# Studies of the control of plasma aldosterone concentration in normal man: *II. Effect of dietary potassium and acute potassium infusion*

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Regardless of dietary intake, increases of serum potassium of 0.5-1.5 mEq/liter above preinfusion levels were usually associated with significant increments in plasma aldosterone concentration. Our data agree with previous evidence that the potassium ion stimulates the adrenal cortex directly to secrete aldosterone. Peripheral renin activity did not increase after the potassium infusion. Plasma cortisol and corticosterone levels generally followed the expected diurnal decline during the infusion, implying that ACTH secretion did not increase.

The plasma aldosterone response to incremental changes in serum potassium was linear on each of the four diets. The slopes of these linear relationships increased significantly when the potassium intake was increased from 40 to 200 mEq. No increase in slope occurred on either potassium intake when dietary sodium was restricted from 200 to 10 mEq. Thus, identical increases in serum potassium were associated with greater increments in plasma aldosterone above preinfusion levels […]



# Studies of the Control of Plasma Aldosterone Concentration in Normal Man

## II. EFFECT OF DIETARY POTASSIUM AND ACUTE POTASSIUM INFUSION

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ABSTRACT The responses of plasma aldosterone, cortisol, and corticosterone to an infusion of 75 mEq of potassium chloride over 120 min were studied in 10 normal subjects. Five subjects were fed a 10 mEq and five a 200 mEq sodium diet, while all subjects ingested 40 mEq and 200 mEq potassium sequentially. Two potassium infusions were performed in each subject when in balance on a fixed sodium intake and low and then high potassium diets.

Regardless of dietary intake, increases of serum potassium of 0.5–1.5 mEq/liter above preinfusion levels were usually associated with significant increments in plasma aldosterone concentration. Our data agree with previous evidence that the potassium ion stimulates the adrenal cortex directly to secrete aldosterone. Peripheral renin activity did not increase after the potassium infusion. Plasma cortisol and corticosterone levels generally followed the expected diurnal decline during the infusion, implying that ACTH secretion did not increase.

The plasma aldosterone response to incremental changes in serum potassium was linear on each of the four diets. The slopes of these linear relationships increased significantly when the potassium intake was increased from 40 to 200 mEq. No increase in slope occurred on either potassium intake when dietary sodium was restricted from 200 to 10 mEq. Thus, identical increases in serum potassium were associated with greater increments in plasma aldosterone above preinfusion levels on either sodium intake when the 200 mEq potassium diet was compared with the 40 mEq potassium intake.

## INTRODUCTION

Previous studies have defined an important role for the potassium ion in the regulation of aldosterone secretion. In the dog (1) and sheep (2), infusion of potassium into the adrenal artery increased the secretion of aldosterone. In man, on low or normal sodium intakes, potassium loading has been associated with increased urinary excretion or secretion of aldosterone (3–7). In man, however, acute changes in aldosterone secretion in response to small changes in serum potassium have not been documented. The present study reports the response of plasma aldosterone, cortisol, and corticosterone after an i.v. infusion of potassium chloride on varied sodium and potassium intakes.

## METHODS

10 normal volunteers, eight males and two females, ages 21–34 were admitted to The Clinical Center of the Peter Bent Brigham Hospital. Complete history and physical examination and routine laboratory tests were within normal limits. All subjects denied use of drugs of any type in the weeks immediately preceding admission. Informed consent was obtained in all cases.

All subjects received a constant sodium intake during the entire hospitalization. Five subjects received a 200 mEq sodium diet and the other five received a 10 mEq sodium diet. In addition, all patients received a diet containing 40 mEq potassium during the first 6 or 7 days of hospitalization

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TABLE I

*Response of Plasma Levels of Aldosterone, Corticosterone, and Cortisol in Normal Subjects in Balance on a 10 mEq Sodium (40 mEq or 200 mEq $K^+$) Diet to an Infusion of Potassium Chloride (0.62 mEq/min for 120 min)*

