

Potassium Balance and the Control of Renin Secretion

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ABSTRACT Plasma renin activity and renin substrate were measured in nine groups of rats which were maintained for 7 wk on diets in which the proportions of sodium and potassium were varied.

Balance data indicated that the highest dietary intake of potassium employed (92 mEq K⁺/100 g food) consistently induced sodium depletion. With less consistency, the highest sodium intake employed (52 mEq Na⁺/100 g food) tended to induce potassium depletion.

In accordance with previous reports, sodium deprivation induced significant increases in plasma renin activity. But the present results indicated that changes in potassium intake exerted a highly significant modulating influence on this characteristic response. The results describe an inverse relationship between potassium administration and the concurrent level of plasma renin activity. The highest serum renin levels of all occurred in the potassium-depleted animals and the usual renin response to sodium deprivation was virtually abolished in the presence of a high potassium diet.

Neither the suppressing effect of K⁺ administration nor the stimulating effect of K⁺ depletion on plasma renin activity could be explained in terms of any predicted changes in aldosterone secretion or observed changes in sodium balance. Therefore, the effect seems to be mediated by a direct influence of potassium ions on renal renin secretion, perhaps via induced changes in sodium load to the macula densa.

These studies point to an important role for potassium in the regulation of renin secretion. The results in turn raise the possibility that renin secretion per se may be importantly involved in effecting potassium conservation and potassium elimination. The means by which these interactions are finally mediated remain to be clarified.

INTRODUCTION

In recent years the role of the renin-angiotensin-aldosterone system in regulation of sodium balance has been

greatly clarified. In man (1, 2) and other species (3, 4) the stimulation of aldosterone secretion by angiotensin has been well established and increases in plasma renin activity and plasma angiotensin have been shown to be inversely related to the sodium intake (5, 6). Observations such as these define a close relationship between this renal-adrenal hormonal system and the regulation of sodium balance.

However, despite the fact that sodium and potassium metabolism are closely interconnected, little is known about the possible influence of changes in potassium metabolism on renin secretion and on angiotensin formation. It has been well established that increases in plasma potassium levels can directly stimulate aldosterone secretion (7-11) and that potassium depletion can sharply reduce aldosterone secretion (10). However, observations in the course of clinical studies suggest that these effects of potassium on aldosterone secretion are not mediated via any corresponding change in plasma renin activity. Thus, in a variety of clinical situations we have actually observed marked increases in plasma renin activity in states of potassium depletion associated with very low aldosterone secretion and we have also observed suppression of plasma renin activity after potassium administration with stimulation of aldosterone secretion (12). Both of these effects of potassium on renin activity can occur without apparent changes in sodium balance. Somewhat similar observations have been described by Veyrat, Brunner, Manning, and Muller (13). Furthermore, more recently, Dluhy, Wolf, Christlieb, Hickler, and Lauer (14) and Vander (15) have described an acute depression of renal renin secretion by potassium infusions.

The present study was designed to extend and clarify these relationships by employing an animal model in which more drastic and rigidly controlled changes in both potassium and sodium balance could be imposed. The results of this study demonstrate a significant and discrete influence of changes in potassium balance with changes in plasma potassium concentration on the level of plasma renin activity.

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METHODS

Male Holtzman rats weighing between 275 and 285 g were divided into nine groups of 10 animals each. The nine groups were designed to encompass all possible combinations of three arbitrary levels of dietary intake defined as low, medium, or high, for both sodium and potassium (Table I).

All animals were fed a basic diet which contained 60% cerulose, 24% vitamin-free casein, 2% Alphacel, 10% Mazola oil, 4% salt mix, and adequate amounts of all vitamins. All diets contained the same amounts of magnesium (0.05%) and trace elements were present as follows (per kg of diet): ferric citrate (1100 mg), $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$ (240 mg), $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (160 mg), $\text{MnSO}_4 \cdot \text{H}_2\text{O}$ (980 mg), KI (1.2 mg), and NaF (40 mg). Each group of animals was fed a diet containing different percentages of sodium and potassium (Table I). Variations in sodium-to-potassium ratios were achieved by using different salts of these elements. Adjustments in the total quantity of salt mix to keep it as close as possible to 4% of the diets were made by altering the amount of Alphacel whenever necessary, e.g., adding Alphacel to salt mix to make it equal to 4% of the diet. When salt mix was more than 4% of the diet, Alphacel in the amount of excess salt was subtracted to maintain the same percentages of fat, carbohydrate, and protein.

