Distal Renal Tubular Acidosis and the Potassium Enigma

Daniel Batlle, K.M.L.S.T. Moorthi, William Schlueter, and Neil Kurtzman

Severe hypokalemia is a central feature of the classic type of distal renal tubular acidosis (RTA), both in hereditary and acquired forms. In the past decade, many of the genetic defects associated with the hereditary types of distal RTA have been identified and have been the subject of a number of reviews. These genetic advances have expanded our understanding of the molecular mechanisms that lead to distal RTA. In this article, we review data published in the literature on plasma potassium from patients with inherited forms of distal RTA. The degree of hypokalemia varies depending on whether the disease is autosomal autosomal-recessive or dominant, but, interestingly, it occurs in defects caused by mutations in genes encoding the AE-1 exchanger, the carbonic anhydrase II gene, and genes encoding different subunits of the H+ adenosine triphosphatase. This shows that a unique defect involving the H+/K+-adenosine triphosphatase leading to renal potassium wastage cannot explain the hypokalemia seen in virtually all types of classic distal RTA.
Semin Nephrol 26:471-478 © 2006 Elsevier Inc. All rights reserved.

KEYWORDS distal renal tubular acidosis, hypokalemia, potassium, gene mutations

The renal tubular acidosis (RTA) syndromes encompass a disparate group of tubular transport defects that have in common the inability to secrete H+, a defect that is disproportionately large in relation to any reduction in the glomerular filtration rate.[1-16] This inability results in failure to excrete acid in the form of NH4+ and titratable acids or to recapture all filtered HCO3-, and leads to chronic metabolic acidosis. Many of the genetic defects associated with the hereditary types of both proximal and distal RTA have been identified and have been the subject of a number of reviews.[7,11,16-18] Distal RTA can present with low, normal, or high plasma [K+]. The defects leading to these 2 types, and the corresponding clinical features, are quite different. In this article, we provide an update on the hypokalemic types of distal RTA and discuss possible mechanisms leading to renal potassium wastage.

Overview of the Distal RTA Syndrome

Excretion of sufficient nonvolatile acid to match daily endogenous production is accomplished in the distal nephron by H+ secretion. Secretion of H+ at this site results in acid excretion by titrating filtered buffers destined for excretion, such as phosphate, creatinine, and uric acid, and by combining with NH3 to form NH4+, thereby trapping it in the urine. In the absence of these buffers, secretion of H+ would quickly produce a limiting transtubular [H+] gradient in the collecting tubule. In human beings this gradient (a minimum urine pH of 4.5) would allow the excretion of only 0.03 mEq of H+/L of urine. Thus, the presence of urinary buffers is essential to excrete the 50 to 70 mEq of H+ needed daily to maintain acid balance. A defect in distal H+ secretion is present in type I RTA, reducing the maximal transtubular [H+] gradient. This defect, in turn, results in a decrease in both NH4+ and titratable acid excretion. Reduced net acid excretion leads to a positive acid balance and the development of a hyperchloremic metabolic acidosis.[16]

An inability to secrete H+ and thus decrease urine pH normally (ie, <5.5), in the face of spontaneous acidemia, no matter how severe, is the hallmark of type I RTA. Patients with type I RTA often present with nephrocalcinosis and kidney stones, or both. A decrease in citrate excretion and an increase in calcium excretion are the predisposing factors for these complications.

Classic distal RTA may occur as a primary entity or may be acquired as a result of renal tubule involvement in a variety of renal diseases, systemic conditions, or drugs. In children, distal RTA usually occurs as a primary entity, whereas in

From the Division of Nephrology/Hypertension, Northwestern University Feinberg School of Medicine, Chicago, IL; and the Department of Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, TX.
Address reprint requests to Daniel Batlle, MD, 303 East Chicago Ave, 4-701 Tarry, Chicago, IL 60611-3008. E-mail: d-batlle@northwestern.edu

adults it is frequently an acquired disease.[16] Hypergamma-globulinemia, autoimmune disorders with renal involvement such as Sjögren's syndrome, lupus, and disorders of calcium metabolism are among the causes of acquired distal RTA. The primary type of distal RTA can present sporadically, but often is inherited in a dominant or autosomal-recessive pattern, as discussed later.

