Metabolic acidosis accompanying potassium deprivation

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A close relationship between renal potassium and hydrogen ion excretion has been recognized for many years. In early experiments potassium chloride depletion was shown to result in metabolic alkalosis and a "paradoxical" aciduria; potassium chloride loading, on the other hand, was reported to result in an alkaline urine. Since both K+ and H+ are known to be secreted in the distal nephron, these observations led to the hypothesis that in this section of the nephron potassium and hydrogen ions compete for secretion by an ion pump which preferentially transfers the more abundant ion into the tubular fluid (4-7). This simple and popular hypothesis became strongly entrenched in physiological teaching and still represents one of the best remembered items of physiological lore by many not actively involved in this area of renal physiology.

Situations in which potassium and hydrogen ion secretion behaves in a manner opposite to that predicted by the existence of a pump for which these ions compete have been known for some time, for instance, ammonium chloride acidosis (20, 25) and aldosterone administration (3, 23), but in recent years several developments have forced reevaluation of the concept of K+-H+ competition. During the course of balance studies on dogs in which dietary potassium content was varied, it was noted that removal of potassium from the diet is accompanied by a prompt decrease in the excretion of ammonium and titratable acid. Further investigation showed that these changes in H+ excretion are associated with an increase in urine pH which is sustained as long as the diet is free of potassium. Over several days the positive H+ balance which results from the decrease in net H+ excretion leads to a mild systemic metabolic acidosis which, by increasing NH4+ excretion, then increases net acid excretion until it approximates the control value.

METHODS

Details of the balance method used in these experiments have been published previously (10). In brief, mongrel dogs were maintained in metabolic cages on 30 g/kg per day of a synthetic diet which is practically electrolyte free, and in particular contains less than 0.2 meq/kg of potassium. The diet was supplemented with known amounts of several salts according to one of two protocols, A or B, as described in the next paragraph. All of the daily ration of food was eaten by each animal. Jugular venous blood samples were obtained at intervals of 2-3 days and analyzed for sodium, potassium, chloride, bicarbonate, pH, urea nitrogen, and creatinine. Urine was collected under mineral oil with thymol and phenylmercuric nitrate as preservatives. Urine titratable acid, ammonium, bicarbonate, sodium,
Some CO₂ loss from the specimen. pH values of refrigerated urine under mineral oil with preservatives showed a slightly higher pH in the stored urine, presumably due to some CO₂ loss from the specimen. pH values of refrigerated samples were stable for over 1 wk. Analytical methods are the same as those described previously (10).

The electrolyte composition of the diet in protocols A and B is shown in Table 1. In protocol A the experiment was divided into the following periods:

Period I. Control period. During the first 8-11 days, each dog was maintained on 30 g/kg per day of the electrolyte-free diet supplemented with 30 meq potassium chloride and 30 meq sodium phosphate, pH 7.4.

Period II. Potassium deprivation. Potassium chloride was removed from the diet and 30 meq sodium chloride were substituted during the second period which lasted 13 or 14 days; the first 3 and last 3 days of this period are defined as Periods IIA and IIB, respectively.

Period III. Recovery. The diet of Period I was resumed, restoring potassium intake.

Period IV. High sodium intake. In two dogs after a 9-day recovery period, 30 meq sodium chloride were added to the control diet without altering the potassium content.

In protocol B, Periods I and III contained also 30 meq of sodium chloride. Potassium chloride was removed from the diet in Period II without making any other change in electrolyte composition (Table 1). The duration of Periods I, II, and III with this protocol was 9, 7, and 4 days, respectively.

**RESULTS**

Figure 1 shows the results of a representative experiment using protocol A. The horizontal lines in each section of the figure represent the average excretion rates for the control period. Daily values are shown as deviations above or below the average control value except for potassium excretion which is given as the total excretion rate per period.