After the nine groups were habituated to their respective diets for 5 days, a 12 day balance study was begun using 45 animals (5 from each group). During this time food and fluid consumptions were measured daily and urine and feces collected every 2 days. Spillage of food was taken into account in the calculation of food consumption. During the balance period each rat was kept in an individual stainless steel metabolism cage designed to separate urine from feces. To facilitate the collection of urine, the funnel portion of the

cage was coated with paraffin. After fecal matter was removed the cages were rinsed with distilled water to remove any urine that might have remained on the cages. The washings were pooled with the urine and made up to known volume. Sodium and potassium determinations using a flame photometer were made on urine directly and on feces following ashing at 650°C and dilution to a known volume.

After completion of the balance study these animals along with the others were maintained on the same regimen for an additional 35 days at which time they were all sacrificed by decapitation. Aorta blood was collected from each animal into a beaker containing added thrombin and allowed to clot. The serum was separated promptly and stored frozen. All animals were weighed on days 1, 6, 18, 32, and at the time of sacrifice (day 53).

Sodium and potassium concentrations were measured on each individual serum sample. For the estimation of serum renin activity and renin substrate concentration equal parts of nonhemolyzed serum from each rat in each group were pooled to make up a total pooled volume of at least 10 ml. This relatively large volume of pooled serum was necessary for the requirements of an earlier method used in our laboratory (16). Results obtained with this earlier method in a pilot study of the present experiment are not reported here. However, these results were directionally entirely similar to those obtained with a newer and more sensitive method utilized herein. In the method employed for estimation of plasma renin activity (17) 2.7 ml of serum were added to 0.3 ml of a solution containing 0.03 M disodium EDTA, 1.5 M phosphate buffer, and 2% neomycin sulphate. Before incubation at 37°C the pH was adjusted to 5.7 and 0.03 ml diisopropylfluorophosphate (DFP) was added to give a concentration of 1:2000. After incubation for 16 hr

TABLE I
Plan of Experimental Groups and the Significance of the Changes Observed in Serum Sodium and Potassium

Sodium intake (mEq/100 g food) ...	Serum sodium (mEq/liter)			Serum potassium (mEq/liter)		
	Low (0.52)	Med. (5.2)	High (52)	Low (0.52)	Med. (5.2)	High (52)
Potassium intake (mEq/100 g food)						
High (92)	III 138	VI 135	IX 139	III 6.6*	VI 6.0*	IX 6.0‡
Med. (9.2)	II 140	V 139	VIII 136§	II 6.2‡	V 5.8‡	VIII 6.1
Low (0.92)	I 143	IV 138	VII 139	I 5.3	IV 4.6§	VII 3.3¶

* Means <0.01, represents probability value as compared to lowest potassium intake.

‡ Means <0.001, represents probability value as compared to lowest potassium intake.

§ Means <0.05, represents probability value as compared to lowest sodium intake.

|| Means <0.05, represents probability value as compared to lowest potassium intake.

¶ Means <0.001, represents probability value as compared to lowest sodium intake.

the samples were rapidly frozen and stored for future pressor bioassay in the rat. The mean values obtained for plasma renin activity are expressed as nanograms angiotensin generated per ml of serum per hour of incubation. The pressor activity of each sample was assayed from four to six times.

