Renal

HYPERKALEMIC DISTAL RENAL TUBULAR ACIDOSIS

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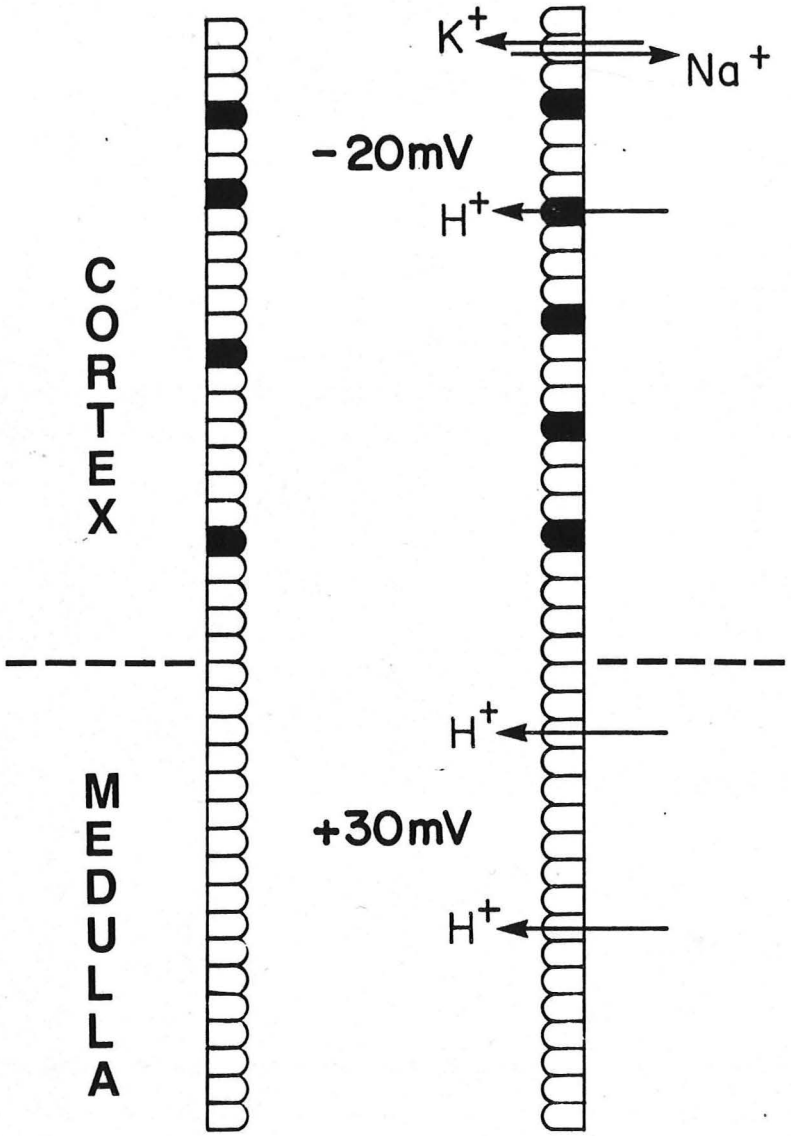
June 6, 1985



HYPERKALEMIC DISTAL RTA

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INTRODUCTION

Hyperkalemic distal renal tubular acidosis (HDRTA), also known as type IV RTA, is a common disorder in patients with mild to moderate chronic renal insufficiency particularly when tubulointerstitial nephritis is present. It is now recognized as the most prevalent type of renal tubular acidosis. In contradistinction to classical distal RTA (Type I) associated with hypokalemia and proximal RTA (Type II) associated with normo- or hypokalemia, Type IV RTA features hyperkalemia as a predominant finding. This review will concentrate specifically on the etiology, pathophysiology, clinical spectrum and treatment of HDRTA.

I. History

Hyperkalemic hyperchloremic distal renal tubular acidosis encompasses a broad spectrum of potential defects of renal acidification, the nature of which evolved from observations on the clinical syndrome of hyperkalemia associated with hypoaldosteronism.

In 1957, Hudson, Chobanian, and Relman reported a syndrome of hyperkalemia-induced Stokes-Adams attacks and selective hypomineralocorticoidism in an elderly man (1). Hyperkalemia and hyponatremia in their patient were corrected by a high NaCl intake combined with intramuscular administration of the synthetic mineralocorticoid hormone deoxycorticosterone acetate. Renal function and cortisol excretion rates were normal, but both baseline and stimulated aldosterone excretion rates were markedly reduced. Thus, these investigators described the first case of isolated hypoaldosteronism in man. In the late 1950's and early 1960's, several case reports of isolated hypoaldosteronism similar to the one described by Hudson et al. appeared in the literature (2-7). Up until this time, hyporeninemic states resulting in

impaired aldosterone secretion had not been documented. In 1972, Perez, Siegel, and Schreiner reported hyperkalemia in association with hyporenenemia and hypoaldosteronism in a 59 year-old diabetic woman with chronic renal insufficiency (8). Simultaneously, Schambelan, Stockigt, and Biglieri reported six patients with unexplained hyperkalemia, moderately impaired renal function, reduced urinary aldosterone metabolite excretion rates, and subnormal baseline as well as stimulated (upright posture, sodium depletion) plasma renin activity and concentration values (9). These investigators suggested that the observed renin deficiency perhaps represented an acquired abnormality of the juxtaglomerular apparatus. Subsequently, studies of patients with hypoaldosteronism and impaired renin secretion began to focus on the origin of hyperchloremic metabolic acidosis, a frequent additional finding in hypoaldosteronism. Thus, in 1976, Szylman et al. demonstrated the role of hyperkalemia- induced suppression of renal ammoniagenesis as an important pathogenetic factor in the renal acidification defect (10). In 1977, Sebastian and co-workers established the role of mineralocorticoid deficiency as an additional independent factor in the pathogenesis of hyperchloremic metabolic acidosis (11). In 1980, Schambelan et al. studied patients with mild to moderate chronic renal insufficiency of diverse pathophysiological origin in whom hyperkalemia and hyperchloremic metabolic acidosis were observed (12). They documented four important observations: 1) hypoaldosteronism occurs commonly in hyperkalemic patients with chronic renal insufficiency; 2) some patients with hyperkalemic, hyperchloremic metabolic acidosis and chronic renal insufficiency are not hypoaldosteronemic; 3) when present hypoaldosteronism may occur in the absence of hyporeninemia in some patients; and 4) the pathogenesis of renal hyperkalemia in some patients with the syndrome may be due to factors independent of hypoaldosteronism.

It is now well recognized that chronic hyperkalemia, hyperchloremic metabolic acidosis may be associated with primary defects in renal tubular hydrogen ion and potassium transport independent of aldosterone levels in individuals with normal and impaired renal function (13, 14).

II. Definition

Hyperkalemic distal renal tubular acidosis (HDRTA) is a syndrome in which impaired renal excretion of potassium and hydrogen ions, owing to deranged distal nephron ion transport, results in hyperkalemia and hyperchloremic metabolic acidosis. The syndrome occurs most often in association with mild to moderate renal insufficiency; however, the magnitude of hyperkalemia and acidosis are disproportionately severe for the observed degree of renal insufficiency.

III. Distinction of HDRTA (or Type IV RTA) from Classical Distal RTA (or Type I RTA)

HDRTA or Type IV RTA can be distinguished from Type I RTA on the basis of several important characteristics. First and foremost, patients with Type IV RTA are distinguished from patients with Type I RTA on the basis of plasma potassium concentration which is abnormally high in the former and abnormally low in the latter. Second, in Type IV RTA mild to moderate chronic renal insufficiency is almost always present whereas in Type I RTA renal function is normal or only mildly impaired. Third, in most cases of Type IV RTA the urine pH measured during spontaneous acidosis is appropriately low (i.e., <5.5), whereas urine pH during spontaneous (or induced) acidosis in Type I RTA fails to decrease appropriately (i.e., >5.5, often in the 6.0-6.5 range). Fourth, metabolic acidosis in Type IV is mild with plasma bicarbonate concentration

rarely below 15 mEq/L, but in Type I RTA acidosis is often severe with plasma bicarbonate concentrations below 15 mEq/L.

It should also be remembered that Type IV RTA is a much more common form of RTA than Type I and is therefore more likely to be encountered.

IV. Classification of HDRTA

Hyperkalemic distal RTA is classified on the basis of an association with or independence from aldosterone deficiency as shown in Table 1. It should be noted that in most instances this disorder is associated with some form of chronic renal insufficiency. Furthermore, whatever the underlying etiology the findings of hyperkalemia and metabolic acidosis can be accounted for on the basis of deranged ion transport in the distal nephron.

V. Normal Potassium and Acid-Base Physiology

Whole Body Potassium Homeostasis

Potassium balance is maintained by renal excretory mechanisms under normal circumstances. As shown in Figure 1 under steady-state conditions, 90-95% of daily dietary potassium load is excreted in the urine. Gastrointestinal excretion accounts for only 5-10% of this load when renal function is normal but can adaptively increase if renal function becomes impaired (up to 30-40% of dietary load). Total body potassium amounts to about 3500 mEq most of which (about 98%) is confined to the intracellular compartment. The remaining 2% is, of course, located in the extracellular fluid at a concentration of approximately 4.0 mEq/L.

TABLE 1

CLASSIFICATION OF HYPERKALEMIC DISTAL RTA

A. Associated with Aldosterone Deficiency
   1. Addison's Disease
   2. Bilateral Adrenalectomy
   3. Adrenal Zona Glomerulosa Enzyme Defects
      a. Congenital
         1) Corticosterone Methyl Oxidase I & II Deficiencies
         2) 21-Hydroxylase Deficiency
      b. Acquired
         1) Corticosterone-O-Methyl Oxidase Deficiency
   4. Hyporeninemia
      a. Associated with Chronic Renal Insufficiency
      b. Secondary to Drugs
         1) Non-Steroidal Anti-Inflammatory Agents
         2) β-Blockers
   5. Chronic Heparin Therapy
   6. Combined selective aldosterone deficiency and tubular defect

B. Not Associated with Aldosterone Deficiency
   1. Chronic Renal Insufficiency
      a. Tubulointerstitial Nephritis
         1) Diabetes Mellitus
         2) SS Nephropathy
         3) SLE Nephritis
         4) Transplant Rejection
         5) Idiopathic
         6) Sjögren's
         7) Obstructive Uropathy
   2. Pseudohypoaldosteronism Type I
   3. Pseudohypoaldosteronism Type II
   4. Medications
      a. Amiloride
      b. Lithium Carbonate
      c. Spironolactone
      d. Triamterene

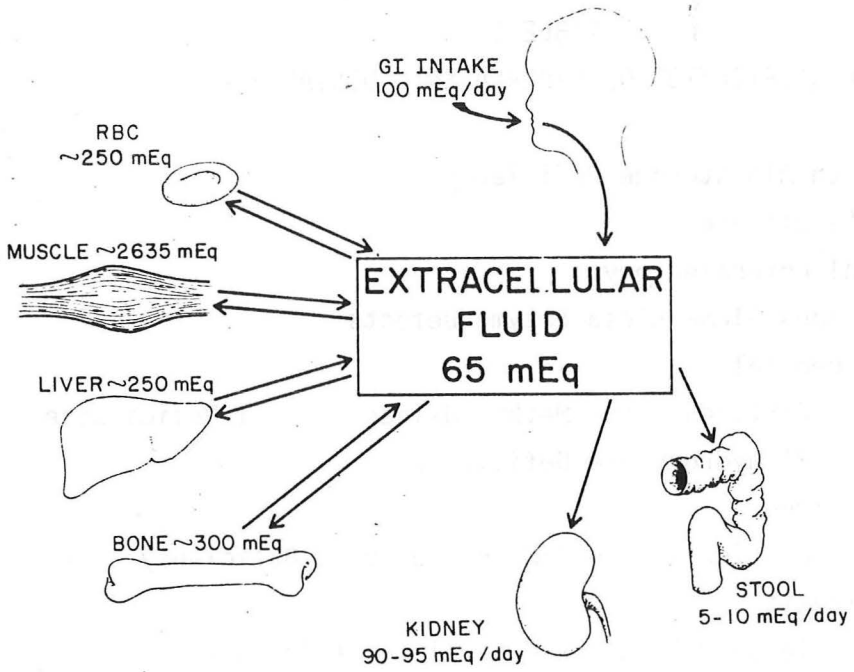


FIG. 1. Schematic representation of total body potassium distribution and the maintenance of potassium homeostasis in healthy subjects. See text for a detailed discussion. From ref. 53

Overall Response to Alterations in Potassium Intake

Plasma potassium concentration is regulated within a narrow range by both renal and extrarenal mechanisms. A number of hormonal and neural mechanisms interact to achieve this fine balance such that plasma K^+ varies by only a fraction of a milliequivalent per liter under normal conditions. For example, when an acute exogenous potassium load is administered by an oral or intravenous route the attendant increase in plasma K^+ directly stimulates the release of insulin from the pancreas and aldosterone from the adrenal gland whitch act in concert to drive potassium into the muscle and liver cells thereby providing an extrarenal disposal mechanism. Further, β-adrenergic activity by way of catecholamines also potentiate tissue potassium uptake. In addition renal excretion of potassium is enhanced by several mechanisms (see below). Conversely, when potassium intake is decreased potassium leaves the cells to enter the extracellular space and simultaneoulsy renal excretion is attenuated.

It is beyond the scope of this article to discuss potassium balance in great detail, however, three points should be kept in mind: 1) the kidney plays a central role in overall potassium balance; 2) net dietary potassium intake impacts on renal mechanisms of potassium and hydrogen ion excretion; and 3) the occurrence of sustained hyperkalemia indicates an impairment in renal potassium excretion.

