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### Research Article

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Potassium repletion resulted in a prompt decrease in renin activity to predepletion values.

This study indicates that potassium deficiency has a stimulatory effect on renin release that is independent of any effect on sodium balance.

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# Effects of Chronic Potassium Deficiency on Plasma Renin Activity

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**ABSTRACT** Serial determinations of plasma renin activity, sodium balance, urinary potassium excretion rate, and plasma sodium and potassium concentration were done in five dogs during dietary-induced potassium depletion and repletion. Duration of depletion for the different animals ranged from 5 to 7 wk.

Plasma renin activity increased in all animals during depletion, with rises being demonstrated as early as the 1st depletion day in two of the dogs. Maximum values in the five dogs were recorded from the 2nd to the 28th day of depletion. Early in depletion, changes in renin activity did not correlate with changes in sodium balance. Late in the course of depletion, plasma renin activity decreased concurrently with a progressive retention of sodium. However, in every case increased renin activity persisted throughout depletion despite development of sodium retention sufficient to inhibit renin release in normal dogs.

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## INTRODUCTION

Several recent studies have demonstrated that increased plasma potassium concentration or positive potassium balance exerts an important inhibitory effect on renin secretion. The administration of KCl to salt-depleted human subjects (1-4) or patients with renovascular hypertension (4) caused a decrease in plasma renin activity. A patient with idiopathic hyperkalemia and decreased plasma renin responded to potassium-depleting agents with a return to normal plasma potassium con-

centration and renin activity (5). Renal intra-arterial infusion of KCl in anesthetized dogs inhibited renin secretion (6, 7). Conversely, the possibility that decreased plasma potassium concentration or a negative potassium balance may stimulate renin secretion is suggested by the finding that correction of potassium deficiency in subjects who have been simultaneously depleted of both potassium and sodium caused a 50% fall in plasma renin (3).

The present experiments were designed to study chronic changes in plasma renin activity in conscious dogs during the course of dietary potassium deprivation and repletion. Sodium balance was also followed in order to gain further information in the interaction between potassium balance and renin secretion.

## METHODS

Five female mongrel dogs, weighing 10-23 kg, were studied during dietary-induced potassium depletion and repletion. An episiotomy was done on each dog to facilitate catheterization of the urinary bladder. The dogs were kept in metabolism cages throughout the experiment so that urinary electrolyte excretion could be determined.

The dogs were fed 200 g/day of a potassium-deficient diet (General Biochemicals, Div., Chagrin Falls, Ohio, Hartroft formulation) with added sodium chloride so that the total sodium intake was 45 mEq/day. During a control period of at least 3 wk the diet was supplemented with 40 mEq/day of potassium chloride. The supplemental KCl was then withdrawn for a depletion period of from 5 to 7 wk, after which 40 mEq/day of KCl were again added during a repletion period of 2-4 wk. The weight of all the dogs became essentially constant during the control period and did not change appreciably during depletion or repletion.

Serial measurements of plasma renin activity, sodium balance, urinary potassium excretion, and plasma sodium and potassium concentrations were made during the control, depletion, and repletion periods. The dogs were trained to lie quietly for  $\frac{1}{2}$  hr before the plasma samples were obtained. All blood samples were obtained during the postabsorptive state at the same time each day to avoid possible effects of diurnal variations. The red cells from all blood samples were resuspended in isotonic saline to the original hematocrit and returned to the animals.

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TABLE I  
*Potassium Intake and Urinary Excretion during the  
Predepletion Control Period*

| Dog No. | Length of control period | Total K <sup>+</sup> intake | Total urinary K <sup>+</sup> excretion | Estimated daily extrarenal K <sup>+</sup> loss |
|---------|--------------------------|-----------------------------|--|--|
|         | days                     | mEq                         | mEq                                    | mEq  |
| 1       | 24                       | 1080                        | 1001                                   | 3.3  |
| 2       | 24                       | 1080                        | 1022                                   | 2.4  |
| 3       | 21                       | 945                         | 867                                    | 3.7  |
| 4       | 21                       | 945                         | 836                                    | 5.2  |
| 5       | 21                       | 945                         | 850                                    | 4.5  |

Plasma renin activities were determined by a modification (8) of the method of Boucher, Veyrat, de Champlain, and Genest (9). This method measures renin indirectly by assaying the quantity of angiotensin generated during a 3 hr plasma incubation under standardized conditions. Accordingly, renin activities are expressed as angiotensin equivalents in nanograms per milliliter of plasma. The lower limit of sensitivity for this method is about 0.5–1.0 ng/ml.

