Factors related to potassium transport in chronic stable renal disease in man

T. KAHN, D. M. KAJI, G. NICOLIS, L. R. KRAKOFF AND R. M. STEIN

Departments of Renal Disease, Hypertension and Endocrinology, Bronx Veterans Administration Hospital and Mount Sinai School of Medicine, City University of New York, New York, U.S.A.

(Received 26 September 1977; accepted 7 February 1978)

Summary

1. The inter-relationships between plasma aldosterone, plasma renin activity, potassium excretion and plasma potassium were evaluated in subjects with normal and decreased glomerular filtration rate.

2. In seven studies of healthy control subjects and 12 studies of patients with renal disease, daily urine collections, plasma aldosterone and plasma renin activity were measured on a free diet for 5–10 days and subsequently during the administration of 50 mmol of potassium chloride daily for 5 days. Plasma aldosterone was also measured in 22 hospital patients with normal glomerular filtration rate and 24 patients with reduced glomerular filtration rate.

3. Plasma aldosterone was similar in base-line conditions in patients with or without renal disease and increased similarly during the administration of potassium chloride, suggesting that potassium excretion in patients with reduced glomerular filtration rate probably does not depend primarily upon increased aldosterone.

4. Plasma renin activity increased similarly in control subjects and patients with renal disease during the administration of 50 mmol of potassium chloride/day, but plasma renin activity did not increase when 100 mmol of potassium chloride/day was given to control subjects.

5. With the administration of 50 mmol of potassium chloride/day mean daily potassium excretion increased similarly in control subjects and patients with renal disease but plasma potassium increased significantly (4.7 to 5.4 mmol/l) only in patients with renal disease, suggesting that their uptake of potassium into cells was impaired.

Key words: aldosterone, plasma potassium, potassium excretion, renin.

Abbreviations: GFR, glomerular filtration rate; PRA, plasma renin activity.

Introduction

Patients with chronic stable renal disease usually maintain a normal plasma potassium. The mechanisms whereby they are able to excrete normal quantities of potassium despite a marked reduction in functioning nephrons remain uncertain. Earlier studies indicated that increased aldosterone maintained potassium excretion (Cope & Pearson, 1963; Kleeman, Okun & Heller, 1966), but more recent studies have not confirmed this (Schrier & Regal, 1972; Weidmann, Maxwell, Rowe, Winer & Massry, 1975). We have found similar plasma renin activities for a given level of sodium excretion in patients with chronic renal disease and in subjects with normal renal function; plasma renin activity was also appropriately suppressed in response to volume expansion (Kahn, Mohammad, Bornia, Stein & Krakoff, 1975). We have now further investigated the relationship between potassium excretion, plasma potassium, plasma renin activity and aldosterone in control subjects and in
patients with chronic stable renal disease not requiring dialysis.

**Methods**

**Group 1**

*Patients with chronic renal disease.* (1) Base-line studies. Ten patients with chronic renal disease and normal plasma potassium were studied. They were clinically stable, had no oedema, and maintained a steady weight on their free diet. No patient was receiving any treatment known to affect the variables being studied. Twenty-four hour urine collections were made for 5–10 days. Blood for aldosterone, plasma renin activity (PRA) and plasma potassium was obtained on several occasions at noon preprandially after the subject had been ambulatory. (2) Addition of 50 mmol of potassium. Twelve studies were performed on the 10 subjects, one subject being studied on three separate occasions. Each subject ingested 25 mmol of potassium chloride at 08.00 hours and 15.30 hours for 5 days.

*Normal subjects.* Six subjects with no known renal disease were studied on a free diet. (1) Base-line studies. Twenty-four hour urine collections were made for 5–10 days. (2) Addition of 50 mmol of potassium. Seven studies were performed on the six subjects who ingested 25 mmol of potassium chloride at 08.00 hours and 15.30 hours for a period of 5 days. (3) Addition of 100 mmol of potassium. Seven studies were performed on the six subjects who ingested 25 mmol of potassium chloride at 08.00, 12.30, 15.30 and 19.30 hours for 5 days. Blood was obtained at noon, preprandially, after ambulation.

**Group 2**

Forty-six hospital patients with a range of glomerular filtration rates of 4–189 ml/min, and not receiving any treatment known to affect PRA or aldosterone, were studied. They were on a free diet, were clinically stable with steady weight and no oedema. Twenty-four hour urine collections were made for 3–5 days. Blood for PRA and plasma aldosterone was taken between 07.00 and 09.00 hours while the patient was fasting and had remained in bed since midnight. PRA values in these subjects have been previously reported (Kahn et al., 1975). Signed informed consent was obtained from each subject and this study was approved by the Human Experimentation Committee of this institution.

