Control of excretion of potassium: lessons from studies during prolonged total fasting in human subjects

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Renal Division, National Defense Medical Center, Taipei, Taiwan, Republic of China; McGill Nutrition and Food Science Centre, Royal Victoria Hospital, McGill University, Montreal, Quebec; and Division of Nephrology, St. Michael’s Hospital, University of Toronto, Toronto, Ontario, Canada M5B 1A6

Lin, Shih-Hua, Surinder Cheema-Dhadli, Manjula Gowrishankar, Errol B. Marliss, Kamel S. Kamel, and Mitchell L. Halperin. Control of excretion of potassium: lessons from studies during prolonged total fasting in human subjects. Am. J. Physiol. 273 (Renal Physiol. 42): F796–F800, 1997.—A deficit of K⁺ of close to 300 mmol develops in the first 2 wk of fasting, but little further excretion of K⁺ occurs, despite high levels of aldosterone and the delivery of ketoacid anions that are not reabsorbed in the distal nephron. Our purpose was to evaluate how aldosterone could have primarily NaCl-retaining, rather than kaliuretic, properties in this setting. To evaluate the role of distal delivery of Na⁺, four fasted subjects received an acute infusion of NaCl to induce a natriuresis. To assess the role of distal delivery of HCO₃⁻, five fasted subjects were given an infusion containing NaHCO₃. The natriuresis induced by an infusion of NaCl caused only a small rise in the rate of excretion of K⁺ (0.8 ± 0.1 to 1.9 ± 0.3 mmol/h); in contrast, when HCO₃⁻ replaced Cl⁻ in the infusion, K⁺ excretion rose to 8.3 ± 2.2 mmol/h, despite little excretion of HCO₃⁻ (urine, pH 5.8) and similar rates of excretion of Na⁺. The transtubular K⁺ concentration gradient was 19 ± 3 with HCO₃⁻ and 6 ± 2 with NaCl. We conclude that the infusion of NaHCO₃ led to an increase in K⁺ excretion, likely reflecting an increased rate of distal K⁺ secretion. With a low distal delivery of HCO₃⁻, aldosterone acts as a NaCl-retaining, rather than a kaliuretic, hormone.

Aldosterone; bicarbonate; ketoacidosis; sodium

Development of physiological mechanisms to adapt to prolonged periods of total lack of food is one of the most primitive yet essential strategies that have permitted the human species to survive. Understanding the basis for these critical adaptive responses could reveal the importance of control mechanisms that operate in a variety of clinical settings. In this study, we addressed the control of K⁺ homeostasis in prolonged total fasting.

A key element in the physiology of prolonged fasting is the need to provide a fat-derived fuel (fat stores are abundant) to displace the need of the brain for glucose as an energy substrate (a supply of glucose now depends on gluconeogenesis from indispensable protein; reviewed in Ref. 2). The water-soluble, fat-derived fuel is, for the most part, the ketone bodies, β-hydroxybutyrate (β-HB⁻). It takes <1 wk to develop the near steady state characterized by a modest degree of ketosis (β-HB⁻ in the 5–7 mM range) and acidemia (pH 7.34, 19–21 mM HCO₃⁻) (2, 21). Subsequently, renal adaptive mechanisms become paramount (6, 11, 15, 18, 21, 23). The kidney filters 750–1,000 mmol of β-HB⁻ each day, and 15–20% of this filtered load is excreted (21). The consequences of the excretion of β-HB⁻ on the excretion of cations such as Na⁺, K⁺, and NH₄⁺ in chronic fasting have been well characterized (6, 11, 15, 18, 21, 23). They can be summarized as follows: during the first 2 wk of fasting, a large deficit of Na⁺ develops (close to 350 mmol), but over the subsequent period of fasting, there is little additional excretion of Na⁺. Similarly, there is also a large initial kaliuresis (close to 300 mmol) (7, 22). However, renal mechanisms for conservation of K⁺ are less efficient than for Na⁺, and there is a continuing mild progression in the negative balance for K⁺. Without a K⁺ supplement, a mild degree of hypokalemia develops despite the relative hypoinsulinemia, a hormonal setting characterized by a shift of K⁺ from cells (30).

The question we address in this study is, what is responsible for the low rate of kaliuresis in subjects who have continued their total caloric deprivation for 2 wk? This low rate of kaliuresis occurred despite the presence of two factors that should augment it: high levels of aldosterone (4, 6, 18) and the delivery to the distal nephron of anions (β-HB⁻) that are not reabsorbed in these nephron segments (13, 29). Results indicate that two factors seemed to limit the excretion of K⁺ in these subjects: a low distal delivery of Na⁺ (minor factor) and a low distal delivery of HCO₃⁻ (major factor). These results will be discussed in a fashion that integrates K⁺ and acid-base physiology with the aim of suggesting how aldosterone can continue to promote the electroneutral reabsorption of NaCl while avoiding its kaliuretic action in prolonged total fasting.