Renin substrate concentration was estimated by the addition of an excess of angiotensinase-free hog renin. For this, 0.2 ml of serum was incubated with 0.2 ml of standard hog renin in the presence of EDTA, phosphate buffer, and neomycin sulphate in proportions indicated. The solution was diluted to 2 ml with isotonic saline and incubated for 1 hr at 37°C. The samples were then placed in boiling water for 10 min, centrifuged, and the supernatant bioassayed in the rat.

In this study the balance data and the serum electrolytes were analyzed by analysis of variance.

RESULTS

The results of these experiments are presented in Tables I-III and certain features are illustrated in Figs. 1-5.

General effects. In all of the groups the animals appeared healthy throughout. However, growth rate was retarded in certain of the groups (Fig. 1). A normal growth rate was observed in groups II, V, VI, and VIII. There was slight retardation of growth in groups III, IV, and VII and a marked retardation in groups I and IX. The failure of growth in the latter two groups occurred despite a similar caloric intake (Table III).

Patterns of renal excretion of sodium and potassium and analysis of balance data. These data are plotted in Fig. 2 and tabulated in Tables II and III for the average of the five animals of each group utilized for the 12 day balance period.

In general expected changes in sodium and potassium balance were observed among the various groups (Fig. 2). However, it should be noted that the high potassium intake caused significant natriuresis in both the sodium-depleted rats and also in those rats on the normal sodium diet. Thus, groups III and VI were both in negative sodium balance and lost more sodium than groups I or IV. Furthermore, even in those rats eating the high salt diet the high potassium intake reduced the positive sodium balance and produced more natriuresis than in animals eating a normal K⁺ intake (groups VIII and IX). In contrast, virtually no sodium was lost in the urine of sodium-depleted and normal rats which were not receiving the high potassium intake (groups I and IV).

A second trend observed was the tendency for increasing the amounts of dietary sodium to induce kaliuresis. This trend was not nearly as consistent as the first trend noted above. However, it was apparent when groups IV and VII, and VI and IX were compared. In each case an increase in the sodium intake caused a significant reduction in potassium balance. In addition it is of interest to note that increasing the intake of either sodium or potassium had little effect on the absorption of the other ion (Table II).

TABLE II
Sodium and Potassium Balances

Group No.	Sodium (mEq)			
	Intake	Fecal	Absorbed	Urine
I lo Na lo K	0.94	1.09	-0.15	0.95
II lo Na m K	1.00	0.53	0.47	0.40
III lo Na hi K	0.91	0.61	0.30	3.48
IV m Na lo K	9.15	1.08	8.06	5.6
V m Na m K	9.61	1.36	8.25	7.1
VI m Na hi K	11.43	1.14	10.29	13.0
VII hi Na lo K	92.50	6.09	86.4	77.1
VIII hi Na m K	111.71	7.75	104.0	84.7
IX hi Na hi K	112.96	3.99	109.0	106.1

Potassium (mEq)				
I lo Na lo K	1.65	0.87	0.78	0.52
IV m Na lo K	1.61	0.24	1.37	0.66
VII hi Na lo K	1.63	0.57	1.06	1.65
II lo Na m K	17.6	1.1	16.5	14.6
V m Na m K	16.9	1.3	15.6	11.6
VIII hi Na m K	19.7	1.3	18.4	13.7
III lo Na hi K	160	6.0	154	144
VI m Na hi K	202	7.0	195	169
IX hi Na hi K	199	5.9	193	186

All values are the mean of five animals for the entire 12 day period.

In the analysis of these experiments it should be appreciated that, as might be expected, the balance data derived from those animals receiving the high sodium or high potassium diets become inherently considerably less accurate, because differences in total balance of the order of a few milliequivalents (which could be significant biologically) are less apparent when the measured urinary excretion of these cations is already very high.

In summary, the balance data indicate that high potassium diets tended to be natriuretic and that high sodium diets occasionally tended to be kaliuretic. These two effects were more apparent in those groups of animals which were oriented towards a maximum conservation of the other of the two cations.

