Lin, Shih-Hua, Surinder Cheema-Dhadli, Manjula Gowrishankar, Errol B. Marliss, Kamei S. Kamei, 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 kaliuresis 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.

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 indispensible 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 β-HB⁻. 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; Ayerst 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 HCO3− 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 HCO3− over 6 h in a second study. Analytic techniques. Blood samples were drawn anaerobically for immediate assay of pH and PCO2. Urine was collected without preservative, and its pH and PCO2 were measured immediately; the concentration of HCO3− in the urine was calculated using a pK of 6.10, and a solubility factor for CO2 with the infusion of NaCl, and one containing HCO3−, there was no significant change in the urine flow rate (Table 2). The kaliuresis was greater when HCO3− 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 HCO3− (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+

---

**Table 1. Values in plasma and urine in prolonged fasting**

<table>
<thead>
<tr>
<th></th>
<th>Fed</th>
<th>Prolonged Fasting</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.39 ± 0.01</td>
<td>7.34 ± 0.01</td>
</tr>
<tr>
<td>HCO3−</td>
<td>25 ± 1</td>
<td>21 ± 1</td>
</tr>
<tr>
<td>β-Hydroxybutyrate</td>
<td>&lt;0.1</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Na+</td>
<td>140 ± 1</td>
<td>130 ± 30</td>
</tr>
<tr>
<td>K+</td>
<td>4.3 ± 0.2</td>
<td>48 ± 8</td>
</tr>
<tr>
<td>Cl−</td>
<td>102 ± 1</td>
<td>127 ± 32</td>
</tr>
<tr>
<td>Creatinine</td>
<td>70 ± 4</td>
<td>14.0 ± 1</td>
</tr>
<tr>
<td>NH4+</td>
<td></td>
<td>138 ± 11</td>
</tr>
</tbody>
</table>

Values are means ± SE. Values in fed (n = 9) and prolonged fasted subjects (n = 9) are from 24 h urines. During prolonged fasting, the only oral supplements were water and 16 mmol KCl. Units in plasma are mM, except for creatinine, which is in µM. Units for urine are mmol/day.

---

**Fig. 1 Effect of an acute infusion of NaCl on urine pH during prolonged fasting.** For details, see METHODS. Subjects (n = 4) received an infusion of NaCl beginning at time 0 and lasted 6 h. Urine was provided hourly. Data from each subject are connected by line.
during chronic fasting. This model is of interest for three major reasons. First, the adaptations developed for survival during prolonged deprivation of food are critically important and therefore must have been established very early on in human evolution. Second, this is an example of a clinical setting where the rate of excretion of K\(^+\) is low, but there are factors present that could augment the excretion of K\(^+\): a high level of aldosterone (4, 6, 18) and the delivery of anions (\(\beta\)-HB\(^-\)) that are not reabsorbed in the distal nephron. Third, by revealing the control mechanisms that operate in this setting, perhaps insights can be gained into understanding the pathophysiology of clinical disorders with a dyskalemia resulting from an altered rate of excretion of K\(^+\).

Balance data for Na\(^+\) and K\(^+\) during total fasting place the antinatriuresis and the antikaliuresis in perspective. Subjects who fast for >1 wk have cumulative negative balances that are close to 350 mmol for Na\(^+\) (6, 15, 23) and close to 300 mmol for K\(^+\) (7, 22). Although these subjects typically have normal value for plasma Na\(^+\) concentration ([Na\(^+\)]) they are modestly hypokalemic if no supplements of K\(^+\) are given (7).

The physiological response to a deficit of Na\(^+\) is to have a maximum renal conservation of Na\(^+\) and Cl\(^-\). Indeed, the rate of excretion of Na\(^+\) in our subjects was very small (3–8 mmol/day, Table 1) and typical of that found in other studies (6, 15, 23). Part of this renal response for maximal conservation of Na\(^+\) involves aldosterone. The well-established mechanism begins with extracellular fluid volume contraction, which leads to the release of renin and thereby an increase in the production of angiotensin II (reviewed in Ref. 14). This latter compound stimulates the zona glomerulosa of the adrenal cortex to release aldosterone (19). Aldosterone acts primarily on the principal cell of the CCD, and the response is activation of the epithelial Na\(^+\) channel in its luminal membrane (29). If Cl\(^-\) are reabsorbed along with Na\(^+\), this system will be absolutely beneficial for survival (electroneutral reabsorption for Na\(^+\); Fig. 2A). Alternatively, if Na\(^+\) were reabsorbed in an electrogenic fashion (i.e., without Cl\(^-\)), there could be continued 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

