

Effect of Potassium Deficiency on the Reabsorption of Bicarbonate in the Proximal Tubule of the Rat Kidney *

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Potassium deficiency accelerates the secretion of H^+ ions by the kidney; in consequence the net excretion of acid (ammonia and titratable acid-bicarbonate) into the urine and the capacity to reabsorb filtered HCO_3^- are increased (1-7). Although the precise mechanism involved has not been identified, Berliner, Kennedy, and Orloff (8), on the basis of the demonstrated reciprocal relationship between H^+ and K^+ secretion, proposed that these ions compete for a common secretory pathway in the distal nephron. Consequently, K^+ depletion, by lowering the concentration of K^+ at the competitive secretory site, would facilitate H^+ secretion and increase the capacity of the distal tubule to reabsorb HCO_3^- (9).

Certain observations, however, are difficult to reconcile with the theory of competitive inhibition. Rector, Buttram, and Seldin (10) found that the inhibitory effects of K^+ administration on HCO_3^- reabsorption could not be overcome by raising intracellular H^+ concentration by respiratory acidosis. This observation, which is not consistent with the theory of competitive inhibition between H^+ and K^+ , suggests that K^+ might reduce H^+ secretion by either noncompetitive inhibition or by alkalizing the renal tubular cells. If alterations of intracellular K^+ were capable of changing the pH of renal tubular cells, two consequences might follow: first, the inverse relationship between H^+ and

K^+ secretion could be the result of reciprocal changes in the intracellular concentrations of these two ions in the distal nephron, rather than competition for a common secretory pathway; second, by altering the pH of proximal tubular cells, changes in intracellular K^+ might influence H^+ secretion even though this area of the nephron is not a site of K^+ secretion.

The present experiments in rats were designed to investigate whether K^+ deficiency accelerates H^+ secretion in the distal nephron only, where K^+ is known to be secreted (11), or also in the proximal tubule, where we (12), as well as others (11, 13), have demonstrated that K^+ is reabsorbed but not secreted. If the HCO_3^- reabsorptive capacity of the distal, but not the proximal tubule, were increased, the concentration of HCO_3^- in plasma and in glomerular filtrate would be maintained at a concentration far above the proximal reabsorptive capacity. Consequently, as $NaCl$ and H_2O were reabsorbed in the proximal tubule, the concentration of the unreabsorbed bicarbonate would rise, and proximal tubular fluid would become more alkaline than blood. In contrast, if the HCO_3^- reabsorptive capacity of the proximal tubule were increased either alone or with a proportionate increase in distal reabsorptive capacity, the concentration of HCO_3^- in plasma and glomerular filtrate would be maintained at a level near, but not exceeding, the proximal reabsorptive capacity. Therefore, the relative rates of $NaHCO_3$, $NaCl$, and H_2O reabsorption would be similar to those of normal rats, and the concentration of HCO_3^- in proximal fluid should fall below that in plasma, as it does normally. These two possibilities were examined by comparing the concentration of HCO_3^- in proximal tubular fluid in K^+ -deficient, alkalotic rats with that in normal rats and in rats made acutely alkalotic by an infusion of $NaHCO_3$.

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TABLE I
Treatment and plasma composition of the experimental groups

Group	No. of rats	Treatment	Plasma*			
			[K]	pH	CO ₂ content	Pco ₂
			mEq/L		mEq/L	mm Hg
I Normal	10	None	4.5 ±0.2	7.39 ±0.04	26.6 ±2.5	40 ±2
II NaHCO ₃	11	0.15 M NaHCO ₃ infusion for 2 hours	3.8 ±0.2	7.57 ±0.05	39.8 ±3.5	45 ±3
III Potassium-deficient	17	SEDD† + Na ₂ SO ₄ + DOCA‡ for 7 days	1.7 ±0.3	7.55 ±0.03	38.3 ±2.3	44 ±3

* Mean values ± SD.

† Standard electrolyte-deficient diet.

‡ Desoxycorticosterone acetate.

