Sodium Wasting in Potassium Depletion: 
The Role of Aldosterone

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INTRODUCTION

Impaired renal conservation of sodium (Na) has been reported in potassium (K)-depleted humans and experimental animals when challenged with sodium restriction(1-3); however, the magnitude, duration, or mechanism of this phenomenon have never been clearly defined.

It is known that potassium depletion depresses aldosterone secretion and that sodium restriction stimulates it(1,4-7). Johnson et al.(1) have reported transient sodium wasting in potassium-depleted humans after sodium restriction. Urinary aldosterone excretion was markedly depressed at the time of maximum sodium wasting and was elevated by the time sodium balance had spontaneously returned to normal. Cannon(4) reported similar results. These studies suggest that the impairment of sodium conservation in potassium depletion might be the result of depressed aldosterone secretion which accompanies potassium depletion.

It is significant that impaired sodium conservation associated with potassium depletion has been reported only in the face of severe sodium restriction. Potassium depletion in the presence of adequate sodium intake results in sodium retention with excess sodium accumulating in cells and extracellular fluid(1,3,8-10). Hollander(11) has suggested that the apparent defect in renal sodium conservation might well be explained by the excretion of the higher

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than normal quantities of sodium which have been retained in muscle and extracellular fluid.

The present study has examined sodium balance in potassium-depleted rats, its relationship to endogenous aldosterone secretion, and the effect of exogeneously administered mineralocorticoid.

METHODS

I. Experimental Design

Albino male Sprague-Dawley rats were divided into four groups.

Group I. Sodium balance during dietary potassium depletion followed by sodium restriction. Twelve rats weighing 158–195 g were placed on a normal-Na, low-K diet for 6 days followed by 10 days of a low-Na, low-K diet before killing.

Group II. The effect of deoxycorticosterone acetate on sodium wasting. Eleven rats weighing between 290 and 377 g were divided into two subgroups, five control and six experimental, which were treated as follows:

Subgroup II-E (experimental). Twelve days of normal-Na, low-K diet including 5 days of daily intramuscular injections of 0.5 mg deoxycorticosterone acetate (DOCA) in sesame oil at the beginning of the experiment. This was followed by 7 days of low-Na, low-K diet with one 1 M injection of 0.5 mg DOCA on day 18 and killing on day 19.

Subgroup II-C (control). Twelve days of normal diet including 5 days of 1 M injections of 0.1 cc of sterile saline at the beginning of the experiment. This was followed by 7 days of low-Na, normal-K diet with one injection of 0.5 mg of DOCA on day 18 and killing on day 19.

Group III. Correlation of sodium balance with aldosterone secretion in potassium depletion with subsequent sodium restriction. Eight rats weighing 171–201 g were placed on a normal-Na, low-K diet for 11 days including 5 days of daily injections of 0.5 mg DOCA in sesame oil at the beginning of the experiment. This was followed by 9 days of low-Na, low-K diet before killing on day 20.

Group IV. Correlation of sodium balance with aldosterone secretion when sodium is restricted during the course of potassium depletion. Twelve rats weighing 139–159 grams were placed on a low-Na, low-K diet for 26 days. Killing schedule: day 14, two rats; day 21, two rats; day 24, five rats; day 26, three rats.

II. Analytical Procedures

During balance studies, animals were maintained in individual metabolic cages with screens so placed as to deflect feces, and urine was collected under mineral oil. Daily food consumption was recorded and demineralized water was provided ad libitum. Daily urine volumes were recorded and aliquots were analyzed for Na and K concentration by indirect flame photometry.

1 Doca acetate. Organon.
At the time of killing, each rat was anesthetized with IP sodium pentobarbital and the abdominal cavity was opened. Approximately 5 cc of blood were aspirated from the abdominal aorta and approximately 4 g of thigh muscle were removed. Serum Na and K concentrations were determined by indirect flame photometry and urea nitrogen determinations were done on a Technicon AutoAnalyzer. Muscle samples were dried, extracted three times with anhydrous ether, ground, and digested with nitric acid. Aliquots of the digest were analyzed for Na and K content by indirect flame photometry.

Synthetic diets were made up according to the protocol of Manitius, et al. (2). These diets were analyzed for Na and K content by flame photometry after nitric acid digestion (Table 1).

Aldosterone secretion rates were determined on lumboadrenal venous blood samples by the double-isotope derivative technique of Kliman and Peterson (12).

RESULTS

As has been shown before, potassium depletion results in polyuria, hypokalemia, sodium retention with increased muscle content of sodium, decreased muscle content of potassium, and mild elevation of blood urea nitrogen. Serum sodium concentration is unaffected by simple potassium depletion. These changes are summarized in Table 2.

