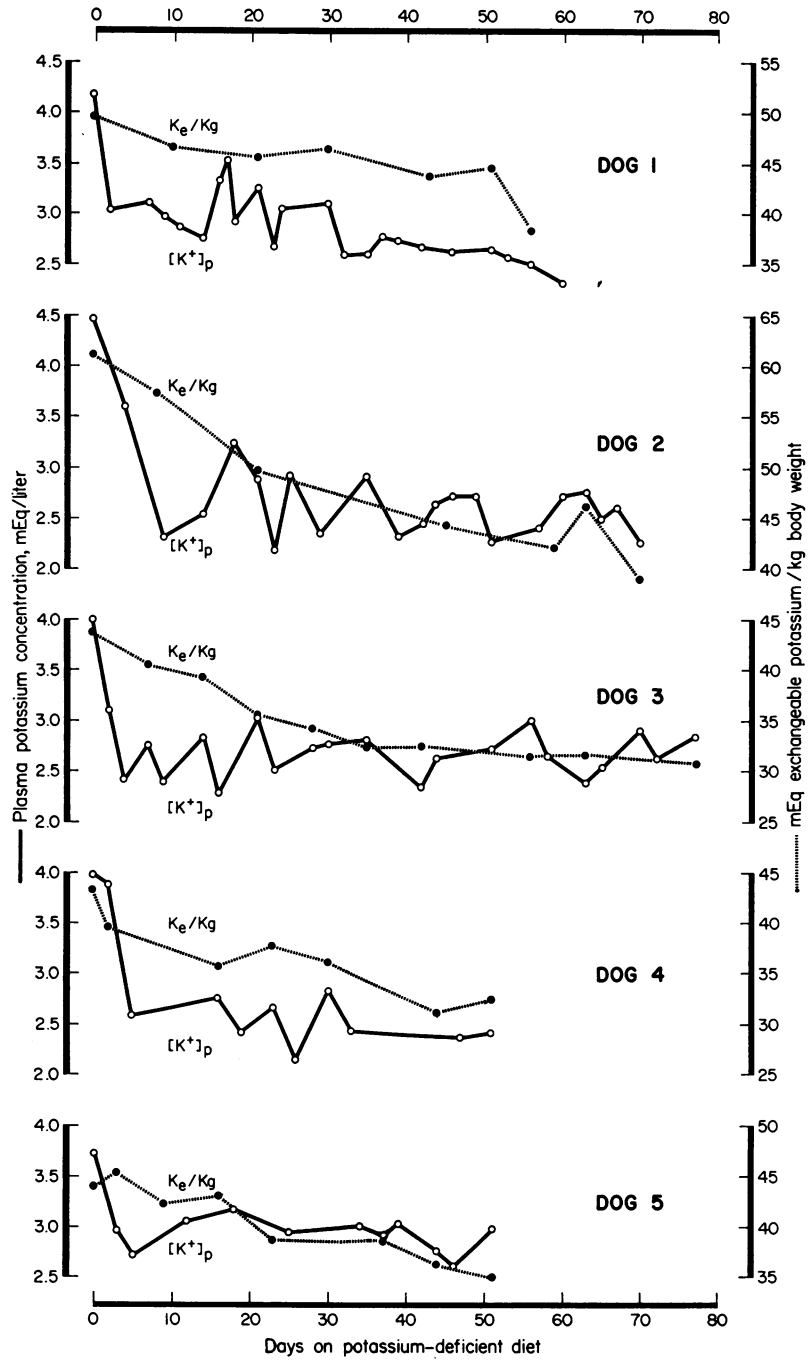

FIGURE 2 Exchangeable potassium per kilogram body weight, and plasma potassium concentration as a function of the duration of potassium depletion for dogs 1–5. Values at day zero are the average of the predepletion values.

ficiency on glucose Tm have been reported. In two of three dogs that were depleted by restriction of dietary potassium and administration of desoxycorticosterone acetate (DOCA), Beskind and Mudge (4) found filtration rate and Tm_g to be unchanged from their control values after 2 wk of depletion. In the third dog filtration rate was decreased by 12% and Tm_g reduced by 19% after 2 wk depletion. Since only two measurements were made for each dog during depletion, and the results obtained for the three dogs were inconsistent, the findings

were not conclusive. Giebisch and Lozano (1) reported that glucose Tm's were unchanged in two dogs after the administration of DOCA. However, since they did not present their data or the details of their experiments it is difficult to interpret their findings. Our finding of substantial decreases in Tm_g in all seven dogs leaves little doubt that potassium deficiency reduces Tm_g.

