ROLE OF WATER BALANCE IN THE ENHANCED POTASSIUM EXCRETION AND HYPOKALAEMIA OF RATS WITH DIABETES INSIPIDUS

By EMMA FERNÁNDEZ-REPOLLET, MANUEL MARTÍNEZ-MALDONADO AND SUSAN OPAVA-STITZER*

From the Departments of Physiology and Medicine, University of Puerto Rico School of Medicine, and Medical Service, San Juan Veterans Administration Hospital, San Juan, Puerto Rico 00936

SUMMARY

1. The role of water balance in the hypokalaemia of rats with diabetes insipidus (DI rats) was studied.

2. After a 3-day balance study DI rats had a lower muscle potassium content, and plasma [K⁺], and the urinary excretion of potassium in response to oral KCl loading was reduced when compared to normal rats. The hypokalaemia was found to be associated with elevated concentrations of potassium in renal medulla and papilla when compared to values in normal Long-Evans rats.

3. During a 9-day balance study urinary potassium excretion was higher than that of normal rats on days 1–3, but not different on days 4–9; this transient elevation was observed in DI rats on normal, high and low potassium diets. On a low potassium diet the urinary potassium excretion of DI rats fell to minimal levels, making unlikely the existence of a renal defect in potassium handling.

4. Muscle potassium content and plasma [K⁺] were normal after 9 days in metabolism cages. This spontaneous reversal of the hypokalaemia of DI rats was associated with increased water content of renal medulla and papilla, and decreased potassium concentration in these zones.

5. The effect of acute mild dehydration on potassium handling of DI rats was evaluated. Water deprivation for 1–8 hr was sufficient to raise the urinary potassium excretion of DI rats above that of DI rats drinking ad lib. Renal tissue [K⁺] was significantly increased after 8 hr of dehydration. Water deprivation also enhanced the response of DI rats to an oral KCl load. Two days of chronic dehydration in the form of water rationing also significantly enhanced the urinary potassium excretion of DI rats.

6. These data suggest that chronic mild dehydration may be responsible for the modest potassium deficiency observed in DI rats via alterations in renal tissue [K⁺] and consequently in urinary potassium excretion. Correction of dehydration during prolonged periods in metabolism cages may account for the spontaneous reversal of the hypokalaemic condition.
INTRODUCTION

It has been reported that rats of the Brattleboro strain with hereditary hypothalamic diabetes insipidus (DI rats) are hypokalaemic despite partial adrenal insufficiency (Mohring, Mohring, Dauda & Haack, 1974). High tubular flow rates in the distal convoluted tubule secondary to ADH deficiency have been implicated as the cause of this hypokalaemia (Mohring et al. 1974; Reineck, Osgood, Ferris & Stein, 1975) presumably by enhancing distal K secretion. Several studies have shown that increased distal flow rate increases K secretion (Khuri, Weiderhold, Streider & Giebisch, 1975; Kunau, Webb & Borman, 1974; Malnic, Klose & Giebisch, 1964; Malnic, Klose & Giebisch, 1966a, b). In water diuresis, however, a situation analogous in some respects to diabetes insipidus, K secretion has not been shown to be increased (Ali & Pickford, 1958; Evans, Hughes-Jones, Milne & Steiner, 1964; Urbach, Phelps, Steiger & Bellet, 1953). Thus it seems likely that other factors may account for the hypokalaemia observed in diabetes insipidus.

The present study was designed to investigate whether the potassium deficiency in DI rats is associated with inappropriately high potassium excretion, and if so, to attempt to determine the cause of this enhanced excretion. In view of the finding that DI rats may be in a state of chronic mild dehydration, as indicated by elevated plasma sodium concentration and osmolality (Valtin & Schroeder, 1964; Valtin, 1967), and diminished arterial pressure (Gross, Dauda, Kazda, Kyncl, Mohring & Orth, 1972), and since cellular dehydration is known to enhance urinary potassium excretion (Butler, McKhann, & Gamble, 1933; Wiley & Wiley, 1933; Elkinton & Winkler, 1943; Painter, Holmes & Gregersen, 1947; Mudge, Foulks & Gilman, 1950), we have evaluated the role of water balance in the hypokalaemia of diabetes insipidus. Part of the work has been presented to the American Federation for Clinical Research (Opava-Stitzer, Fernández & Martínez-Maldonado, 1977).