Using aseptic techniques, the urinary bladder was catheterized each day to insure accurate urine collections. Plasma and urinary sodium and potassium concentrations were measured by flame photometry. Balance studies during the control period indicated that the daily urinary sodium ion excretion for the five dogs averaged from 2 to 5 mEq less than dietary intake (Table I). It was assumed that this difference represented sodium loss from the gastrointestinal tract, and the value for each dog was applied as a correction in calculating the cumulative sodium balances from urinary excretion during depletion and repletion.

At the end of the repletion period, the kidneys were removed for histological examination.

## RESULTS

Values for plasma sodium and potassium concentrations, plasma renin activity, and cumulative sodium balance obtained for the five dogs of this study are shown in Figs. 1–5. Plasma potassium concentration decreased rapidly during the first 5–10 days of depletion, and then stabilized at 2–3 mEq/liter. It returned to control levels by the 5th day of repletion. Plasma sodium concen-

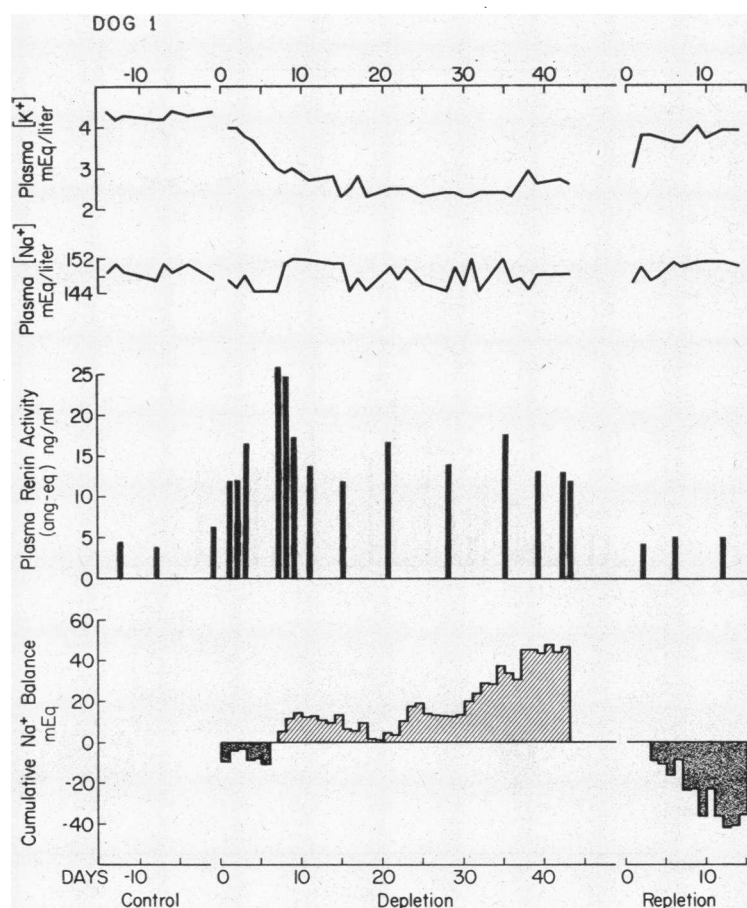


FIGURE 1 Plasma renin activity, cumulative sodium balance, and plasma sodium and potassium concentrations for dog 1 during potassium depletion and repletion. Cumulative sodium balances start at zero at the beginning of both depletion and repletion.

tration did not show any systematic changes during depletion or repletion. Cumulative sodium balance became negative during the first few days of depletion in four of the five animals. However, by the 8th day of depletion each of the animals had developed a positive sodium balance which persisted throughout the remainder of the depletion period. The net retention of sodium in the dogs at the end of the depletion period was in the range of 40–60 mEq. Repletion resulted in a prompt increase in urinary sodium excretion, such that the animals had lost most of the retained sodium after 2 wk of repletion.