Balance studies in Groups I and II show that sodium retention becomes marked 3–4 days after potassium depletion is initiated with urinary excretion of sodium being one-half to one-third of intake (Fig. 1). Normal rats challenged with sodium restriction are able to reduce urinary excretion of sodium to levels which equal sodium intake and thus achieve sodium balance in 3–4 days. In contrast, when potassium-depleted rats are similarly challenged, there ensues a period of sodium wasting which does not return to normal balance until 8–10 days after sodium restriction (Fig. 2). In Group II (Fig. 2), 6 days after sodium re-

| TABLE 1 |
|-----------------------|------|------|
| SODIUM AND POTASSIUM CONTENT OF DIETS |
| Experiment | Diet | Na(μ equiv/g) | K(μ equiv/g) |
| I | High Na, low K | 315.0 | 1.7 |
| | Low Na, low K | 2.0 | 2.3 |
| II | High Na, low K | 315.0 | 1.7 |
| | Low Na, low K | 2.0 | 2.3 |
| | Low Na, normal K | 2.5 | 74.5 |
| | Normal (Purina Rat Chow) | 182.0 | 184.0 |
| III | High Na, low K | 315.0 | 1.7 |
| | Low Na, low K | 2.0 | 1.0 |
| IV | Low Na, low K | 2.0 | 1.0 |
striction, when control rats had already achieved sodium balance, the urinary sodium excretion in potassium-depleted rats was more than three times intake.

The effect of exogenous mineralocorticoid on sodium balance is depicted in Fig. 2. After injection of DOCA, potassium-depleted rats (Group II-E) dramatically reduced urinary sodium excretion by one-half that on the previous day (from 47.6 to 24.0 μequiv/day). In control rats, which were essentially in normal

| TABLE 2 |
|---|
| **ANALYSIS OF BLOOD AND MUSCLE SAMPLES** |
| **Group** | **Na (meq/liter)** | **K (meq/liter)** | **BUN (mg/dl)** | **FBS (mg/dl)** |
| I (K-depleted) | 5.3 ± 0.08 | 15.7 ± 0.14 | 7.5 ± 0.44 | 7.5 ± 0.44 |
| II-C (Control) | 5.3 ± 0.15 | 25.1 ± 0.44 | 7.5 ± 0.44 | 7.5 ± 0.44 |
| II-E (K-depleted) | 5.3 ± 0.15 | 25.1 ± 0.44 | 7.5 ± 0.44 | 7.5 ± 0.44 |
| III (K-depleted) | 5.3 ± 0.15 | 25.1 ± 0.44 | 7.5 ± 0.44 | 7.5 ± 0.44 |
| IV (K-Na depleted) | 5.3 ± 0.15 | 25.1 ± 0.44 | 7.5 ± 0.44 | 7.5 ± 0.44 |

*All not killed at the same time.**

Note: All values represent mean ± SEM, n = 6 except for group IV, n = 5.
Fig. 1. Daily sodium and potassium balance in microequivalents per day during potassium depletion followed by sodium restriction. Group I. Mean values. Sodium balance becomes increasingly positive on adequate sodium intake with reversal to negative sodium balance after superimposed sodium restriction.

Fig. 2. Sodium balance in Groups II and III. Rats in Group II were given DOCA on day 6 of sodium restriction. Rats in Group III were not given DOCA. Note the rapid restoration of sodium balance after sodium restriction in control rats (II-C), the persistent sodium wasting followed by rapid restoration of sodium balance with DOCA in potassium-depleted rats (II-E) and the persistent sodium wasting in potassium-depleted rats with gradual achievement of normal sodium balance in the absence of DOCA. (III). Aldosterone secretion rates were markedly depressed at the time normal sodium balance occurred in this group.
sodium balance (Group II-C), the response was significantly less marked (from 24.0 to 20.4 μequiv/day).

Studies of aldosterone secretion rates (Table 3) show that simple sodium restriction results in elevated aldosterone secretion (17.3 ng/min compared to 4.0 ng/min in normal controls); whereas, potassium-depleted rats which had achieved normal sodium balance spontaneously after 9 days of sodium restriction (Group III) were found to have depressed aldosterone secretion rates in the range of one-tenth normal levels (0.3 ng/min) at a time when normal sodium balance had been achieved (Table 3).

Sodium wasting occurs only if potassium depletion is carried out in the presence of adequate sodium intake (Fig. 3). When sodium is restricted from the beginning of potassium depletion (Group IV), sodium does not accumulate in muscle and there is never a period of negative sodium balance despite profound potassium depletion (Table 3). Interestingly, aldosterone secretion rates measured in two of these animals were comparable to those of controls, but low relative to sodium-depleted rats (Table 3).

DISCUSSION

Impaired renal sodium conservation in potassium depletion has been reported(1–3,8,14) but little is known of its mechanism, magnitude, or duration. It is well known that potassium depletion depresses aldosterone secretion(1,5,6) thus suggesting an etiologic factor. The present study reflects upon several features of renal sodium conservation in the potassium-depleted rat, its relationship to endogenous aldosterone secretion, and the effect of exogenous mineralocorticoid.

| TABLE 3 | Aldosterone Secretion Rates |
|---------|-----------------------------|
| Normal rats\textsuperscript{a} | 4.0 ± 0.5 \( n=20 \) |
| Normal rats after 10 days of sodium restriction\textsuperscript{a} | 17.3 ± 2.2 \( n=8 \) \( P<0.001 \) |
| Potassium-depleted rats after 9 days of sodium restriction (have achieved normal sodium balance) Group III | 0.3 ± 0.08 \( n=8 \) \( P<0.001 \) |
| Rats after 26 days of simultaneous sodium and potassium depletion Group IV | 3.9 ± 0.3 \( n=2 \) |