Hydrogen Ion Homeostasis

Interplay Between Diet, Kidneys, and Lungs

Cellular metabolism of dietary foodstuffs gives rise to fixed acids (non-volatile or non-carbonic acid) which require renal excretion as shown in Figure 2. This amount of acid is referred to as the endogenous acid production. Adult humans produce between 0.7--1.5 mEq/kg/day of endogenous

RELATIONSHIP BETWEEN ENDOGENOUS ACID PRODUCTION AND URINARY NET ACID EXCRETION UNDER STEADY-STATE CONDITIONS

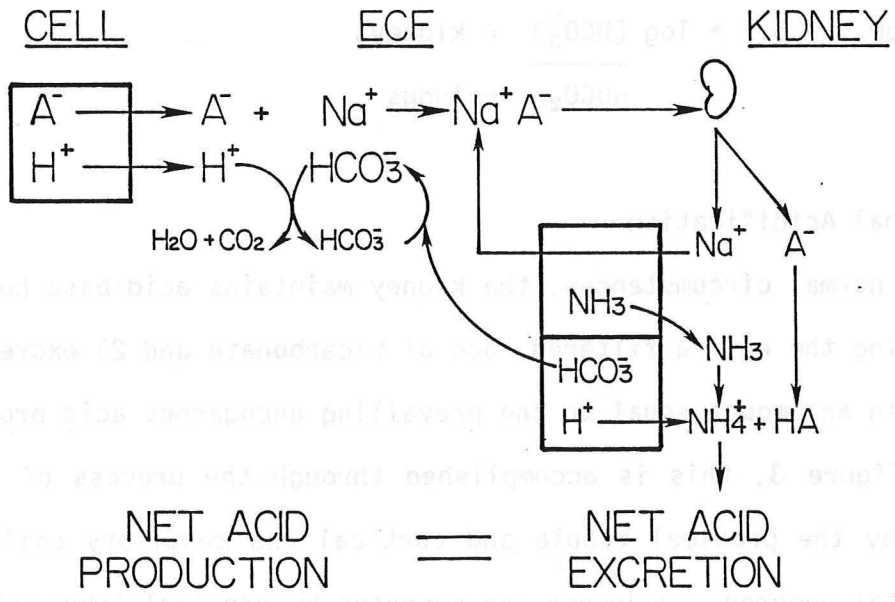


Figure 2

acid when ingesting an average American diet. Fixed acids derive from three sources: 1) sulfur containing amino acids, 2) incompletely metabolized CHO and fat giving rise to organic acids and 3) from phosphoproteins containing cationic amino groups. When the fixed acids enter the extracellular fluid space, bicarbonate is neutralized and the sodium salt of the acid is formed. The sodium salts are filtered by the kidney and excreted along with hydrogen ions (in the form of ammonium and dihydrogen phosphate) generated by the renal tubular epithelium. The amount of acid excreted by the kidney on a daily basis can be calculated from the algebraic sum of urinary ammonium and titratable acid less any bicarbonate and is referred to as the net acid excretion. In the steady-state, net acid excretion rate will equal the endogenous acid production rate and plasma bicarbonate concentration remains constant. The lungs serve to regulate the arterial pCO_2 at a constant level such that the arterial blood hydrogen ion concentration remains relatively constant. These three variables are related by the familiar Henderson-Hasselbalch equation shown below:

$$pH = 6.1 + \log \frac{[HCO_3^-]}{\alpha pCO_2} \quad \begin{matrix} \leftarrow \text{kidneys} \\ \leftarrow \text{lungs} \end{matrix}$$

Overall Renal Acidification

Under normal circumstances, the kidney maintains acid-base homeostasis by 1) reclaiming the entire filtered load of bicarbonate and 2) excreting acid in the urine in an amount equal to the prevailing endogenous acid production. As shown in Figure 3, this is accomplished through the process of hydrogen ion secretion by the proximal tubule and cortical and medullary collecting ducts of the distal nephron. Hydrogen ion secreted by proximal tubular cells

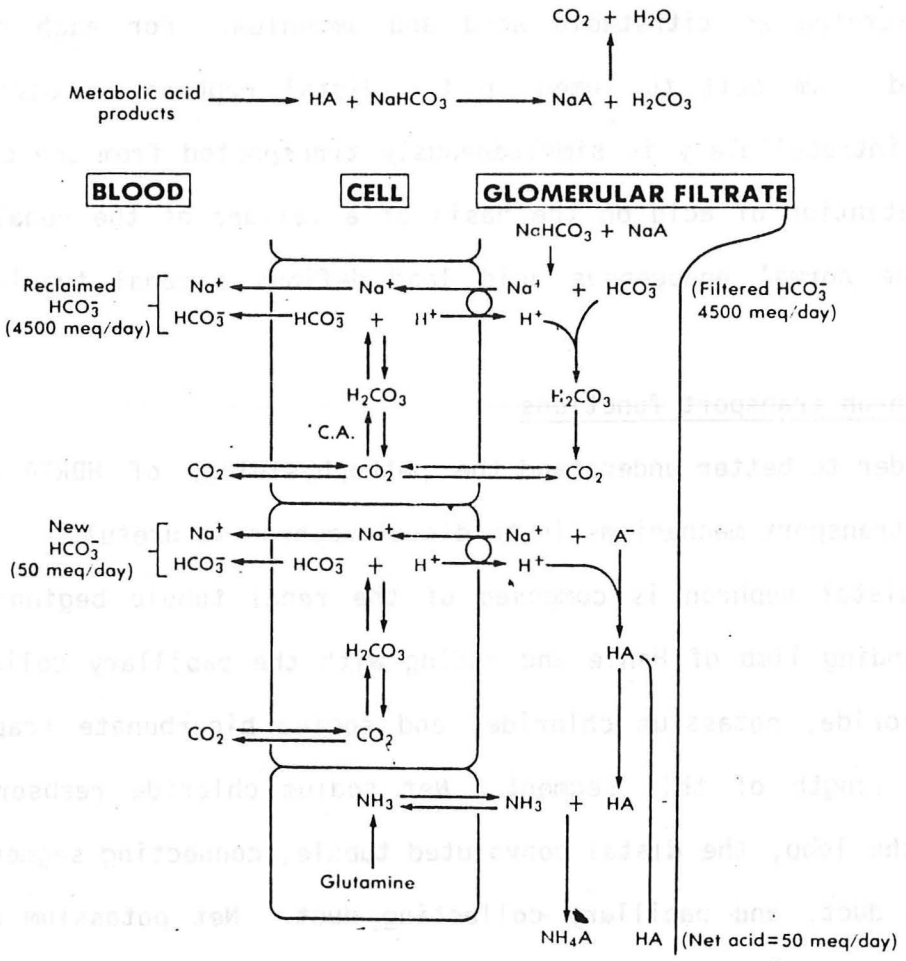


Figure 3 Normal renal acidification: Distribution of secreted hydrogen ion between bicarbonate reabsorption and net acid excretion.

combines with luminal bicarbonate ions, resulting in the formation of carbonic acid. Under the catalytic influence of luminal carbonic anhydrase, carbonic acid dehydrates to form CO_2 and water. CO_2 diffuses from the lumen into the cell where it combines with a hydroxyl ion to reform a bicarbonate ion. Bicarbonate is then transported out of the cell into the peritubular blood. This process in the proximal tubule is responsible for approximately 80% of the filtered blood of bicarbonate. The remainder of the filtered bicarbonate

is reabsorbed in the loop of Henle and collecting ducts. In the distal nephron, hydrogen ion secreted into the lumen combines with available buffers and is excreted as titratable acid and ammonium. For each hydrogen ion transported from cell to lumen in the distal nephron, a bicarbonate ion generated intracellulary is simultaneously transported from the cell into the blood. Retention of acid on the basis of a failure of the renal tubules to excrete the normal endogenous acid load defines a renal tubular acidosis.

Distal nephron transport functions

In order to better understand the pathophysiology of HDRTA a review of basic ion transport mechanisms in th distal nephron is useful.

The distal nephron is composed of the renal tubule beginning with the thick ascending limb of Henle and ending with the papillary collecting duct. Sodium chloride, potassium chloride, and sodium bicarbonate transport occur along the length of this segment. Net sodium chloride reabsorption takes place in the loop, the distal convoluted tubule, connecting segment, cortical collecting duct, and papillary collecting duct. Net potassium reabsorption occurs along the medullary and cortical thick ascending limb segments and to a smaller extent in the medullary collecting duct, but undergoes net secretion in the distal convolution and cortical collecting duct segments. Hydrogen ion secretion occurs in the thick ascending limb of Henle's loop and in the cortical, medullary, and papillary collecting duct segments.

Sodium Transport

In the medullary and cortical thick ascending limb, sodium is reabsorbed passively as a consequence of active chloride transport which, in turn, generates a lumen-positive transepithelial potential difference in these

segments. In consequence, the luminal sodium concentration decreases along the length of the thick limb. In the post-macula densa portion of the distal nephron, active sodium transport accounts for the further reduction in luminal sodium concentration as detected by experimental micropuncture techniques. In these segments, sodium enters the apical cell membrane through putative sodium channels down a lumen-to-cell concentration gradient and is actively transported out of the cell across the peritubular cell membrane via membrane-bound Na^+-K^+ ATPase. The activity of this enzyme increases in response to the transient increase in cell sodium activity owing to luminal sodium entry. Sodium transport in this manner generates a lumen-negative transepithelial potential difference observed in the distal convoluted tubule, cortical collecting duct segments.

In the CCD in particular, sodium transport is modulated by mineralocorticoid hormone (MCH): an increase in MCH activity enhances transepithelial sodium transport and increases the magnitude of the lumen-negative transepithelial potential difference; conversely, the absence of MCH greatly reduces the magnitude of sodium reabsorption and transepithelial potential in this segment. Figure 4 depicts a model of aldosterone stimulated sodium transport in the CCD. It has been postulated that MCH stimulates sodium reabsorption by increasing the number of available sodium channels in the luminal membrane which secondarily stimulates Na^+-K^+ ATPase actively, as described above. An increase in luminal sodium concentrarion by virtue of enhanced delivery to the distal nephron increases sodium reabsorption by increasing the lumen-to-cell sodium concentration gradient. The enhanced reabsorption under these conditions, however, is modulated by the prevailing level of MCH activity. The capacity of this system to increase sodium transport is evidenced by the reduction in urinary sodium concentration to

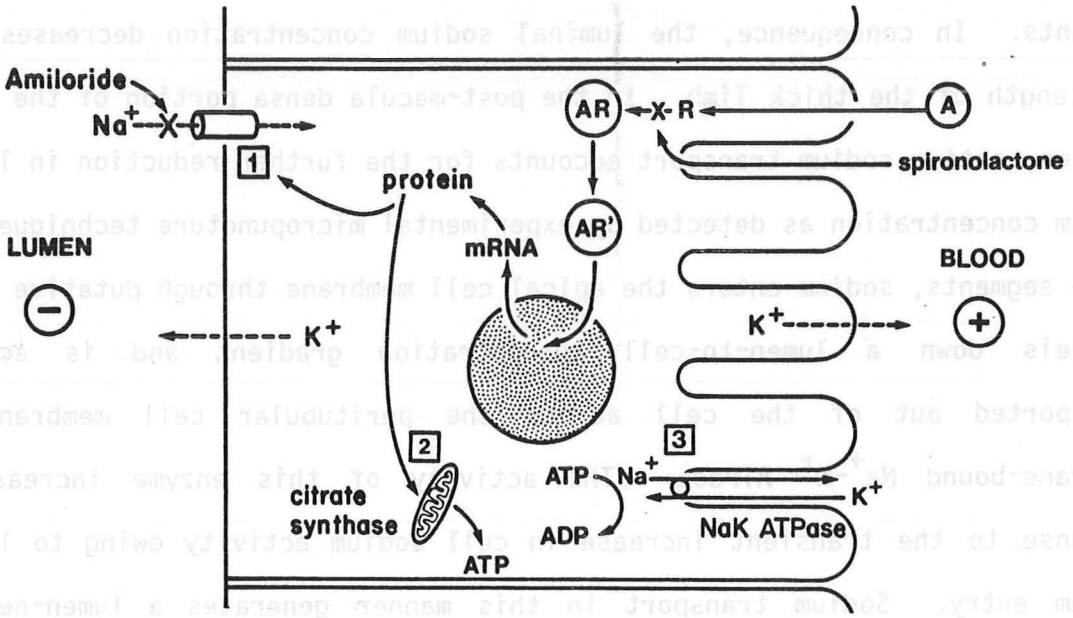


Fig. 4 Model for aldosterone-stimulated Na^+ and K^+ transport. The effect of aldosterone in the cortical collecting tubule cell Aldosterone *(A)* interacts with a cytoplasmic mineralocorticoid receptor. This aldosterone-receptor interaction may be blocked by spironolactone. The aldosterone-receptor complex activates specific regions of nuclear chromatin to produce messenger RNA which is then translated into several proteins. One such protein is a permease which increases the permeability of the luminal membrane to sodium. In addition, enzymes involved in energy production may also be stimulated. It has been demonstrated that activation of the Na^+-K^+ ATPase system on the basolateral surface [3] is dependent on increased intracellular Na^+ concentration resulting from the permease effect. Blockage of Na^+ entry by amiloride prevents aldosterone-induced increases of Na^+-K^+ ATPase. From ref. 54.

less than 1 mEq/L during periods of high MCH activity (e.g., low sodium diet, volume depletion). The relative affinity of the distal nephron to reabsorb sodium as modulated by MCH activity and dietary sodium intake has been phenomenologically referred to as the distal sodium "avidity".

Chloride Transport

Chloride is actively reabsorbed in the thick ascending limb, generating the lumen-positive potential difference in this segment, as previously mentioned. In the post-macula densa distal nephron, the lumen-negative potential difference favors chloride reabsorption. In addition, like sodium, MCH also enhances chloride reabsorption in the CCD; however, the relative increase in sodium, as compared to chloride transport induced by MCH, in part explains the net increase in magnitude of the lumen-negative potential. The

relative permeabilities of Na^+ and Cl in the CCD segment in large part determine the magnitude of the transepithelial potential difference.

It has been observed that chronic potassium depletion results in depressed distal chloride reabsorption presumably by impairing chloride permeability in the collecting duct. Furthermore, chronic K^+ depletion has been shown to impair the augmented chloride reabsorption induced by chornic MCH stimulation. In this manner, chronic K^+ depletion may augment the lumen-negative potential difference which favors the transport of hydrogen ion into the lumen.

Potassium Transport

Net Potassium reabsorption takes place in the thick ascending limb of Henle coupled with the transport of Na^+ and Cl^- ions. Inhibitors of NaCl transport in this segment decrease potassium transport concomitantly. In addition, recent evidence suggests that acute alterations in plasma potassium concentration reduce potassium transport across the medullary portion of the thick ascending limb. In the distal convoluted tubule, net potassium reabsorption occurs under normal circumstances, but in the connecting segment and cortical collecting duct, net potassium secretion occurs under normal physiologic conditions. Slight net potassium reabsorption occurs in the medullary collecting duct. Potassium secretion in the distal nephron occurs in two steps as shown in Figure 5: 1) K^+ is actively transported into the cell across the peritubular membrane via Na^+-K^+ ATPase; and 2) it exits across the apical membrane down an electrochemical gradient into the lumen of the DCT and CCT. Factors that alter the net secretory flux of potassium in these segments serve to maintain potassium homeostasis. For example, during chronic potassium loading urinary potassium excretion rises in large part owing to a

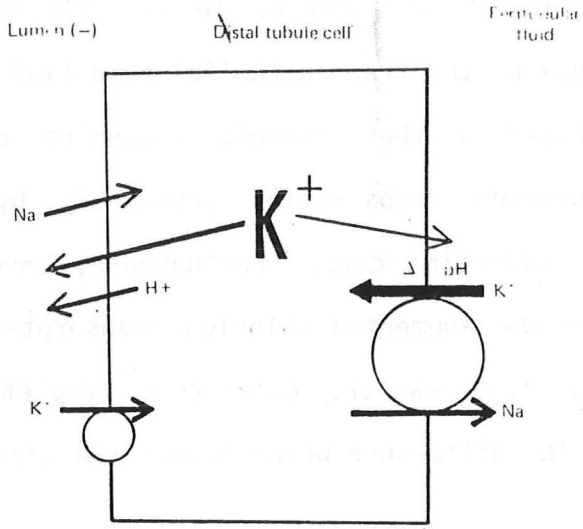


Fig. 5. Schematic representation of potassium secretion by the distal tubule.

sharp rise in net distal nephron potassium secretion. Conversely, dietary potassium restriction is associated with a fall in urinary potassium excretion and a reduction in distal potassium secretion in both the distal tubule and CCD. In the distal tubule, net potassium flux is reversed so that net potassium reabsorption becomes evident during dietary K depletion.