Table 2. Effect of an infusion of NaCl or NaHCO\(_3\) on excretion of K\(^+\)

<table>
<thead>
<tr>
<th>Urine</th>
<th>Before</th>
<th>NaCl</th>
<th>NaHCO(_3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>5.7 ± 0.1†</td>
<td>5.2 ± 0.1†</td>
<td>5.8 ± 0.2</td>
</tr>
<tr>
<td>Flow rate, ml/min</td>
<td>2.1 ± 0.2</td>
<td>1.4 ± 0.4</td>
<td>1.7 ± 0.3</td>
</tr>
<tr>
<td>Na(^+), mM</td>
<td>3 ± 0.1</td>
<td>20 ± 5*</td>
<td>25 ± 4*</td>
</tr>
<tr>
<td>Na(^+), mmol/h</td>
<td>0.4 ± 0.1</td>
<td>1.6 ± 0.4*</td>
<td>2.5 ± 0.4*</td>
</tr>
<tr>
<td>K(^+), mM</td>
<td>6 ± 2</td>
<td>25 ± 6</td>
<td>76 ± 12†</td>
</tr>
<tr>
<td>K(^+), mmol/h</td>
<td>0.8 ± 0.1</td>
<td>1.9 ± 0.3*</td>
<td>8.3 ± 2.2†</td>
</tr>
<tr>
<td>Cl(^-), mM</td>
<td>8 ± 1.3</td>
<td>10 ± 8*</td>
<td>66 ± 15*</td>
</tr>
<tr>
<td>Cl(^-), mmol/h</td>
<td>1.0 ± 0.2</td>
<td>4.9 ± 1.7*</td>
<td>6.7 ± 2.4*</td>
</tr>
<tr>
<td>TTKG, mmol/h</td>
<td>2 ± 1</td>
<td>6 ± 2*</td>
<td>19 ± 3†</td>
</tr>
</tbody>
</table>

Values are means ± SE for fasted subjects infused with NaCl (n = 4) and NaHCO\(_3\) (n = 5). For details, see METHODS. For ease of presentation, all values before infusion are presented as a single column (Before); for statistical analyses, values before and after the infusion of Na\(^+\) salts were compared by paired analysis. TTKG, transtubular K\(^+\) concentration gradient. * P < 0.05 for the effect of NaCl or NaHCO\(_3\); † P < 0.05 comparing NaHCO\(_3\) vs. NaCl.

Fig. 2. A: aldosterone and augmented reabsorption of NaCl. Adrenal gland is depicted by triangular structure. One secretagogue for release of aldosterone is angiotensin II. Angiotensin II, by stimulating the reabsorption of HCO\(_3\) in the proximal and distal convoluted tubules, diminishes delivery of HCO\(_3\) to the cortical collecting duct (CCD), and thereby a kaliuresis is not promoted. B: aldosterone and augmented secretion of K. Critical point here is that distal delivery of HCO\(_3\) augments K\(^+\) excretion if aldosterone leads to an "open" Na\(^+\) ion channel in luminal membrane of CCD. Because hyperkalemia depresses proximal reabsorption of HCO\(_3\), aldosterone would cause electrolytic reabsorption of Na\(^+\) in the CCD if HCO\(_3\) retards the reabsorption of Cl\(^-\) in this nephron segment.
rise (0.8 to 1.9 mmol/h) in the rate of excretion of K\(^+\). Hence, other mechanisms were probably operating to curtail the rate of excretion of K\(^+\).

When examining the excretion of K\(^+\) in normal subjects, we were struck by the fact that the presence of bicarbonaturia was strongly correlated with the rate of excretion of K\(^+\) provided that aldosterone was present (3, 25). In more detail, HCO\(_3\)\(^-\) led to a high [K\(^+\)] in the terminal CCD, whereas a rise in flow rate in the CCD was not a consistent finding. For example, the maximum value for the TTKG was close to 10 in HCO\(_3\)-free urine, whereas it was close to 20 when there was bicarbonaturia (3, 27). In the diurnal period, the time of urine, whereas it was near 1200 h, the time of the alkaline tide (25). Moreover, giving 9-α-fludrocortisone in the evening did not lead to a high TTKG, unless the subjects consumed NaHCO\(_3\) or took a carbonic anhydrase inhibitor type of diuretic (acetazolamide) (25). Accordingly, we wished to evaluate whether delivery of HCO\(_3\) to the distal nephron in prolonged fasting could make the endogenous aldosterone increase the kaliuresis by raising the [K\(^+\)] of CCD.