Methods

Microperfusion studies were performed on three groups of male Sprague-Dawley rats. Groups I and II were fed rat pellet diet and tap water. Group I received no further treatment. Group II rats were infused with 0.15 M NaHCO₃ at the rate of 0.1 ml per minute for 2 hours before collecting any samples of tubular fluid; the infusion was continued during the collection periods. This 2-hour infusion period permitted the blood pH and plasma HCO₃⁻ concentrations to attain reasonably stable values. Group III rats were made K⁺ deficient by feeding them a standard electrolyte-deficient diet containing 1 mM Na₂SO₄ daily and injecting 5 mg desoxycorticosterone acetate (DOCA) in oil intramuscularly daily for 7 days. All animals were fasted for 18 hours before the experiment to permit complete excretion of the dietary Na₂SO₄; the last injection of DOCA was 24 hours before the microperfusion study.

The rats were anesthetized with sodium pentobarbital and prepared for microperfusion as previously described (12), except that the left kidney was exposed through a flank incision. Samples of tubular fluid were aspirated into quinhydrone microelectrodes for the measurement of pH. The site of collection was determined by microdissection after injecting the tubule with latex. At the end of the experiment blood was collected from the abdominal aorta for measurement of pH, CO₂ content, and K⁺.

The concentration of HCO₃⁻ in tubular fluid was estimated by the following technique. The pH of tubular fluid was measured with quinhydrone microelectrodes prepared as described by Pierce and Montgomery (14). Immediately before use the microelectrodes were filled with mineral oil that had been equilibrated with 5% CO₂. Samples aspirated into the tip of the pipette-electrode quickly equilibrated to the same Pco₂ as the mineral oil. The electrode tips were sealed by dipping them into egg albumin. The voltage difference between the quinhy-

drone electrode and a saturated KCl-calomel reference electrode was measured at 37° C, with a General-Radio electrometer. The pH was calculated from the formula given by Pierce and Montgomery (14). Since the pH of these samples was measured at a constant Pco₂ of approximately 40 mm Hg in the electrode rather than at the actual Pco₂ of plasma, the measured value was not the true intratubular pH, but represented instead a measure of the HCO₃⁻ concentration in the tubular fluid (15). The concentration of HCO₃⁻ in tubular fluid was calculated from the quinhydrone pH and the known Pco₂ of the mineral oil in the electrode by the Henderson-Hasselbalch equation.

In an additional series of experiments in four rats made alkalotic by NaHCO₃ infusion, the effect of acute reductions in glomerular filtration rate (GFR) on proximal acidification was investigated. Proximal HCO₃⁻ concentration was measured in the same tubule before and after constricting the aorta above the renal arteries. A silk ligature was passed around the aorta and threaded through a small glass capillary tube; when the ligature protruding from the capillary was tied around a small glass rod and twisted, the aorta was gently pulled against

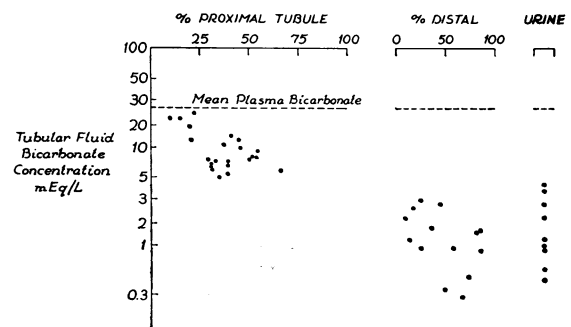


FIG. 1. CONCENTRATION OF BICARBONATE IN TUBULAR FLUID AND URINE IN NORMAL RATS.