TABLE 2

Collecting Duct Conditions that Result in Increased Urine Potassium Excretion

Increased flow through collecting duct
Increased availability of Na^+ for reabsorption in collecting duct
Increased avidity of collecting duct for Na^+ reabsorption
Na^+ depletion
Hyperaldosteronism
Decreased availability of Cl^- for reabsorption in the collecting duct without corresponding decreased availability of Na^+
Increased intracellular K^+ concentration in collecting duct
Metabolic alkalosis
K^+ feeding
Increased Na^+-K^+-ATPase activity
Carbonic anhydrase inhibition
? Hyperaldosteronism
Increased luminal membrane potassium permeability
Hyperaldosteronism
Increased luminal pH

Factors Affecting K^+ Secretion

As shown in Table 2 a number of factors may serve to increase net potassium secretion. First, it has been demonstrated that increasing distal sodium delivery enhances potassium secretion in the distal tubule (Fig. 6b). Second, when the electrical potential difference (lumen-negative) is

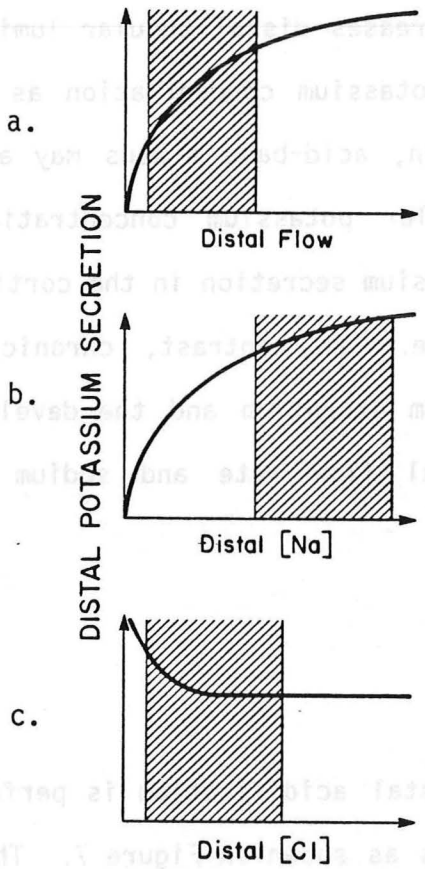


Fig. 6. Separate effects on distal potassium secretion of flow rate, luminal sodium concentration or luminal chloride concentration.

experimentally increased in the DCT and CCT, net potassium secretion increases in both of these segments. Third, an increase in luminal flow rate increases potassium secretion presumably by lowering the luminal K^+ concentration thereby enhancing the cell-lumen K^+ concentration gradient favoring K^+ secretion (Fig. 6a). Fourth, induction of acute hyperkalemia is associated with an increase in distal tubule potassium secretion rate and an increase in potassium excretion. Fifth, dietary potassium intake has a major effect on net potassium secretion: high potassium intake markedly increases and a low potassium intake markedly decreases distal tubular luminal potassium concentration as well as urinary potassium concentration as compared to a normal potassium intake. In addition, acid-base status may affect renal potassium excretion by altering cellular potassium concentration. Acute metabolic acidosis decreases renal potassium secretion in the cortical collecting tubule and distal convoluted tubule. In contrast, chronic extrarenal acidosis results in increased potassium excretion and the development of hypokalemia probably by increasing distal flow rate and sodium delivery during the generation phase.

Hydrogen Ion Secretion

Site and General Mechanism

The major portion of distal acidification is performed by the cortical and medullary collecting ducts as shown in Figure 7. The epithelium in these nephron segments displays relatively low permeabilities for several ions, including hydrogen, and are thereby referred to as "tight" epithelia. This property permits establishment and maintenance of relatively large transepithelial pH gradients in these segments. The excretion of net acid is dependent upon the capacity of the distal nephron to achieve such a gradient.

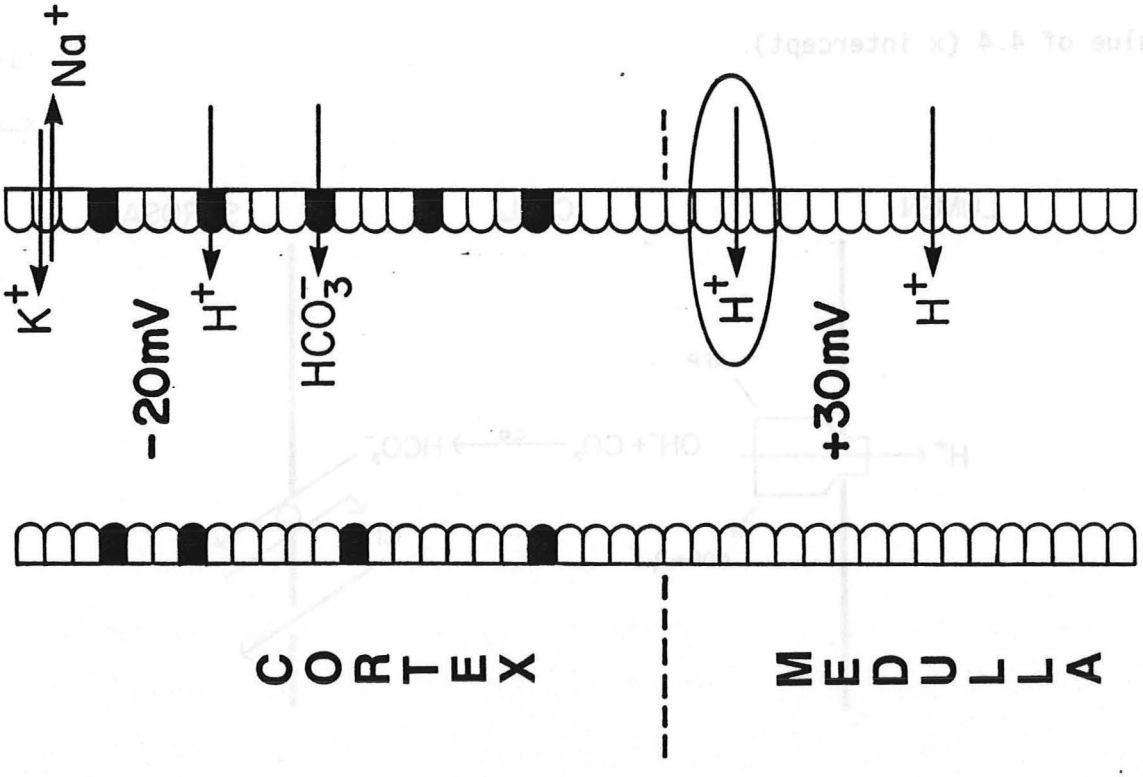

MAJOR TRANSPORT PROCESSES IN CORTICAL AND MEDULLARY COLLECTING DUCTS
Na+
K+
-20mV
H+
HCO3-
H+
+30mV
H+
CORTEX
MEDULLA

Figure 7

Hydrogen ion secretion is accomplished by proton translocating ATPase situated on the apical membrane. Proton secretion is thus an energy requiring process and secretion of protons across the apical membrane generates an elctrical gradient indicating that proton transport is electrogenic. The ATPases, or "pumps", utilize ATP as an energy source to drive hydrogen ion secretion. As shown in Figure 8, hydrogen ions derived from water hydrolysis provide substrate for the pumps responsible for H^+ secretion in both cortical and medullary collecting duct cells. Secretion of hydorgen ion by the distal nephron results in the formation of a transepithe-lial hydrogen ion concentration gradient which at maximum capacity is about three pH units. As shown in Figure 9, the hydrogen ion transport rate (J_H) is maximal when luminal pH is equal to blood (y intercept) and is limited by the pH gradient as it falls to zero (in a linear fashion) when the luminal pH approaches a value of 4.4 (x intercept).

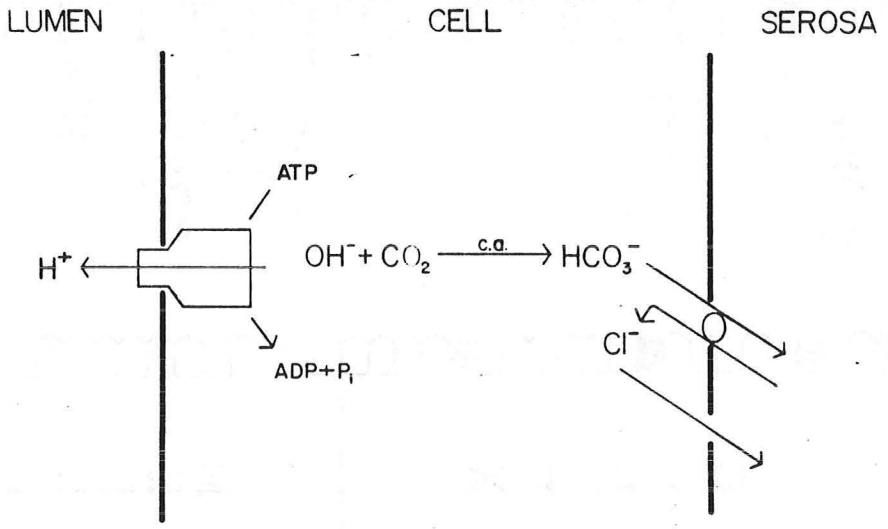


Figure 8. Cellular organization of urinary acidification in a tight epithelium: collecting duct.

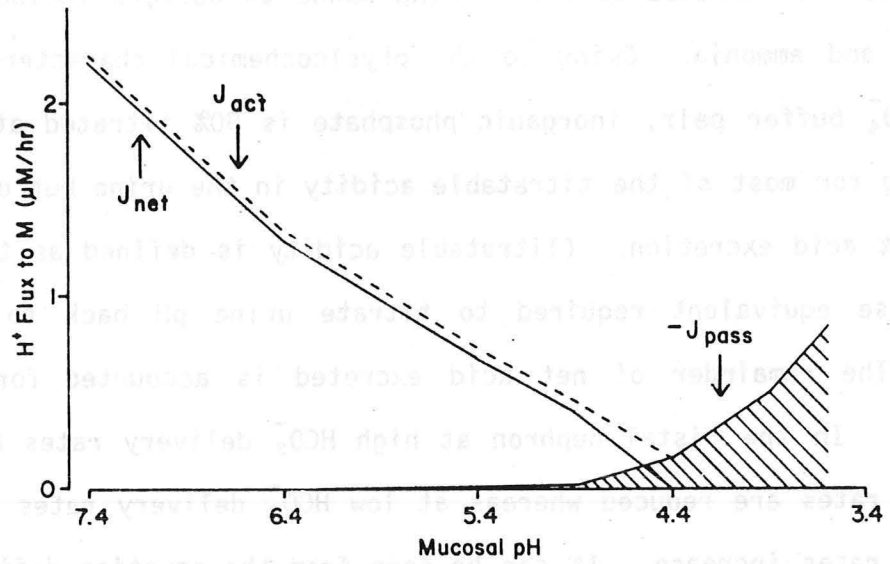


Figure 9. Active H^+ transport against pH gradients. J_{net} represents the net rate of H^+ secretion measured by pH stat titration. The rate of back diffusion is indicated by J_{pass} (shaded area). The active component of transport J_{act} is indicated by the dashed line. (Ref. 55)

Net Acid Excretion (NAE)

In order to achieve net acid excretion rates sufficient to maintain H^+ ion balance, the distal nephron must be capable of establishing and maintaining the large transepithelial pH gradient of up to 3 pH units. Net acid excretion rate is defined as the sum of ammonium plus titratable acid minus bicarbonate as shown:

$$NAE = NH_4^+ + TA - HCO_3^-.$$

This capacity depends on several factors including intact pumps, availability of luminal non-bicarbonate buffer for titration of secreted H^+ and relative rates of delivery of Na^+ and HCO_3^- to the distal acidifying sites. Due to the low pKa of fixed acids (e.g., sulfuric acid derived from meat), secreted

protons must be excreted by first being bound to buffers including inorganic phosphate and ammonia. Owing to the physicochemical characteristics of the $HPO_4^{2-}/H_2PO_4^-$ buffer pair, inorganic phosphate is 90% titrated at a pH of 5.8 accounting for most of the titratable acidity in the urine but only about 50% of the net acid excretion. (Titratable acidity is defined as that amount of strong base equivalent required to titrate urine pH back to that of the blood.) The remainder of net acid excreted is accounted for by ammonium excretion. In the distal nephron at high HCO_3^- delivery rates $H_2PO_4^-$ and NH_4^+ excretion rates are reduced whereas at low HCO_3^- delivery rates $H_2PO_4^-$ and NH_4 excretion rates increase. It can be seen from the equation defining NAE that limitation of non-bicarbonate buffer availability for secreted H^+ ion can limit net acid excretion. In certain instances buffer limitation may be severe enough to result in systemic metabolic acidosis.