Effects on serum sodium and potassium concentrations. The trends indicated by the balance data were supported by changes observed in the serum electrolyte values (Table I). Firstly, the kaliuretic effect of sodium administration was reflected by its tendency to retard hyperkalemia in the potassium-fed animals and to promote hypokalemia in the potassium-depleted groups. As expected the highest levels of serum potassium were observed in the three groups of animals receiving the high

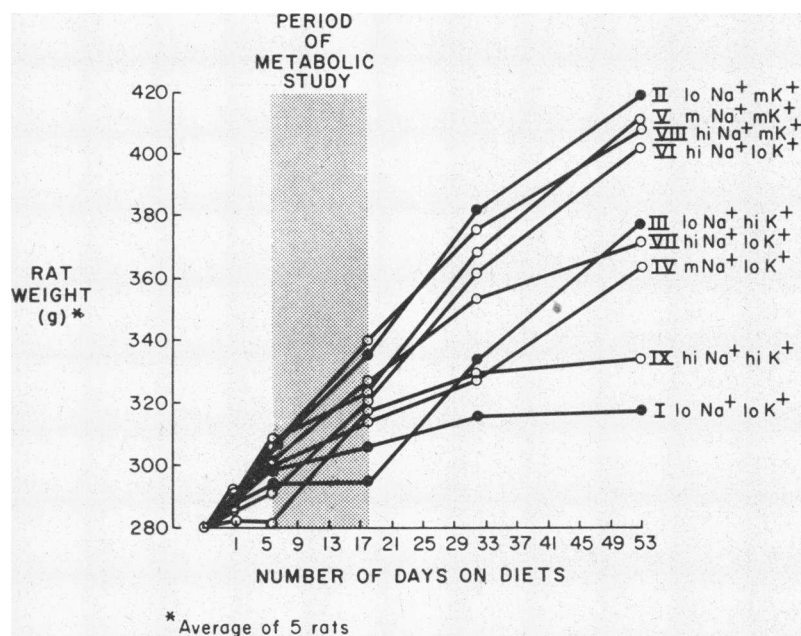


FIGURE 1 Growth rates of the nine groups of rats. lo = low; m = medium; hi = high.

potassium diet. However, when sodium was provided in the diet (groups IV and VII as compared to group I) increasing degrees of sodium administration produced significant graded reductions in the serum potassium concentrations. This effect was most apparent in those animals receiving the lowest potassium intake.

In general the serum sodium seemed to be affected by increasing potassium intake, thus increasing potassium was associated with a gradual fall in serum sodium. However, these changes were only significant when comparing groups VII and VIII. The exception to this

trend appears in group IX where a high potassium intake, in the face of a high sodium diet, did not induce a relatively lower serum sodium. Unlike the changes in serum potassium, the changes in serum sodium were proportionally much smaller. Furthermore, it should also be noted that the highest serum sodium values were actually observed in the three groups of rats receiving the lowest dietary intake of sodium.

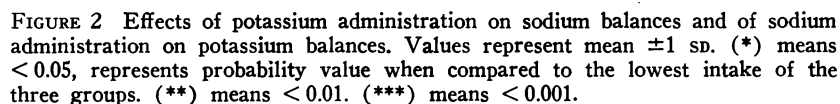
Effects on serum renin activity and on the concentration of renin substrate. These results are presented in Table III and in Figs. 3, 4, and 5. Since the variability

TABLE III
Balance Data, Food and Fluid Intake, Renin Activity, and Renin Substrate Measurements

Group No.	Food intake	Fluid intake	Balance		Plasma Renin activity	Renin substrate
			Sodium	Potassium		
	g	ml	mEq	mEq	ng/ml/hr	ng/ml
I lo Na lo K	179	378	-0.74	0.26	6.0	308
II lo Na m K	191	327	0.07	1.9	3.3	407
III lo Na hi K	174	571	-3.18	9.6	1.6	372
IV m Na lo K	175	401	2.5	0.72	2.7	372
V m Na m K	184	347	1.5	4.0	1.1	345
VI m Na hi K	219	574	-2.7	26	0.9	405
VII hi Na lo K	177	343	9.3	-0.59	2.8	376
VIII hi Na m K	214	425	19.3	4.7	1.5	408
IX hi Na hi K	216	829	2.9	7.3	3.7	371

All values are the mean of five animals for the entire 12 day period.