Plasma renin activity increased during potassium depletion, with marked rises being demonstrated as early as the 1st depletion day in two of the animals (dogs 1 and 4). Maximum renin activities in the five dogs were recorded from the 2nd to the 28th day of depletion. The early changes in renin activity did not appear to

correlate with changes in sodium balance. Late in the course of depletion, when sodium retention was maximum, renin activity tended to decrease, but did not return to control levels. Renin activities did return to control levels promptly after repletion was started.

Average daily urinary potassium excretion rates for the five dogs are shown in Fig. 6. Daily excretion during the control period was from 1 to 2 mEq less than intake. A marked decrease in urinary potassium output occurred during the 1st day of depletion, and by the 15th day average urinary excretion was less than 1 mEq/day. Repletion was accompanied by a rapid increase in potassium output, with a return to near control values by the 10th day of repletion.

Histological examination showed the kidneys from all of the dogs to be essentially normal.

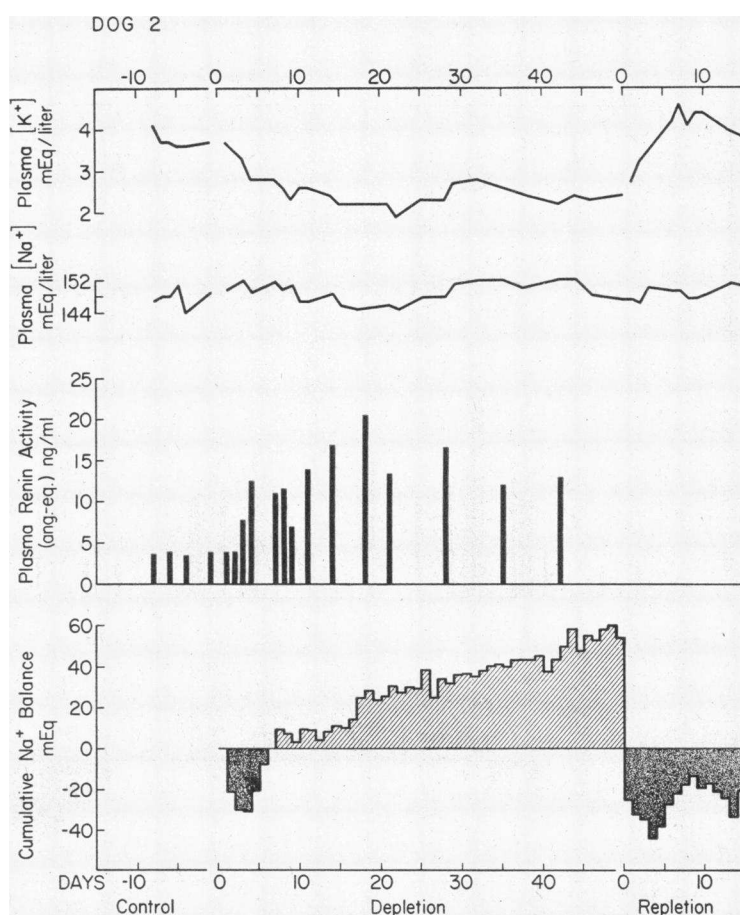


FIGURE 2 Plasma renin activity, cumulative sodium balance, and plasma sodium and potassium concentrations for dog 2 during potassium depletion and repletion. Cumulative sodium balances start at zero at the beginning of both depletion and repletion.