Factors Affecting Hydrogen Ion Secretion

Transepithelial Potential

Experimental observations in the isolated tubule have demonstrated that the lumen negative transepithelial potential difference in the cortical collecting tubule modulates the net acidification rate of this segment. Thus, an increase in lumen negativity increases and a decrease in lumen negativity decreases net hydrogen ion secretion through alterations in the electrical gradient for H^+ movement into the tubular lumen. Factors which may increase the lumen negativity include the rate of distal sodium delivery, the reabsorbability of the anion accompanying sodium, and the availability of mineralocorticoid hormone. An example of how altering transepithelial potential difference by changing the nature of the anion delivered to the distal nephron and thereby influencing net acid excretion is shown in Figure

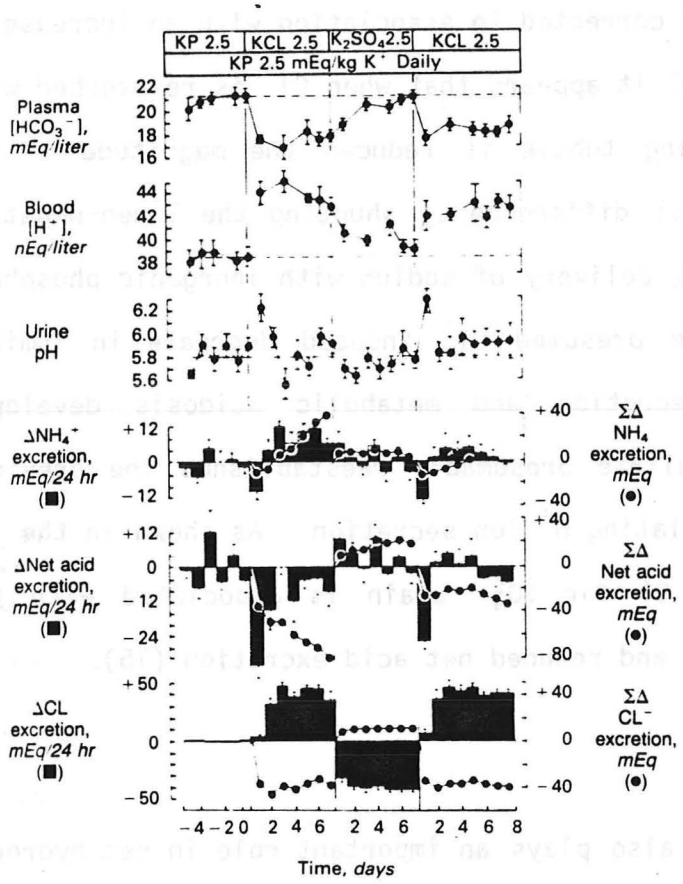


Fig. 10. Intact dogs volume depleted and kept on a zero Na^+ intake have normal acid-base status during the period when fed KP (upper left panel). When KCl is substituted for ½ of KP metabolic acidosis develops in association with a fall in net acid excretion. Acidosis is corrected by equivalent SO_4^{2-} substitution for dietary chloride.

10. The figure depicts intact volume-depleted dogs maintained on a constant sodium chloride-free diet so that distal sodium avidity is sharply increased. In the control period, normal plasma acid-base and electrolyte composition and steady net acid excretion rates are present (far left panel). Under these conditions distal sodium delivery is low and phosphate, a relatively non-reabsorbable anion, is the anion accompanying any sodium delivered to the distal nephron. In addition, aldosterone levels are increased. When chloride, a more reabsorbable anion, is substituted for a portion of dietary phosphate, metabolic acidosis develops in association with

a significant fall in net acid excretion (second panel from left). However, when sulfate, a poorly reabsorbable anion, is subsequently substituted for chloride in the diet, acidosis is corrected in association with an increase in net acid excretion. In this model it appears that when Cl^- is reabsorbed with sodium in the cortical collecting tubule it reduces the magnitude of the negative transepithelial potential difference by shunting the lumen-negative potential previously generated by delivery of sodium with inorganic phosphate (a non-reabsorbable anion). The presumed Cl^- induced decrease in luminal negativity then retards H^+ secretion and metabolic acidosis develops. Replacement of chloride with sulfate presumably reestablishes the previous luminal negativity, thereby stimulating H^+ ion secretion. As shown in the far right panel, resubstitution of Cl for SO_4^{2-} again is associated with the development of metabolic acidosis and reduced net acid excretion (15).

Buffer Availability

Luminal buffer availability also plays an important role in net hydrogen ion secretion and net acid excretion. The major urinary buffers within the physiologic pH range include bicarbonate, monohydrogen phosphate (HPO_4^{2-}), and ammonia. These buffers compete for titration of secreted hydrogen ion, once all bicarbonate is reabsorbed from the luminal fluid, secreted H^+ is titrated by ammonia and phosphate. Restriction of buffer availability in the luminal fluid results in a reduction in net acid excretion as establishment of the maximal transepithelial hydrogen ion concentration gradient is achieved rapidly in the absence of buffer. It should be noted that even at maximal phosphate excretion rates titratable acid excretion is insufficient to maintain normal net acid excretion. In order to excrete the normal endogenous load of fixed acid, the kidney synthesizes ammonia which freely diffuses into

the lumen where it is protonated and trapped as ammonium (due to its poor diffuseability). A scheme of ammonium transport is shown in Figure 11. Factors which alter ammoniagenesis may have a profound effect on urinary buffer and net acid excretion rates. Potassium is known to play an important role in renal ammoniagenesis: hypokalemia stimulates, and hyperkalemia suppresses, renal ammonia production. This effect of hyperkalemia on renal

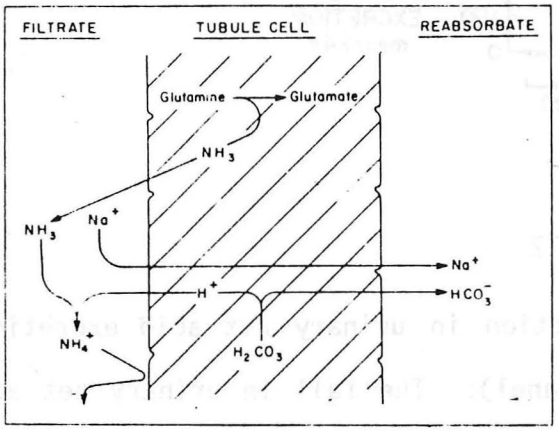
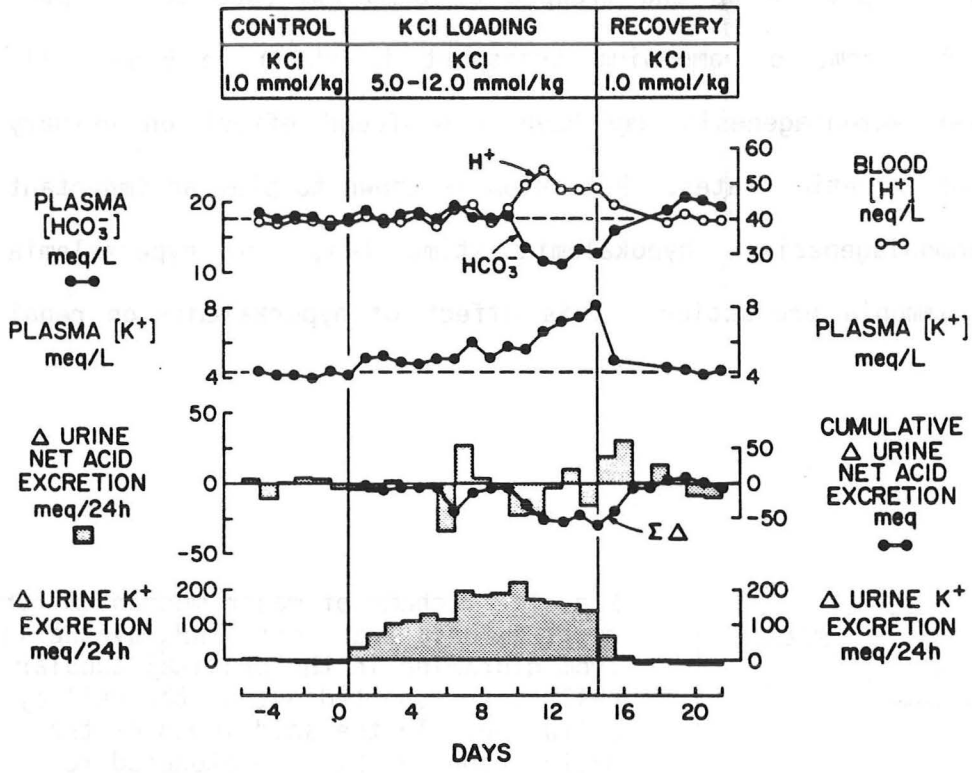


Fig. 11. Scheme of major mechanism for renal ammonia transport. NH_3 synthesized from glutamine in the proximal tubular cell is transported out of the cell by diffusion. In the acid lumen of the distal nephron NH_3 is protonated to form ammonium (poorly diffuseable) and is subsequently excreted into the urine.

acidification is important in the pathogenesis of hyperkalemic distal RTA. An example of how reduced urinary buffer availability may alter renal acidification is shown in Figure 12. Adrenalectomized, fixed-steroid, replaced dogs ingesting a constant, normal NaCl, phosphate-restricted diet achieve normal and steady plasma and urinary acid-base composition (left panel). When the animals are made hyperkalemic by increasing the dietary potassium load with potassium chloride, hyperkalemia and hyperchloremic metabolic acidosis occur



Effect of chronic oral KCl loading on plasma and urinary acid-base and electrolyte composition in a representative fixed steroid-replaced ADX dog of *group IA*. ΣΔ values (closed circles) represent cumulative change in excretion from control mean.

From ref. 16

FIGURE 12

and persist in association with a reduction in urinary net acid excretion. Renal tubular acidosis occurs (middle panel). The fall in urinary net acid excretion rate is accounted for on the basis of a fall in urinary ammonium excretion (since urinary phosphate excretion is negligible on a low phosphate diet). Removal of excess potassium from the diet results in a normalization of plasma and urinary acid-base composition (right panel) (16).

Mineralocorticoid Hormone

Mineralocorticoid hormone (MCH) also plays an important role in distal nephron acidification. First, MCH indirectly increases hydrogen ion transport in the cortical collecting tubule by enhancing luminal negativity as a result of augmented sodium reabsorption (relative to chloride reabsorption). Second, MCH appears to increase hydrogen ion secretion by a mechanism independent of

sodium transport in both the cortical and medullary collecting ducts. In contrast to the CCT, the MCT normally exhibits a lumen-positive transepithelial potential difference which is attributable to hydrogen ion secretion (recall that the MCT does not reabsorb sodium to any appreciable extent). Both chronic in vivo and acute in vitro stimulation with MCH enhance MCT acidification rate. Figure 13 depicts the dual effects of aldosterone on H^+ secretion. The important regulatory role of MCH in maintaining normal acid-base homeostasis has been demonstrated in adrenalectomized humans maintained on chronic oral miner-alocorticoid and glucocorticoid replacement. As shown in Figure 14, when MCH (fludrocortisone) is discontinued in an adrenalectomized patient kept on a constant normal sodium intake and constant diet, plasma total CO_2 falls and plasma potassium concentration increases in