Acquired Distal RTA

The acquired form of classic distal RTA is seen in a variety of conditions. This disorder may develop in up to 50% of patients with Sjögren's syndrome and hyperglobulinemic purpura.[19,20] The mechanism by which hyperglobulinemia causes distal RTA is not known, but it is independent of the class or quantity of abnormal circulating globulin.[20] In patients with Sjögren's syndrome, high levels of serum gamma globulin, serum protein, and serum b-2 microglobulin are the best predictors of the development of classic distal RTA.[21] Classic distal RTA also has been reported in patients with cryoglobulinemia,[22] fibrosing alveolitis,[23] thyroiditis and Grave's disease,[24] systemic lupus erythematosus,[25,26] primary biliary cirrhosis,[27] chronic active hepatitis,[28-30] and multiple myeloma.[31] Distal RTA also is seen in patients with chronic renal allograft rejection.[32,33]

Patients with primary hyperparathyroidism appear to develop distal RTA only after they develop nephrocalcinosis.[34,35] Similarly, patients with vitamin D intoxication, hyperthyroidism, idiopathic hypercalciuria, medullary sponge kidney, and Fabry's disease who do not have nephrocalcinosis do not develop distal RTA.[36-41] The deposition of calcium in the renal medulla and in the cortical regions adjacent to the collecting ducts appears to be the primary mechanism causing impaired distal acidification in disorders of calcium metabolism.[42-44]

Inherited Distal RTA

Both autosomal-dominant and autosomal-recessive patterns of inheritance occur in patients with hereditary distal RTA; the mode of inheritance affects the clinical presentation and severity. Autosomal-recessive distal RTA occurs early in life and frequently is associated with a family history of consanguinity.[7] The phenotypic features include osteopetrosis, deafness, and mental retardation, and typically the clinical phenotype is more severe than autosomal-dominant distal RTA. Hypokalemia, metabolic acidosis, nephrocalcinosis, renal calculi, and growth retardation are seen in both autosomal-recessive and dominant distal RTA, but tend to be more severe and more common in patients with autosomal-recessive distal RTA.

Metabolic acidosis is the key determinant of delayed growth. If metabolic acidosis occurs early in life and is untreated, significant growth retardation can be seen in both autosomal-dominant and autosomal-recessive distal RTA. Because the genetic defects responsible for autosomal-dominant and autosomal-recessive distal RTA are better character-

ized, it may be possible to establish clinical correlates with each of the specific genetic defects.

Incomplete Distal RTA

Incomplete type 1 RTA is a syndrome manifested by an inability to maximally decrease urinary pH after acid loading in patients in whom metabolic acidosis does not develop spontaneously.[45,46] It has been described with both hereditary and acquired types of distal RTA. For instance, relatives of patients with identified autosomal-dominant distal RTA caused by mutations in the AE1 gene (see later) often have an incomplete distal RTA.[47] Chronic interstitial nephritis, kidney stones, medullary sponge kidney, and lithium therapy are a few causes of acquired incomplete distal RTA. Ammonium excretion is normal or only slightly reduced and these patients also may have low urinary citrate excretion. The cause of the low urinary excretion of citrate has been ascribed to enhanced proximal tubule reabsorption driven by the presence of subclinical acidosis.

In patients on chronic lithium therapy, HCO_3- administration fails to increase urine partial pressure of carbon dioxide (pCO_2), a sign of impaired collecting duct H+ secretion (see later), even though they retain the ability to decrease urine pH after NH_4Cl loading.[48] These patients usually do not develop a metabolic acidosis, indicating that their defect in H+ secretion is mild. Lithium therapy, at therapeutic plasma levels, consistently causes this type of incomplete distal RTA.[48] A similar pattern is described in patients with a variety of disorders, who thus appear to have an incomplete form of incomplete distal RTA.

Pathophysiology

The collecting duct has 3 distinct functional segments: cortical, outer medullary, and inner medullary. The cortical collecting duct has the capacity for both H+ and HCO_3- secretion. The outer medullary collecting duct has the highest capacity for H+ secretion, whereas the inner medullary collecting duct has a lower capacity. Throughout the collecting duct, H+ secretion is accomplished by active transport, provided by H+-adenosine triphosphatase (ATPase) and H+/K+-ATPase. Both transporters are located in the apical membrane of α-intercalated cells. Apical H+ secretion generates HCO_3- inside the intercalated cell, which exits via a Cl-/HCO_3- exchanger (AE1) located on the basolateral membrane. The SLC4 gene family includes at least 3 Na+ independent Cl-/HCO_3- exchanger genes and multiple Na+/HCO_3- cotransporter and Na+-dependent anion exchanger genes.[49,50] The most extensively studied among them are the Na+-independent anion exchangers, AE1, AE2, and AE3, all of which are expressed in kidney. The AE1 gene encodes eAE1 (band 3), the major intrinsic protein of the erythrocyte, as well as kAE1, the basolateral Cl-/HCO_3- exchanger of the acid-secreting α-intercalated cell. Mutations in AE1 are responsible for some forms of heritable distal RTA.