METHODS

Experimental animals

All studies were performed in Long-Evans hooded rats of the Brattleboro strain homozygous for the hypothalamic diabetes insipidus trait (DI rats) and in normal Long-Evans hooded rats, except for KCl loading and K depletion studies in which normal albino rats were used. Both sexes were used and body weights ranged from 150 to 350 g.

Balance studies

Prior to any balance study each rat was placed in a metabolism cage (ACME Research Products AC-5062, Chicago) for an equilibration period of 60–65 hr. Balance studies consisted of daily measurement of body weight, food and water intake and urine volume, osmolality, sodium and potassium concentration.

Fifteen DI rats and fifteen Long-Evans rats were placed in metabolism cages for an equilibration period as described above. After 3 days of study, four DI and four Long-Evans rats were killed for measurement of potassium concentration in plasma; potassium and water content of gastrocnemius; and [K+] and water content of renal cortex, medulla and papilla. The rest of the rats were studied for a total of 9 days, at the end of which four DI and four Long-Evans rats were killed for blood and tissue analysis. Plasma [K+] and muscle potassium content were also measured in five DI rats taken directly from their habitation cages.
KCl loading studies

Twelve DI rats and twelve normal rats were placed in individual metabolism cages for a 3-day balance study. On the morning of the fourth day the animals were then placed in clean metabolic cages and allowed to drink water ad libitum but deprived of food. Urine was collected for a 2 hr control period. The rats were then divided into four groups which received NaCl or KCl by gavage as follows:

Group 1: six DI rats which received 200 µmole K+/100 g body wt. as a hypertonic solution (400 m-osmolar) of KCl.
Group 2: six DI rats which received 200 µmole Na+/100 g body wt. as a hypertonic solution (400 m-osmolar) of NaCl.
Group 3: six normal rats which received the same KCl load as DI rats in group 1.
Group 4: six normal rats which received the same amount of saline as DI rats in group 2.

After gavage urine was collected from DI rats at 2 hr intervals and from normal rats at 4 hr intervals for 8 hr. Urine volume and potassium excretion were measured for each 2 hr period. Prior to the control period and between subsequent periods, complete bladder emptying was ensured by inducing urination with an ether-impregnated gauze placed over the nose of each rat.

Altered dietary potassium intake

Potassium-free diet

Twelve DI rats and twelve normal rats were placed in metabolism cages for one week prior to a 4-day control balance study. They were fed Purina laboratory chow (K+: 0.92%, Na+: 0.46%). Six of the DI rats and six of the normal rats were then placed on a potassium-free diet (General Biochemicals) for 6 weeks. Corn starch was added to the diet (10% by weight) to prevent diarrhoea. The remaining rats were continued on a normal diet which consisted of the potassium-free diet + 10% corn starch + 1.2 g KCl/100 g of food. At the end of the sixth week the animals were placed in metabolism cages for a 4-day balance study. Four rats from each group were killed at the end of the study for analysis of plasma and gastrocnemius muscle.

High potassium diet

Twelve DI rats eating Purina laboratory chow were placed in metabolism cages for one week prior to a 4-day control balance study. Six of the rats were then placed on a high potassium diet (ground Purina chow + 15 g KCl/100 g of chow) for 4 weeks. The remaining rats continued eating rat chow alone. At the end of the fourth week a 6 day balance study was carried out.

Dehydration studies

Acute dehydration

Twelve DI rats were studied for 3 days in metabolism cages. On the fourth day the rats were fasted for 2 hr, after which a 1 hr control urine sample was obtained from each rat. Water was then removed from half of the rats. Urine samples were collected at 1 hr intervals for 5 hr; urine flow rate and potassium excretion were determined for each period. At the end of the study the rats were killed for analysis of blood, kidney and muscle.