Urine and plasma were analysed for sodium and potassium by flame photometer, and creatinine by Technicon Auto-analyzer. PRA and plasma aldosterone were analysed by radioimmunoassay (Krakoff, 1973; Varsano-Aharon & Ulick, 1975). Endogenous creatinine clearance was used as a measure of glomerular filtration rate (GFR). Results were analysed by using a paired t-test.

**Results**

**Group 1**

Results are summarized in Table 1 and Figs. 1–3. Plasma values are averages of two to five specimens obtained in each period and urinary values are an average of all collections in that period. Weight and blood pressure remained stable in all subjects. In the normal control subjects base-line potassium excretion averaged 62 mmol/24 h, and with the addition of 50 mmol of potassium chloride potassium excretion increased by an average of 30 mmol/24 h (Fig. 1, Table 1). In the patients with chronic renal disease potassium excretion averaged 45 mmol/24 h in base-line studies and with the administration of 50 mmol of potassium chloride the mean increase in potassium excretion was 31 mmol/24 h, the same as in control subjects. During the administration of 50 mmol of potassium chloride plasma potassium did not change significantly in control subjects but increased significantly in patients with renal disease from mean value of 4.7 mmol/l to 5.4 mmol/l ($P < 0.001$). Even with the administration of 100 mmol of potassium chloride to control subjects plasma potassium increased only from 4.7 to 4.9 mmol/l (Table 1).

The response of plasma aldosterone to a supplement of 50 mmol of potassium chloride is shown in Fig. 2. The mean plasma aldosterone of control subjects increased from 41.7 to 51.0 pmol/100 ml but the increase was not statistically significant. In patients with renal disease the mean plasma aldosterone increased from 35.2 to 50.0 pmol/100 ml ($P < 0.001$). Neither the base-line plasma aldosterone values nor the values obtained with the administration of potassium differed significantly between these two groups. The plasma aldosterone concentrations obtained with the administration of 100 mmol of potassium chloride to normal subjects were not significantly higher than those noted with the administration of 50 mmol of potassium, but in six of seven studies plasma aldosterone increased ($P < 0.10$) (Table 1).
Potassium in renal disease

Mean base-line PRA values were also similar in both groups although the range was much larger in those with renal disease (Fig. 3, Table 1). In response to the administration of 50 mmol of potassium chloride PRA increased significantly in both groups. The administration of 100 mmol of potassium chloride to control subjects did not, however, result in a significant increase in PRA (Table 1).

Group 2

The studies were made in 22 subjects who had a GFR above 80 ml/min (mean 119 ± 36 ml/min) and 24 subjects with a GFR below 80 ml/min (mean 36 ± 23 ml/min). Plasma aldosterone concentrations were similar in the 'low GFR' group and the 'normal GFR' group (Fig. 4). No relationship was noted between plasma aldosterone and the level of base-line potassium excretion with or with-
FIG. 2. Average plasma aldosterone values for each individual in normal subjects and subjects with chronic stable renal disease during base-line conditions and during the addition of 50 mmol of potassium chloride/day. Mean values for the entire group are represented by horizontal bars.

FIG. 3. Average plasma renin activity (PRA: pmol of angiotensin 1 h⁻¹ ml⁻¹) in each individual in normal subjects and normokalaemic subjects with chronic stable renal disease during base-line conditions and during the administration of 50 mmol of potassium chloride/day. Mean values for the entire group are shown by horizontal bars.

FIG. 4. Plasma aldosterone concentration plotted against mean daily potassium excretion in 19 subjects with GFR > 80 ml/min (△) and 19 subjects with GFR < 80 ml/min (●). The equation for the linear regression line of the high GFR group is \( y = -0.025x + 55 \), for the low GFR group is \( y = 0.125x + 42 \), and for the groups taken together is \( y = 0.1x + 47 \). None of these lines has significant correlation coefficients.

out renal disease. No relationship between plasma aldosterone and PRA was detected. Similarly, there was no apparent relationship between plasma aldosterone and PRA or potassium excretion in the group I studies under base-line conditions.

Discussion

The interrelationship between potassium excretion, plasma potassium, aldosterone and PRA has not been studied extensively in patients with chronic stable non-oliguric renal disease. The present studies were performed on subjects ingesting their normal diet and with the addition of 50 mmol of potassium chloride to the daily intake. The lower mean values of sodium and potassium excretion in the patients with chronic renal disease in the base-line studies reflect their lower intake of electrolytes, as others have observed (Gonick, Kleeman, Rubini & Maxwell, 1971; Knolph, Gauntner, VanStone & Bauer, 1977). Restricting the electrolyte intake in control subjects or increasing the electrolyte intake in patients with chronic renal disease to obtain similar levels of electrolyte excretion would necessarily alter the base-line conditions and might change the responsiveness to a stimulus such as potassium administration. We therefore chose to study these subjects under baseline conditions on their usual electrolyte intake.