During the control period potassium intake was 30 meq/day and the urinary excretion rate was 24 meq/day; presumably loss of potassium in the stool accounted for the difference between intake and urinary output, but stools were not analyzed in these experiments. On day 10 potassium was removed from the diet, and in the next 2 days potassium excretion fell to less than 3 meq/day and remained there for the remainder of the potassium deprivation period. Total urinary potassium loss in this experiment during Period II was 36 meq. Plasma potassium concentration, not shown in the figure, averaged 3.4 ± 0.4 meq/liter (7 determinations) during the deprivation period as compared to 3.9 ± 0.3 meq/liter (5 determinations) in Period I.

On restoration of potassium to the diet on day 23, potassium excretion remained low for several days, then rose to the control level by about the 5th day. Extracellular volume, calculated from changes in chloride balance, increased in Period II by 130 ± 190 ml, a change which was not significant. Average urine volume in Period II was 391 ± 82 ml/day, a decrease of 74 ml from Period I; there was no significant difference between urine volumes in Periods II and III.

Potassium deprivation was associated with a higher urine pH than during the control period. In the experiment of Fig. 1, average urine pH during Period I was 6.48, in Period II it was 6.67. Accompanying this rise were decreases in ammonium, titratable acid, and net H⁺ excretion which averaged, respectively, 5.8, 2.6, and 8.3 meq/day less during the first 3 days of Period II than in the last 5 days of the control period. The positive H⁺ balance accumulating over several days resulted in a gradual increase in plasma HCO₃⁻, which fell from 27 to 20 meq/liter by the end of Period II. Blood pH (not shown) fell correspondingly from 7.42 to 7.37. The average daily H⁺ excretion for Period II was 46.8 ± 5.6 meq/day, during Period I it was 53.4 ± 7.0 meq/day. The alterations in urine pH and titratable acid excretion persisted as long as potassium deprivation continued. However, as the result of stimulation of renal ammonia production by the mild chronic metabolic aci-
dosis, NH₄⁺ excretion increased slowly, and during the last 3 days of Period II it averaged 35.9 meq/day, compared to a control rate of 37.3 meq/day.

When potassium was restored to the diet, the changes observed in Period II rapidly reversed. On the 2nd day of Period III urine pH began to fall and reached a minimum of less than 6.0 on the 4th day. Ammonium, and to a lesser extent, titratable acid excretion rose in company with the fall in urine pH. At their peak on the 4th day, net H⁺ and NH₄⁺ excretion exceeded the control average by over 50%. The large increase in H⁺ loss quickly eliminated the positive H⁺ balance accumulated during K⁺ deprivation, and the metabolic acidosis which had gradually developed in Period II was corrected in about 5 days.

Table 2 summarizes the data from all the protocol A experiments and shows that the changes illustrated in the one experiment of Fig. 1 represent significant differences (P < 0.05) when the entire set of experiments is considered. Because the duration of urine collections was not always exactly 24 h and varied slightly from animal to animal, excretion rates were added together for several days and are expressed in the table as average milliequivalents per hour. The values shown for Period I are the averages for the last 5 days of the control period; those for Period III are for the first 4 days after potassium was put back in the diet.

In response to potassium deprivation, potassium fell to low levels in the urine. Urine pH rose and net H⁺, NH₄⁺, and titratable acid excretion fell (Period IIA). Urine bicarbonate showed no change. An important observation not discernible in the table is that urine pH rose within the 1st day after removing K⁺ from the diet; the average urine pH on the 1st day of Period II was 6.56 ± 0.08 compared to the control value of 6.25 ± 0.15; this rise was accompanied by appropriate decreases in NH₄⁺ and titratable acid excretion, verifying the occurrence of this prompt pH change. By the latter part of this period (Period IIIB), plasma HCO₃⁻ had fallen, urine pH was still high (6.52), and titratable acid was low (0.51 meq/h), but NH₄⁺ excretion had risen to or slightly above the control level and because of this rise, net H⁺ excretion was close to normal. Plasma potassium concentration changed from an average control value of 3.74 ± 0.13 to 3.23 ± 0.16 meq/liter during Period II; in four dogs the potassium concentration was measured on the 1st day of Period II and was 3.25 ± 0.06 meq/liter at this time compared to an average control value in these animals of 3.71 ± 0.15 meq/liter. Restoration of K⁺ in the diet resulted in a decrease in urine pH to slightly below the control level and in concomitant increases in excretion of NH₄⁺, titratable acid, and net H⁺. While titratable acid excretion rose only to the control level, NH₄⁺ excretion became much greater than in Period I.