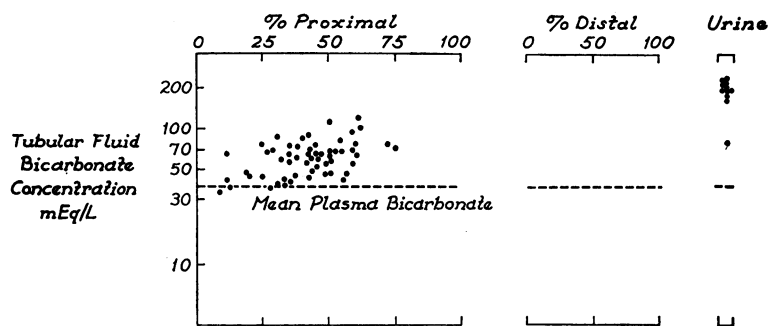


FIG. 2. CONCENTRATION OF BICARBONATE IN TUBULAR FLUID AND URINE IN RATS INFUSED WITH 0.15 M NaHCO_3 FOR 2 HOURS.

the glass tube. The degree of constriction was monitored by measuring the femoral blood pressure through a small polyethylene cannula with a Satham strain gauge and a Sanborn Twin-Viso recorder. Preliminary experiments established that reducing femoral blood pressure to approximately 60 mm Hg lowered GFR by 50 to 65%. During the control periods 0.15 M NaHCO_3 was infused at a rate of 0.1 ml per minute and inulin at a rate of 1 mg per minute; after aortic constriction the infusion rates were reduced to 0.05 ml per minute for NaHCO_3 and 0.5 mg per minute for inulin. Before and after aortic constriction blood was sampled from the jugular vein, and timed urine samples were collected from a bladder catheter for the measurement of inulin, pH, and CO_2 content.

Blood and urine pH were measured in a Beckman anaerobic glass electrode at 37°C with a Vibron pH meter. The CO_2 contents were measured by the Natelson microgasometer. Serum K^+ was determined by an internal standard flame photometer. Inulin in blood and urine was measured by the method of Walser, Davidson, and Orloff (16).

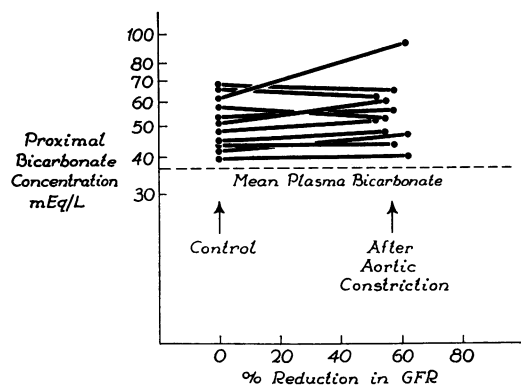


FIG. 3. EFFECT OF ACUTE REDUCTIONS IN GLOMERULAR FILTRATION RATE (GFR) ON PROXIMAL BICARBONATE CONCENTRATION IN RATS INFUSED WITH NaHCO_3 . The bicarbonate concentrations from the same tubule before and after aortic constriction are connected by the solid lines. Only measurements from the middle third of the tubule are shown.

Results

The plasma composition of the three groups is shown in Table I. At the end of the micropuncture experiments the rats in group 1 had values for blood pH, plasma Pco_2 content, and K^+ concentration that were very similar to those obtained in rats in our laboratory not subjected to the micropuncture procedures. In group II the infusion of 0.15 M NaHCO_3 for 2 hours before and during the experiment resulted in a severe metabolic alkalosis: blood pH of 7.57 ± 0.05 (SD), plasma CO_2 content of 39.8 ± 3.5 mmoles per L, and plasma Pco_2 of 45 ± 3 mm Hg. As expected, acute metabolic alkalosis caused a slight fall in the concentration of plasma K^+ to 3.8 ± 0.2 mEq per L. In group III the severe hypokalemia of 1.7 ± 0.3 mEq per L was associated with a marked metabolic alkalosis, with an acid-base composition almost identical to that in group II: blood pH, 7.55 ± 0.03 ; plasma CO_2 content, 38.3 ± 2.3 mmoles per L; and plasma Pco_2 , 44 ± 3 mm Hg.