\( \text{\textsuperscript{a} ± = Standard error of the mean.} \)

\( \text{\textsuperscript{P} values from Student’s t test.} \)
Aldosterone and Na Wasting in K Depletion

Potassium depletion is known to alter sodium balance (1,3,10). In the presence of adequate sodium intake, potassium depletion results in marked sodium retention (Fig. 1) with much of this sodium being retained in muscle. If restriction of sodium intake is then imposed, there follows a period of sodium wasting. The duration of this sodium wasting is approximately twice as long in the potassium-depleted rat as in the normal rat similarly challenged with sodium restriction. This is depicted in Fig. 2 which shows control rats achieving normal sodium balance 5 days after sodium restriction whereas potassium-depleted rats required 9 days to do the same. The return of sodium balance can be significantly hastened by the administration of exogenous mineralocorticoid, DOCA, (Fig. 2), but this does not prove mineralocorticoid deficiency as the etiologic factor for sodium wasting.

The studies of Johnson et al. (1) demonstrate transient sodium wasting in potassium-depleted humans after sodium deprivation, with urinary aldosterone excretion being depressed at the time of maximum sodium wasting and increased above control levels by the time sodium balance had spontaneously returned to normal. One might speculate that sodium wasting is the result of depressed aldosterone secretion in potassium depletion and that normal sodium balance can be achieved only when aldosterone secretion had returned to normal levels; however, the present study does not bear this out. Aldosterone secretion rates measured in potassium-depleted rats which had achieved normal sodium balance spontaneously after 9 days of sodium restriction were markedly depressed to less than one-tenth of normal values. This clearly demonstrates that normal sodium balance can be achieved despite depressed aldosterone secretion and thus implicates a factor other than aldosterone in the sodium wasting of potassium depletion.

A different sequence of events occurs if sodium is restricted from the beginning of potassium depletion. In this situation, muscle sodium content does not become elevated and sodium wasting does not occur even though animals become profoundly potassium depleted. Interestingly, aldosterone secretion measured in two of these animals was normal, apparently indicating that prolonged combined sodium and potassium depletion have counterbalancing effects on aldosterone secretion. This observation has been corroborated by Boyd et al. (15).
Hollander(11) has suggested that apparent sodium wasting in potassium depletion may be the result of previous sodium retention in tissues and extracellular fluid. The present study supports the concept that excess urinary sodium excretion after sodium restriction in potassium depletion is actually the redistribution of previously accumulated sodium from muscle to extracellular fluid and its subsequent excretion in the urine. If this is the case, it becomes clear that only a portion of accumulated sodium is redistributed since normal sodium balance can be achieved in the face of persistently elevated muscle sodium.

Potassium depletion in the presence of adequate sodium intake favors entry of sodium into the cells in exchange for potassium; however, when sodium restriction is superimposed, the direction of the intracellular–extracellular sodium equilibrium changes with an efflux of sodium from the cells. When potassium depletion is carried out with concomitant sodium restriction, sodium does not accumulate in muscle and sodium wasting does not occur.

The present study demonstrates that sodium wasting associated with potassium depletion terminates spontaneously in the face of markedly depressed aldosterone secretion, thus suggesting etiologic factors other than aldosterone. The precise details of the intermediary mechanisms involved await further clarification.

**SUMMARY**

Sodium balance was studied in potassium-depleted rats and was correlated with aldosterone secretion rates and the administration of deoxycorticosterone acetate (DOCA).

Potassium-depleted rats maintained on adequate sodium intake are in striking positive sodium balance and accumulate much of this sodium in muscle (muscle sodium of 7.8 mequiv/100g FFDS in controls as compared with 16.7 mequiv/100g FFDS in potassium-depleted rats).

When challenged with sodium restriction, these potassium-depleted rats exhibit a significant negative sodium balance which gradually returns to normal balance in approximately 9 days. Return to normal conservation is hastened by the administration of DOCA, but balance is restored without DOCA at the end of day 9 despite the presence of a markedly depressed aldosterone secretion rate (17.3 ng/min in sodium-restricted controls compared to 0.33 ng/min in potassium-depleted rats with sodium restriction for the same duration as controls).

When potassium depletion is accompanied by sodium restriction from the outset, however, marked sodium retention does not occur, muscle sodium does not increase, and sodium wasting does not develop.

These results suggest that the apparent defect in renal sodium conservation, when potassium-depleted rats previously on adequate sodium intake are challenged with sodium restriction, can be explained by the redistribution of previously accumulated sodium in muscle into the extracellular space and its subsequent excretion by the kidney.

These studies clearly demonstrate that, although this phenomenon of apparent
sodium wasting is acutely responsive to exogenous mineralocorticoid, it is not the result of depressed aldosterone secretion associated with potassium depletion. The sodium wasting is returned to normal when the previously accumulated muscle sodium is partially depleted and normal sodium conservation can be maintained in the presence of markedly depressed aldosterone secretion.

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