Methods

Human subjects. The study protocols were approved by the ethics committee for experiments in human subjects. Seven females and two males [age, 33 ± 2 (range 21–48 yr), initial body weight, 122 ± 7 kg] were admitted for prolonged (2–4 wk) therapeutic fasting for a severe degree of obesity. They volunteered for the study after being informed of its purpose, nature, and possible consequences. None had diabetes mellitus, gout, renal, hepatic, or cardiovascular disorders, nor had they received medications that could have influenced the present results.

During fasting, subjects maintained a daily oral intake of at least 1,500 ml of water. They were also given 16 mmol KCl (Slowk; Ciba Pharmaceuticals, Dorval, PQ, Canada) to avoid a severe degree of hypokalemia; they also received a daily multivitamin preparation (Beminal; Aayerst Laboratories, Don Mills, ON, Canada). Measurement of electrolytes and metabolites in venous blood, renal function tests, and an electrocar-
Infusion studies. The purpose of the first study was to examine whether a low distal delivery of Na\(^+\) is the limiting factor for K\(^+\) secretion in the cortical collecting duct (CCD) after 2 wk of fasting. To control for possible mixing of urines with different Na\(^+\) and K\(^+\) excretion rates, an acute infusion protocol was used. Four of the subjects were given an acute infusion of 2 liters containing 300 mmol Na\(^+\), 80 mmol K\(^+\), and 380 mmol Cl\(^-\) over 6 h, with all the infusions starting at 0900 h. Prior to the infusion, subjects drank at least 0.5 liter of water so that they could void hourly on request for the 6-h period. To evaluate whether distal delivery of HCO\(_3\)\(^-\) was also a factor that might influence the excretion of K\(^+\) in this setting, five additional subjects were given an intravenous infusion of 2 liters containing 300 mmol Na\(^+\), 80 mmol K\(^+\), 230 mmol Cl\(^-\), and 150 mmol HCO\(_3\)\(^-\) over 6 h in a second study.

Analytic techniques. Blood samples were drawn anaerobically for immediate assay of pH and P\(_{CO_2}\). Urine was collected without preservative, and its pH and P\(_{CO_2}\) were measured immediately; the concentration of HCO\(_3\)\(^-\) in the urine was calculated using a pH of 6.10, and a solubility factor for CO\(_2\) corrected for ionic strength as previously described (3). A portion of blood and urine were each mixed immediately with an equal volume of 10% perchloric acid at 4°C for determination of \(\beta\)-HB\(^-\). Assays for Na\(^+\), K\(^+\), Cl\(^-\), pH, P\(_{CO_2}\), total CO\(_2\), urea, creatinine, osmolality, \(\beta\)-HB\(^-\), and NH\(_4\)\(^+\) were performed as previously described (11, 12).

Calculations. The transtubular K\(^+\) concentration ([K\(^+\)]\(_{\text{urine}}\)/[K\(^+\)]\(_{\text{plasma}}\)) gradient (TTKG) was calculated using the following formula (8)

\[
\text{TTKG} = \frac{[\text{K}^+]_{\text{urine}}}{[\text{K}^+]_{\text{plasma}}} \times \frac{\text{osmol}}{\text{plasma}}
\]

Statistical analysis. This was performed using the paired two-tailed Student's t-test. \(P < 0.05\) was considered to be a statistically significant difference.

RESULTS

At 2 wk of fasting, the subjects had a mild degree of metabolic acidosis (pH 7.34 ± 0.01, 21 ± 1 mM HCO\(_3\)\(^-\)), hypokalemia (3.5 ± 0.1 mM), and an elevated level \(\beta\)-HB\(^-\) in plasma (4.6 ± 0.4 mM). Their urine pH was close to 6.0, in agreement with previous observations (18, 22), and NH\(_4\)\(^+\) and \(\beta\)-HB\(^-\) were the predominant urine solutes in the 24-h period (Table 1).

To evaluate whether a low distal delivery of Na\(^+\) might limit secretion of K\(^+\) in the collecting ducts, subjects were given an intravenous load of NaCl. Prior to the administration of Na\(^+\), the rate of excretion of Na\(^+\) was 0.4 ± 0.1 mmol/h, whereas that of K\(^+\) was 0.8 ± 0.1 mmol/h. When the rate of excretion of Na\(^+\) rose to 1.6 mmol/h, there was a small rise in the rate of excretion of K\(^+\) to 1.9 mmol/h and a significant decline in urine pH from 5.7 to 5.2 (Fig. 1 and Table 2). Net K\(^+\) secretion in the terminal CCD was evaluated using the noninvasive semiquantitative tool, TTKG. The TTKG rose from 2 ± 1 to 6 ± 2 with the infusion of NaCl, and there was no significant change in the urine flow rate (Table 2).