| Patient | Age | Sex | | Time (*min*) of infusion, 40 mEq $K^+$ | | | | | Time (*min*) of infusion, 200 mEq $K^+$ | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 0 | 30 | 90 | 120 | 300 | 0 | 30 | 90 | 120 | 300 |
| | *yr* | | | | | | | | | | | | |
| P. W. | 21 | M | Aldosterone | 45 | 55 | 88 | 122 | 24 | 96 | 169 | 178 | 184 | 44 |
| | | | Corticosterone | 0.67 | 0.21 | 0.16 | 0.16 | 0.03 | 1.0 | 0.47 | 0.15 | 0.08 | 0.1 |
| | | | Cortisol | 20 | 16 | 9 | 8 | 5 | 17 | 12 | 8 | 6 | 3 |
| | | | Potassium | 4.1 | 5.1 | 5.9 | 6.1 | 4.5 | 4.4 | 5.0 | 5.5 | 5.7 | 5.1 |
| M. C. | 24 | M | Aldosterone | 41 | 46 | 51 | 65 | 31 | 124 | 150 | 213 | 314 | 65 |
| | | | Corticosterone | 1.3 | 1.1 | 0.47 | 0.21 | 0.35 | 1.3 | 0.54 | 0.18 | 0.26 | 0.23 |
| | | | Cortisol | 30 | 25 | 19 | 18 | 14 | 32 | 16 | 14 | 11 | 9 |
| | | | Potassium | 4.3 | 4.8 | 5.3 | 5.6 | 4.8 | 4.5 | 5.3 | 5.6 | 6.0 | 4.5 |
| L. Hou. | 25 | M | Aldosterone | 30 | 36 | 39 | 55 | 70 | 82 | 83 | 136 | 131 | 54 |
| | | | Corticosterone | 1.06 | 0.40 | 0.33 | 0.29 | 0.33 | 0.71 | 0.27 | 0.29 | 0.60 | 0.1 |
| | | | Cortisol | 27 | 21 | 22 | 19 | 11 | 22 | 15 | 8 | 17 | 6 |
| | | | Potassium | 4.1 | 5.0 | 5.6 | 6.5 | 4.8 | 4.6 | 5.3 | 5.9 | 6.3 | 4.5 |
| P. S. | 21 | M | Aldosterone | 117 | 128 | 131 | 151 | 147 | 141 | 184 | 199 | 238 | 151 |
| | | | Corticosterone | 0.76 | 0.78 | 0.43 | 0.55 | 0.33 | 0.52 | 0.50 | 0.44 | 0.34 | 0.40 |
| | | | Cortisol | 20 | 15 | 8 | 10 | 6 | 20 | 17 | 11 | 10 | 9 |
| | | | Potassium | 3.8 | 4.9 | 5.7 | 6.2 | 4.5 | 4.2 | 5.0 | 6.2 | 6.1 | 4.5 |
| A. T. | 21 | M | Aldosterone | 103 | 121 | 138 | — | 36 | 87 | 100 | 128 | 103 | 38 |
| | | | Corticosterone | 0.75 | 0.72 | 0.40 | — | 0.21 | 0.70 | 0.68 | 0.42 | 0.22 | 0.19 |
| | | | Cortisol | 19 | 14 | 12 | — | 5 | 19 | 17 | 12 | 10 | 6 |
| | | | Potassium | 4.1 | 4.8 | 5.5 | 5.8 | 4.6 | 4.0 | 4.4 | 5.0 | 5.2 | 4.3 |
| Mean ±SEM | | | Aldosterone | 67±16 | 77±18 | 89±18 | 98±18 | 62±20 | 106±10 | 137±18 | 171±15 | 194±34 | 70±19 |
| | | | Corticosterone | 0.91±0.11 | 0.64±0.14 | 0.36±0.05 | 0.30±0.07 | 0.25±0.06 | 0.85±0.12 | 0.49±0.06 | 0.30±0.05 | 0.30±0.08 | 0.20±0.05 |
| | | | Cortisol | 23±2 | 18±2 | 14±2 | 14±2 | 8.2±1.6 | 22±2 | 15±1 | 11±1 | 11±2 | 6.6±1.0 |
| | | | Potassium | 4.1±0.1 | 4.9±0.1 | 5.6±0.1 | 6.0±0.2 | 4.6±0.1 | 4.3±0.1 | 5.0±0.2 | 5.6±0.2 | 5.9±0.2 | 4.6±0.1 |

Aldosterone levels expressed in nanograms per 100 ml; corticosterone and cortisol in micrograms per 100 ml; and potassium in millequivalents per liter.

and then 200 mEq potassium during the last 8–10 days of hospitalization. An acute i.v. load of 75 mEq of potassium chloride was administered to each subject when he was in balance on the 40 mEq potassium diet and in an identical fashion when he was in balance on the 200 mEq potassium diet. A physician was in attendance at all times during all infusions. The potassium was infused over a 120 min period beginning at 9 a.m. in all cases. Blood for plasma aldosterone, corticosterone, and cortisol and serum potassium was drawn before the infusion and at 30, 90, and 120 min during the infusion as well as 3 hr after the conclusion of the infusion. Peripheral plasma renin activity was determined at the beginning and end of the infusion.