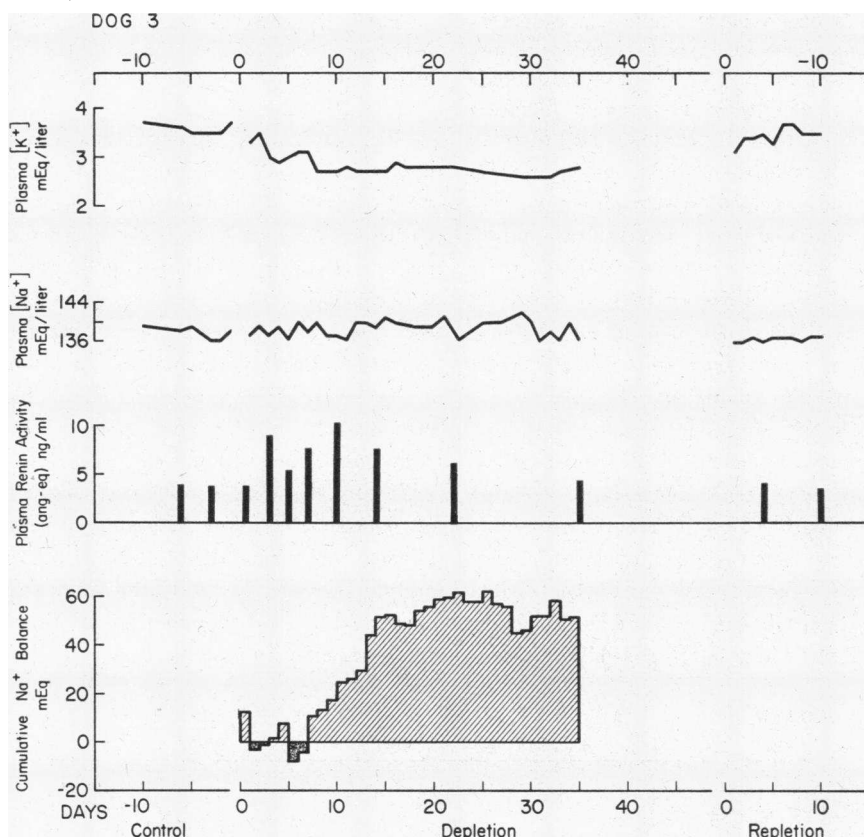


FIGURE 3 Plasma renin activity, cumulative sodium balance, and plasma sodium and potassium concentrations for dog 3 during potassium depletion and repletion. Cumulative sodium balances start at zero at the beginning of both depletion and repletion.

## DISCUSSION

These data demonstrate that chronic potassium deprivation consistently results in increased plasma renin activity and that this effect cannot be attributed solely to changes in sodium balance. Three of the five dogs showed an early sodium loss which might have contributed to the initial rise in renin activity. However, in every case increased renin activity persisted despite an ultimate degree of sodium retention which normally would be expected to inhibit renin release (10). Indeed, the pattern of changes in renin does suggest that the stimulatory effect of potassium deficit on renin release was in part offset by the inhibitory effect of sodium retention. Each animal had its maximum plasma renin during the first 24 days, after which there was a decrease toward control values as sodium retention progressed. In all of the dogs, however, plasma renin remained elevated throughout the entire period of potassium deprivation. This is in contrast to the renin suppression that occurs despite marked potassium depletion in patients with primary aldosteronism (11). It may be that very

long-standing positive sodium balance such as is seen in that disease is adequate to dominate renin control mechanisms. The prompt reduction in plasma renin activity after repletion was started, at a time when the animals were losing sodium, is further evidence for an independent action of potassium on renin secretion. It is evident that much more work will be required to quantify the relative contributions of potassium and sodium balance to the control of renin secretion under a variety of conditions. It should be noted that in all of our experiments there were changes in chloride intake concurrent with potassium ion depletion or repletion.

What is the mechanism by which potassium depletion stimulates renin release? Previous studies (6, 7) utilizing renal intra-arterial infusion of KCl have demonstrated that increased renin release in potassium deficiency is due to a direct effect of reduced plasma potassium on the kidney. The precise mechanism cannot be determined from the present experiments. One possibility is that potassium exerts a direct effect on the juxtaglomerular cells. A second possibility involves the

macula densa, since micropuncture studies have demonstrated that potassium depletion is associated with decreased delivery of sodium from the proximal tubule (12, 13) secondary to decreased glomerular filtration rate (GFR) and/or increased proximal reabsorption (12). The resulting decrease in sodium delivery to the macula densa might be expected to stimulate renin release (14). Finally, the increased renin release might be directly related to increased renal resistance during potassium depletion (15). However, this is unlikely to be the sole or major stimulus since during the first few days of depletion, renin is greatly elevated while renal blood flow is still almost unchanged (16).