The concentration of HCO_3^- in tubular fluid and

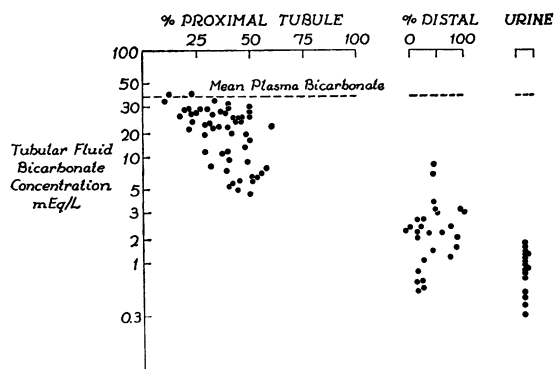


FIG. 4. CONCENTRATION OF BICARBONATE IN TUBULAR FLUID AND URINE IN POTASSIUM-DEFICIENT RATS.

urine in the normal rats (group I) is shown in Figure 1. The concentration of HCO_3^- in proximal tubular fluid progressively fell, reaching values as low as 5 mEq per L. The average HCO_3^- concentration in the middle third of the proximal tubule was 7.5 ± 2.2 mEq per L. These results are similar to those reported by Gottschalk, Lassiter, and Mylle (17).

In the rats made acutely alkalotic by the infusion of NaHCO_3 (group II), the concentration of HCO_3^- in proximal tubular fluid rose to a level significantly higher than that in plasma (Figure 2). In the middle third of the proximal tubule the HCO_3^- concentration in every sample was higher than in plasma, averaging 57.8 ± 13.5 mEq per L.

Acutely lowering GFR had no effect on proximal bicarbonate concentration in the rats given NaHCO_3 (Figure 3). Aortic constriction reduced the GFR by 50 to 60%. Blood pH, CO_2 content, and PCO_2 were the same before and after aortic constriction. Despite the marked reduction in GFR the concentration of HCO_3^- in individual proximal tubules was essentially the same after aortic constriction as before.

In contrast to results obtained in the acutely alkalotic rats, the concentration of HCO_3^- in proximal tubular fluid in the rats with hypokalemic alkalosis was lower than in plasma (Figure 4). In the middle third of the proximal tubule the HCO_3^- concentration of every sample was lower than that of plasma, falling from a mean concentration of 37.2 ± 2.3 mEq per L in plasma to a mean concentration of 17.8 ± 7.5 mEq per L in

tubular fluid (Table II). The fluid entering the distal tubule contained almost no HCO_3^- , indicating that virtually all the filtered HCO_3^- had been reabsorbed in more proximal segments of the nephron.

Discussion

In the normal rat filtered HCO_3^- is reabsorbed in the proximal convoluted tubule at a rate relatively faster than the isosmotic reabsorption of water; consequently the concentration of HCO_3^- in the fluid issuing from the proximal tubule is less than that of plasma. In contrast, during acute alkalosis the concentration of HCO_3^- in plasma and glomerular filtrate exceeds the proximal reabsorptive capacity, so that as water is reabsorbed isosmotically (secondary to NaCl reabsorption), the unreabsorbed HCO_3^- is concentrated to a level above that in plasma.

These results clearly indicate that the concentration of HCO_3^- in the fluid leaving the proximal tubule is determined not only by the rate of HCO_3^- reabsorption (R_{NaHCO_3}), but also by the rate of water reabsorption and the concentration of HCO_3^- in glomerular filtrate ($[\text{HCO}_3^-]_{\text{GF}}$). Since NaCl and NaHCO_3 are the principal osmotically active solutes whose removal promotes the isosmotic reabsorption of water, the directional changes in the HCO_3^- concentration in tubular fluid ($[\text{HCO}_3^-]_{\text{TF}}$) can best be expressed in terms of the relative rates of NaCl and NaHCO_3 reabsorption. For purposes of this discussion, the term relative rate is defined as the rate of reabsorption of a particular sodium salt divided by its concentration in glomerular filtrate. The relative rates for NaCl and NaHCO_3 reabsorption are $R_{\text{NaCl}}/[\text{NaCl}]_{\text{GF}}$ and $R_{\text{NaHCO}_3}/[\text{NaHCO}_3]_{\text{GF}}$, respectively.