Intercalated cells constitute 40% of the cells in the distal nephron, and exist in 2 forms: one secretes H+ using H

ATPase-(a-type) and the other is involved in HCO_3- secretion (b-type). The α-intercalated cell is abundant in the outer medullary collecting duct, but also is present in the cortical collecting duct. The α-intercalated cell has an H+-ATPase in the apical membrane and a Cl-/HCO_3- exchanger (AE1) in the basolateral membrane The β-intercalated cell, found only in the cortical collecting tubule, secretes HCO_3- into the tubule lumen via a Cl-/HCO_3- exchanger in the apical membrane and has an H+-ATPase on the basolateral membrane.[51-54] The identity of the luminal Cl-/HCO_3- exchanger has been a matter of debate. It has been proposed that an isoform of the anion exchanger, AE4, performs this function in the rabbit kidney and that pendrin accomplishes this function in the mouse.[55] The expression and possibly the function of AE4 is species specific. In rats and in mice, AE4 functions as a Cl-/HCO_3- exchanger in the basolateral membrane of α-intercalated cells, whereas in rabbits AE4 is localized to the apical and lateral membranes and may contribute to HCO_3-secretion.[55] Pendrin is an apical Cl-/HCO_3- exchanger encoded by the PDS gene[45,56] and may have an essential role in Cl- reabsorption and HCO_3- secretion.[45] To date no mutations in the pendrin gene have been identified in patients with proximal or distal RTA. It is reasonable to postulate that some patients with pendrin mutations, who usually present with goiter,[57] may have a mild renal phenotype that will require provocative tests of urinary acidification for its identification.

Principal cells constitute 60% of the cells in the distal tubule and collecting tubules and are involved in water and Na+ reabsorption, and in K+ secretion.[58] The lumen-negative transepithelial potential created by Na+ reabsorption via the apical membrane Na+ channel epithelial sodium channel (ENaC) then promotes either passive Cl-reabsorption through the paracellular pathway or K+ secretion through K+ channels [primarily renal outer medullary potassium channel (ROMK)] in the apical membrane. The lumen-negative potential generated by Na+ reabsorption in principal cells also favors H+ secretion by neighboring α-intercalated cells.

Unlike the proximal tubule, the collecting duct contains only the type II isoenzyme (cytosolic carbonic anhydrase enzyme [CA II]) in the cytosol of intercalated cells. As noted earlier, this isoform also is found in the cytosol of proximal tubule cells, as well as in bone, brain, and retina.[43,59,60] Defects in cytosolic CA II have been reported to cause a mixed type of RTA (see CA II Gene Mutations section later).[43]

The potential mechanisms underlying distal RTA are outlined later.

H+-ATPase Defects

Defects in H+-ATPase have long been postulated as the key mechanism for distal RTA.[3-7,11-13] This hypothesis is supported by showing the absence of apical H+-ATPase staining in renal biopsy specimens from patients with distal RTA associated with Sjögren's syndrome.[61,62] In one of these reports, physiologic tests were consistent with a secretory defect type of distal RTA.[61] In fact, genetic defects in H+-ATPase now

have been identified in hereditary distal RTA (see Molecular Pathogenesis section).[63-65]

Rate-Dependent Defects

The term *rate-dependent defect* is used to designate abnormalities in H+ secretion that are secondary to abnormalities in the transport of other ions in the collecting duct. For example, a decrease in the ability to generate a negative lumen potential, as a result of either impaired Na+ reabsorption or enhanced Cl- reabsorption, will decrease H+ secretion in this segment of the nephron. Such a defect is likely to decrease K+ secretion as well (see hyperkalemic distal RTA), and is unlikely to be responsible for type I RTA. The availability of buffers (eg, NH3, HPO4-) is critically important for the secretion of the H+ to be effective in excreting adequate amounts of acid. Thus, reduction in a urinary buffer such as NH3, as seen in chronic hyperkalemic states, limits the rate of H+ excretion and results in a form of hyperkalemic distal RTA or contributes to it. The H+-ATPase also is responsive to aldosterone, and thus aldosterone deficiency can slow the rate of H+ secretion by this transporter, leading to a rate-dependent form of RTA.