EFFECT OF SODIUM ON POTASSIUM BALANCE



In accordance with numerous previous reports, sodium deprivation produced significant increases in serum renin levels (Table III). Thus, on the medium K⁺ intake sodium deprivation caused a significant increase in renin activity from 1.1 to 3.3 ng/ml per hr. However, it was also clear from the data that changes in the potassium intake exerted a highly significant modulating influence on this characteristic renin response (Fig. 3). Thus, on the high potassium intake the typical response to sodium depletion was greatly attenuated. The control value for serum renin was lower (0.9 ng/ml per hr) and it increased to only 1.6 ng/ml per hr despite an even greater degree of sodium depletion associated with the high K⁺ administration (see above). Moreover, the basal renin level as well as its response to sodium depletion

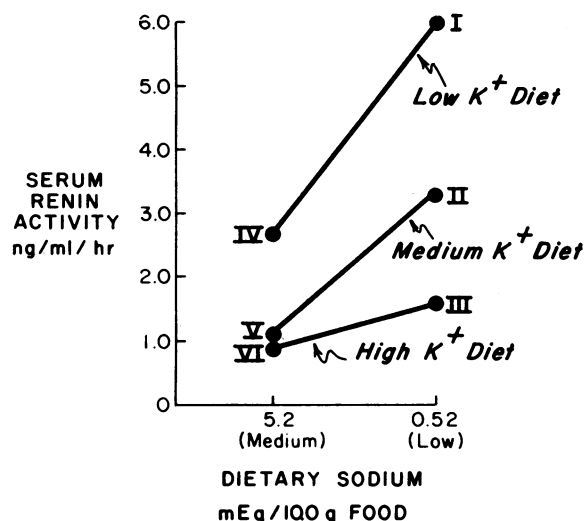


FIGURE 3 The usual plasma renin response to sodium depletion is blunted by increases in the dietary potassium intake.

was greatly augmented by potassium depletion. In this latter situation sodium depletion caused the values to rise from 2.7 to 6.0 ng/ml per hr. It should be noted that the highest of all renin values occurred in the low K⁺, low Na⁺ dietary group. Furthermore, in group III (high K⁺, low Na⁺ group) the values were practically normal and were actually lower than those observed in animals receiving a normal Na⁺, low K⁺ diet (group IV).

The suppression of plasma renin by potassium administration in the three groups of animals maintained on a low sodium diet is depicted in Figs. 4 and 5. The plots illustrate a reciprocal relationship between dietary potassium and serum renin levels and also between serum potassium and serum renin levels. This reciprocal relationship between potassium balance and serum renin obtained in the face of the slightly natriuretic and hyponatremic effects induced by the potassium administration, effects which would be expected to operate to increase plasma renin.

In a previous report it was found that, in the rat, administration of large excess of sodium chloride did not suppress plasma renin levels below what was observed with moderate amounts of sodium in the diet (18). In this regard it is of interest to note that in the present study all three groups of animals given the high sodium intake exhibited serum renin levels of the same order of magnitude as the corresponding groups given only the medium dietary sodium intake. The exception again was group IX. The discrepancy in this group may reflect an unphysiological consequence of the extremely high solute loads.

DISCUSSION

The present relatively long-term balance studies define an impressive inverse relationship between, on the one hand, potassium administration, plasma potassium concentration, the rate of urinary potassium excretion, and potassium balance, and, on the other hand, the concurrent level of serum renin activity.

The influence of changes in potassium metabolism on circulating renin levels could not be explained as a consequence of any induced changes in sodium balance. Indeed, the suppressing effect of potassium administration on renin activity was often observed despite the fact that the potassium feeding occasionally induced some sodium depletion and hyponatremia. Furthermore, the striking increases in serum renin activity associated with K⁺ depletion were never associated with a sodium diuresis and in some situations may in fact have occurred despite an induced sodium retention.