Plasma aldosterone concentration was similar under basal conditions in control subjects and in
the patients with chronic renal disease both in the upright and recumbent position. No relationship was observed under basal conditions between plasma aldosterone and potassium excretion whatever the GFR (Fig. 4). With 50 mmol of potassium chloride plasma aldosterone values were still similar in both groups. The fact that the increase in plasma aldosterone in response to 50 mmol of potassium chloride reached statistical significance only in patients with renal disease may indicate a difference in responsiveness of plasma aldosterone in the two groups. These studies confirm that aldosterone is normal in patients with chronic renal disease (Schrier & Regal, 1972; Weidmann et al., 1975) and support the view that other factors play a major role in maintaining potassium excretion when GFR is reduced (Schultze, Taggart, Shapiro, Pennell, Caglar & Bricker, 1971).

A supplement of 50 mmol of potassium chloride resulted in an increase in PRA in both normal and azotaemic patients. Earlier studies found that potassium-loading depressed PRA (Brunner, Baer, Sealey, Ledingham & Laragh, 1970; Dluhy, Underwood & Williams, 1970). The conflict of evidence may be explained by the larger amounts of potassium given in earlier studies and by the fact that their PRA was generally stimulated by a low sodium intake. The fact that a supplement of 100 mmol of potassium chloride did not significantly increase the PRA of our control subjects suggests that the response may depend upon the precise amount of potassium given. Studies of Addisonian patients found that the administration of 200 mmol of potassium chloride did not depress PRA, and suggested therefore that a fall in PRA in response to a large potassium supplement depends upon an increase in aldosterone provoked by the large dose of potassium (Miller, Waterhouse, Owens & Cohen, 1975). A supplement of 50 mmol of potassium chloride administered to normal subjects on a zero electrolyte diet did not alter PRA (Bauer, Gauntner, Nolph & VanStone, 1977). Inhibition of PRA in response to potassium chloride loading may specifically depend primarily upon more chloride reaching the macula densa (Kotchen, Galla & Luke, 1976). It seems reasonable therefore to suggest that a small amount of potassium chloride may increase PRA by one mechanism and a larger load may depress PRA by another.

Potassium excretion increased similarly in control subjects and patients with renal disease in response to 50 mmol of potassium chloride. Nevertheless, plasma potassium increased significantly from 4.7 to 5.4 mmol/l in the azotaemic subjects and did not change significantly in the control subjects. Indeed, the plasma potassium increased only minimally in the control subjects in response to 100 mmol of potassium chloride when potassium excretion increased by a mean of 72 mmol/24 h. The higher plasma potassium in the patients with renal disease cannot be attributed to progressive retention of potassium since mean daily potassium excretion was similar in both groups and faecal losses are if anything increased in patients with renal insufficiency (Hayes, McLeod & Robinson, 1967). Plasma aldosterone concentrations were similar in both groups but reduced responsiveness to aldosterone in renal failure cannot be excluded. In normal animals (Hiatt, Miller & Katayanagi, 1975; Petit, Vick & Swander, 1975) and man (Moore-Ede, Meguid, Fitzpatrick, Ball & Boydén, 1976) the initial response to the administration of potassium appears to be rapid uptake into the cells before excretion in the urine. The higher plasma potassium 4 h after the administration of potassium thus probably indicates a defect in transporting potassium into cells. Several observations suggest a potassium transport defect in renal failure: potassium concentration is reduced in leucocytes (Patrick, Jones, Bradford & Gaunt, 1972), sodium concentration is elevated in erythrocytes (Welt, Smith, Dunn, Czerwinski, Proctor, Cole, Balfe & Gitelman, 1967) and muscle potassium concentration is low in azotaemic patients (Bilbrey, Carter, White, Schilling & Knochel, 1973). Uraemic dogs have impaired cellular potassium uptake (Hiatt, Chapman, Davidson, Scheinkopf & Miller, 1976). Our studies of azotaemic patients whose plasma potassium is persistently high despite normal concentrations of aldosterone and normal potassium excretion also suggest a potassium transport defect (Kahn, Kaji, Krakoff, Stein & Nicolis, 1976).

Although a direct correlation between PRA and plasma aldosterone has been reported in patients with end-stage renal failure before dialysis (Weidmann, Maxwell & Lupu, 1973; Vetter, Zarubar, Armbruster, Beckerhoff, Nussberger, Furrer, Fontana & Siegenthaler, 1977) we did not find a significant correlation between PRA and plasma aldosterone values in subjects with normal or reduced GFR.

Acknowledgments

We thank John Torelli, Bernice Middleton, Linda Conception and Katherine Felton for technical assistance and Evelyn Shapiro for secretarial
assistance. This work was supported by the General Medical Research Service of the Veterans Administration, NIH USPHS HL 13595 and NIH AM-16317.

References