Backleak

An abnormal increase in H+ permeability in the apical membrane of collecting duct cells, resulting in backleak of secreted H+, is a postulated mechanism for distal RTA that once was accepted widely. The administration of amphotericin, however, provides the only known model for such a defect.[66] In the turtle urinary bladder and in mammalian collecting tubules, the application of amphotericin to the mucosal (or apical membrane) side results in H+ back-diffusion (lumen to blood).[67] The drug also increases K+ permeability but not HCO_3- permeability. Toluene initially was believed to cause a permeability defect as well. Unlike amphotericin, however, toluene does not reduce the pH gradient generated across the turtle bladder, suggesting that it does not cause H+ back-diffusion.[68] In human beings exposed to toluene, urine P_{CO_2} does not increase normally after $NaHCO_3$ loading, indicating a diminished rate of H+ secretion by the collecting tubules.[68] Another mechanism that could mimic a permeability defect is mistargeting of the Cl-/HCO_3- exchanger to the apical rather than basolateral membrane of the α-intercalated cell. This would cause the intercalated cell to operate as a b-type cell with enhanced HCO_3- secretion (see AE1 Gene Mutations later).

Molecular Pathogenesis

The hereditary form of distal RTA has received increased attention recently because of dramatic advances in the understanding of its genetic basis.[69-72] Mutations have been identified in the genes encoding the anion exchanger (AE1), cytosolic carbonic anhydrase enzyme (CA II), and H+-ATPase (B1 and A4 subunits).
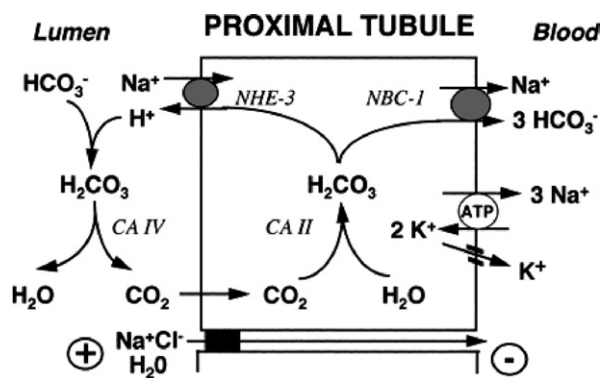
Figure 1 Collecting duct α-intercalated cell showing the H+ ATPase and the H+/K+ ATPase pumps on the apical membrane and the anion exchanger (AE-1 or Cl-/HCO$_3$- exchanger) and Na+/K+ AT-Pase on the basolateral membrane. Under normal conditions, the H+/K+ ATPase is the major pump secreting H+ into the tubule lumen, where it combines with phosphate and ammonia to accomplish acid excretion. Reprinted with permission from Rodriguez Soriano.[11]

AE1 Gene Mutations

The AE1 gene was targeted as a potential candidate gene for hereditary distal RTA because H+ secretion by the α-intercalated cell requires simultaneous HCO$_3$- exit through the basolateral membrane, via the Cl-/HCO$_3$- exchanger (Fig 1). Malfunction of AE1 could result in a decrease in H+ secretion in the collecting duct. The AE1 knockout mouse lacks AE1 immunostaining in α-intercalated cells, a finding consistent with a role for AE1 defects as a potential cause of a distal RTA.[73] Functional studies revealing impaired distal acidification or even the presence of metabolic acidosis, however, have not been reported in this mouse model.

The AE gene family has at least 3 members, with the AE1 (also known as *band 3*, *SCL4A1*, or *EPB3*) gene being the most abundant. In the collecting duct, the basolateral Cl/HCO$_3$-exchanger protein is encoded by the AE1 gene, present on chromosome 7, and this same gene gives rise to the erythrocyte Cl-/HCO$_3$- exchanger. The kidney form of AE1 differs from the erythrocyte form in that it is truncated at the amino terminus, lacking exons 1 to 3.[74]

Mutations in the gene encoding the erythrocyte Cl-/HCO$_3$-exchanger have been described in autosomal-dominant distal RTA.[69-71] The AE1 mutation most frequently found in affected members was a single base change resulting in a missense mutation (Arg $\rightarrow$ His) at codon 589 (R589S). A second mutation at codon 589, R589H, was found in several unrelated families with autosomal-dominant distal RTA.[71] The exact mechanism by which the AE1 mutations R589H and R589S cause autosomal-dominant distal RTA remains to be elucidated.[7,75] Insertion of the HCO$_3^-$/Cl$^-$ exchanger into the apical, rather than the basolateral, membrane (ie, mistargeting) could negate the H+ ions pumped by the H+-AT-Pase or H+/K+-ATPase. Among individuals with autosomal-dominant distal RTA, correlation between genotype and phenotype has not been apparent. A family with the R589C mutation was reported in which the father had severe

nephrocalcinosis, lithiasis, and isosthenuria, but no metabolic acidosis.[20] By contrast, the patient's daughter was acidotic, hypokalemic, and hypercalciuric, but without nephrocalcinosis. Thus, the clinical phenotype can be altered by modifier genes, some of which themselves may be RTA genes. Deafness has not been reported with dominant distal RTA and AE1 gene mutations, which makes it a useful distinguishing clinical feature.