In the preceding experiments potassium was replaced by sodium during the deprivation period, keeping chloride intake constant, and it was possible that the observed effects on acid excretion were due to the extra dietary sodium rather than to removal of potassium. To evaluate this possibility, in two experiments 9 days after restoring potassium, 30 meq/day of NaCl were added to the diet without changing the potassium content. The results are shown in Fig. 2. A marginal increase (0.12 in experiment 1 and 0.15 in experiment 2) occurred in average urine pH. However, net H⁺ excretion did not decrease, indicating that the change in urine pH was insignificant. Thus, addition of NaCl to the diet alone did not reproduce the changes in acid excretion observed when NaCl was substituted for KCl in the diet.

In order to confirm that removal of potassium ion was responsible for the changes described above, another group of experiments was performed using a different protocol. In contrast to protocol A, in which potassium was replaced with an equimolar amount of sodium, in the second set of experiments (protocol B) potassium chloride was removed from the diet but the sodium content was not changed. Table 3 shows the changes in average urine pH and net H⁺ excretion for the three periods in each of the four dogs studied. In one animal (#4) the control (Period I) urine pH was higher and the net H⁺ excretion rate was lower than in the other dogs, and no change in these measurements occurred in Period II when potassium chloride was withdrawn. However, even in this animal restoration of potassium chloride caused urine pH to fall and net H⁺ excretion to rise. In the other three experiments responses identical to those observed with protocol A were obtained. Urine pH rose significantly when potassium chloride was removed (Period II) and fell when it was put back in the diet (Period IV).
Chronic metabolic acidosis is accompanied by an increase in urine pH and acid excretion. The development of acidosis lends further credence to the described changes in urine pH which, through different mechanisms, produces a decreased net H+ excretion, and a positive H+ balance ensues if acid production rate remains constant, as it presumably did in these experiments. Persistence of this positive H+ balance eventually restores net H+ excretion approximately to the control level so that H+ excretion once again nearly equals H+ production rate.

Further evidence for the changes observed during potassium deprivation are the large changes in all parameters of H+ excretion which result when K+ is reintroduced into the diet. Urine pH falls, titratable acid excretion returns to normal, and net H+ and NH4+ excretions rise temporarily above control values so that the gradually accumulating alterations in acid balance which developed during 13 days of K+ deprivation are corrected within 4-5 days after potassium intake is restored. The much greater relative increase in NH4+ excretion than in titratable acid excretion present during the first few days after resuming K+ intake can be attributed to the fact that both the enhancement of NH4+ production by acidosis and its suppression upon cessation of the acidotic stimulus are slow changes requiring several days for complete development (25, 27). Thus, NH4+ production is still high when urine pH falls sharply after K+ is added to the diet and a high rate of NH4+ excretion occurs for several days.