It has been reported that glomerular filtration rate and glucose Tm change proportionately in dogs when their state of hydration is altered by infusion of isotonic saline or the administration of diuretics and hypertonic dextrose solution (19). Van Liew, Deetjen, and Boylan (20) found that Tm_g was proportional to filtration rate over a wide range of filtration rates in normal rats. However, in all of our animals the rate of decrease of Tm_g was greater than the rate at which inulin clearance

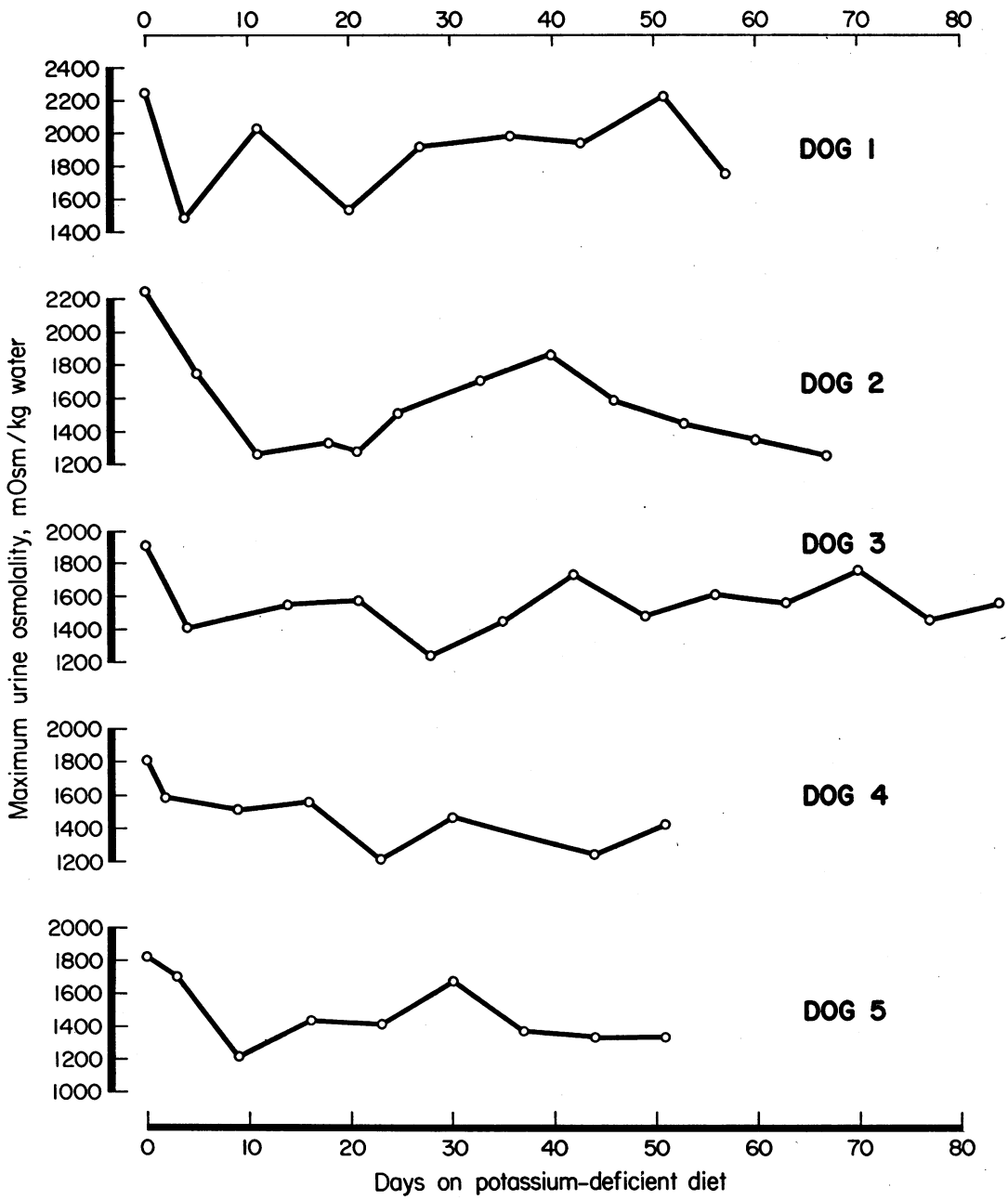

FIGURE 3 Urine osmolality after 18 hr dehydration as a function of the duration of potassium depletion for dogs 1–5. Values at day zero are the average of the predepletion values.