From these studies, it appears that AE1 gene mutations are responsible for the autosomal-dominant type of distal RTA. Mutations in AE1 also cause hereditary spherocytosis and ovalocytosis. However, these conditions usually are not associated with distal RTA, and conversely distal RTA is not associated with abnormal red cell fragility.[21] Mutations in AE1 also have been identified as a major cause of autosomal-recessive distal RTA in southern Asia, but not as yet in the Western hemisphere. Compound heterozygosity of AE1 mutations has been associated with Southeast Asian ovalocytosis and distal RTA, and homozygosity of AE1 mutations has been associated with distal RTA and hemolytic anemia.

CA II Gene Mutations

The CA II gene is located at q22 on chromosome 8. At least 12 different mutations have been identified to date in different kindreds with distal RTA.[76-79] The syndrome of CA II deficiency, caused by these mutations, has a varied phenotypic presentation and has been diagnosed in a variety of ethnic backgrounds. It is particularly common in Arab populations of the Middle East. More than 70% of the reported cases of CA II deficiency syndrome are from these populations, probably the result of both a high rate of consanguineous marriages and an increased frequency of the CA II deficiency allele.[76]

Deficiency of CA II is also the primary defect underlying the autosomal-recessive syndromes of osteopetrosis, renal tubular acidosis, and cerebral calcification.[43,69] This disorder causes a proximal, distal, or a mixed pattern of proximal and distal RTA (type III RTA). Early onset of hypokalemia, paroxysmal muscle weakness, moderate to severe mental retardation, and growth retardation are the other associated manifestations.

H+-ATPase Gene Mutations

In patients with hereditary distal RTA, mutations in the genes encoding this key enzyme first were reported by Karet et al,[63] who studied 31 unrelated kindreds with a autosomal-recessive form of hereditary distal RTA associated with sensorineural hearing loss, screening for mutations in the ATP6V1B1 gene, which encodes the B1 subunit of H+-AT-Pase. This gene was found to be defective in 19 of the 31 total kindreds. None of these mutations were found among 36 unaffected control subjects. The finding of 15 independent mutations showing specificity for distal RTA and cosegregating with the disease constitutes proof that mutations in ATP6V1B1 cause autosomal-recessive distal RTA. These ATP6B1 mutations are likely to disrupt the structure or abrogate the production of the normal B1 subunit protein.[63]

The results of genetic analysis for ATP6B1 mutations in 13 kindreds with hereditary autosomal-recessive distal RTA with normal hearing also were reported by the same group.[80] No mutations at this gene locus were associated with distal RTA in these kindreds. A genome-wide linkage search revealed a new locus, however, at chromosome 7q33 to 34, in 9 of the 13 kindreds.[80] A gene, ATP6V0A4, encoding a novel kidney-specific H+-ATPase pump accessory subunit, the A4 subunit, was shown to be involved. These 9 kindreds were screened, and 8 were found to have different homozygous mutations in the ATP6V0A4 gene.[64] Other kindreds with this form of RTA did not show linkage to either ATP6V0A4 or to ATP6V1B1, which implies the existence of additional mutations at different loci in this disorder. More recently, the same group investigated 26 new kindreds with autosomal-recessive distal RTA and reported 7 novel ATP6V0A4 mutations.[65] They also reported the development of mild hearing loss, usually in young adulthood, as opposed to the severe hearing loss that usually occurs in childhood in ATP6V1B1 mutations.[65]

Expression studies showed the ATP6V0A4 gene product in α-intercalated cells in the kidney[64] and within the human inner ear.[65] Although the involvement of the A4 subunit in distal RTA shows that it must be essential for proper H+-ATPase pump function in the kidney, its role within the multisubunit pump structure remains unclear. In yeast, some mutations showed that this subunit is important for the assembly of the H+-ATPase, whereas other mutations had greater effects on ATPase activity and H+ transport.

The foregoing shows that ATP6V1B1 mutations are associated with autosomal-recessive distal RTA and severe deafness in childhood, whereas ATP6V0A4 mutations are associated with mild hearing loss that develops later, in early adulthood. Some families with primary autosomal-recessive distal RTA do not link to either ATP6V1B1 or ATP6V0A4. There are numerous other candidate genes for autosomal-recessive distal RTA, including the genes for all known subunits of the H+-ATPase or genes whose products are required for the trafficking of this transporter to the apical membrane.[21] The regulation of the H+/ATPase and another acid base transporters has been reviewed recently and will not be discussed here further.[7,16-18,81-83]

Why is Plasma Potassium Low in Classic Distal RTA?