Because HCO\(_3\)\(^-\) excretion is associated with a higher rate of excretion of K\(^+\) (3) and the infusion of NaCl led to a fall in HCO\(_3\)\(^-\) excretion (fall in urine pH, Fig. 1), a second protocol was employed to determine whether distal delivery of HCO\(_3\) could be an important modulator of the excretion of K\(^+\) in these subjects. When the rate of excretion of Na\(^+\) was not statistically significantly different during the infusion of NaCl and the one containing HCO\(_3\), there was no significant change in the urine flow rate (Table 2). The kaliuresis was greater when HCO\(_3\) was added to the infusate (8.3 vs. 1.9 mmol/h, respectively, Table 2). The TTKG was much higher in the subjects infused with the solution containing HCO\(_3\) (19 ± 3 and 6 ± 2, respectively, Table 2); there was no change in plasma [K\(^-\)]. These data suggest that the delivery of Na\(^+\) to the CCD was only one factor that influenced the rate of excretion of K\(^+\) in this setting.

DISCUSSION

The principal focus of this study was to examine factors that might limit the rate of excretion of K\(^+\)
continue excessive excretion of $K^+$, and this response is not a desirable one (Fig. 2B). How aldosterone could "select" electroneutral rather than electrogenic reabsorption of $Na^+$ in the CCD during chronic fasting will be considered here.

The simplest possible mechanism to limit the excretion of $Na^+$ and $K^+$ is to limit the delivery of $Na^+$ to the distal nephron. For this to be an effective mechanism, the $[Na^+]$ in the luminal fluid would have to be considerably less than 10–15 mM, the concentration that results in half-maximal secretion of $K^+$ in the CCD of the rat (9). It is possible, however, that such a low distal delivery of $Na^+$ could compromise the excretion of $NH_3$ or that of $K^+$, if a need for its excretion arose (e.g., cell necrosis). As shown in Table 2, when distal delivery of $Na^+$ was present ($Na^+$ excretion rose), there was only a modest...
Accordingly, we wished to evaluate whether delivery of a diuretic (acetazolamide) would be expected to augment a kaliuresis. We envision two additional mechanisms operating now. First, to the extent aldosterone was secreted in the CCD, it must be reabsorbed downstream in the medullary collecting duct because its excretion was low even when NaCl was infused (Table 2). An H⁺-K⁺-ATPase can carry out this function (28), albeit at a cost of extra ATP turnover. For this process to function, there must be a luminal H⁺ ion acceptor, and, in this case, the acceptor for H⁺ is NH₄⁺. The net result would be the excretion of NH₄⁺ and β-HB⁻ in a 1:1 stoichiometry, while minimizing a further deficit of Na⁺ or K⁺.

The second area to consider with respect to the distal delivery of Na⁺ and β-HB⁻ is distal H⁺ secretion. The fact that the urine pH fell when Na⁺ excretion rose (Fig. 1, Table 2) suggests that a low distal delivery of Na⁺ could also limit distal H⁺ secretion in steady state. Again, the secretion of H⁺, which are largely converted to NH₄⁺, permits the eventual urine to be Na⁺ and K⁺ poor, having NH₄⁺ plus β-HB⁻ as its principal constituents.

Perspectives for Disease States

The results of this study underscore the possible importance of HCO₃⁻ in the CCD as a factor that can augment the excretion of K⁺ when abundant Na⁺ is delivered and aldosterone is present. At times, there will be excessive delivery of HCO₃⁻ to the kidney, and this can cause a high rate of excretion of K⁺. Examples include vomiting or treating patients with proximal renal tubular acidosis (RTA) with large amounts of alkaline salts. At times, the kaliuresis can be augmented because of lower reabsorption of HCO₃⁻ in the PCT (acetazolamide, hyperkalemia), whereas, at other times, there could be lower secretion of H⁺ in the distal nephron (excessive kaliuresis in distal RTA; Ref. 24). This “cross-talk” between the proximal and distal nephron in which HCO₃⁻ reabsorption in the PCT is correlated with the net secretion of K⁺ in the CCD is consistent with the known influence of hypokalemia to stimulate and hyperkalemia to inhibit the proximal reabsorption of HCO₃⁻ (reviewed in Ref. 10) (Fig. 2B).

To summarize, when aldosterone is to function as a hormone which should enhance the electroneutral reabsorption of NaCl, having angiotensin II as its secretagogue is a logical choice (Fig. 2A). In contrast, when the function of aldosterone is to promote the excretion of K⁺, having hyperkalemia as its secretagogue is also logical, because hyperkalemia can augment the delivery of HCO₃⁻ to the distal nephron (Fig. 2B).

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