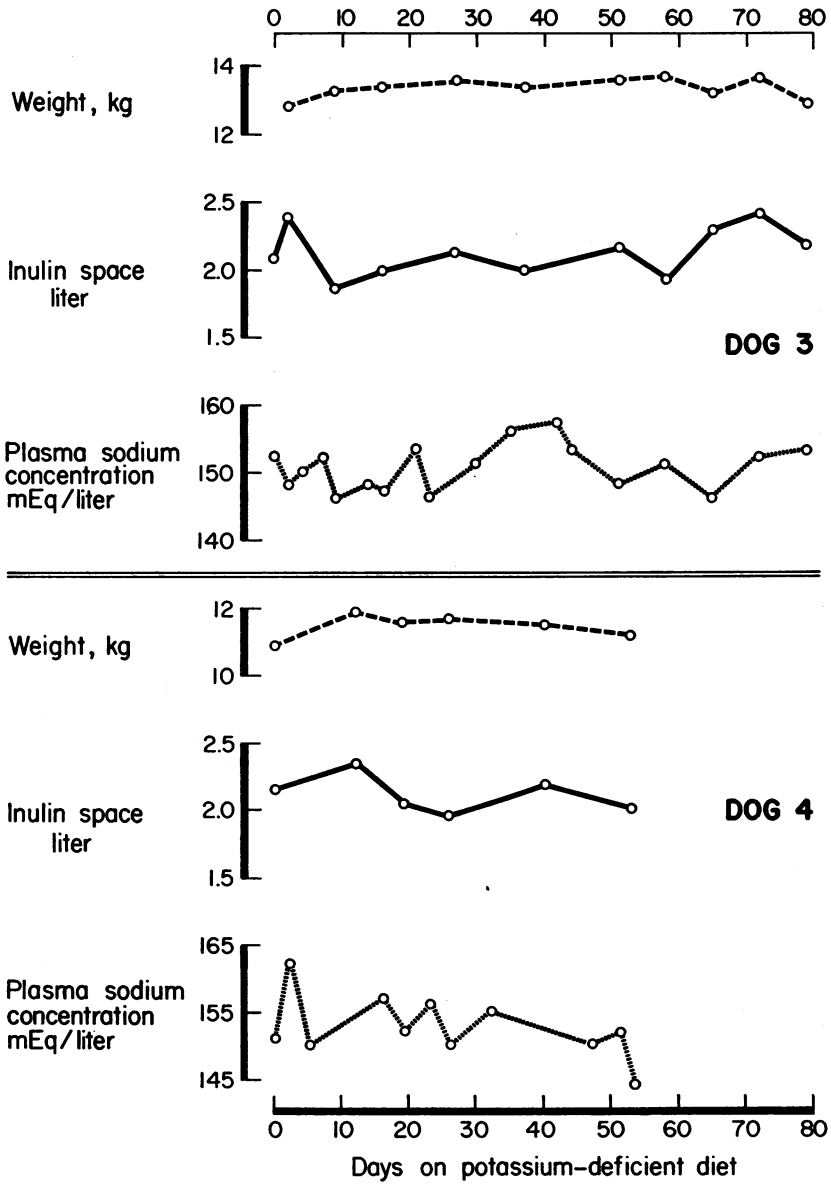

FIGURE 4 Body weight, inulin distribution space, and plasma sodium concentration as a function of duration of potassium depletion for dogs 3 and 4. Values at day zero are the average of the predepletion values.

decreased. Thus it is likely that the decrease in tubular reabsorptive capacity for glucose was not due to decreased filtration only, but that a defect in the cellular transport mechanism for glucose was also present. This is consistent with the histological evidence of changes in proximal tubular cells, and also with the finding (5) of decreased T_{mPAH} in potassium deficiency, since PAH is secreted in the same tubular region in which glucose is reabsorbed.