The classic form of RTA usually is accompanied by hypokalemia, which results from renal K wastage. A permeability defect, causing passive K secretion, would readily explain it because it occurs with amphotericin B administration.[66,67] Because the permeability defect, as a mechanism of distal RTA, seems unique to amphotericin B, alternative explanations are required.[68] It is important to note that hypokalemia is a central feature of hereditary forms of distal RTA in which the molecular mechanism is now known (see later). Potassium wastage in the absence of an abnormal collecting tubule permeability for potassium could result from accelerated potassium secretion in the face of impaired H+ secretion. The enhancement of K secretion could be driven by secondary hyperaldosteronism, which may be a feature of distal RTA.[84,85] Aldosterone oversecretion could be expected as a result of sodium wastage, which has been documented in some patients with distal RTA.[84,85] Although this may be a reasonable explanation, it is nevertheless intriguing that some patients present with striking hypokalemia although others do not. Further, it is unlikely that aldosterone levels would be increased in the face of protracted potassium depletion, which suppresses its secretion and, indeed, few studies have reported aldosterone data from patients with severe hypokalemic distal RTA. It is therefore possible that factors other than secondary hyperaldosteronism are responsible for the development of severe hypokalemia, at least in some cases of distal RTA.

A particularly attractive mechanism that could account for hypokalemia is the existence of a defect in the renal K+/H+ ATPase pump.[86] Renal K+ excretion is determined not only by active K+ secretion localized largely to the distal tubule and cortical collecting tubule, but also by active K+ absorption localized, at least in part, to the outer medullary collecting tubule.[87,88] Under conditions of dietary K+ deprivation or extrarenal K+ wastage, profound K+ depletion would ensue unless there was a compensatory increase in K+ absorptive flux in more terminal nephron segments. Activation of K+ conservation in the outer medullary collecting tubule prevents further K+ wastage while producing enhanced proton secretion.[87] If the K+/H+ ATPase pump in the medullary collecting tubule were defective in distal RTA, one would expect the development of both hypokalemia and metabolic acidosis. Thus, the classic features of RTA could be explained readily by such a defective mechanism.

Such a mechanism was proposed after the observation that administration of vanadate to rats, a nonspecific inhibitor of the H+/K+-ATPase, resulted in hypokalemia and metabolic acidosis similar to that seen in patients with classic RTA.[86] Moreover, in some patients with distal RTA, gastric hypoactivity has been documented.[89] This would suggest the existence of a defective H+/K+ ATPase of both gastric parietal cells and renal collecting tubule cells. A partial defect in this pump could explain well the development of both hypokalemia and metabolic acidosis, especially under conditions of dietary K deprivation or enhanced extrarenal losses. In this regard, it is intriguing that the occurrence of severe hypokalemic RTA in the Northeastern part of Thailand peaks in the summer months.[90] Heat exposure in the summer could initiate potassium depletion, which would be aggravated by defective renal conservation as a result of a K+/H+ ATPase defect. Simpson and Schwartz[91] described a case report of an infant with hypokalemic distal RTA, the pathophysiology of which was proposed to be a deficiency or defect in the colonic H+, K+-ATPase activity. However, there are no genetic probes available to confirm this proposition. In the absence of a direct genetic analysis, a role of the H+/K+-ATPase in causing distal RTA, with severe hypokalemia, in our opinion, remains an attractive but unproven possibility.

Moreover, the administration of vanadate and another

Table 1 Summary of Selected Studies Including Patients with Hereditary DRTA with Molecular Diagnosis