If the relative rates of NaCl and NaHCO_3 reabsorption were equal, $[\text{Cl}^-]_{\text{TF}}$ and $[\text{HCO}_3^-]_{\text{TF}}$ would not change, remaining equal to their concentrations in plasma and glomerular filtrate. If, on the other hand, the relative rate for NaHCO_3 were greater than that for NaCl , $[\text{HCO}_3^-]_{\text{TF}}$ would fall below and $[\text{Cl}^-]_{\text{TF}}$ would rise above their respective concentrations in plasma, whereas if the relative rate for NaHCO_3 were less than that for NaCl , then $[\text{HCO}_3^-]_{\text{TF}}$ would rise and $[\text{Cl}^-]_{\text{TF}}$ would fall.

TABLE II
Effect of potassium deficiency on acidification of proximal tubular fluid

Group	Plasma		Proximal tubule*	
	pH	$[\text{HCO}_3^-]$ mEq/L	pH†	$[\text{HCO}_3^-]$ mEq/L
I Normal	7.39 ± 0.04	25.4 ± 2.5	6.88 ± 0.12	7.5 ± 2.2
II NaHCO_3	7.57 ± 0.05	38.5 ± 3.5	7.75 ± 0.15	57.8 ± 13.5
III Potassium-deficient	7.55 ± 0.03	37.2 ± 2.3	7.15 ± 0.27	17.8 ± 7.5

* Mean \pm SD in middle third of proximal tubule.

† Quinhydrone pH of sample equilibrated with 5% CO_2 .

Changes in $[\text{NaHCO}_3]_{\text{GF}}$ and $[\text{NaCl}]_{\text{GF}}$ would influence the directional change in $[\text{HCO}_3^-]_{\text{TF}}$ only if R_{NaHCO_3} and R_{NaCl} were not linearly related to $[\text{NaHCO}_3]_{\text{GF}}$ and $[\text{NaCl}]_{\text{GF}}$. If R_{NaHCO_3} and R_{NaCl} were both linearly related to $[\text{NaHCO}_3]_{\text{GF}}$ and $[\text{NaCl}]_{\text{GF}}$, respectively, then the relationship between $R_{\text{NaHCO}_3}/[\text{NaHCO}_3]_{\text{GF}}$ and $R_{\text{NaCl}}/[\text{NaCl}]_{\text{GF}}$ obviously would not change as the composition of the glomerular filtrate was altered. From currently available micropuncture data R_{NaCl} does in fact appear to be a linear function of $[\text{NaCl}]_{\text{GF}}$. Giebisch, Klose, and Windhager (18) and Lassiter, Gottschalk, and Mylle (19) found that raising $[\text{NaCl}]_{\text{GF}}$ by the infusion of 5% saline resulted in proportionate increases in R_{NaCl} . Clearance studies, however, clearly reveal that the over-all tubular reabsorption of NaHCO_3 does not increase linearly as $[\text{NaHCO}_3]_{\text{GF}}$ is elevated and, instead, exhibits a reabsorptive maximum (20). The present studies also indicate that proximal R_{NaHCO_3} is a nonlinear function of $[\text{NaHCO}_3]_{\text{GF}}$; therefore, changes in $[\text{NaHCO}_3]_{\text{GF}}$ do alter the directional changes in proximal $[\text{HCO}_3^-]_{\text{TF}}$.

In the normal rats $[\text{HCO}_3^-]_{\text{TF}}$ in proximal tubular fluid fell below that in plasma to a level of about 7.5 mEq per L. Thus, in these normal rats, the relative rate of NaHCO_3 reabsorption exceeded that for NaCl . As $[\text{NaHCO}_3]_{\text{GF}}$ was acutely elevated by the infusion of NaHCO_3 , the directional change in $[\text{HCO}_3^-]_{\text{TF}}$ reversed, and $[\text{HCO}_3^-]_{\text{TF}}$ rose to approximately 58 mEq per L or roughly 1.5 times the concentration in plasma and glomerular filtrate. In the acutely alkalotic rats, therefore, the relative rate of NaHCO_3 reabsorption was less than that for NaCl . This clearly indicates that R_{NaHCO_3} did not increase in linear fashion as $[\text{NaHCO}_3]_{\text{GF}}$ was raised, but instead exhibited saturation kinetics.