All of the animals in this study were retaining sodium by the 2nd wk of potassium depletion. The existence of sodium retention during chronic potassium depletion has been reported previously (17, 18). The retention may be due, in part, to the progressive reduction in glomerular filtration rate which occurs during potassium depletion (16), and perhaps to an increased tubular reabsorption (12) as well. The latter possibility is con-

sistent with the results of acute studies in dogs in which it was found that elevation of plasma potassium acted directly upon the kidney to inhibit sodium reabsorption (7).

The pattern of urinary potassium excretion during potassium depletion observed in these experiments is very similar to that reported by Lemieux, Warren, and Gervais (19), and illustrates the ability of the canine kidney to conserve this ion. The difference of 1–2 mEq between daily intake and excretion rates observed during the control period presumably represents fecal excretion. Fecal potassium loss must be a major cause of the relatively large deficits in total exchangeable potassium which have been reported in dietary-induced potassium deficiency in the dog (16).

Finally, it should also be emphasized that the existence of potassium control of renin secretion further complicates understanding of the control of aldosterone secretion since the direct effect of potassium on the adrenal cortex (20, 21) is opposed by its indirect effect via the renin-angiotensin system.

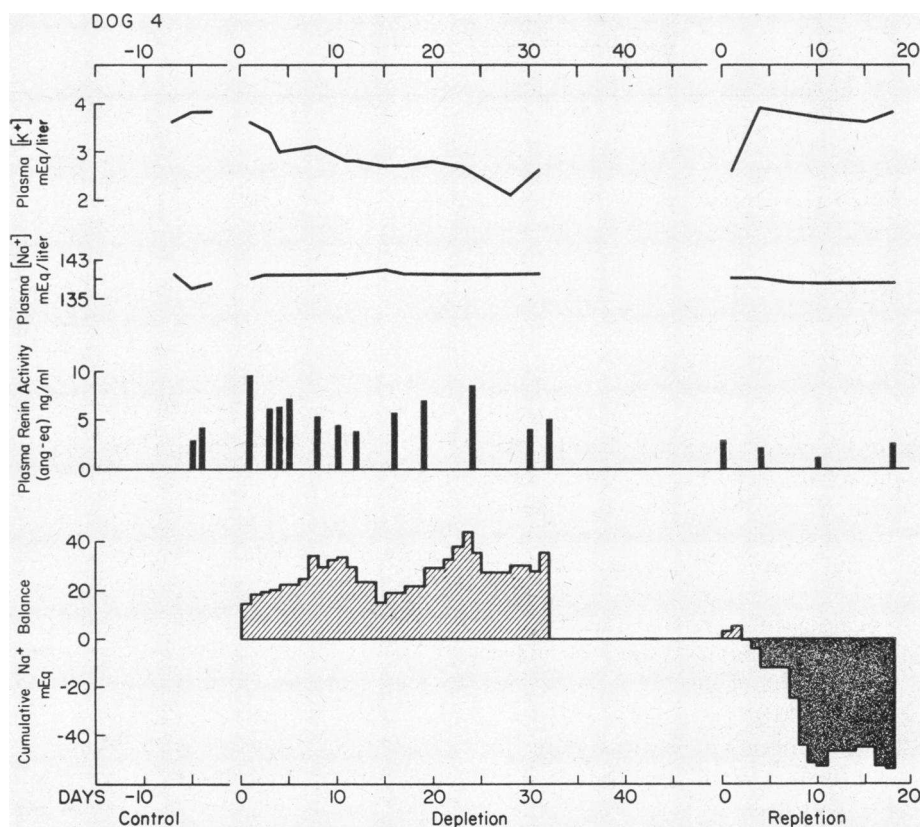


FIGURE 4 Plasma renin activity, cumulative sodium balance, and plasma sodium and potassium concentrations for dog 4 during potassium depletion and repletion. Cumulative sodium balances start at zero at the beginning of both depletion and repletion.