Plasma aldosterone, corticosterone, and cortisol were measured by displacement analysis techniques as previously described from this laboratory (8). In brief, the three steroids are first separated on a Bush 5 system. The steroids are eluted and the corticosterone and aldosterone are determined by radioimmunoassay using antibodies specifically directed against these two steroids. The cortisol is measured by a competitive protein binding method similar to that described by Nugent and Mayes (9). The values obtained with plasma from adrenalectomized patients are below the sensitivity of the method for cortisol and corticosterone and at the 4 pg level for aldosterone. The sensitivity of the cortisol assay system is 0.2 ng per binding tube; for the corticosterone assay, 0.02 ng per binding tube; and for the aldosterone assay, 0.002 ng per binding tube. Coefficient of variation is between 7 and 11% at a level 10 times the sensitivity for the three assays. Recovery of added steroid from each assay is the same, ranging between 85 and 110%. The cortisol, corticosterone, and aldosterone values in 12 samples were significantly correlated ($P < 0.001$) when compared with a double isotope derivative method. Peripheral renin activity (PRA)[1] was measured by a modification of the method of Boucher, Veyrat, deChamplain, and Genest (10) as previously described (11).

Statistical analyses were performed by either the Student's or the paired $t$ test or by least squares regression analysis as described in Snedecor and Cochran (12), utilizing a General Electric 635 computer. Results are reported as mean ±SE of the mean unless otherwise indicated.

## RESULTS

*Urine electrolyte excretion.* On the day before the potassium infusion, the following mean urinary excretion values were obtained. On the 10 mEq sodium/40 mEq potassium diet, mean urine excretion was 9±2 mEq sodium and 38±3 mEq potassium/24 hr, while on the 10 mEq sodium/200 mEq potassium diet the mean values were 7±1 mEq sodium and 149±8 mEq potassium/24 hr. On the 200 mEq sodium intake, mean urine excretion on the 40 mEq potassium intake was 185±13 mEq sodium and 30±3 mEq potassium/24 hr, while on the 200 mEq potassium intake the excretion

[1] *Abbreviation used in this paper:* PRA, peripheral renin activity.

TABLE II

*Response of Plasma Levels of Aldosterone, Corticosterone, and Cortisol in Normal Subjects in Balance on a 200 mEq Sodium (40 mEq or 200 mEq $K^+$) Diet to an Infusion of Potassium Chloride (0.62 mEq/min for 120 min)*

| Patient | Age | Sex | | Time (*min*) of infusion, 40 mEq $K^+$ | | | | | Time (*min*) of infusion, 200 mEq $K^+$ | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 0 | 30 | 90 | 120 | 300 | 0 | 30 | 90 | 120 | 300 |
| | *yr* | | | | | | | | | | | | |
| M. Q. | 21 | F | Aldosterone | 3.9 | 10 | 22 | 22 | 8.5 | 19 | 86 | 171 | 138 | 22 |
| | | | Corticosterone | 0.60 | 0.85 | 0.28 | 0.32 | 0.06 | 0.31 | 0.35 | 0.20 | 0.23 | 0.09 |
| | | | Cortisol | 19 | 13 | 16 | 15 | 5 | 18 | 25 | 12 | 13 | 11 |
| | | | Potassium | 3.7 | 4.1 | 5.4 | 5.7 | 3.8 | 4.0 | 4.8 | 5.5 | 5.5 | 4.2 |
| B. C. | 22 | M | Aldosterone | 4.1 | 19 | 43 | 42 | 13 | 40 | 51 | 71 | 58 | 23 |
| | | | Corticosterone | 0.5 | 0.54 | 0.49 | 0.48 | 0.18 | 0.34 | 0.33 | 0.27 | 0.24 | 0.24 |
| | | | Cortisol | 18 | 22 | 23 | 19 | 17 | 19 | 17 | 15 | 12 | 11 |
| | | | Potassium | 4.2 | 4.8 | 5.5 | 5.6 | 5.0 | 4.2 | 4.8 | 5.2 | 5.5 | 4.4 |
| L. Her. | 22 | F | Aldosterone | 3.8 | 14 | 22 | 37 | — | 3.3 | 12 | 17 | 61 | — |
| | | | Corticosterone | 0.54 | 0.21 | 0.05 | 0.15 | — | 0.49 | 0.74 | 0.42 | 0.28 | — |
| | | | Cortisol | 16 | 18 | 15 | 12 | — | 14 | 16 | 14 | 10 | — |
| | | | Potassium | 4.3 | 4.8 | 6.2 | 6.0 | — | 4.3 | 5.0 | 5.4 | 6.0 | — |
| E. P. | 26 | M | Aldosterone | 4.6 | 11 | 8.4 | 10 | 7.2 | 3.7 | 5 | 22 | 29 | 18 |
| | | | Corticosterone | 1.1 | 1.6 | 1.3 | 1.3 | 1.6 | 0.38 | 0.25 | 0.29 | 0.24 | 0.21 |
| | | | Cortisol | 21 | 21 | 16 | 17 | 16 | 20 | 16 | 12 | 7 | 6 |
| | | | Potassium | 3.8 | 4.3 | 4.7 | 4.9 | 4.4 | 4.4 | 4.2 | 4.9 | 5.4 | 4.8 |
| A. B. | 22 | M | Aldosterone | 4.0 | 10 | 17 | 31 | 22 | 47 | 38 | 70 | 88 | 19 |
| | | | Corticosterone | 1.5 | 1.0 | 0.41 | 0.23 | 0.11 | 0.82 | 0.23 | 0.27 | 0.18 | 0.15 |
| | | | Cortisol | 25 | 18 | 15 | 7 | 10 | 26 | 14 | 9 | 10 | 5 |
| | | | Potassium | 4.1 | 4.6 | 5.7 | 6.3 | — | 3.9 | 4.5 | 5.3 | 5.9 | 3.8 |
| Mean ±SEM | | | Aldosterone | 4.1±0.1 | 12.8±1.6 | 23±5 | 28±5 | 12.5±2.6 | 23±8 | 38±14 | 70±25 | 75±17 | 21±1 |
| | | | Corticosterone | 0.85±0.17 | 0.84±0.20 | 0.47±0.19 | 0.50±0.18 | 0.49±0.32 | 0.47±0.08 | 0.38±0.09 | 0.29±0.03 | 0.23±0.01 | 0.17±0.03 |
| | | | Cortisol | 20±1 | 18±2 | 17±1 | 14±2 | 12±2 | 19±2 | 18±2 | 12±1 | 10±1 | 8.3±1.2 |
| | | | Potassium | 4.0±0.1 | 4.5±0.2 | 5.5±0.1 | 5.7±0.1 | 4.4±0.2 | 4.2±0.1 | 4.7±0.1 | 5.3±0.1 | 5.7±0.1 | 4.3±0.1 |