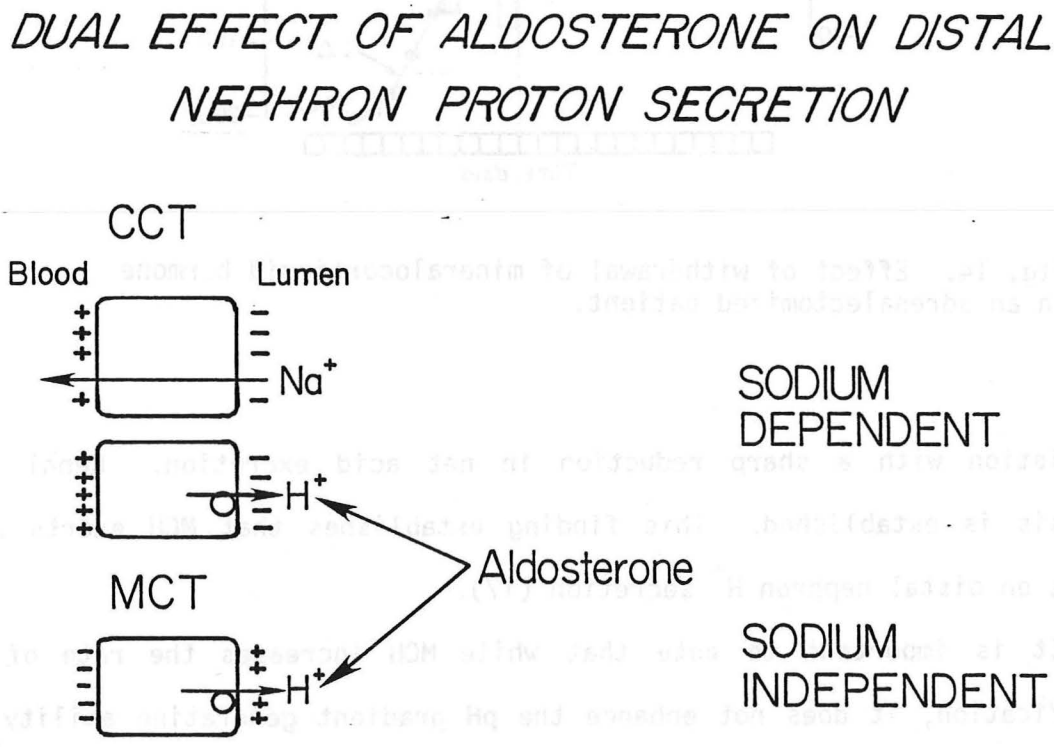


Figure 13

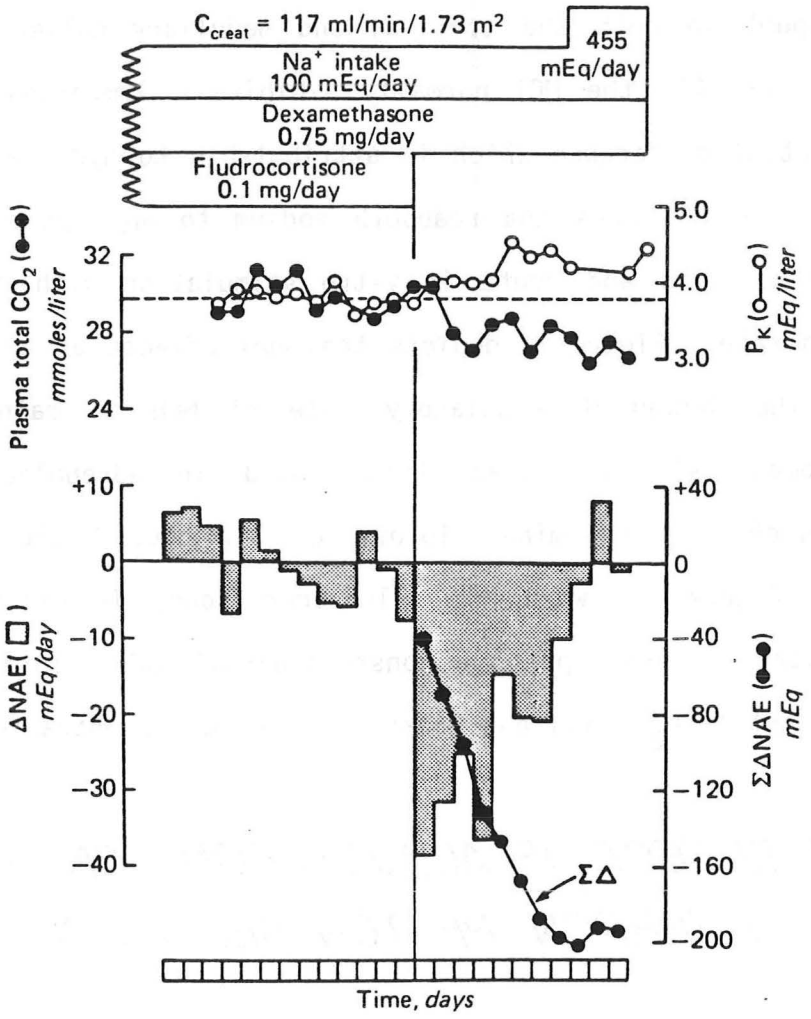
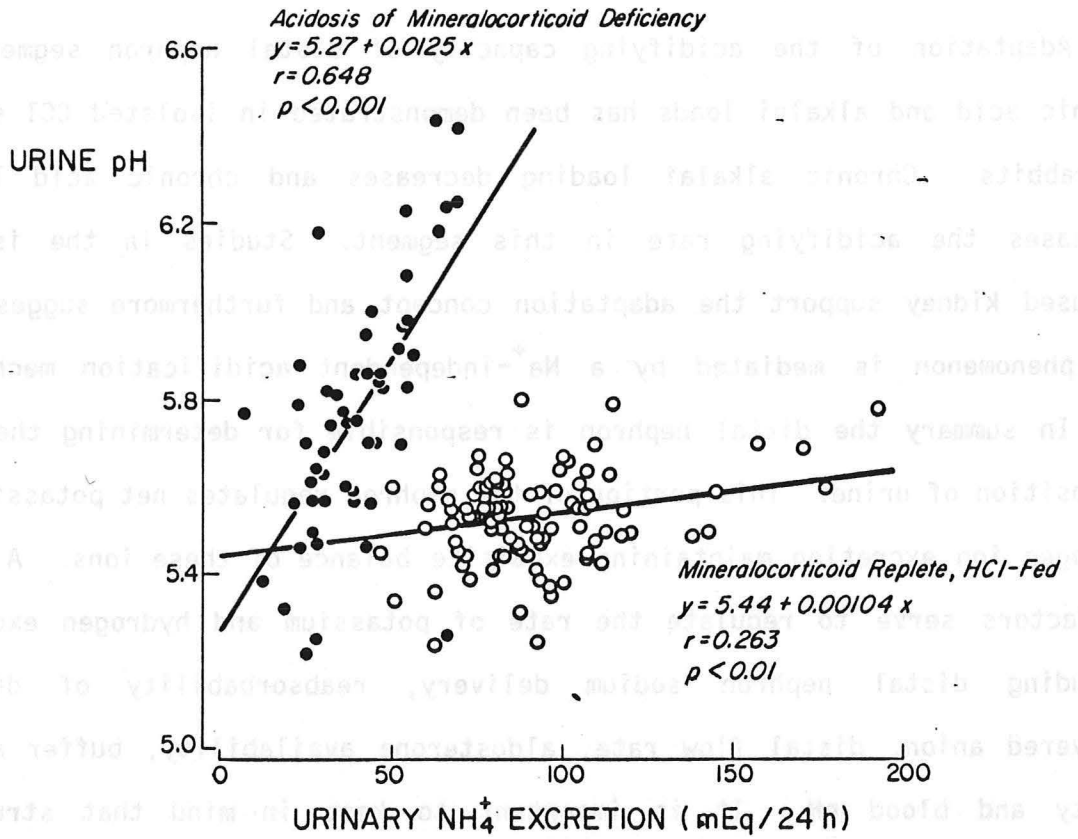


Fig. 14. Effect of withdrawal of mineralocorticoid hormone in an adrenalectomized patient.

association with a sharp reduction in net acid excretion. Renal tubular acidosis is established. This finding establishes that MCH exerts a tonic effect on distal nephron H^+ secretion (17).

It is important to note that while MCH increases the rate of distal acidification, it does not enhance the pH gradient generating ability of the epithelium. This fact has been shown both in vitro in the turtle bladder, a model of the mammalian collecting duct epithelium as well as in vivo in

experimentally induced MCH deficiency in dogs. As shown in Figure 15, urinary pH is plotted as a function of urinary ammonium excretion rates in two groups of chronically acidotic dogs: mineralocorticoid deficient, glucocorticoid replete animals (upper line) and intact HCl-fed animals. The MCH deficient animals exhibit a higher urinary pH at high urinary ammonium excretion rates as compared to intact HCl-fed animals, indicating a reduced renal acidifying capacity. Note, however, that at very low buffer excretion rates, the minimal achievable urinary pH is the same for MCH deficient and intact HCl-fed groups, indicating that the ability to generate and maintain a steep hydrogen ion concentration gradient across the distal epithelium is independent of MCH



Urine pH as a function of urinary ammonium excretion during steady-state acidosis in dogs that were mineralocorticoid-deficient (●) and mineralocorticoid-replete (○). (From Hulter, H. N., et al.: Impaired renal H^+ secretion and NH_3 production in mineralocorticoid-deficient glucocorticoid-replete dogs. Am. J. Physiol. 232:F136, 1977.)

Figure 15

activity. Phenomenologically, this finding indicates that MCH does not alter the force of the hydrogen ion secretory pump (the "proton-motive" force) but appears instead to facilitate proton movement through the pump pathway.

Blood pH

Acute alterations in arterial blood pH can alter net acid secretion by the distal nephron. In both in vivo and in vitro studies in the medullary and cortical collecting tubules respectively acute decreases in blood pH stimulate hydrogen ion secretion (18,19). In association with enhanced proton secretion ammonium excretion rates increase acutely in studies examining excretion of acid by the whole kidney (20).

Adaptation of the acidifying capacity of distal nephron segments to chronic acid and alkalai loads has been demonstrated in isolated CCT studies in rabbits. Chronic alkalai loading decreases and chronic acid loading increases the acidifying rate in this segment. Studies in the isolated perfused kidney support the adaptation concept and furthermore suggest that the phenomenon is mediated by a Na^+-independent acidification mechanism.

In summary the distal nephron is responsible for determining the final composition of urine. This portion of the nephron regulates net potassium and hydrogen ion excretion maintaining exquisite balance of these ions. A number of factors serve to regulate the rate of potassium and hydrogen excretion including distal nephron sodium delivery, reabsorbability of distally delivered anion, distal flow rate, aldosterone availability, buffer availability and blood pH. It is important to keep in mind that structural integrity of the distal nephron is a prerequisite to maintenance of normal function. When the kidney fails to excrete net acid at a rate equal to endogenous acid production in the absence of advanced renal failure renal tubular acidosis occurs.

Pathogenesis and Pathophysiology of HDRTA

A. HDRTA Associated with Aldosterone Deficiency

1. Impaired Renin Secretory Capacity

Renin is elaborated from the myoepithelial cells of the afferent arteriole portion of the juxtaglomerular apparatus and enters the circulation acting on angiotensinogen to generate angiotensin I. Angiotensin I in turn is acted on by the converting enzyme in the lung to form angiotensin II. Angiotensin II, in addition to its other effects, is a potent secretagogue for aldosterone produced in the zona glomerulosa of the adrenal gland. Aldosterone has multiple target sites; in addition to regulating renal Na^+-K^+ and H^+ balance, it facilitates extrarenal cellular uptake of extracellular potassium.

Renin release is controlled by several factors including renal perfusion pressure, β-adrenergic activity, body potassium stores, distal Na^+ (or Cl^-) delivery and renal prostaglandin levels. In response to volume depletion, upright posture and dietary sodium restriction renin secretion rises and an increase in plasma renin activity (PRA) and a parallel increase in plasma aldosterone level occurs. Conversely under conditions of volume expansion, supine posture or high dietary sodium intake renin secretion, PRA and plasma aldosterone levels decrease.

A chronic impairment in renin secretion by whatever mechanism may engender a state of hypoaldosteronism sufficient to produce a syndrome of chronic mineralocorticoid hormone deficiency. In some patients with selective hypoaldosteronism, plasma renin activity is subnormal and fails to increase normally in response to low Na^+ diet, volume depletion, and postural change maneuvers. Plasma renin concentration is also reduced in most patients despite a normal or supranormal level of renin substrate. These observations

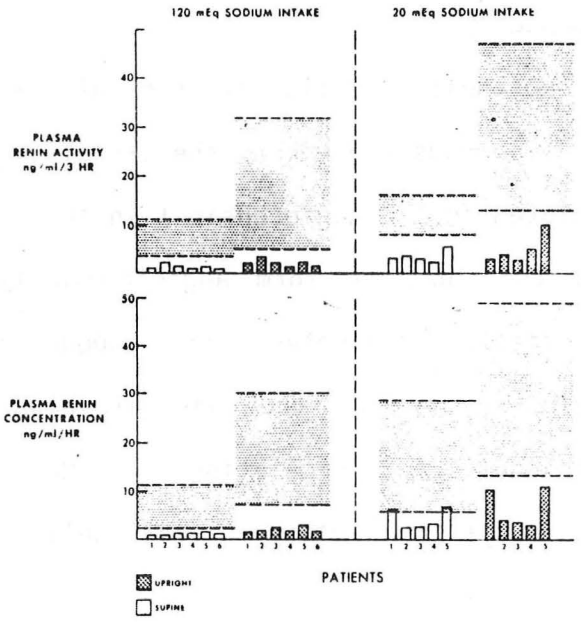


Fig. 16. Supine and upright levels of plasma renin activity and concentration obtained on normal sodium (120 mEq) and low sodium (20 mEq or less) intakes in 6 patients with isolated hypoaldosteronism. Ranges for normal subjects under the same study conditions are shown in the stippled areas. From Ref. 9.

are depicted in Figure 16. In a small subset of patients who do exhibit a normal postural increase in plasma renin activity, a parallel increase in plasma aldosterone level has been observed. Moreover, plasma aldosterone levels correlate positively with plasma renin activity determinations in patients. Furthermore, plasma aldosterone levels increase in patients in response to intravenous infusion of angiotensin II. In addition, adrenal output of aldosterone increases normally in response to ACTH infusion and potassium loading. Finally, adrenal cortisol and other non-aldosterone corticosteroid plasma and urinary metabolite levels are not reduced in the hyporeninemic group of patients. Taken together, these observations strongly support a primary role for impaired renin secretory capicity in the pathogenesis of this syndrome.

It is interesting to note, however, that plasma aldosterone levels in many patients with hyporeninemic hypoaldosteronism are higher for any given plasma renin activity as compared to normals, reflecting the effect of persistent hyperkalemia per se on adrenal aldosterone output. Nevertheless, the finding of a "normal" plasma aldosterone concentration in a hyporeninemic patient with chronic hyperkalemia suggests that adrenal aldosterone output is physiologically subnormal.

Pathogenesis of Hyporeninemia

The pathogenesis of hyporeninemia has not been clearly elucidated. It is important to recognize that renin secretion is known to decrease with advancing age concomitant with decline in renal function observed with normal aging. In diabetic patients, it has been suggested that arteriosclerosis of the juxtaglomerular apparatus, a commonly observed lesion in patients with advancing diabetic nephropathy, impairs renin secretory capacity. In addition, subnormal β-adrenergic stimulation of renin may also occur in diabetics as a result of autonomic neuropathy. A third possibility is the recent demonstration that an abnormal, inactive renin molecule (found in plasma of diabetics with renal insufficiency) is secreted by the JGA and evokes a subnormal aldosterone secretion rate. Fourth, in two of four patients with chronic renal insufficiency, hyporeninemic hypoaldosteronism, ECF volume expansion, and increased total exchangeable sodium and hypertension studied by OH et al., treatment with furosemide produced sustained diminution in ECF volume and a gradual increase in plasma renin activity and plasma aldosterone levels (21). These observations suggested that salt and water retention associated with renal disease results in a volume expansion-mediated reduction in renal renin secretion.

A further possible explanation for hyporeninemia has arisen from clinical case reports of reversible hyperkalemia accompanying the chronic oral administration of non-steroidal anti-inflammatory agents (22). Protaglandins, including PGE_2 and prostacyclin, are known renin secretagogues; inhibition of renal cyclooxygenase activity and prostaglandin production may result in impaired renin secretion sufficient to induce hyporeninemic hypoaldosteronism accompanied by hyperkalemia and hyperchloremic metabolic acidosis (23,24). Whether diminished PGE_2 production or activity might occur in chronic renal insufficiency in the absence of exogenous cyclooxygenase inhibitors to an extent sufficient to impair renin secretion has not been determined. A preliminary report by Lee et al has suggested that reduced renal prostacyclin generation is responsible for hyporeninemia in some patients with this syndrome (25). Table 3 lists the possible pathogenetic factors responsible for hyporeninemia.

TABLE 3

Pathogenesis of Hyporeninemia
In Hyperkalemic Distal RTA

1. Arteriosclerosis of the juxtaglomerular apparatus
2. Autonomic neuropathy
3. Abnormal renin molecule
4. Volume expansion
5. Decreased renal prostaglandin production

Normal Renin Secretory Capacity

Selective aldosterone deficiency may also result from a primary adrenal defect in some instances, and several reports indicate that both congenital and acquired forms of enzyme defects in the aldosterone biosynthetic pathway exist (25-30). Individuals with such defects may have normal or depressed renal function and exhibit variable hyperkalemia as the prominent clinical feature. Table 4 lists some of the reported defects in aldosterone biosynthesis resulting in isolated hypoaldosteronism. The pathogenesis of acquired enzyme deficiencies remains unknown. The clinical presentation of patients with inherited and acquired aldosterone biosynthetic defects is similar to that of hypoaldosteronism due to hyporeninemia: hyperkalemia is the predominant feature; metabolic acidosis is usually mild if present at all. An important clinical feature of these patients is the demonstration of restored renal potassium and hydrogen excretory function after chronic administration of synthetic mineralocorticoid hormone.

It should also be added that normoreninemic hypoaldosteronemia in patients with chronic renal insufficiency may also be due to a primary adrenal defect.

Pathophysiologic Consequences of Hypoaldosteronism

Hyperkalemia

Hypoaldosteronism is a hyperkalemia producing factor by virtue of its effect to reduce distal nephron potassium secretion. Aldosterone deficiency may impair distal K^+ secretion in at least two ways. First, it has been observed that MCH deficiency is associated with a marked decrease in the electrical potential difference (P.D.) in the distal segments responsible for

TABLE 4

Isolated Hypoaldosteronism Due to Congenital
And Acquired Adrenal Zona Glomerulosa Biosynthetic Defects

Clinical Presentation	Hyperreninemia	Salt Wasting	Origin	Putative Enzyme Defect	Author
Hyperkalemia	+	+	Acquired	? corticosterone methyl oxidase (CMO)	Williams et al, 1983
Dehydration	+	+	Familial	CMO I or II	Rösler et al, 1977
Postural Hypotension	+	+	Familial	CMO I or II	Rösler et al, 1977
Hyperkalemia	+	+	Familial	CMO I or II	Veldhuis, 1980
Hyperkalemia	-	-	Acquired	? 18 hydroxylase	Vagnucci, 1969

potassium secretion. This may result from a primary decrease in apical cell sodium permeability and lowered intracellular sodium concentration which in turn decreases the activity of peritubular membrane-bound Na^+-K^+ ATPase. A fall in the lumen-negative P.D. would decrease the passive driving force for potassium movement from cell to lumen. Second, MCH deficiency may decrease the K^+ permeability of the cell secondarily reducing potassium conductance across the epithelium which in the steady state would cause a decrease in net potassium secretory rate.