In a similar experiment, the effect of dehydration on the response of twelve DI rats to KCl loading was studied. On the day following a 3-day balance study food was removed from all of the rats and water from half of the rats. Following a 2 hr control urine collection all of the rats were given 200 µequiv K+/100 g body wt. by gavage as a hypertonic solution of KCl (400 m-osmolar). Urine was collected at 2 hr intervals for 8 hr. Complete bladder emptying was insured by inducing urination with ether.

Chronic dehydration

Six DI rats underwent a 4-day balance study during which the average 24 hr water intake was calculated for each rat. Over the following 2 days of study each rat was allowed, daily, 7/8 of his prior average daily water intake. Half of this ration was provided in the morning, half in the afternoon.
Analyses

Tissue preparation

**Muscle.** Gastrocnemius muscle was excised and weighed immediately for determination of tissue wet weight. After drying to constant weight (48 h at 70–85 °C) the tissue was ground and redried to constant weight. An overnight ether extraction was then performed and the defatted tissue subjected to digestion by 0.75 N-HNO₃ (5 ml./0.1 g defatted tissue). For analysis of potassium concentration the HNO₃ solution was diluted 1:10 in lithium solution and read directly in a flame photometer. Results were expressed as m-mole/kg fat-free dry wt.

**Kidney.** Immediately after killing the left kidney was excised and rapidly separated into cortex, medulla, and papilla. Tissue wet weight was immediately determined. As with gastrocnemius, the samples were then dried to constant weight, ground, and redried to constant weight. The ground tissue was digested with 0.75 N-HNO₃ and diluted in lithium solution for flame photometry.

Potassium and osmolality

Potassium concentration in plasma, urine and tissue was determined by flame photometry (Radiometer Model FLM-2E). Urine osmolality was determined by freezing point depression in an Advanced Instruments osmometer (Model 8731 L).

Statistical methods

Data were analysed using paired *t* and Student's *t* tests, utilizing the statistics programme supplied by Hewlett-Packard for their programmable calculator (Model 9100 B).

RESULTS

Balance studies

As shown in Fig. 1 the daily urinary potassium excretion was higher in DI than in Long-Evans rats on the first 4 days of balance studies. On days 5–9 urinary potassium excretion of DI rats had fallen to a value not significantly different from that of normal rats. During the period of augmented potassium excretion, plasma [K⁺] was significantly reduced compared to Long-Evans rats (3.7 ± 0.2 mM vs. 4.3 ± 0.2 mM, respectively; *P* < 0.01) but by the end of the 9-day study it had increased to 4.3 ± 0.2 mM, a value not significantly different from that measured in Long-Evans rats at the same time (4.3 ± 0.1 mM). Fig. 1 also illustrates the food intake of DI and Long-Evans rats during 9 days of study. Food intake of DI rats was significantly higher than that of Long-Evans rats on all but 2 days of study. There was no difference between the average food intake of DI rats on days 1–4 and 5–9.

Four DI rats taken directly from their habitation cages had an average plasma [K⁺] of 3.6 ± 0.1 mM, not significantly different from that of DI rats after 3 days in metabolism cages (3.7 ± 0.2 mM).

Table 1 records the electrolyte and water content of kidney and muscle of DI and Long-Evans rats after 3 and 9 days in metabolism cages. As shown in this Table, the reversal of the hypokalaemia of DI rats at 9 days was associated with a significant reppletion of potassium in muscle, indicated by the increased potassium content and [K⁺] in gastrocnemius muscle after 9 days, as compared to measurements made after only 3 days in metabolism cages. Potassium concentration of renal medulla and papilla was higher in DI than in normal rats at 3 days. At the end of 9 days, however, there was no significant difference between DI and Long-Evans rats with respect to
Fig. 1. Urinary potassium excretion and food intake during a 9-day balance study in Long–Evans (LE) \((n = 11)\) and DI \((n = 11)\) rats. Vertical bars indicate s.e. of the mean. + \(P < 0.05\) when compared to LE rats on the same day. *\(P < 0.05\) when compared to the average of days 1–3 in the same rats.