Potassium deficiency obviously altered the response of proximal R_{NaHCO_3} to increased $[\text{NaHCO}_3]_{\text{GF}}$. At the same high $[\text{NaHCO}_3]_{\text{GF}}$ as was present in the rats given NaHCO_3 (Table II), $[\text{HCO}_3^-]_{\text{TF}}$ fell below that in plasma and glomerular filtrate. The relative rate of NaHCO_3 reabsorption, therefore, exceeded that for NaCl despite the high $[\text{NaHCO}_3]_{\text{GF}}$. Since the $[\text{NaHCO}_3]_{\text{GF}}$ and $[\text{NaCl}]_{\text{GF}}$ were approximately the same in the K^+ -deficient rats and the rats infused with NaHCO_3 , the reabsorptive ratio $R_{\text{NaHCO}_3}/$

R_{NaCl} must have been greater in the K^+ -deficient than in the acutely alkalotic rats.

Several factors might have been responsible for the relative increase in proximal NaHCO_3 reabsorption in the K^+ -deficient rats. Holliday, Eagan, and Wirth (21) have reported that K^+ deficiency depresses the GFR in rats. It is conceivable, therefore, that the increased proximal acidification in the K^+ -deficient rats might have been the consequence of a fall in GFR. On an *a priori* basis, however, it is difficult to predict the effect of reduced GFR on proximal acidification, since clearance studies on intact animals have demonstrated that the reabsorption of both NaCl (22) and NaHCO_3 (20) tend to decrease as GFR falls. Such studies, however, do not indicate the relative contributions of the proximal and distal nephron, nor do they establish the relative magnitudes in the reduction in NaCl and NaHCO_3 reabsorption as GFR is decreased. For a reduction in GFR to account for the proximal acidification in the K^+ -deficient rats, it would be necessary that R_{NaCl} be depressed to a greater extent than R_{NaHCO_3} , so that the reabsorptive ratio $R_{\text{NaHCO}_3}/R_{\text{NaCl}}$ is increased. Therefore, to elucidate the role of GFR, if any, in proximal acidification, GFR was reduced 50 to 60% by constricting the aorta in rats made acutely alkalotic by an infusion of NaHCO_3 (Figure 3). Despite these marked reductions in GFR the tubular fluid remained alkaline. This must mean that a reduction in GFR depresses R_{NaCl} and R_{NaHCO_3} to the same extent and therefore cannot lower the concentration of HCO_3^- in proximal tubular fluid. It is concluded that acidification of proximal tubular fluid in K^+ deficiency cannot be due to a fall in GFR.

Since variations in plasma CO_2 tension are known to influence the capacity to reabsorb filtered HCO_3^- , the mild hypercapnia (Table I) observed in the hypokalemic rats might account in part for the relative increase in R_{NaHCO_3} . However, this cannot account for the relatively greater R_{NaHCO_3} in the hypokalemic rats, since the plasma CO_2 tensions were identical in the rats made alkalotic with NaHCO_3 and the rats with hypokalemic alkalosis (Table I). These experiments indicate, therefore, that K^+ deficiency per se is in some way responsible for the increased R_{NaHCO_3} relative to R_{NaCl} in the proximal convoluted tubule.