Clinically, impaired renal K secretion owing to hypoaldosteronism is manifest by a decrease in renal potassium clearance. Under steady-state conditions when dietary potassium intake is constant, urinary potassium excretion rate can be taken as a reflection of the net dietary load (i.e., diet-stool potassium). In patients with hyperkalemia and distal RTA associated with chronic renal insufficiency it has been shown that the serum K^+ concentration increases linearly with increases in dietary potassium intake (Fig. 17, closed symbols). Hyperkalemia per se stimulates adrenal aldosterone output, thus the level of hypoaldosteronism observed in patients with chronic

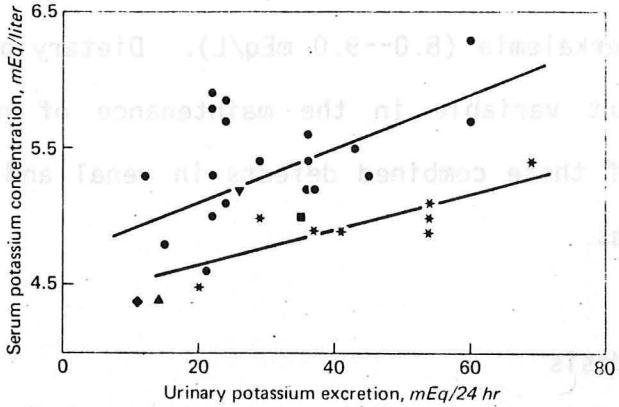


Figure 17. Relationship between serum K^+ concentration and urinary potassium excretion in 2 groups of patients with HDRTA. Solid symbols denote patients with hypoaldosteronism and asterisks denote patients without hypoaldosteronism. Taken from ref. 11. (See text for details.)

renal insufficiency depends in part on the degree of hyperkalemia. In patients with hyperkalemia and chronic renal insufficiency not associated with hypoaldosteronism a direct relationship between serum K^+ concentration and urinary K excretion also exists (Fig. 17, asterisks). As shown in Figure 17 patients with hypoaldosteronism (closed symbols) have a greater degree of hyperkalemia for any level of urinary K^+ excretion as compared to patients without hypoaldosteronism (asterisks). Taken together these data suggest that the degree of impairment in renal potassium excretion in patients with hyperkalemia and chronic renal insufficiency is a function of the relative degree of subnormal aldosterone output since many patients with "normal" aldosterone levels have plasma levels lower than expected for the degree of hyperkalemia they exhibit.

It should be emphasized that diabetes and hypoaldosteronism together are associated with more severe hyperkalemia. The concomitant deficiency of insulin renders these patients subject to impaired extrarenal potassium clearance, particularly when potassium loads are imposed. In addition insulin may be required in order for the K^+ mediated increase in adrenal aldosterone output. In these individuals, severe acute hyperglycemia may be associated with malignant hyperkalemia (8.0--9.0 mEq/L). Dietary potassium intake is an especially important variable in the maintenance of normokalemia in these patients because of these combined defects in renal and extrarenal potassium clearance mechanisms.

Metabolic acidosis

The outstanding feature of metabolic acidosis in hyperkalemic distal RTA is the occurrence of impaired renal acidification out of proportion to the degree of concomitant renal insufficiency. Metabolic acidosis is thus of the

hyperchloremic form wherein the anion gap remains normal in contrast to the acidosis of renal failure in which a high anion gap is present. These observations have led to studies focusing on the role of hypoaldosteronism as an important pathogenetic factor in the generation and maintenance of acidosis. Metabolic acidosis in Type IV RTA with hypoaldosteronism is attributable to at least two factors: aldosterone deficiency and hyperkalemia.

Role of Hypoaldosteronism in Metabolic Acidosis

Aldosterone exerts a tonic stimulus to renal acidification by two mechanisms. First, by enhancing sodium reabsorption in the cortical collecting duct and, thereby, increasing luminal electronegativity, the driving force for proton secretion is simultaneously increased. Second, aldosterone stimualtes net acidification in the medullary (as well as the cortical) collecting duct by a sodium-independent transport mechanism. It might be considered that aldosterone deficiency by engendering volume depletion would limit distal sodium delivery and therefore compromise distal nephron hydrogen ion secretion. Several studies have now provided evidence that aldosterone deficiency is a sodium-independent acidosis-producing factor. First, metabolic acidosis in hypoaldosteronism persists even in patients who have adequate distal sodium delivery as estimated by normal or high urinary sodium excretion rates. Second, experimental MCH deficiency in dogs is associated with chronic metabolic acidosis and reduced net acid excretion even when volume depletion and weight loss are prevented by massively increasing dietary sodium intake (31). Taken together with the known effect of MCH to alter proton secretion in both CCT and MCT by sodium-independent mechanisms it is clear that MCH deficiency per se can generate renal metabolic acidosis.

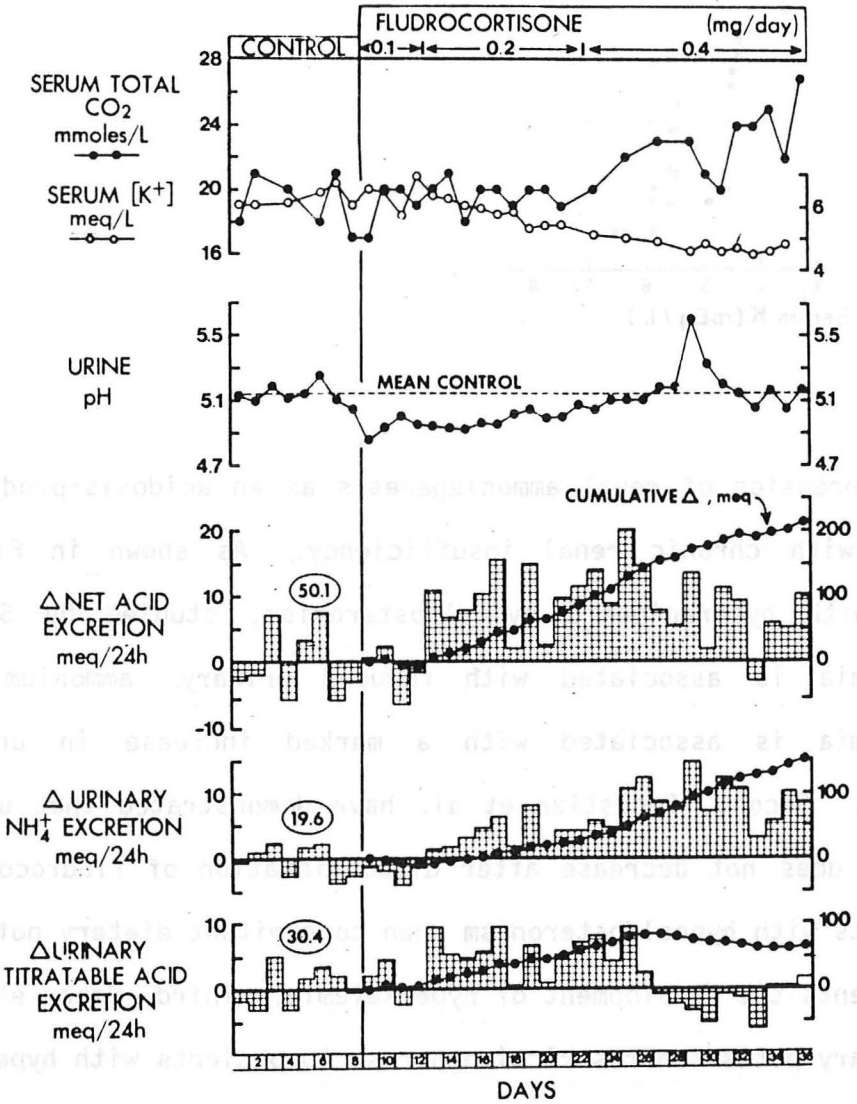
Amelioration of spontaneous acidosis in humans with hyporeninemic hypoaldosteronism chronically administered fludrocortisone, a synthetic mineralocorticoid hormone, has been demonstrated by Sebastian et al. The effect of chronic oral fludrocortisone administration on plasma and urinary acid-base composition in a patient with hyporeninemic hypoaldosteronism is shown in Figure 18. While on a constant diet, spontaneous acidosis and mild hyperkalemia are present. After fludrocortisone is begun, acidosis and hyperkalemia improve in association with a fall in urinary pH and increases in urinary net acid, ammonium, and titratable acid excretion rates. Conversely, when fludrocortisone therapy is discontinued in a patient with hyporeninemic hypoaldosteronism, metabolic acidosis and hyperkalemia occur in association with an increase in urinary pH and decreases in urinary net acid, ammonium, and titratable acid excretion rates. Taken together these studies strongly support an independent role for MCH deficiency in the generation of renal metabolic acidosis observed in this form of HDRTA.

Role of Hyperkalemia in Metabolic Acidosis

Hyperkalemia is also an independent renal acidosis-producing factor by virtue of two potential mechanisms. First, hyperkalemia reduces renal ammonia production. Recent in vitro studies in rat and dog renal slices and dog tubules have demonstrated that impaired ammoniagenesis occurs when bathing media potassium concentration is increased (32). Furthermore, decreased urinary ammonium excretion accompanies chronic oral potassium loading in both humans and dogs, suggesting that the availability of ammonia for titration of secreted H^+ ion is reduced. A reduction in ammoniagenesis in vivo might result in impaired distal acidification by virtue of reduced buffer availability for titration. Several human studies support the notion of hyperka-

Figure 18

EFFECT OF FLUDROCORTISONE ON POTASSIUM ACID-BASE STATUS OF A PATIENT WITH ISOLATED HYPOALDOSTERONISM



Effect of oral administration of 9α-fluorohydrocortisone on serum carbon dioxide and potassium concentration, urine pH, urinary titratable acid, ammonium, and net acid excretion in a patient with hyporeninemic hypoaldosteronism and chronic renal insufficiency (creatinine clearance 35 ml/min per 1.73 m^2). Systemic acidosis had not previously been treated. In the three bottom panels the hatched bars represent the difference between the measured value of acid excretion and the mean pre-9α-fluorohydrocortisone value; the magnitude of these differences is indicated by the scale on the left-hand side of the panel. For reference, the mean control value is designated by the numerals within the ellipses. The accumulated values of the daily differences are depicted by the solid circles and are indicated by the scale on the right-hand side of the panel.

From ref. 11.

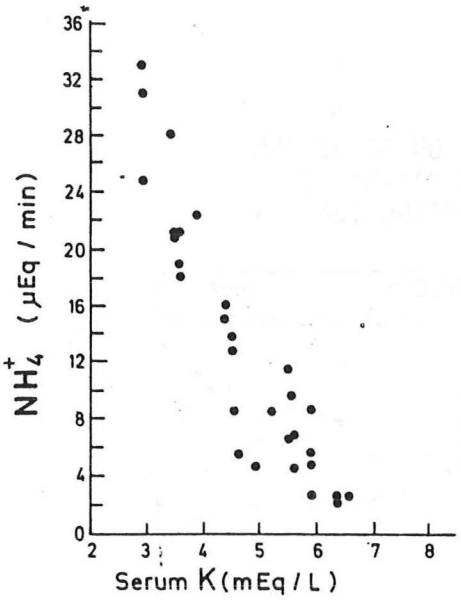


Fig. 19. Relationship between urinary ammonium and serum K^+ excretion in a patient with isolated hypoalsosteronism.

lemic suppression of renal ammoniagenesis as an acidosis-producing factor in patients with chronic renal insufficiency. As shown in Figure 19, in a patient with hyporeninemic hypoaldosteronism, studied by Szylman et al., hyperkalemia is associated with reduced urinary ammonium excretion and normokalemia is associated with a marked increase in urinary ammonium excretion. Second, Sebastian et al. have demonstrated that urinary ammonium excretion does not decrease after discontinuation of fludrocortisone therapy in patients with hypoaldosteronism when concomitant dietary potassium restriction prevents the development of hyperkalemia. Third, Maher et al. have shown that dietary potassium restriction per se in patients with hyperkalemic distal RTA results in correction of hyperkalemia, an increase in urinary ammonium excretion, and amelioration of metabolic acidosis (33). Taken together, these findings indicate that hyperkalemia plays an important role in the

pathogenesis and magnitude of metabolic acidosis in patients with hyperkalemic distal RTA.

In addition to the renal effects, chronic hyperkalemia may have an extrarenal acidosis producing effect by causing a transcellular shift of hydrogen ion from cells to the extracellular compartment. This effect would tend to worsen acidemia by increasing the blood H^+ ion concentration. Figure 20 summarizes the effects of hyperkalemia on metabolic acidosis in hypoaldosteronism.

HDRTA Without Aldosterone Deficiency

Chronic Tubulointerstitial Nephritis

HDRTA occurs commonly in patients with chronic tubulointerstitial nephritis (TIN) of diverse pathophysiological origin including sickle cell nephropathy, diabetes mellitus, SLE, Sjogrens syndrome, toxin-induced, hypertensive nephrosclerosis, analgesic nephropathy and in chronic obstructive uropathy among others. In these disorders combined hydrogen ion and potassium secretory defects may occur with or wihout salt-wasting. The relationship between TIN and transport defects remains speculative since the mechanism of defective transport in this disorder has not been elucidated. For example, it is not certain whether disturbed membrane architecture, cellular energy supply or some factor or factors produced by inflammation might alter transport function across the epithelium.