Study	Mutation	Subjects	Serum K+ Range, mmol/L	Mean K+, mmol/L	Serum HCO₃ Range, mmol/L	Mean HCO₃, mmol/L	Blood pH Range	Mean Blood pH
Bruce et al,[47] 1997	AE1	18	2.1–4.2	3.59 ± 0.55	14.0–25.0	20.44 ± 3.15	—	
Karet et al,[71] 1998	AE1	6	3.4–4.6	4.00 ± 0.47	17.4–20.1	19.23 ± 0.93	7.29–7.38	7.33 ± 0.04
Stover et al,[65] 2002	ATP6V1B1	12	1.8–4.3	3.05 ± 0.67	8.0–17.4	13.60 ± 3.19	7.12–7.31	7.22 ± 0.08
Stover et al,[65] 2002	ATP6V0A4	23	1.3–4.4	2.99 ± 0.83	4.0–17.8	10.96 ± 3.95	6.72–7.99	7.23 ± 0.23
Karet et al,[71] 1998	AE 1	24	1.58–4.5	2.74 ± 0.63	4.8–15.5	11.07 ± 3.04	7.07–7.30	7.18 ± 0.07
Karet et al,[80] 1999	ATP6N1B	13	1.6–3.5	2.65 ± 0.54	5.5–16.0	10.78 ± 3.48	7.10–7.25	7.18 ± 0.06
Smith et al,[64] 2000	ATP6N1B	9	2.1–3.1	2.58 ± 0.39	5.5–16.0	9.9 ± 3.91	7.10–7.25	7.16 ± 0.06
Ruf et al,[94] 2003	ATP6B1	15	2.2–5.2	3.13 ± 0.92	7.8–12.5	10.70 ± 1.60	7.04–7.31	7.20 ± 0.07

compound that more specifically inhibits H+/K+ ATPase to rats resulted in marked inhibition of H+/K+-ATPase in collecting ducts from both K+-repleted and K+-depleted rats.[92] These animals, however, did not develop overt hypokalemia or metabolic acidosis so that a picture of complete distal RTA could not be shown. Interestingly, urine NH4 excretion was reduced, suggesting impaired distal acidification (Batlle et al, 1991, unpublished data). Daily urine K+ excretion was not different from that of controls, further suggesting that renal K+ concentration could be achieved effectively despite inhibition of the renal H+/K+ ATPase pump. In a H+/K+ ATPase knock out model it was later shown that K+ concentration is impaired in the colon but not in the kidney.[93]

A strong argument against the H+/K+-ATPase hypothesis is the finding that severe hypokalemia occurs in hereditary types of RTA in which the molecular defect is now known.[47,64,65,71,80,94] We have summarized the cumulative findings of 7 different reports, each looking at patients affected with either the autosomal-dominant or autosomal-recessive pattern of inheritance of distal RTA (Table 1). Individuals with an autosomal-recessive pattern of distal RTA in general had serum potassium levels lower than those with an autosomal-dominant inheritance and this difference was statistically significant. In addition, a similarly significant difference was seen in the mean serum bicarbonate levels and the mean pH when the 2 groups of patients were compared (Fig 2). Although all these studies have shown varying degrees of hypokalemia in affected individuals, it is interesting to note the differences in plasma potassium, bicarbonate, and pH based on the type of hereditary pattern of distal RTA (Table 1). The finding of hypokalemia in patients in whom the defect is caused by a mutation of the H+ATPase, the AEI, or the carbonic anhydrase 2 genes clearly suggests that the mechanism of potassium wastage is not secondary to a primary defect in distal RTA. Perhaps when H+ secretion is impaired by whatever mechanism, there is concomitant amplification of potassium secretory mechanisms, involving either the potassium channel, ROMK, or the sodium channel ENaC. This hypothesis should be tested.

In summary, all the forms of hereditary distal RTA usually are associated with hypokalemia from renal potassium wasting. The degree of hypokalemia seems to vary depending on whether the disease was autosomal-recessive or dominant. The most severe hypokalemia usually has been documented in patients with mutations in the genes encoding the ATP6B1 and ATP6VOA4 subunits of the H+ATPase pump.

Because patients with the same transport defect may be hypokalemic or normokalemic, it also is possible that there are additional transport abnormalities present in some hypokalemic patients that have yet to be defined.
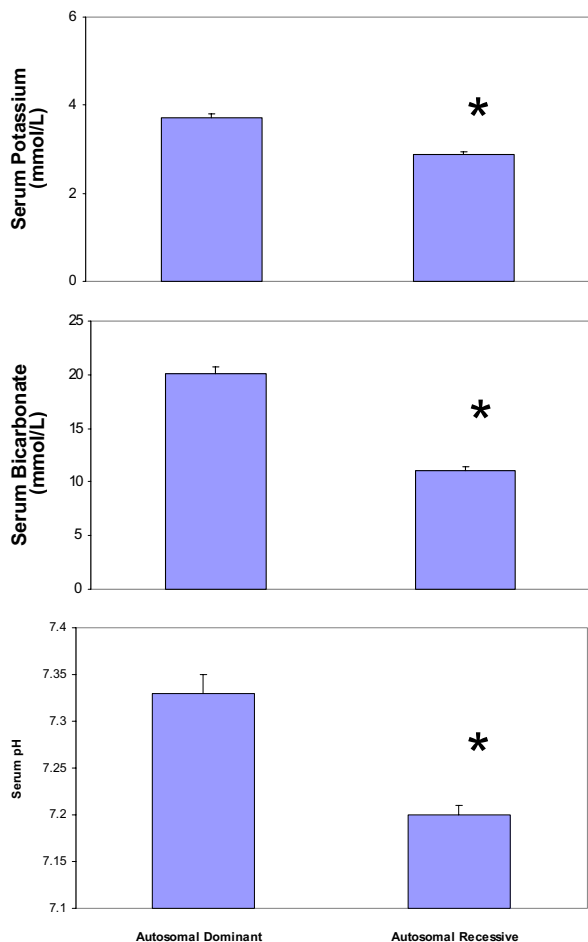