Previous studies have shown that potassium chloride deprivation results in metabolic alkalosis; in the present experiments, potassium deprivation resulted in metabolic acidosis. How can these apparently contradictory results be reconciled? The experimental protocols differ significantly between the two situations. In former studies of potassium chloride depletion, large imbalances in potassium were sought and various methods, such as potent diuretics (17) or mineralocorticoid administration (2, 12, 13), were used to force potassium loss. These agents influenced hydrogen ion excretion, but it is more likely that the accompanying depletion of chloride ion is the major factor responsible for metabolic alkalosis (26). In our experiments using protocol A, chloride intake was kept constant and potassium excretion was not forced. While a slight negative potassium balance developed during the course of the potassium deprivation period, the degree of this imbalance is small compared to that produced in previous studies of potassium chloride depletion. In addition, development of a negative potassium balance is not responsible for the increase in urine pH since this increase develops within the 1st day after removing potassium, before any significant change in potassium balance has occurred.

In regard to these earlier studies of potassium chloride depletion, it is of interest to note that a metabolic acidosis was actually observed under conditions of K+ deprivation, although the authors made no comment on the appearance of this acid-base disorder (10, 18). When potassium chloride-depleted animals with metabolic alkalosis were repleted with chloride but not potassium, producing animals depleted only of potassium ion, the metabolic alkalosis subsided and was replaced by a mild metabolic acidosis. The results of the present study predict that these potassium-deprived animals had a higher than normal urine pH, an abnormality which would account for the appearance of the observed metabolic acidosis.

While any explanation of the mechanism underlying the
change in \( \mathrm{H}^+ \) secretion following potassium deprivation must be speculative at this time, two possibilities deserve discussion. A major factor regulating distal potassium secretion is the electrical gradient across the tubular cells (16). If the \( \mathrm{K}^+ \) is removed from the diet, its excretion rate begins to decrease promptly, possibly as the result of an increase in the negative potential difference between the lumen and the interior of cells of the distal tubule. Under other experimental conditions, changes in \( \mathrm{H}^+ \) excretion have been attributed to alterations in the electrical gradient across the distal tubule (11), and a change in potential difference induced by \( \mathrm{K}^+ \) deprivation could decrease net \( \mathrm{H}^+ \) excretion. If active \( \mathrm{H}^+ \) secretion, which almost certainly occurs in the distal nephron, remained constant, then an increase in passive reabsorption of \( \mathrm{H}^+ \) in response to a change in electrical gradient would decrease net \( \mathrm{H}^+ \) secretion and might account for the results of our experiments.

Another factor which can influence both \( \mathrm{K}^+ \) and \( \mathrm{H}^+ \) excretion is aldosterone. Aldosterone administration has been shown to increase both \( \mathrm{K}^+ \) and \( \mathrm{H}^+ \) excretion (3, 23), although its effects on the latter have not been carefully evaluated. Presumably a reduction in aldosterone secretion could have the opposite effect, reducing the excretion of both ions. Plasma \( \mathrm{K}^+ \) concentration is known to regulate aldosterone secretion by a mechanism independent of the renin-angiotensin system (9, 14), and some evidence suggests that aldosterone secretion is extremely sensitive to the plasma level of \( \mathrm{K}^+ \), small changes in concentration of this ion resulting in significant alterations in aldosterone release (8). In order for a decrease in aldosterone production to account for the increase in urine pH following \( \mathrm{K}^+ \) deprivation, plasma \( \mathrm{K}^+ \) and aldosterone secretion should decrease within the 1st day after discontinuing \( \mathrm{K}^+ \) administration. In four animals in which plasma \( \mathrm{K}^+ \) was measured on the 1st day of \( \mathrm{K}^+ \) deprivation, the concentration of this ion was 0.46 ± 0.14 meq/liter less than during the control period. Thus, a fall in aldosterone production in response to this change in \( \mathrm{K}^+ \) level could have occurred promptly enough to affect urine pH on the 1st day of \( \mathrm{K}^+ \) deprivation.

Previously we have pointed out that regulation of urine pH, which is of paramount importance in determining both ammonium and titratable acid excretion and thus in maintaining hydrogen ion homeostasis, is one of the most poorly understood aspects of renal acid-base physiology (27). The present study adds a further item to the list of factors which must be considered in attempting to analyze the mechanisms which control urine pH.

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