It is interesting to note that the significant changes in sodium balance due to different potassium intakes were reflected in only minor changes in serum sodium concentration while the less consistent changes in potassium balance due to different sodium intakes were associated with significant changes in serum potassium. Perhaps this is due to the fact that changes in sodium balance are usually reflected in changes in extracellular fluid volume, which entails little change in serum sodium concentration, while changes in potassium balance do not affect extracellular fluid volume and so are reflected in changes in serum potassium concentration.

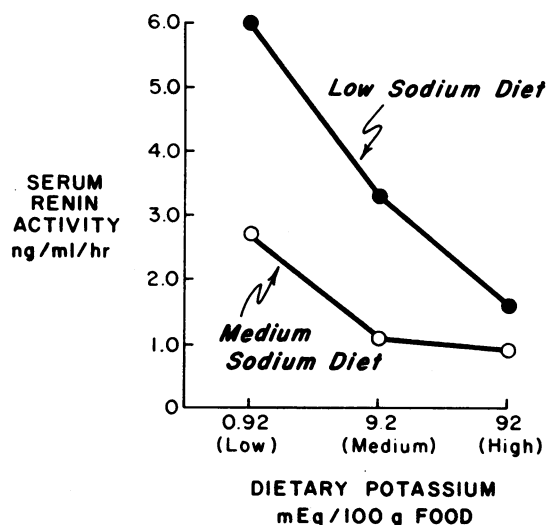


FIGURE 4 Relationship between plasma renin activity and sodium and potassium intake. The plot illustrates an inverse relationship between dietary potassium and plasma renin. The relationship obtains with either a low or a normal sodium intake.

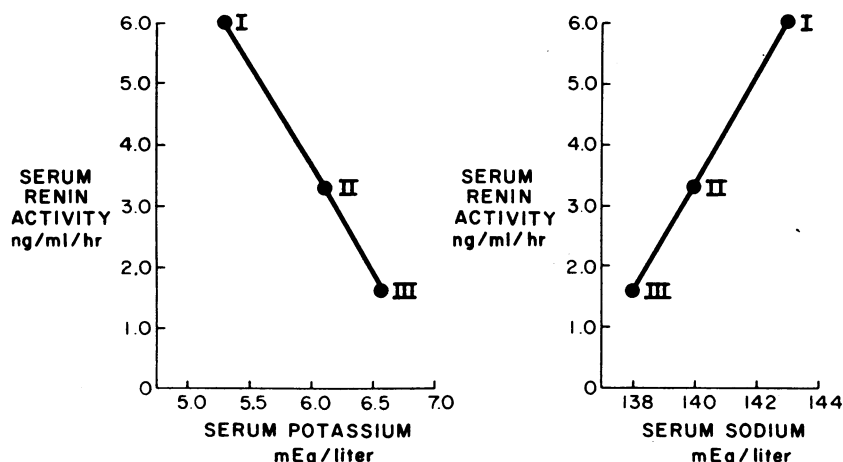


FIGURE 5 Serum renin activity related to plasma K^+ and to plasma Na^+ values in sodium-depleted rats which were fed three different levels of dietary K^+ . A reciprocal relationship between serum renin activity and the serum potassium level is apparent. A direct relationship between serum sodium and renin activity is also plotted. However, the changes in serum sodium are proportionally much smaller than those induced in serum K^+ and are not statistically significant.

In six of the nine groups of the present study a close reciprocal relationship obtained between serum renin levels and potassium administration. However, before assigning an important role for potassium in the regulation of renin secretion it is necessary to reconcile the failure of the very high sodium diet in the three groups of rats which received it to produce an expected suppression of renin. Quantitative considerations indicate that the amount of sodium chosen for this diet when translated by weight to larger species might have been extremely unphysiological. Thus, the solute load in this group would, by weight in man, represent an intake of greater than 1000 mEq for both sodium and potassium. In the present experiment these high levels of dietary sodium appeared to exert a K^+ -depleting effect which may ultimately have been the cardinal influence in producing the paradoxical or seemingly inappropriate hyperreninemia observed in these three groups. Failure of the higher sodium diet to suppress plasma renin levels beyond that observed with normal salt intake is also in keeping with a previous report (18). Such observations raise the possibility that, in the rat at least, plasma renin cannot be reduced below a certain minimum level by sodium administration.