Aldosterone levels are expressed in nanograms per 100 ml; corticosterone and cortisol in micrograms per 100 ml; and potassium in milliequivalents per liter.

was 155±16 mEq sodium and 150±8 mEq potassium/24 hr. The mean increase urinary excretion of potassium on the day of infusion ranged from 44–59 mEq/24 hr but was not significantly different on any of the four diets.

*Responses of serum potassium and sodium.* On the 10 mEq sodium diet, preinfusion serum potassium levels were higher in four of five subjects on the 200 mEq potassium compared to the 40 mEq potassium diet but the mean values were not significantly different (4.3±0.1 mEq/liter vs. 4.1±0.1 mEq/liter) (Table I). On the 200 mEq sodium diet, the preinfusion serum potassium levels in two of five subjects were higher on the 200 mEq potassium intake but again the mean levels were not significantly different (Table II).

The range of mean serum potassium increments above basal levels on all four diets after the infusion of 75 mEq of potassium chloride was 1.5–1.9 mEq/liter. The highest value recorded in any subject at the termination of the infusion was 6.5 mEq/liter. Although in four of five subjects on the 10 mEq sodium intake, the increment of serum potassium from 0 to 120 min was smaller on the 200 mEq potassium diet than on the 40 mEq potassium diet (Table I), the means of the differences in increments were not significant. On the 200 mEq sodium intake, all five subjects had smaller increments in serum potassium from 0 to 120 min on the 200 mEq potassium compared with the 40 mEq potassium diet. Using the *t* test for paired data, the means of the differences of the increments were significant ($P < 0.05$).

Preinfusion serum sodium values on all four diets were not significantly different from each other. In all cases, serum sodium fell significantly ($P < 0.02$) during the infusion, presumably secondary to dilution by the potassium chloride solution and the 0.45% saline used to keep open the i.v. lines. The mean fall was 2.8±0.6 mEq/liter for 10 patients on the 40 mEq potassium intake; and 2.5±0.4 mEq/liter for the 10 patients on the 200 mEq potassium diet.