**TABLE 1.** Tissue potassium and water content in kidney and muscle of DI and Long–Evans (LE) rats after 3 and 9 days in metabolism cages

<table>
<thead>
<tr>
<th>Tissue</th>
<th>3-day values</th>
<th>9-day values</th>
<th>[K+]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>K content (m-mole/kg fat-free dry wt.)</td>
<td>H₂O content (ml/100 g wet wt)</td>
<td>(mm)</td>
</tr>
<tr>
<td>Medulla</td>
<td>DI 406 ± 10*</td>
<td>79·2 ± 1·0</td>
<td>104·7 ± 4·5**</td>
</tr>
<tr>
<td></td>
<td>LE 378 ± 1</td>
<td>82·9 ± 0·9</td>
<td>77·9 ± 2·8</td>
</tr>
<tr>
<td>Papilla</td>
<td>DI 392 ± 4*</td>
<td>80·7 ± 0·4</td>
<td>89·2 ± 3·0*</td>
</tr>
<tr>
<td></td>
<td>LE 339 ± 17</td>
<td>81·5 ± 0·8</td>
<td>77·5 ± 3·8</td>
</tr>
<tr>
<td>Gastrocnemius</td>
<td>DI 442 ± 8*</td>
<td>75·6 ± 0·2</td>
<td>137·1 ± 0·7**</td>
</tr>
<tr>
<td></td>
<td>LE 465 ± 8</td>
<td>75·7 ± 0·4</td>
<td>143·2 ± 1·4</td>
</tr>
</tbody>
</table>

All values are means ± s.e. of mean. \(n = 4\) for each group.

* Significantly different from Long–Evans rats in the same study, *\(P < 0.05\), **\(P < 0.01\).
† Significantly different from 3-day values in the same group, \(P < 0.05\).
any of the parameters measured. Water content of renal medulla and papilla of DI rats increased significantly and [K+] of these zones decreased significantly between 3 days and 9 days in metabolism cages. No differences in water or electrolyte content were observed in cortex of DI or Long–Evans rats between 3 and 9 days, nor between DI and Long–Evans rats measured at 3 or 9 days. Muscle potassium content of four DI rats taken directly from their habitation cages was 362 ± 6 m-mole/kg fat-free dry wt. significantly lower (P < 0·01) than that of DI rats after 3 days in metabolism cages (442 ± 8).

KCl loading studies

This experiment was designed to verify the potassium deficiency in DI rats and to observe the response of these rats to KCl loading.

DI rats did not excrete a KCl load as well as normal rats. Urinary potassium excretion of DI rats was higher (93·8 ± 10·2 μmole/hr) than that of normal rats (33·8 ± 28·1, P < 0·05) during the 2 hr control period prior to KCl loading. At 0–4 and 4–8 hr after loading, potassium excretion of DI rats was 95·3 ± 8·9 and 49·5 ± 6·7, respectively, significantly lower than the corresponding values of 143·2 ± 15·4 (P < 0·05) and 86·5 ± 9·6 (P < 0·01) respectively in normal rats. By 8 hr after KCl loading DI rats had excreted a total of 372 ± 53 μmole of potassium compared to 722 ± 90 μmole excreted by normal rats (P < 0·01). These values were obtained by subtracting the cumulative potassium excretion of DI and normal rats receiving saline from the potassium excretion of KCl-loaded DI and normal rats respectively.

Although DI rats had a diminished capacity to excrete a KCl load compared to normal rats, KCl loading did significantly increase urinary potassium output in DI rats compared to DI rats receiving saline. The average cumulative potassium output in DI rats receiving a KCl load (613·7 ± 52·5 μmole/8 hr) was significantly higher than that in DI rats receiving saline (241·0 ± 22·0 μmole/8 hr; P < 0·01).

Altered dietary potassium intake

Potassium-free diet

This study was performed to determine whether a primary renal defect in potassium handling was responsible for the hypokalaemia in DI rats. On a low potassium diet DI rats were able to reduce their potassium excretion significantly compared to values on a normal diet. The reduction in potassium excretion represented a decrease to only 0·6% of the excretion on a normal diet and resulted in a potassium excretion (10·7 ± 1·1 μmole/24 hr/100 g body wt.) significantly lower than that of normal rats (27·3 ± 3·0 μmole/24 hr/100 g body wt.) on the same diet, P < 0·01. Normal rats reduced their potassium output to 2·0% of their excretion on a normal diet.