It is not possible to make a direct correlation of the change in clearance values with decreases in exchangeable potassium, since the measurements were not made simultaneously. However, since clearances and exchangeable potassium declined proportionately in each dog, the changes in renal function appear to be directly related to the changes in total body potassium. In interpreting measurements of total exchangeable body potassium, the over-all nutritional state of the animal must be considered, since potassium capacity changes with body protein stores (21). In our animals an essentially constant nutritional state was achieved throughout the experiment, as evidenced by constant food intake and

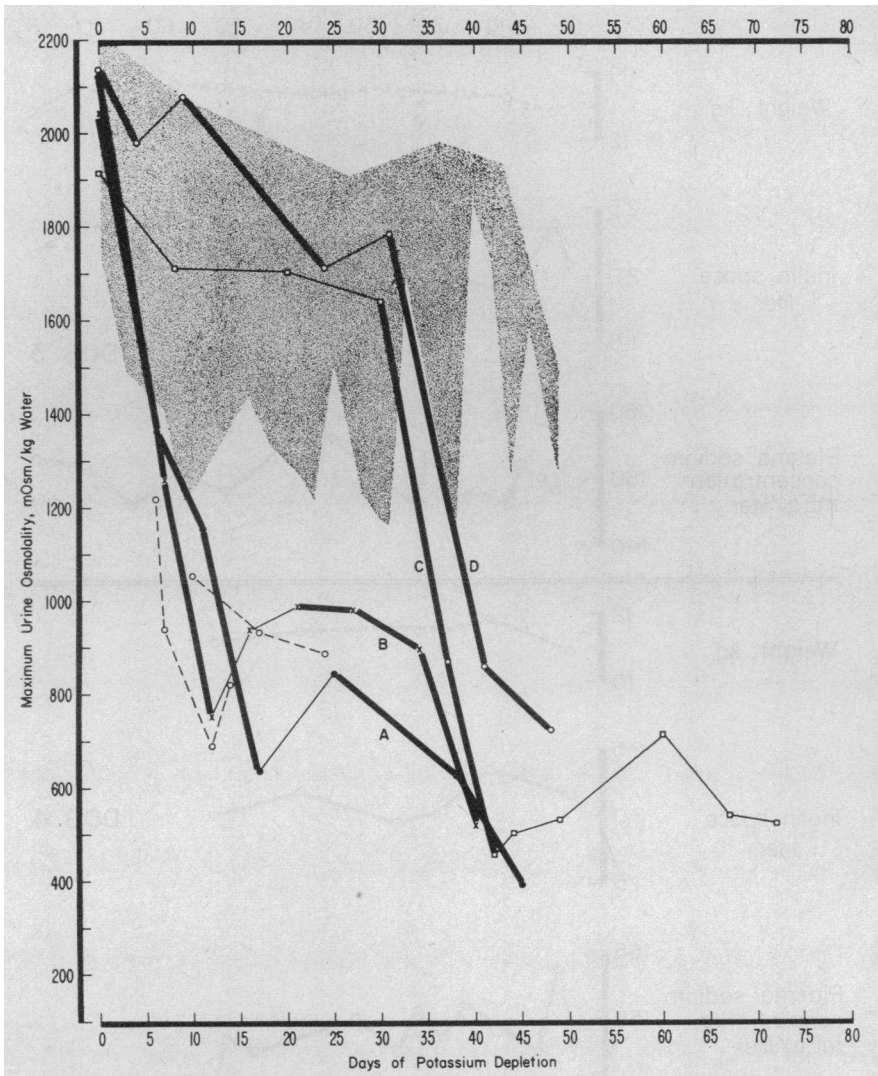

FIGURE 5 Maximum urine osmolality after 18 hr dehydration for dogs treated with potassium-deficient diet and 0.5 mg/kg per day of intramuscular desoxycorticosterone acetate (DOCA). Periods during which DOCA was given are indicated by heavy lines connecting the data points. The shaded area includes data points for maximum urine osmolalities obtained for the seven dogs that were treated with diet alone. The dotted lines connect the data points reported by Giebisch and Lozano, *J. Clin. Invest.* (1) for dogs treated with 1.0 mg DOCA/kg per day.