*Response of peripheral renin activity.* No significant differences in supine PRA were seen before and after potassium infusion on any diet. However, there was a tendency for PRA to fall on the 10 mEq sodium intake both by the end of the potassium infusion and when the potassium content of the diet was increased from 40 to 200 mEq. On the 200 mEq sodium/40 mEq potassium intake, mean preinfusion PRA was 208±44

ng/100 ml per 3 hr and postinfusion PRA 235±49 ng/100 ml per 3 hr. On 200 mEq sodium/200 mEq potassium, mean PRA was 290±25 ng/100 ml per 3 hr (preinfusion) and 287±25 ng/100 ml per 3 hr (postinfusion). On 10 mEq sodium/40 mEq potassium intake, mean preinfusion PRA was 1442±590 ng/100 ml per 3 hr and postinfusion PRA was 1090±207 ng/100 ml per 3 hr. Mean preinfusion PRA on the 10 mEq sodium/200 mEq potassium diet was 1007±169 ng/100 ml per 3 hr and postinfusion PRA was 740± 116 ng/100 ml per 3 hr.

*Response of plasma cortisol and corticosterone.* On all four diets, plasma cortisol showed the expected diurnal fall from the beginning of the infusion to 3 hr after the infusion. The mean value at zero time ranged from 19±2 to 23±2 μg/100 ml and 3 hr after the end of the infusion, from 6.6±1 to 12±2 μg/100 ml (Tables I and II, and Figs. 1 and 2).

The mean plasma corticosterone before the infusion ranged from 0.47±0.08 to 0.91±0.11 μg/100 ml on the four diets. Like plasma cortisol, plasma corticosterone levels declined during the study with mean values at 300 min ranging from 0.17±0.03 to 0.49±0.32 μg/100 ml.

*Response of plasma aldosterone.* On all four diets, there was a significant, progressive increase in plasma aldosterone concentration during the potassium infusion and a decline when the infusion was terminated. Increases in serum potassium of 0.5–1.5 mEq/liter were usually associated with significant increments in plasma aldosterone levels.

The mean, supine preinfusion plasma aldosterone levels on the 10 mEq sodium diet were significantly different ($P < 0.05$) on the 40 mEq potassium diet (67±16 ng/100 ml) compared with the 200 mEq potassium intake (106±10 ng/100 ml). The peak plasma aldosterone concentration at the termination of the infusion was also significantly greater ($P < 0.01$) on the 200 mEq potassium diet (194±34 ng/100 ml) than on the 40 mEq potassium diet (98±18 ng/100 ml). 3 hr after the infusion was terminated, plasma aldosterone had declined to preinfusion levels on the 40 mEq potassium diet. On the 200 mEq potassium diet, the postinfusion concentration (70±19 ng/100 ml) had significantly ($P < 0.05$) declined below the preinfusion value (106±10 ng/100 ml).

On the 200 mEq sodium diet, plasma aldosterone levels similarly increased when the potassium content of the diet was increased. The mean preinfusion value on the 40 mEq potassium diet (4.1±0.1 ng/100 ml) was significantly lower ($P < 0.01$) than on the 200 mEq potassium diet (23±8 ng/100 ml). The peak response at the termination of the infusion on the 200 mEq potassium diet (75±17 ng/100 ml) was significantly greater ($P < 0.05$) than on the 40 mEq potassium diet (28±5 ng/100 ml) (Table II and Figure 2).

When the potassium content of the diet was constant, preinfusion aldosterone levels were significantly greater

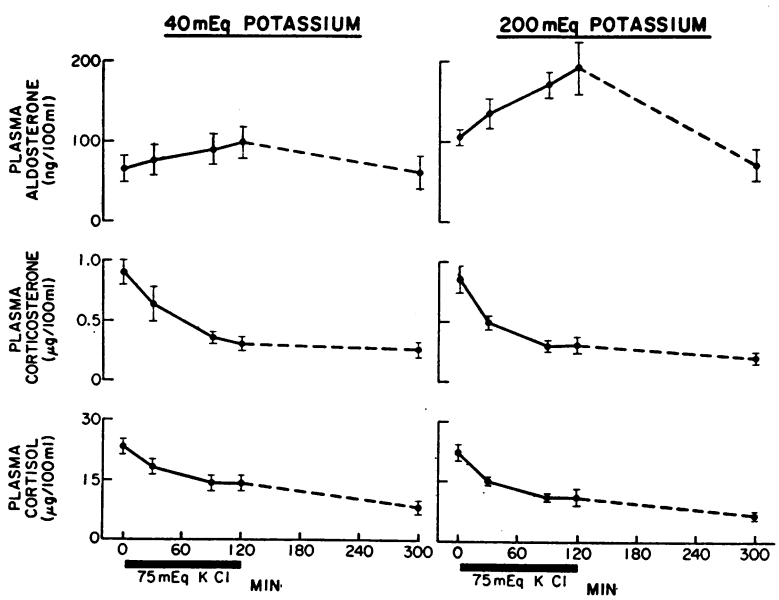


FIGURE 1 Responses of plasma aldosterone, corticosterone, and cortisol to an acute infusion of potassium chloride in normal subjects in balance on 10 mEq sodium (40 mEq or 200 mEq potassium) diets (mean ±SEM).