After 6 weeks on a low potassium diet, potassium content of gastrocnemius in DI rats and normal rats was 303·0 ± 7·5 and 284·9 ± 7·9 m-mole/kg fat-free dry wt. respectively and plasma [K+] was 1·7 ± 0·2 mM in DI rats and 1·6 ± 0·2 mM in normal rats; there were no significant differences between the DI and normal rats.
**High potassium diet**

The pattern of urinary potassium excretion in DI rats on a high potassium diet was studied over a 6 day period. Fig. 2 illustrates the potassium excretion of DI rats over the 6 days of study. Included for comparison are values from DI rats on normal and low potassium diets. Regardless of dietary intake of potassium, the urinary output of potassium always declined significantly (compared to the excretion on day 1) after several days in metabolism cages. The decline occurred earlier (day 3) on a low potassium diet and later (day 5) on a high potassium diet, when compared to a normal diet (day 4).

Potassium content in gastrocnemius muscle on the high potassium diet was $490.8 \pm 20.2$ m-mole/kg fat-free dry wt. and plasma $[K^+]$ was $3.9 \pm 0.3$ mM, values not significantly different from those for Long–Evans rats (Table 1), indicating significant potassium repletion.

**Dehydration studies**

**Acute dehydration**

Fig. 3A depicts the changes in urinary potassium output which resulted from 5 hr of water deprivation in DI rats. The potassium excretion of dehydrated DI rats was higher during all periods after withdrawal of water when compared to that of DI rats drinking *ad lib.*, although there was no difference between these two groups during
the control period. The cumulative potassium output over the 5 hr period of measurement was more than three times higher in the dehydrated group.

Fig. 3B illustrates the effects of dehydration on the response to an oral KCl load in DI rats. KCl loading resulted in an increased potassium excretion both in rats with free access to water and rats deprived of water for 8 hr. Nevertheless the potassium output of dehydrated rats was higher than that of undehydrated rats 4–8 hr after KCl loading and the cumulative potassium output over the 8 hr period of measurement was also significantly greater.

Renal tissue potassium and water content were measured in six rats dehydrated for 5 hr and six rats which had been drinking ad lib. As shown in Table 2, 5 hr of water deprivation in DI rats resulted in a significant increase in [K+] in cortex, medulla, and papilla and reduction in water content of cortex and papilla. There were no significant changes in gastrocnemius muscle as a result of dehydration. In dehydrated rats, the osmolality of a urine sample collected during the hour immediately preceding sacrifice was 419 ± 23 m-osmole/kg H₂O, significantly higher than that of rats drinking ad lib. (127 ± 6; P < 0.001).
Chronic dehydration

The effects of 2 days of water rationing on the potassium output of DI rats was also evaluated in this study. When the rats were limited to 7/8 of their average daily water intake, potassium excretion increased significantly from $1669 \pm 170$ to $1942 \pm 150$ μ equiv/100 g body wt./24 hr, $P < 0.05$. Body weight decreased by an average value of 15% after 2 days, while urinary osmolality increased from $152 \pm 32$ to $326 \pm 14$ m-osmole/kg H$_2$O, $P < 0.01$.