While a connection between potassium metabolism and renin secretion has been demonstrated in this study, the means of its mediation remain incompletely defined. It is well known that potassium administration increases (7-11) and that potassium depletion decreases (7, 10, 11) the adrenal cortical secretion of aldosterone and there is good evidence to suggest that this occurs via a direct adrenal effect of changes in plasma K^+ (7-9).

However, it is not at all likely that the changes in plasma renin produced by changes in dietary potassium described herein could be secondary to induced changes in aldosterone secretion. This is because a number of studies have indicated that the suppression of renin secretion by mineralocorticoids such as deoxycorticosterone or aldosterone is entirely secondary to the sodium retention induced by these steroids (18-20). Furthermore, in the present study, the effects of potassium on plasma renin often occurred in the face of changes in sodium balance which would be expected to have the opposite effect on renin secretion. It therefore seems that changes in potassium balance can induce changes in renin secretion which cannot be explained by any changes which potassium administration or depletion might induce in aldosterone secretion or in sodium balance.

The changes observed could be induced by changes in the cellular uptake of potassium at some critical site. Alternatively, they may result from a direct effect of the plasma potassium concentration, from changes in potassium reabsorption by the proximal tubule leading to modification of a signal in the macula densa cell area (21), or to changes in tubular secretion of potassium into the distal tubule, even though such changes are thought to occur in the distal convoluted tubule at a site beyond the macula densa area (22). Also, because of the close connection between sodium and potassium transport the results observed could also be secondary to subtle changes induced in sodium metabolism. In this regard it should be noted that others have demonstrated increased proximal tubular sodium reabsorption associated with K^+ depletion (23, 24). Such an effect of potassium might op-

erate to stimulate renin secretion by reducing the amount of sodium delivered to the macula densa area. In this context the renin suppression of potassium administration could be explained by postulating a depression of proximal sodium reabsorption and diversion of more sodium to the macula densa area.

The idea that potassium loading suppresses renin secretion by a direct renal effect is supported by infusion (14) and renal perfusion (14, 15) studies. In the latter study it was suggested that the renin suppression resulted from depressed proximal sodium reabsorption and an increased sodium delivery to the macula densa. However, this mechanism may not explain the suppressed renin observed in our long-term studies of K^+ -loaded, Na^+ -depleted animals because in this situation renin remained suppressed even though urine sodium levels (and therefore presumably sodium load to the macula densa) were reduced.

Whatever the mechanisms involved, these observations already have implications in the comprehension of the renin-angiotensin-aldosterone hormonal system which appear to operate for regulation of sodium and potassium balance and of arterial pressure. Thus, it now appears that depletion of either sodium or potassium ions activates the secretion of renin. However, in the former situation aldosterone is also stimulated whereas in the latter it is greatly retarded. Sodium conservation in the face of potassium depletion may not require increased aldosterone secretion because K^+ depletion may increase renal tubular sodium reabsorption by other mechanisms (25).

The renin-angiotensin-aldosterone interaction now appears more complex than other more familiar endocrine systems. Much more work is required for a full understanding of how this hormonal system simultaneously controls sodium and potassium balance. However, there are clinical situations which are in harmony with the observations of this study. For example, we have frequently observed patients with potassium depletion due to alimentary loss who exhibit extremely high plasma renin levels, and at the same time a markedly reduced aldosterone secretion. It is therefore possible that an increased renin activity per se plays a role in the renal conservation of potassium whereas when aldosterone secretion is also increased, the two hormones together operate to promote renal elimination of excesses of potassium.

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