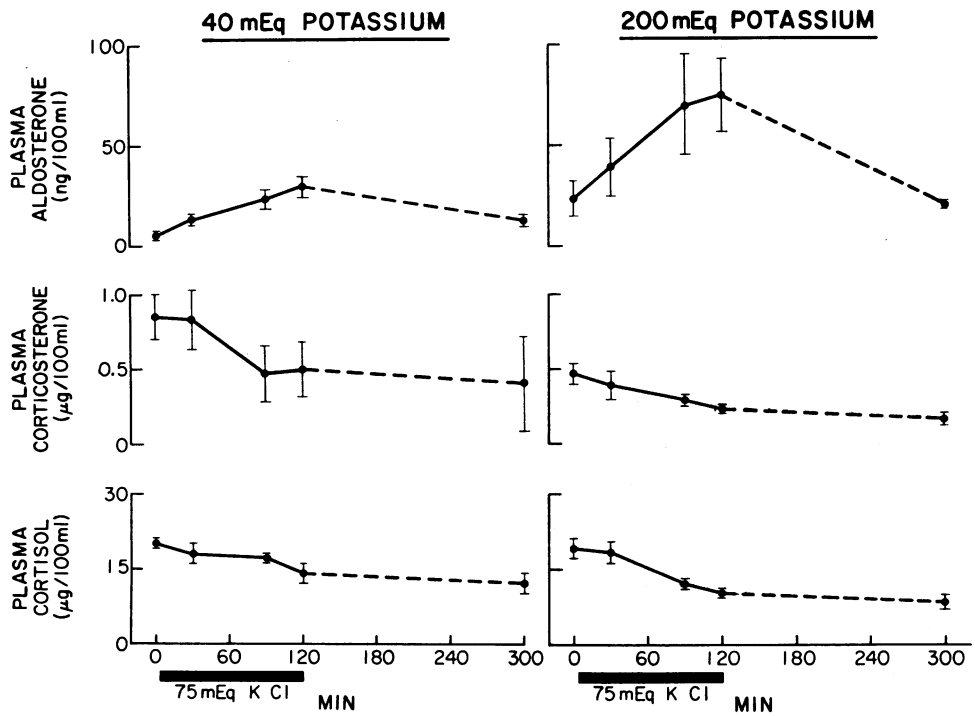


FIGURE 2 Responses of plasma aldosterone, corticosterone, and cortisol to an acute infusion of potassium chloride in normal subjects in balance on 200 mEq sodium (40 mEq or 200 mEq potassium) diets (mean ±SEM).

on the 10 mEq sodium intake. On the 40 mEq potassium intake, plasma aldosterone concentration was 4.1±0.1 ng/100 ml on the 200 mEq sodium diet compared with 67±16 ng/100 ml on the 10 mEq sodium diet (Tables I and II). Basal recumbent plasma aldosterone levels were 23±8 ng/100 ml (200 mEq sodium) and 106±10 ng/100 ml (10 mEq sodium) on the 200 mEq potassium diets.

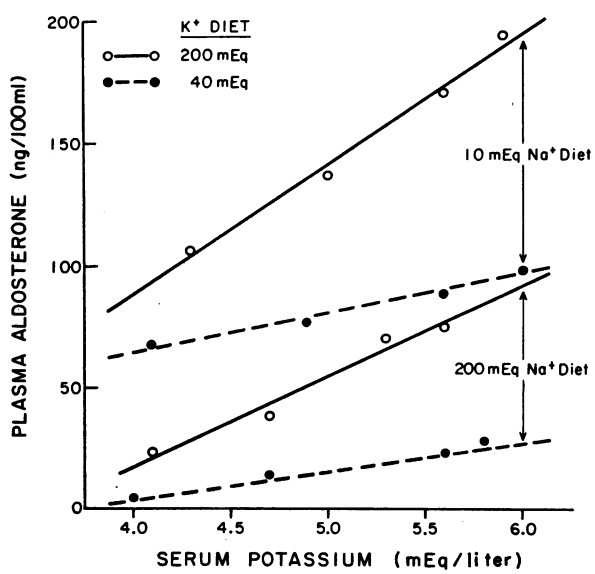


FIGURE 3 The relationship of plasma aldosterone response and serum potassium response to an acute infusion of potassium chloride on varied sodium and potassium intakes.