Potassium deficiency might augment the rate

of NaHCO_3 relative to NaCl reabsorption in one of several ways. One possibility is that, rather than a primary increase in the rate of NaHCO_3 reabsorption, the rate of NaCl reabsorption is decreased. The reabsorption of NaCl is thought to be mediated by an ion exchange pump at the peritubular surface of the cell that pumps Na^+ out of K^+ into the cell, with Cl^- moving passively from lumen to blood (23). It is conceivable, therefore, that a decreased concentration of K^+ in blood would decrease the rate of Na^+ transport out of the cell and consequently decrease NaCl reabsorption. Giebisch and Windhager (24) have reported that lowering the concentration of K^+ in peritubular fluid decreased the rate of proximal Na^+ reabsorption in *Necturus*. Bank and Aynedjian (25), however, have recently found that the percentage of glomerular filtrate reabsorbed in the proximal tubules of K^+ -deficient rats is increased. Unfortunately, this study, while suggestive, is not conclusive; the GFR was reduced in the animals studied by Bank and Aynedjian, so that their results do not necessarily exclude a decrease in the rate of NaCl reabsorption. More important, however, is the fact that K^+ deficiency not only augments proximal acidification but also increases the absolute rate of NaHCO_3 reabsorption (3, 7). Therefore, while a primary decrease in R_{NaCl} could account for the fall in proximal $[\text{HCO}_3^-]_{\text{TF}}$, it could not account for the greatly augmented HCO_3^- reabsorptive capacity associated with K^+ depletion.

It is much more probable, therefore, that the effects of K^+ deficiency on proximal acidification are a reflection of an increase in the rate of H^+ secretion. Since it has previously been shown that K^+ is reabsorbed (11–13), but not secreted in the proximal tubule, this effect cannot be due to competition between H^+ and K^+ at a common secretory site on the luminal surface of the cell. Although it is possible that K^+ inhibits H^+ secretion by some noncompetitive process, it is more likely that K^+ influences H^+ secretion by changing the pH of renal tubular cells. Anderson and Mudge (26) demonstrated that in kidney slices HCO_3^- moves into or out of the cells together with K^+ . Thus, K^+ deficiency might decrease the steady-state concentration of HCO_3^- in the tubular cells so that at any given Pco_2 there would be a lower intracellular pH. As a result of this in-

crease in intracellular H^+ concentration, the secretion of H^+ would be stimulated, thereby augmenting the rate of NaHCO_3 reabsorption.

Potassium deficiency might lower the steady-state concentration of HCO_3^- in the tubular cells by accelerating the rate of removal of HCO_3^- ions. According to current concepts, the HCO_3^- generated in the cell by the combination of H_2CO_3 formation and H^+ secretion moves out of the cell along electrochemical gradients. An important factor in HCO_3^- removal, therefore, would be the potential difference across the peritubular membrane. We have found that the resting membrane potential of skeletal muscle increases from a mean value of 89 ± 1 (SD) mv in normal rats to 97 ± 3 mv in K^+ -deficient rats (27). If similar changes in potential difference occurred across the peritubular surface of the renal epithelial cells, the electrical force driving HCO_3^- out of the cell would be commensurately increased and could therefore result in a decreased steady-state intracellular concentration of HCO_3^- .

Although it is tempting to speculate that K^+ deficiency affects the proximal and distal tubules in a similar fashion, these experiments cast no light on the relation between K^+ and H^+ secretion in the distal nephron. The conclusion that K^+ deficiency augments H^+ secretion in the proximal tubule by lowering intracellular pH cannot be extrapolated to the distal nephron where competition between K^+ and H^+ for a common secretory pathway may well be operative.

Summary

Proximal acidification was investigated by measuring HCO_3^- concentration in tubular fluid in normal rats, rats made acutely alkalotic by an infusion of NaHCO_3 , and rats with hypokalemic alkalosis. The concentration of HCO_3^- in the proximal tubule of normal rats fell to an average value of 7.5 mEq per L, a value significantly lower than that of plasma. Despite a comparable degree of metabolic alkalosis in the rats given NaHCO_3 and the hypokalemic rats, every sample of proximal fluid in the rats given NaHCO_3 had a higher HCO_3^- concentration than plasma, whereas every proximal sample in the hypokalemic rats had a lower HCO_3^- concentration than plasma. This clearly indicates that K^+ deficiency increases

the capacity of the proximal convoluted tubule to reabsorb filtered HCO_3^- . Since K^+ is not secreted in the proximal tubule, the effect of K^+ deficiency cannot be due to decreased competitive inhibition at a common H^+ - K^+ secretory pathway. It is postulated that K^+ depletion stimulates proximal H^+ secretion by producing an intracellular acidosis.

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