little variation in body weight. There was poor correlation between plasma potassium concentration and exchangeable potassium in our study. Thus, measurements of plasma potassium concentration would be expected to be of little use in predicting changes in renal clearances in potassium depletion.

The fact that the deficits in renal function which developed during potassium deficiency were reversed in the two repleted dogs indicates that potassium deficiency was indeed the cause of the decreased renal function. The time required for total correction of the defects was considerably longer than that required for replenishment of potassium stores, a finding which has been reported by Schwartz and Relman (5). The fact that Tm_s recovered more slowly than inulin or PAH clearance is consistent with the hypothesis of a defect in the proximal tubular transport mechanism for glucose in hypokalemia.

The control urine osmolality values that we obtained after 18 hr dehydration are comparable to those found by Giebisch and Lozano (1) after 48 hr dehydration, indicating that the 18 hr period of hydropenia is an adequate test of concentrating ability. There was an

initial fall in concentrating ability in all dogs after institution of the potassium-deficient diet, but the concentrating defect did not progress with increasing time or degree of depletion. No previous studies of the effect of duration or degree of potassium depletion on concentrating ability have been published for the dog, and studies of this question in rats have produced conflicting results. Warner and Hollander (22) depleted rats by feeding potassium-free diets supplemented with different electrolyte solutions so that the degree of depletion at a given time was different for each group. In studies done at 9, 18, and 28 days of depletion, they found good correlation between the potassium concentration in muscle and the reduction in concentrating ability, but no significant change with time in the regression relating maximum urine concentration to muscle potassium content. Their results differ from those of Holliday, Segar, Bright, and Egan (23) in which two groups of rats depleted of potassium for 28 days had similar maximum urine concentrations despite different skeletal muscle potassium concentrations. However, with prolonged depletion (60 and 114 days) the concentrating defect did appear to correlate with the degree of depletion. This finding was probably due to the progressive fibrosis and scarring that appeared with prolonged depletion, even though the potassium deficit was not changing much. Our dogs did not show these histological changes even after 80 days of depletion. Thus our finding of no significant correlation of concentrating ability with either the duration or magnitude of potassium deficiency, in contrast to the reports mentioned above, may be due to species differences. It should be noted that in our experiments there was a correlation between concentrating ability and plasma potassium concentration, in the sense that both variables decreased rapidly at first and then tended to remain relatively constant. Thus extracellular potassium concentration may be an important determinant of concentrating ability in the dog.

The magnitude of the renal concentrating defect found in our experiments with diet-induced depletion was considerably less than that which we have found in dogs treated with potassium-deficient diet plus intermittent periods of DOCA administration (Fig. 5). Upward and downward variations in concentrating ability during the course of depletion appeared to be related to whether or not the animal was receiving DOCA before the time of measurement. After periods in which DOCA was not given, concentrating ability usually rose slightly although the dog was still on the potassium-deficient diet. In dog C no DOCA was given during the first 30 days of depletion. During this time urinary concentrating ability dropped only slightly. Administration of DOCA starting at 30 days of depletion resulted in marked fall in concentrating ability. Maximum concentrating ability in DOCA-treated dogs reported by Giebisch and Lozano (1) and shown by the dotted curves in Fig. 5 was also substantially lower than that found in our diet-depleted animals.

In addition, animals depleted with diet alone did not exhibit as severe polydipsia and polyuria as that found in the steroid-treated animals. The above findings are compatible with the concept that DOCA may have an action on water metabolism independent of its potassium-depleting effect, and they emphasize the need for caution in interpreting the results obtained from animals depleted in different ways.

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