Role of Distal Nephron Transepithelial Potential Difference

The lumen-negative transepithelial potential difference in the late distal tubule and cortical collecting tubule is generated by sodium reabsorption in these segments, as already noted. Recent experimental evidence sug-

ROLE OF HYPERKALEMIA IN METABOLIC ACIDOSIS OF HYPERKALEMIC RTA

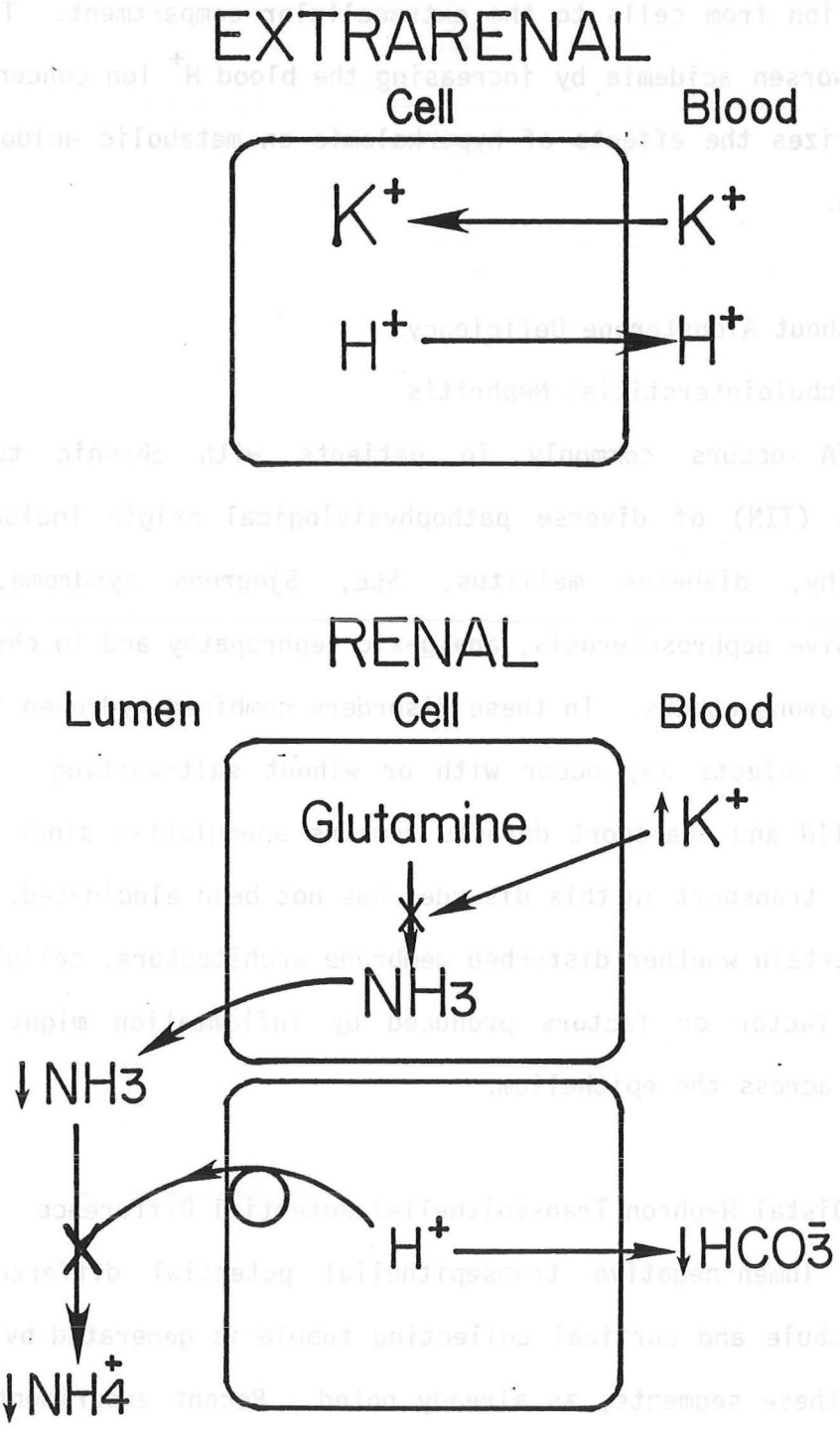


Figure 20

gests that inhibition of sodium reabsorption in the distal nephron reduces the transepithelial potential difference which, in turn, would tend to reduce both net hydrogen ion and net potassium secretion. In the isolated rabbit CCT, ouabain applied to the bathing solution in order to inhibit transepithelial sodium transport, reduces the transepithelial potential difference and simultaneously inhibits net bicarboante reabsorption in these segments. Amiloride, a weak natriuretic agent, exerts its action primarily in the cortical collecting tubule by blocking apical membrane sodium channels. In the rabbit cortical collecting tubule, amiloride inhibits sodium transport, reduces luminal negativity, and simultaneously diminishes net hydrogen ion secretion and potassium secretion. In addition, amiloride inhibits the sodium reabsorptive and potassium secretory responses to exogenous MCH in the CCT in the dog (34). In experimental animal models, chronic amiloride induces an impairment in distal acidification and potassium excretion which, in the dog, is sufficient to result in hyperkalemia and hyperchloremic metabolic acidosis in the absence of renal insufficiency (35). In effect, chronic amiloride administration in dogs appears to result in a reversible form of chronic renal tubular acidosis by virtue of its ability to reduce the transepithelial potential difference in the cortical collecting duct. This particular derangement has been referred to as a "voltage- dependent" defect.

An additional experimental model of impaired distal acidification owing to reduced distal sodium transport (and reduced transepithelial P.D.) has been developed, using lithium chloride (36). In this model, lithium reduces distal sodium transport presumably by competing for cation channels in the apical membrane of the CCT. Inhibition of renal acidification in rats occurs after chronic lithium treatment but can be overcome by infusion of sodium with an impermeant anion such as sulfate. By enhancing luminal negativity, sodium

sulfate infusion restores the lithium-induced reduction in distal nephron proton secretion (37).

Battle et al have reported hyperkalemic distal RTA occurring in the absence of hypoaldosteronism in patients with chronic obstructive uropathy (38). In this subgroup of patients renal hyperkalemia and acidosis may result from a primary defect in tubular secretion of K^+ and H^+ owing to a voltage-dependent defect. Evidence for such a tubular defect is obtained by infusion of sodium sulfate which stimulates distal H^+ and K^+ transport by stimulating distal Na^+ reabsorption. As shown in the left panel of Figure 21, acute intravenous infusion of sodium sulfate fails to lower urine pH in an HDRTA patient indicating an impairment in distal acidifying capacity (see appendix). This defect occurs despite a marked increase in distal sodium delivery reflected by a large (4-fold) increase in fractional sodium excretion (right panel).

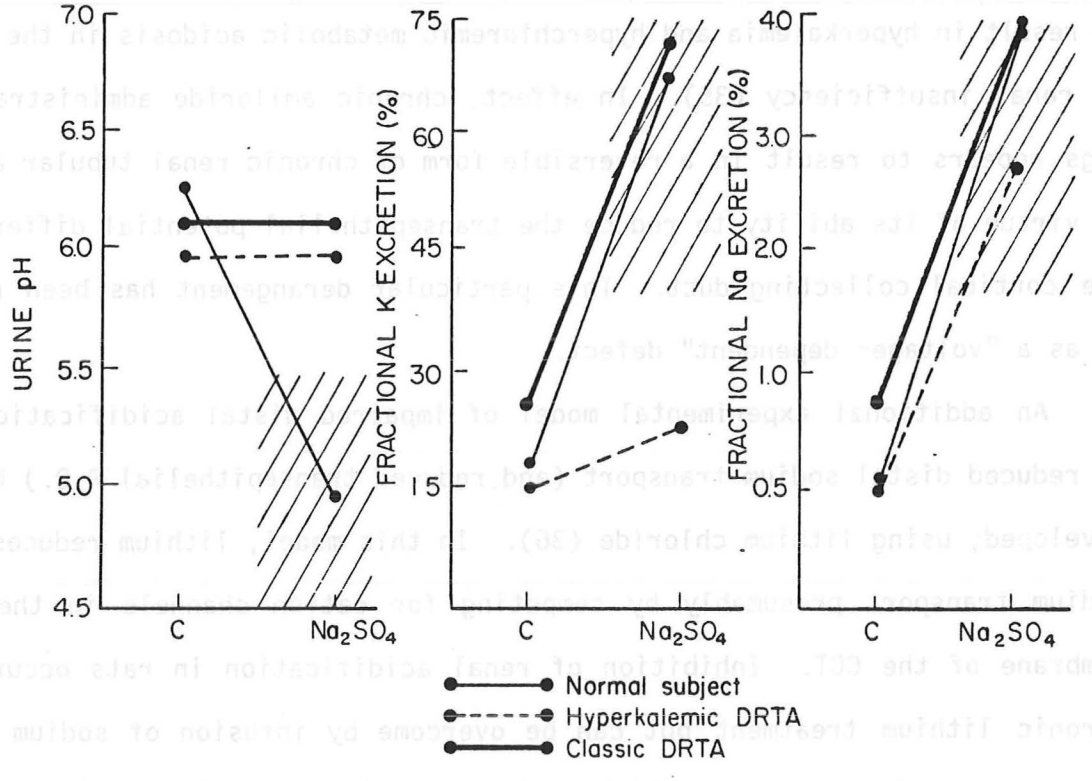


Fig. 21. Responses to Na_2SO_4 infusion in a normal subject, a patient with classic DRTA and a patient with hyperkalemic DRTA: pH, K^+, Na^+

Potassium excretion is also impaired as shown by the failure to increase fractional potassium excretion as compared to normal individuals and patients with classical RTA (middle panel). These observations parallel the findings observed in the experimental distal acidification defect associated with chronic amiloride administration. On this basis, the authors have suggested that obstructive uropathy may represent a human form of a "voltage-dependent" acidification defect. A similar defect has been described in patients with sickle cell nephropathy.

Hyperkalemic distal RTA without salt wasting in association with normal-to-elevated aldosterone concentrations has been described. Schambelan et al have studied one such patient in whom hypertension, hyperkalemia and metabolic acidosis occurred spontaneously (39). After exogenous administration of MCH no effect on renal potassium excretion was observed while the patient ingested a normal NaCl diet. However, when the patient was infused with sodium sulfate or sodium bicarbonate (both of which are poorly reabsorbable anions in the distal nephron), an increase in potassium excretion occurred. Based on these observations, it was postulated that defective potassium excretion results from an abnormally increased distal nephron NaCl reabsorptive rate associated with a reduced transepithelial voltage. The inferred enhancement in distal NaCl reabsorptive rate attenuates the passive driving force for potassium and hydrogen ion secretion and engenders volume expansion and hypertension. Figure 22 depicts a hypothetical model of a distal nephron "chloride shunt" which might represent another human form of a "voltage-dependent" acidification defect.

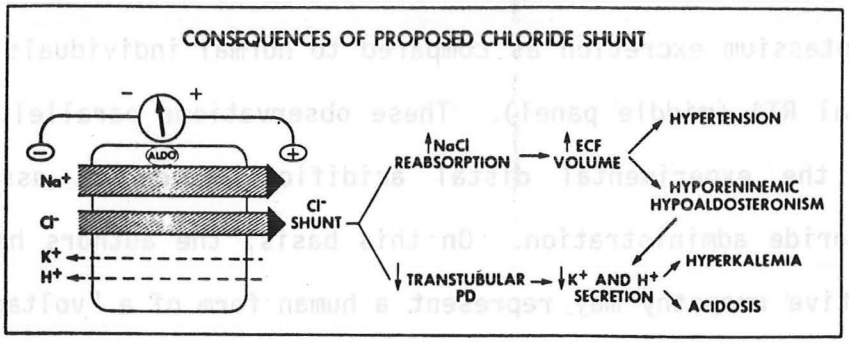


Figure 22

Pseudohypoaldosteronism

Type I

This form of HDRTA is a rare inherited disorder in which the distal nephron is insensitive to aldosterone. As a result renal salt wasting, hyperkalemia and metabolic acidosis accompanied by hyperaldosteronism are present (40,41). Recent studies have shown that extrarenal aldosterone target sites including salivary gland and gut demonstrate resistance to aldosterone (42). The precise cellular defects which account have not been elucidated however exogenous MCH has no effect on renal epithelium in this disorder. It remains uncertain as to whether cytosolic receptor deficiency or nuclear binding of MCH is abnormal.

Defective renal hydrogen ion and potassium excretion may also occur in mineralocorticoid resistant states associated with renal NaCl wasting owing to impaired distal sodium chloride reabsorption. Presumably, a decrease in distal nephron luminal negativity owing to impaired NaCl reabsorption is responsible for the development of hyperkalemia and metabolic acidosis in these patients. For example, hyperkalemia resistant to MCH has been observed in patients with TIN with or without salt-wasting including patients with SS disease post-renal transplant and drug-induced TIN.

Type II

A heterogenous group of disorders observed in both children and adults characterized by hypertension, hyperkalemia, metabolic acidosis and normal or high plasma aldosterone levels has been recognized in the literature (39,43-45). Although a primary defect in distal K^+ secretion was previously thought to be the central factor responsible for this group of disorders, available evidence now suggests that hyperabsorption of NaCl in the distal nephron may be the primary defect in this group of patients. Thus, dietary sodium chloride restriction or thiazide diuretics partially or completely correct hypertension hyperkalemia and acidosis in a number of these patients. These patients do not consistently respond to administration of exogenous MCH by increasing K^+ and H^+ ion excretion, but differ from Type I patients by virtue of exaggerated NaCl retention and hypertension instead of salt wasting observed in those patients. Taken together with normal renal potassium excretory response to Na_2SO_4 infusion the possibility of a "chloride shunt" in the distal nephron of these patients remains an attractive explanation for the distal nephron transport defects observed in this syndrome.

HDRTA Associated with Medications

Chronic oral administration of several medications may mimic the clinical syndrome of HDRTA. Amiloride and lithium carbonate administration as causes of HDRTA have been discussed. Potassium sparing diuretics such as spironolactone and triamterene have been reported to induce a syndrome of hyperkalemic hyperchloremic metabolic acidosis under certain conditions (46,47). It is not clear whether hyperkalemic suppression of renal ammoniagenesis or abnormal epithelial transport of H^+ and/or Na^+ might also be

involved in the pathogenesis of the metabolic derangements seen with these agents. For example spironolactone by blocking aldosterone action could impair H^+ and K^+ excretion by this mechanism. On the other hand, triamterene which inhibits distal nephron sodium reabsorption independent of MCH activity may operate at a cellular cytosolic or membrane site apart from the action of MCH.

Cyclooxygenase inhibitors by inhibiting renal prostaglandin production may secondarily reduce renin secretion sufficient to engender hypoaldosteronism with hyperkalemia and metabolic acidosis.

Chronic heparin therapy is known to inhibit adrenal aldosterone secretion and can cause clinical hypoaldosteronism even when given in "routine" doses (48). The appearance of asymptomatic hyperkalemia in patients treated with heparin for prolonged periods should alert the clinician to the possibility of drug-induced hypoaldosteronism.

Clincal Presentation and Diagnostic Features

The prototypical patient with hyperkalemic distal RTA is in the fifth-to-seventh decades of life, has a long-standing history of diabetes mellitus with a moderate reduction in glomerular filtration rate, usually in the range of 20-60 ml/min. Moderate arterial hypertension is also likely to be present in the typical case. Most patients are asymptomatic and are incidentally discovered to have unexplained hyperkalemia which is usually in the range of 5.5-6.5 mEq/L but may be substantially higher (especially in diabetic individuals). Hypobicarbonatemia and hyperchloremia are present, but the degree of acidemia is mild with blood pH values in the 7.25-7.35 range and plasma bicarbonate concentrations usually in the 18-22 mEq/L range. Whereas most patients are asymptomatic, up to 20-25% of patients present with some

degree of muscle weakness or cardiac arrythmias, owing to hyperkalemia, as the first manifestation of distal RTA. Salt wasting is usually absent and sodium balance is maintained unless dietary sodium is severely restricted (i.e., 10 mEq/d). To confirm that acidemia is present, arterial or "arterialized" blood pH should be measured to exclude chronic respiratory alkalosis as a cause of hypobicarbonatemia.