*Correlation of serum potassium with plasma aldosterone response.* The response of plasma aldosterone to increments in serum potassium on each of the four diets was linear (Fig. 3). However, an identical increase in serum potassium was associated with a greater increase in plasma aldosterone levels above control values when the 200 mEq potassium diet was compared to the 40 mEq potassium intake on either sodium intake. With an increase in serum potassium of 0.5 mEq/liter, the extrapolated increments of plasma aldosterone above control levels on the 200 mEq potassium diets were 26 ng/100 ml (10 mEq sodium) and 20 ng/100 ml (200 mEq sodium) compared with 8.0 ng/100 ml (10 mEq sodium) and 6.5 ng/100 ml (200 mEq sodium) on the 40 mEq potassium intakes.

The calculated slopes of these linear relationships also indicated that the 200 mEq potassium intake, regardless of sodium intake, yielded the steepest slopes. On the 10 mEq sodium/40 mEq potassium diet, the slope (16.5±5.8 ng/100 ml per mEq per liter) was significantly less ($P < 0.05$) than on the 200 mEq po-

tassium diet (52.7±7.3 ng/100 ml per mEq per liter). On the 200 mEq sodium/40 mEq potassium intake, the slope (13.6±1.2 ng/100 ml per mEq per liter) was also significantly less ($P < 0.05$) than the slope on the 200 mEq potassium (37.0±5.5 ng/100 ml per mEq per liter). This significance increased to 0.01 if a paired $t$ test was performed on the slopes with the difference between the slopes being 36.2±6.8 ng/100 ml per mEq per liter on the 10 mEq sodium diet and 23.4±4.3 ng/100 ml per mEq per liter on the 200 mEq sodium diet. However, there was no significant difference in slopes when comparing the results obtained with different sodium intakes and the same potassium diet, either 40 mEq or 200 mEq.

*Symptoms and electrocardiographic data.* Subjective reaction to the infusion was variable with responses varying from no discomfort to mild or moderate pain in the arm containing the catheter.

No disturbances in QRS interval or cardiac rhythm were recorded; a 2–3 mm increase in amplitude of the T wave occurred in most subjects.

## DISCUSSION

The role of the potassium ion in regulating aldosterone secretion in man has not been established. In the dog (1) and sheep (2), the i.v. infusion of potassium chloride or potassium sulfate augmented aldosterone secretion. Previous studies in man on various sodium intakes have demonstrated that aldosterone excretion or secretion increases after oral potassium loading. Since only small increments in plasma potassium were observed when subjects were potassium loaded, Cannon, Ames, and Laragh (13) speculated that the aldosterone stimulating effect of potassium loading was not related to plasma potassium levels. The present studies indicate that in normal man, small progressive increases in serum potassium ranging from 0.5–1.5 mEq/liter are associated with progressive increments in plasma aldosterone.

Previous in vivo studies in the sheep (2) and the hypophysectomized-nephrectomized dog (1) have demonstrated that potassium infusion systemically or directly into the adrenal arterial supply acutely increases the secretion of aldosterone. The latter study indicates that the stimulating effect of the potassium ion is not dependent upon the renin-angiotensin system or ACTH secretion. Additional support for a direct role of the potassium ion in stimulating aldosterone secretion includes in vitro studies utilizing rat adrenal tissue (14–17), beef adrenal slices (18, 19), or isolated rat glomerulosa cells (20) where increasing concentrations of potassium in the incubation media increased the production of aldosterone.

Our studies provide indirect evidence that the potassium ion directly stimulates aldosterone secretion in normal man. Because plasma renin activity declined or did not change by the termination of the potassium infusion, the increase in plasma aldosterone could not be the results of increased plasma renin activity. Mild discomfort at the beginning of the potassium infusion was experienced by some of our subjects and in several patients was associated with elevated cortisol and corticosterone levels. However, in most subjects, cortisol and corticosterone levels declined in a fashion consistent with the diurnal secretion of these steroids. It is, therefore, unlikely that an increase in ACTH secretion in response to stress or even secondary to elevated potassium levels was responsible for the increased aldosterone secretion. We cannot completely exclude this possibility since ACTH levels were not measured. A previous study (21) has also described a diurnal rhythm for aldosterone in recumbent subjects with highest levels occurring at 8 a.m. and progressively declining over the course of the day. Since our studies were performed between 9 a.m. and 2 p.m., when plasma aldosterone would ordinarily be declining, these observed increases cannot be explained by a circadian rhythm. Blair-West et al. (2) and Davis, Urquhart, and Higgins (1) have demonstrated that large decrements in serum sodium may stimulate aldosterone secretion per se or potentiate the response to a hyperkalemic stimulus. In our subjects on all four diets, serum sodium fell slightly but significantly during the infusion. The mean fall, however, was between 2 and 3 mEq/liter, hardly in the range of the hyponatremia cited previously in animal experiments which increased the secretion of aldosterone. Thus, our data support previous in vivo and in vitro studies indicating that the potassium ion can stimulate the adrenal cortex directly to secrete aldosterone.