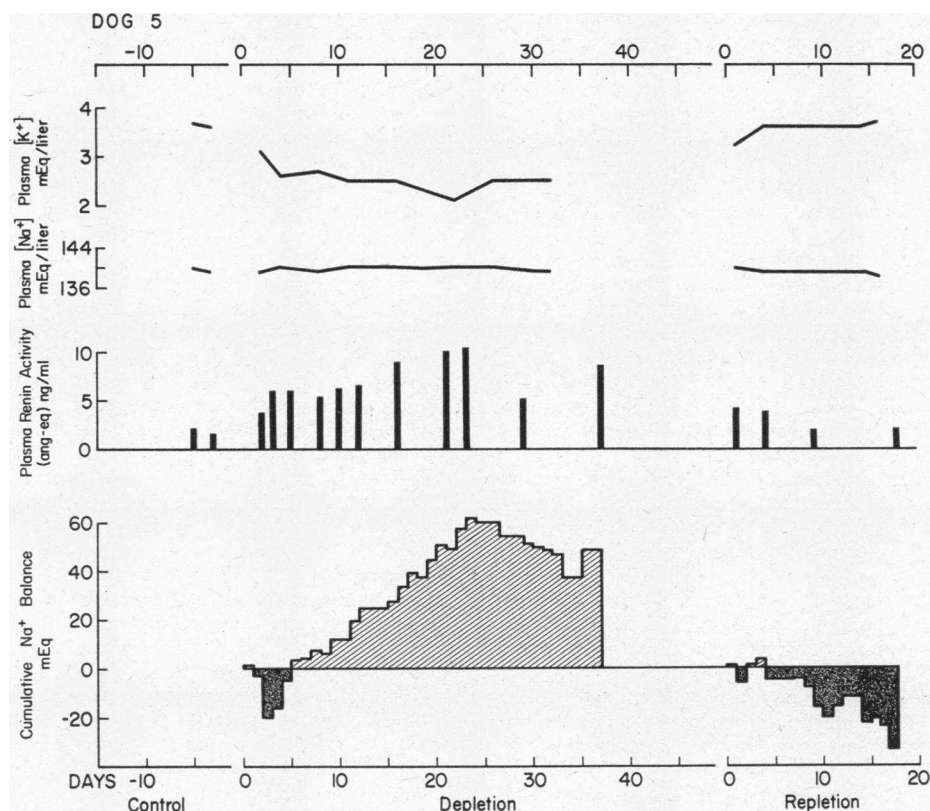


FIGURE 5 Plasma renin activity, cumulative sodium balance, and plasma sodium and potassium concentrations for dog 5 during potassium depletion and repletion. Cumulative sodium balances start at zero at the beginning of both depletion and repletion.

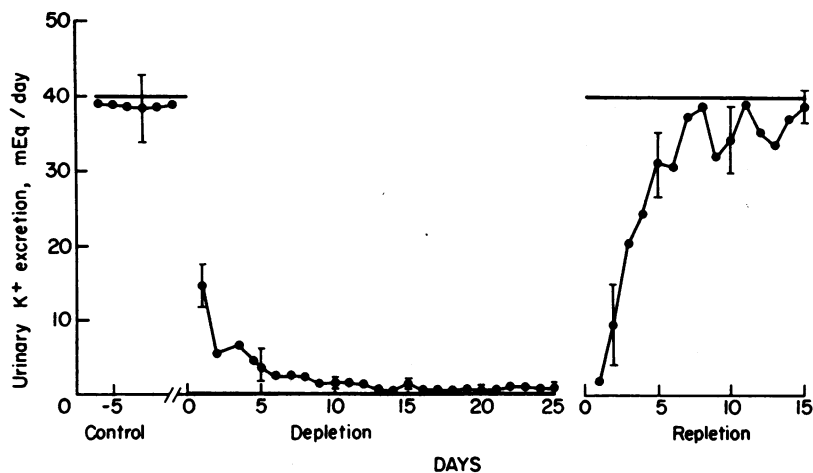


FIGURE 6 Average daily urinary potassium excretion rates for the five dogs during depletion and repletion. Brackets indicate 1 SD above and below the average. Solid horizontal lines show daily intake.

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