Measurement of 24° urine potassium excretion in patients on a constant potassium intake of 60-80 mEq/d (or more) will reveal that net positive potassium balance is present indicating that hyperkalemia is due to impaired renal excretion. Fractional excretion of potassium is reduced in the presence of hyperkalemia and a value of 6% or less in this circumstance is consistent with impaired renal potassium excretion. Since most of these patients maintain the ability to generate a steep H^+ ion gradient between the blood and lumen of the collecting duct, urinary pH is usually low during metabolic acidosis, particularly if hyperkalemia is severe (reflecting a low urinary buffer excretion rate). About 75% of patients with HDRTA exhibit hypoaldosteronism. Measurement of supine and upright plasma renin activity and plasma aldosterone levels reveals that they are below the normal range as pointed out earlier. Typical clinical and biochemical characteristics in this form of HDRTA are shown in Table 5.

Whereas the above description fits to a typical patient with hyporeninemic hypoaldosteronism the diagnosis of HDRTA should be considered in any patient with mild chronic renal insufficiency, hyperkalemia and hyperchloremic acidosis out of proportion to the degree of renal impairment and in whom tubulointerstitial nephritis is a known entity or is strongly suspected on clinical grounds. In the absence of hypoaldosteronism, hyperkalemia and hyperchloremic metabolic acidosis are almost always

TABLE 5

Typical Clinical and Biochemical Characteristics in Patients with Hyperkalemic Distal RTA Associated with Hyporeninemic Hypoaldosteronism

	age (yr)	Ccreat (ml/min)	P.R.A. (ng/ml/hr)		Plasma aldo ng/dl		Serum electrolyte mEq/L			
			Recumbent	upright	Recumbent	upright	Na	K^+	Cl	HCO_3^-
Patients	62	32	0.3	0.6	5.8	8.4	138	5.3	110	19
(N = 23)	±2	±3	±0.1	±0.1	±0.7	±1.6	±1	±0.1	±1	±1
Normals	43	102	1.0	2.4	9.6	20.9	141	4.3	107	25
(N = 29)	±2	±5	±0.1	±0.5	±1.0	±2.1	±1	±1	±1	±1

Adapted from Schambelan et al.
K.I. 17:89, 1980

associated with TIN and rarely with a primary tubular defect (such as the pseudohypoaldosterone syndromes).

Differential Diagnosis

Table 6 lists the differential diagnosis of hyperkalemia. Pseudohyperkalemia can be excluded by simultaneous measurement of both serum and plasma potassium concentrations which reveals that plasma potassium is normal. Extrarenal causes of hyperkalemia, e.g., associated with endogenous or

TABLE 6
DIFFERENTIAL DIAGNOSIS OF HYPERKALEMIA

PSEUDOHYPERKALEMIA--i.e., in vitro hemolysis, thrombocytosis, leukocytosis
EXOGENOUS LOADS
- diet, medications, salt substitutes

ENDOGENOUS LOADS
- hemolysis, crush injury, catabolic states

DECREASED RENAL POTASSIUM EXCRETION
- acute renal failure
- chronic renal failure
  - oliguric end state
    - ECFV depletion--vomiting, diuretics
  - drugs--spironolactone, triamterene, amiloride
  - mineralocorticoid deficiency
    - generalized adrenocortical insufficiency
    - enzymatic defects
    - hyporeninemic
    - tubular unresponsiveness
  - primary defect in renal potassium transport

CELLULAR SHIFT OF POTASSIUM ACIDOSIS
- drugs--succinylcholine, digitalis, arginine
- hyperkalemic periodic paralysis
- hyperglycemia

exogenous loads can usually be excluded by careful history and review of hospital course in hospitalized patients. Acute of chronic renal failure can be diagnosed by measuring glomerular filtration rate which will reveal that severe renal insufficiency (GFR <20 ml/min) is present. In addition acidosis as a cause of hyperkalemia is usually acute and of the high anion gap variety particularly if associated with renal failure. Hyperkalemia due to primary adrenal insufficiency is usually mild and is associated with manifestations of concomitant glucocorticoid deficiency, volume depletion and evidence of hyperpigmentation from excess ACTH. Drug-induced causes of hyperkalemia once again can be excluded by history. It should be emphasized that hyperkalemia with normal renal function or mild renal insufficiency is most often due to some degree of hypoaldosteronism or to relative aldosterone insensitivity since primary tubular transport defects are very rare with the possible exception of the so-called "voltage-dependent" defect (as described in obstructive uropathy and chronic lithium therapy). Two additional points deserve mention. First, it has been reported that in addition to low renin secretory rates some patients also appear to have a primary zona glomerulosa defect which may coexist with chronic renal insufficiency (51). In this regard it is possible that primary defective tubular potassium secretion with hyperkalemia could result in an increase in adrenal aldosterone output and simultaneously reduce renal renin release (or production). If this were the underlying defect the plasma level of aldosterone may fall within the "normal" range but be subnormal for the concomitant level of hyperkalemia. Secondly, in certain instances a primary transport defect and aldosterone deficiency may coexist (38). In this instance simultaneous mineralocorticoid replacement and sodium sulfate infusion fail to lower urine pH and increase urinary potassium excretion.

Treatment

Most patients with this syndrome do not require specific therapy unless they have an intercurrent illness which may exacerbate hyperkalemia and acidosis. Nevertheless, if treatment is required, management of hyperkalemia in HDRTA is the most important aspect of treatment since 1) it tends to be the most prominent feature, 2) hypobicarbonatemia is usually mild, and 3) correcting hyperkalemia may simultaneously correct acidosis. Correction of hyperkalemia alone, as previously noted, will simultaneously improve the metabolic acidosis in most instances. Several modes of therapy are available for lowering plasma potassium concentration.

Diet

As already pointed out, dietary restriction of potassium will reduce plasma potassium concentration in both hypoaldosterone and non-hypoaldosterone forms of HDRTA. Restriction of intake to 40 mEq daily will often reduce plasma potassium without any other maneuver being required. However, severe dietary potassium restriction may become necessary to achieve amelioration of hyperkalemia in some instances, necessitating alternative or additive approaches.

Na^+--K^+ Exchange Resins

Sodium-polystyrene sulfonate (Kayexalate) is a Na^+--K^+ exchange resin that is a useful agent in treating both acute and chronic hyperkalemia. When administered orally with a cathartic agent (usually sorbitol), extracellular potassium is bound to the resin in exchange for sodium on the surface of the resin. This is accomplished as the potassium affinity of the resin is greater than its sodium affinity. Net removal of body potassium is approximately 1

mEq/gram of resin. Daily or alternate day administration of 15-30 grams of Kayexalate along with 100-200 cc of sorbitol will often correct hyperkalemia and partially correct acidosis in HDRTA patients.

Kayexalate may also increase gut absorption of potential base by virtue of its affinity for calcium (which $>K^+$ affinity), providing an additional mechanism for correcting acidosis (49). Kayexalate must be used with caution, particulary in patients with hypertension, congestive heart failure, and expanded extracellular fluid volume since sodium absorbed from the resin may expand volume further.

Diuretics

1. Furosemide inhibits NaCl reabsorption in the thick ascending limb of Henle, thereby enhancing distal flow rate and sodium delivery. It has been shown to increase net acid excretion and potassium excretion in HDRTA especially in patients with hyporeninemic hypoaldosteronism (50). In addition, in some instances where volume expansion suppresses aldosterone secretion, furosemide may increase plasma aldosterone levels while simultaneously increasing delivery of sodium to the cortical collecting duct. Forty to eighty milligram doses of furosemide administered daily are recommended to start in treating both hyperkalemia and acidosis in HDRTA.

2. Thiazide diuretics inhibit NaCl transport primarily in the cortical thick ascending limb of Henle's loop. In HDRTA due to psuedohypoaldosteronism Type II, these agents stimulate renal potassium excretion sufficient to correct hyperkalemia and treat associated hypertension. Fifty to 100 mg/day is the dose range employed to achieve this effect.

Sodium Bicarbonate

Administration of sodium bicarbonate in doses that approximate the daily endogenous acid production rate will ameliorate acidosis. Enhancement of renal potassium excretion also results from $NaHCO_3$ therapy by increasing distal sodium delivery in the presence of poorly reabsorbable anion. In addition, hyperkalemia is also ameliorated by alkalinization of the ECF which results in translocation of potassium to the intracellular compartment. Sodium bicarbonate can be administered as Shohl's solution (one ml = one mEq bicarbonate) or sodium bicarbonate tablets (650 mg tablet contains approximately 7 mEq of bicarbonate) in doses of 1 to 3 mEq/kg/day to effectively treat acidosis and hyperkalemia. Caution must be taken when administering large Na^+ loads to patients with coexisting chronic congestive heart failure.

Synthetic Mineralocorticoid Hormone

Fludrocortisone in doses of 0.1-0.2 mg daily is effective in some patients with hyporeninemic hypoaldosteronism, particularly if sodium wasting is present; however, in some patients very large doses (>0.4 mg/d) are required. Fortunately, in most instances, this agent is not necessary and carries the hazard of expanding volume with its attendant consequences. Since many patients with HDRTA are older and frequently have hypertension or other cardiovascular diseases, this agent is infrequently employed in management.

APPENDIX

Evaluation of Distal Nephron Acidification

The following tests of urinary acidifying capacity are designed to evaluate features of distal nephron proton secretion. In most cases of HDRTA these tests are not required to make the diagnosis but can be helpful if one is interested in determining whether or not a combined defect is present, e.g., defect in epithelial transport and aldosterone deficiency.

1. Ammonium Chloride Loading. Acute oral ammonium chloride administration provides an acififying stimulus to the distal nephron by at least two possible mechanisms. First, by acutely lowering plasma bicarbonate less bicarbonate is delivered distally, and in consequence secreted H^+ is readily titrated by non-bicarbonate buffers. Secondly, a fall in blood pH may stimulate acidification of the luminal fluid of both cortical and medullary collecting ducts by lowering cell pH. This test need only be performed when patients are not spontaneously acidotic and in fact should be avoided if acidosis is present. In addition, NH_4Cl should not be administered to patients with serious liver disease since it may precipitate hepatic encephalopathy.

The test is performed by obtaining 2-3 20 minute anaerobic (under oil) urine collections, then administering NH_4Cl 0.1 gm/kg in capsule form (obtainable from pharmacy if pre-ordered) and waiting 45 minutes to an hour. Urine is then collected at hourly intervals for the next 5 hours. Urine pH of pre- and post-NH_4Cl specimens is then measured. A urine pH below 5.5 by the second to third hour (in association with an increase in net acid excretion) indicates that the distal nephron is capable of generating and maintaining a steep H^+ ion gradient relative to the blood. A value above 5.5 suggests that

an impairment in distal nephron proton secretion exists. It should be noted that reduction in pH to less than 5.5 does not mean that the secretory capacity is normal, rather it only indicates an intact H^+ gradient generating ability. Thus, as previously mentioned most patients with HDRTA are able to lower urine pH when buffer excretion rates are low but they have a defective secretory capacity. In order to examine secretory capacity measurement of urine-blood pCO_2 determined during bicarbonate loading is necessary (see below).

2. Sodium Sulfate Infusion. Acute sodium sulfate infusion provides an acidifying as well as a potassium excretory stimulus under certain circumstances, namely when distal nephron sodium avidity is maximized. In order to maximize distal sodium avidity the combination of a low sodium diet (e.g., $\leq$20 mEq/d) and a pharmacologic dose of mineralocorticoid hormone (oral or parenteral) must be administered to a prospective subject. It is presumed that under these conditions delivery of sodium to the distal nephron accompanied by the non-reabsorbable anion sulfate, permits avid distal sodium (but not sulfate) reabsorption thus generating a strong lumen-negative potential difference. The generation of the strong lumen-negative P.D. facilitates both H^+ and K^+ secretion. The test is performed by placing a subject on a 20 mEq/d Na^+ restriction for 5 days. Twelve to 24 hours before beginning the infusion, 10 mg DOCA is administered IM. Sodium sulfate 0.15 M plus sodium bicarbonate 25 mEq/L is infused at a rate of 8.3 ml/min for a 2 hour period. Urine pH, urinary sodium and potassium concentrations are measured during two to three 30 minute pre-infusion and four 60 minute post-infusion periods beginning 1 hr into the infusion. A urine pH of less than 5.5 signifies a defective gradient generating capacity and in addition implies a secretory defect in H^+ transport which may be due to: 1)

"voltage"-dependent mechanism, 2) to defective hydrogen ion pumps or 3) "back-leak" of protons. With respect to potassium, a 4-10 fold increase in potassium excretion rate above the pre-infusion levels indicates a normal response to the sodium sulfate under these conditions.

3. Determination of U-BpCO_2 in Alkaline Urine. The pCO_2 of alkaline urine produced by intravenous infusion of sodium bicarbonate increases progressively in proportion to the urinary bicarbonate concentration. In normal individuals with intact distal acidification this induces a pCO_2 gradient between urine and blood. It has been shown that generation of this gradient can be explained by slow dehydration of H_2CO_3 formed from titration of luminal HCO_3^- along the distal nephron. The U-BpCO_2 determined under conditions of alkaline diuresis has been used as a qualitative measure of distal nephron hydrogen ion secretory capacity. In patients with defective distal H^+ secretory capacity a subnormal U-BpCO_2 gradient generated during alkaline diuresis, has been demonstrated (52). A U-BpCO_2 gradient of 30 to 40 mmHg is generally observed in normal subjects.

Isotonic sodium bicarbonate infusion in euvolemic subjects at a rate sufficient to result in diuresis with urinary bicarbonate concentrations in the 100-200 mEq/L range is generally sufficient to properly analyze U-BpCO_2. After completion of two 30 minute control urine collections with one mid-point arterial or arterialized blood specimen prior to infusion, an arterial or arterilized blood sample for pCO_2 is obtained at 15 and 45 minute intervals (mid-point of urine collections). Urine must be collected under oil for accurate determination of HCO_3^- and pCO_2 levels. Once urinary bicarbonate is within the appropriate range 4-6 30 minute urine collections are obtained for analysis of HCO_3^- and pCO_2 along with arterilized blood pCO_2 at the midpoint of the third and sixth collections. U-BpCO_2 during infusion of $NaHCO_3$ is

generally in the 30-40 range in normal subjects. Failure to increase U-$BpCO_2$ into the normal range indicates a diminished distal H^+ ion secretory capacity. It should be recalled that this test does not determine H^+ gradient-generating capacity rather it detects an impaired ability to maximally transport H^+ into the distal tubular lumen.

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