**Table 2. Effect of acute dehydration (5 hr) on tissue potassium and water content in kidney and muscle of DI rats**

<table>
<thead>
<tr>
<th></th>
<th>K content (m-mole/kg fat-free dry wt)</th>
<th>H$_2$O content (ml/100 g wet wt)</th>
<th>[K$^+$] (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortex</td>
<td>C 312 ± 7</td>
<td>73.5 ± 0.6</td>
<td>114.6 ± 5.0</td>
</tr>
<tr>
<td></td>
<td>D 320 ± 15</td>
<td>71.7 ± 0.8*</td>
<td>125.0 ± 4.0*</td>
</tr>
<tr>
<td>Medulla</td>
<td>C 361 ± 31</td>
<td>80.0 ± 1.5</td>
<td>98.7 ± 2.0</td>
</tr>
<tr>
<td></td>
<td>D 511 ± 64**</td>
<td>78.0 ± 2.5</td>
<td>152.4 ± 30.0*</td>
</tr>
<tr>
<td>Papilla</td>
<td>C 371 ± 78</td>
<td>84.0 ± 2.0</td>
<td>73.1 ± 2.1</td>
</tr>
<tr>
<td></td>
<td>D 433 ± 84</td>
<td>78.4 ± 2.5**</td>
<td>87.6 ± 2.1**</td>
</tr>
<tr>
<td>Gastrocnemius</td>
<td>C 454 ± 21</td>
<td>75.0 ± 0.6</td>
<td>142.3 ± 6.5</td>
</tr>
<tr>
<td></td>
<td>D 448 ± 15</td>
<td>74.0 ± 0.4</td>
<td>143.9 ± 5.0</td>
</tr>
</tbody>
</table>

C = undehydrated rats, n = 6; D = dehydrated rats, n = 6. Values are means ± S.E. of the mean.

Significantly different from undehydrated rats, *$P < 0.05$, **$P < 0.01$.

**DISCUSSION**

The results of the present study indicate that the mild hypokalaemia previously reported in DI rats (Möhring et al. 1974) is associated with inappropriately high urinary potassium excretion and is a reversible condition, which is corrected spontaneously after several days in metabolism cages. In these studies DI rats were found to be hypokalaemic after a 3 day balance study as evidenced by lower plasma [K$^+$] and muscle potassium content, and a reduced response to KCl loading when compared to normal Long-Evans rats. This hypokalaemia was present at a time when potassium excretion was elevated in comparison to that of Long-Evans rats.

After 9 days in metabolism cages, however, urinary potassium excretion was reduced and muscle potassium content and plasma [K$^+$] increased to values not significantly different from those of Long-Evans rats. These results suggest that the higher potassium output observed in DI rats early in balance studies might be due to environmental factors which can be corrected by placing the rats in metabolism cages where they are housed individually. Measurements made in DI rats taken directly from their regular habitation cages indicate that the hypokalaemia exists before placement in metabolism cages and does not result from adaptation to the new environment. Plasma [K$^+$] in these rats was not different from that measured in DI rats after a 3 day balance study; muscle potassium content was even lower indicating significant potassium repletion during the first 3 days in metabolism cages. It is of
interest to note that our experiments explain the discrepancy between the data of Mohring et al. (1974) and Friedman & Friedman (1965). The latter did not encounter potassium deficiency in Brattleboro rats. Their rats were maintained in metabolism cages for 22–24 days before sacrifice for muscle and plasma analysis.

Since Friedman & Friedman (1965) have shown a greater food intake in DI rats than in normal rats, the contribution of an increased potassium intake to the higher potassium excretion in these rats was evaluated. Our data show that food intake was indeed higher in DI rats than Long–Evans rats but the changes observed in potassium excretion during prolonged periods in metabolism cages did not correlate with changes in food intake. Food intake of DI rats was constant over the 9 days of study, while potassium excretion declined significantly in the latter part of the study (Fig. 1). In addition, a separate study in DI and normal albino rats revealed no difference in food intake between the two groups throughout a 9-day balance study, yet potassium output of DI rats was higher than that of normal rats on the first 3 days of study.

The present studies make unlikely the existence of a primary defect in renal potassium handling in DI rats. When DI rats were kept on a low potassium diet they were able to reduce their potassium excretion to levels even lower than those of normal rats in a similar state of potassium balance. This should not have occurred if a defective renal tubular mechanism was involved in the hypokalaemia, since one would expect this defect to be characterized by a tubular leak (albeit reduced in magnitude on a low potassium diet) resulting in a continuous renal loss of potassium in any state of potassium balance. Although the potassium depletion studies and KCl loading studies were performed using normal albino rats rather than Long–Evans rats for comparison, we have demonstrated that there is no difference between these rats and Long–Evans rats with respect to urinary potassium excretion, muscle Na, K or water content or plasma [K+]; only food intake was higher in these rats.