On either a 200 mEq or 10 mEq sodium intake, mean fasting recumbent preinfusion aldosterone levels increased significantly when the potassium intake was increased. Plasma renin values not only did not increase significantly but ordinarily declined as the potassium content of the diet was increased on either sodium intake. Mean basal preinfusion plasma cortisol and corticosterone levels did not significantly change when the potassium content of the diets was altered, suggesting ACTH secretion did not change. Basal aldosterone secretion may then be regulated by serum potassium levels which usually but not invariably increased as the potassium content of the diet was increased. It is also possible that aldosterone secretion on different potassium intakes is regulated by an alteration in intracellular potassium content.

Previous studies have demonstrated modification of aldosterone secretion in response to ACTH stimulation, angiotensin infusion and potassium loading on high and low sodium intakes. A heightened aldosterone response to ACTH with sodium depletion has been reported in humans (22, 23). High potassium intake can also augment the secretion of aldosterone in response to ACTH infusion (24). The response of the adrenal cortex to potassium loading is also modified by the sodium and potassium balance. Cannon et al. (13) reported that the aldosterone secretory response to potassium administration was enhanced 4- to 10-fold after sodium depletion in normal subjects. The in vitro steroidogenic response of rat adrenal tissue to potassium loading was also found to be related to the previous in vivo sodium and potassium balance status of the animals (14, 15). Funder et al. (25) reported that the degree of augmentation of aldosterone secretion with potassium loading was not different, however, in sodium-repleted compared with sodium-depleted sheep. In our studies, the response of the adrenal cortex to increments in serum potassium was also related to the sodium and potassium balance of the subjects.

On the 40 mEq potassium diets, rises in serum potassium of 1–1.5 mEq/liter were always associated with significant increments in plasma aldosterone concentration. In subjects on a 200 mEq potassium intake, increments of serum potassium of only 0.5 mEq/liter were associated with significant elevations in plasma aldosterone levels. By extrapolation, a 25% increase in plasma aldosterone may occur with as little as 0.2 mEq increase in serum potassium on a 200 mEq potassium intake compared with a 0.9 mEq change on a 40 mEq potassium intake. The response of plasma aldosterone to incremental changes in serum potassium on each of the four diets was linear. However, while the preinfusion and peak plasma aldosterone levels at the end of the infusion were always greater on the 10 mEq sodium diet than on the 200 mEq sodium diet, a change in dietary sodium did not alter the slopes of the plasma aldosterone-serum potassium relationship on either potassium intake. Increasing the dietary potassium intake from 40 to 200 mEq on either sodium intake significantly increased the slopes of the lines ($P < 0.01$) (Fig. 3). Thus, identical increments in serum potassium on either sodium intake produced greater increments in aldosterone secretion above control levels when the dietary potassium intake was 200 mEq rather than 40 mEq.

The dietary levels assigned to our subjects were selected to exaggerate any influence of sodium and potassium balance on the response of plasma aldosterone to potassium loading. Although the dietary potassium intakes were slightly below (40 mEq) or significantly greater (200 mEq) than the average dietary intake (50–100 mEq/day), our subjects were in balance on these diets as evidenced by their urine excretion values and normal basal serum potassium levels. Although it is unlikely that subjects on the 40 mEq potassium intake were potassium depleted, the heightened aldosterone secretion seen on the 200 mEq potassium intake could nevertheless reflect an enhanced secretion of aldosterone on the high potassium diet, a blunted response on the 40 mEq diet, or both. Since potassium infusions were not performed on normal dietary potassium intakes, this question cannot be resolved. However, since it is unlikely that the 40 mEq potassium diet produced significant potassium depletion, it may be anticipated that a slightly higher (normal) potassium intake might yield a slightly greater slope than that seen on the 40 mEq potassium diet.

In our studies, the maximal increases in serum potassium by the termination of the infusion were smaller in 9 of 10 subjects when they ingested 200 mEq of potassium daily than when they consumed 40 mEq of potassium. This could be explained by the more rapid increase in plasma aldosterone concentration on the high potassium diet, thereby facilitating potassium secretion by the distal tubular epithelium. Although urinary potassium excretion could not be measured in our subjects during the potassium infusion, previous studies in the dog (26) and rat (27) have demonstrated an enhanced renal clearance of potassium in animals potassium loaded on high potassium diets.

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