When NaHCO\(_3\) was infused, the rate of excretion of Na\(^+\) was not statistically significantly different from that of the NaCl series, but there was now a high kaliuresis (1.9 vs. 8.3 mmol/h with NaCl and NaHCO\(_3\) infusions, respectively, Table 2). Nevertheless, frank bicarbonaturia was not seen (urine, pH 5.8), and this probably reflects the continuing presence of acidemia, which stimulated the H\(^+\)-adenosinetriphosphatase (H\(^+\)-ATPase) units downstream in the medullary collecting duct, a nephron system with a high density of these proton pumps (reviewed in Ref. 17).

Integrative physiology. It would be desirable in prolonged total fasting to avoid a kaliuresis by having aldosterone promote the electroneutral reabsorption of NaCl. This was accomplished in small part by having a low distal delivery of Na\(^+\) and the previously suggested effect of a deficit of K\(^+\), which leads to electroneutral reabsorption of NaCl in the CCD (27). We speculate that another and very important component of this picture is to have a low distal delivery of HCO\(_3\). Components of this picture are the effects of a mild metabolic acidosis, which both lowers the filtered load of HCO\(_3\) and stimulates the reabsorption of HCO\(_3\) (reviewed in Ref. 1). Having this lower plasma HCO\(_3\) concentration ([HCO\(_3\)]) will ensure a subnormal plasma level of HCO\(_3\) even if HCl is secreted by the stomach (epithelial phase of gastric H\(^+\) secretion) during a fast; this can cause close to a 5 mM rise in the plasma [HCO\(_3\)] (reviewed in Ref. 20). Finally, having angiotensin II as the stimulator of aldosterone release helps avoid distal delivery of HCO\(_3\), because angiotensin II stimulates proximal (5) and distal (16) reabsorption of HCO\(_3\) (Fig. 2A). In fact, Stonebaugh and Schloeder (26) demonstrated a markedly enhanced capacity for proximal reabsorption of HCO\(_3\) in chronic fasting. In addition, having a mild degree of K\(^+\) depletion could augment the reabsorption of HCO\(_3\) in the proximal convoluted tubule (PCT) even further (5). Whatever the mechanism, having both a K\(^+\) deficit and the presence of angiotensin II reduce the distal delivery of HCO\(_3\) could explain why aldosterone could support electroneutral NaCl retention while avoiding a kaliuresis during chronic fasting (Fig. 2A).

In the prolonged fasted state, distal delivery of Na\(^+\) is accompanied by β-HB\(^-\) anions, and reabsorption of Na\(^+\) would be expected to augment a kaliuresis. We envision two additional mechanisms operating now. First, to the extent K\(^+\) 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 NH\(_3\). The net result would be the excretion of NH\(_4\)\(^+\) 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 NH\(_4\), permits the eventual urine to be Na\(^+\) and K\(^+\) poor, having NH\(_4\) plus β-HB\(^-\) as its principal constituents.

Perspectives for Disease States

The results of this study underscore the possible importance of HCO\(_3\) 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 HCO\(_3\) 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 HCO\(_3\) in the CCD as a factor that can cause a high rate of excretion of K\(^+\). This “cross-talk” between the proximal and distal nephron in which HCO\(_3\) reabsorption 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 HCO\(_3\) 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 HCO\(_3\) (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 HCO\(_3\) to the distal nephron (Fig. 2B).

We are extremely grateful to Dr. Harald Sonnenberg for very helpful discussions and suggestions during the preparation of this manuscript. We are also indebted to Stella Tang and Eleanor Singer.
for expert technical assistance and Jolly Mangat for expert secretarial assistance.

This work was supported by Grant no. 5623 from the Medical Research Council of Canada.

Address for reprint requests: M. L. Halperin, Division of Nephrology, St. Michael’s Hospital, 38 Shuter St., Toronto, Ontario, Canada M5B 1A6.

Received 18 February 1997; accepted in final form 16 July 1997.

REFERENCES