During the period of elevated potassium excretion and hypokalaemia, [K+] was elevated in renal medulla and papilla of DI rats compared to normal rats (Table 1). It should be emphasized that in this sense renal tissue potassium content and [K+] did not reflect the general state of potassium deficiency evident in the reduced potassium content of skeletal muscle and plasma [K+]. The elevated [K+] in renal medulla and papilla at this time was most likely responsible for the enhanced potassium excretion in DI rats. It has been shown that the loop of Henle and collecting duct, which constitute the bulk of the papilla, can be sites of net potassium secretion in the rat (Malnic et al. 1964, 1966a, b; Finkelstein & Hayslett, 1974; Silva, Ross, Charnet, Besarab & Epstein, 1975; Jamison, Lacy, Pennel & Sanjana, 1976; Bengele, Evan, McNamara & Alexander, 1978) and hamster (Hierholzer, 1961).

Changes in renal [K+] and water content in DI rats between 3 and 9 days in metabolism cages support the hypothesis that alterations in water balance are involved in the hypokalaemia and in its reversal. While there was significant repletion of potassium in muscle and plasma after 9 days, [K+] in renal medulla and papilla decreased due to significant increases in the water content of these zones. At the end of the 9 day study, when no differences in renal tissue [K+] and water content could be observed between DI and normal rats, there was also no difference between the urinary potassium excretion of the two groups.

We have also studied the effect of both acute and chronic mild dehydration in DI rats. Acute periods of dehydration (1–5 hr) are sufficient to raise potassium output in
DI rats. As shown in Fig. 3A, even 1 hr of water deprivation significantly increased the potassium output of DI rats, compared to DI rats drinking ad lib. Doubtlessly this is due to the elevation in [K+] of renal tissue (cortex, medulla, and papilla) which results from dehydration (Table 2), a finding consistent with that of Valtin (1966) who found increased [K+] in medulla and papilla of DI rats after 12 hr of dehydration. Four to eight hours of dehydration was also found to enhance the excretion of an oral potassium load (Fig. 3B).

The effects of water rationing in DI rats was also studied since this procedure may more accurately reflect conditions which exist in these rats when they are forced to compete with other rats for drinking water. Water rationing resulted in dehydration, as evidenced by a modest decrease in body weight, and was also associated with increased urinary potassium excretion.

In contrast to muscle, the potassium content and [K+] of renal tissue in these rats was elevated rather than diminished during potassium deficiency. In the kidney, changes in water balance, which were not evident in skeletal muscle, seem to have played a major role in the increase in [K+] and therefore the augmentation of potassium excretion. It should be noted, too, that while changes in cortical and papillary [K+] after acute dehydration (Table 2) resulted from changes in water content, the increased [K+] in medulla resulted from an actual increase in potassium content. We have no explanation for this latter finding.

In summary, we have demonstrated the reversible nature of the hypokalaemia in DI rats and its association with a transient elevation in potassium excretion. This elevated potassium excretion does not appear to be due to elevated food intake or to a primary renal defect and is correctable simply by housing the rats individually in metabolism cages. As shown in Fig. 2, the augmented potassium excretion has been observed in widely varying states of potassium balance and is always of a transient nature.

Measurements of renal tissue potassium and water content during and after correction of hypokalaemia in DI rats, and following acute dehydration, support the hypothesis that mild dehydration associated with the condition of diabetes insipidus decreases the water content of renal medulla and papilla, thereby increasing the [K+] of these zones. This could account for the increased potassium output of DI rats, particularly in view of the fact that renal tissue [K+] was normal when urinary potassium output had returned to normal, i.e. after 9 days in metabolism cages. The increased loss of potassium in the urine appears to be responsible for the reversible hypokalaemia in these rats.

This work was supported in part by grant no. RR-8102 of the Division of Research Resources, National Institutes of Health. This study was carried out by E. Fernández-Repollet in partial fulfillment of the requirements for the Masters degree.

REFERENCES