Figure 2 Summary of mean plasma potassium, blood pH, and bicarbonate in patients with distal RTA categorized on the basis of autosomal-dominant or autosomal-recessive patterns of inheritance. Data from studies summarized in Table 1. *Statistically significant difference. (Color version of figure is available online.)

References

1. Mcsherry E, Sebastian A, Morris RCJ: Renal tubular acidosis in infants: The several kinds, including bicarbonate wasting, classic renal tubular acidosis. J Clin Invest 51:499-514, 1972

2. Edelman CM Jr, Rodriguez-Soriano J, Boichis H: An isolated defect in renal bicarbonate reabsorption as a cause of hyperchloremic acidosis. J Pediatr 67:946, 1965

3. Arruda JAL, Kurtzman NA: Mechanisms and classification of deranged distal urinary acidification. Am J Physiol 239:F515-F523, 1980

4. Batlle DC, Kurtzman NA: Distal renal tubular acidosis: Pathogenesis and classification. Am J Kidney Dis 1:328-344, 1982

5. Batlle D, Flores G: Underlying defects in distal renal tubular acidosis: New understandings. Am J Kidney Dis 27:896-915, 1996

6. Kurtzman NA: Renal tubular acidosis: A constellation of syndromes. Hosp Pract 22:173-178, 181, 1987

7. Batlle D, Ghanekar H, Jain S, et al: Hereditary distal renal tubular acidosis: New understandings. Annu Rev Med 52:471-484, 2001

8. Batlle DC: Segmental characterization of defects in collecting tubule acidification. Kidney Int 30:546-554, 1986

9. Schlueter W, Keilani T, Hizon M, et al: On the mechanism of impaired distal acidification in hyperkalemic renal tubular acidosis—evaluation with amiloride and bumetanide. J Am Soc Nephrol 3:953-964, 1992

10. Batlle DC: Sodium dependent urinary acidification in patients with aldosterone deficiency and in adrenalectomized rates: Effect of furosemide. Metabolism 35:852-860, 1986

11. Rodriguez Soriano J: Renal tubular acidosis: The clinical entity. J Am Soc Nephrol 13:2160-2170, 2002

12. Sebastian A, Schambelan M, Lindenfeld S: Amelioration of metabolic acidosis with fludrocortisone therapy in hyporeninemic hypoaldosteronism. N Engl J Med 197:576-583, 1977

13. Batlle DC, Arruda JA, Kurtzman NA: Hyperkalemic distal renal tubular acidosis associated with obstructive uropathy. N Engl J Med 304:373-380, 1981

14. Batlle DC: Hyperkalemic hyperchloremic metabolic acidosis associated with selective aldosterone deficiency and distal renal tubular acidosis. Semin Nephrol 1:260-273, 1981

15. Batlle DC, Itsarayoungyen K, Arruda JA: Hyperkalemic hyperchloremic metabolic acidosis in sickle cell hemoglobinopathies. Am J Med 72:188-192, 1982

16. Moorthi KMLST, Batlle D: Renal tubular acidosis, in Gennari FJ, Adrogue HJ, Galla JH, et al (eds): Acid Base Disorders and Their Treatment. Taylor and Francis, Boston, MA, 2005, pp 417-467

17. Alper SL: Genetic diseases of acid base transporters. Ann Rev Physiol 64:899-923, 2002

18. Karet FE: Inherited distal renal tubular acidosis. J Am Soc Nephrol 13:2178-2184, 2002

19. Marquez-Julio A, Rapoport A, Wilansky DL, et al: Purpura associated with hypergammaglobulinemia, renal tubular acidosis and osteomalacia. CMAJ 116:53-58, 1977

20. Morris RCJ, Fudenberg HH: Impaired renal acidification in patients with hypergammaglobulinemia. Medicine (Baltimore) 46:57-69, 1967

21. Pertovaara M, Korpela M, Pasternack A: Factors predictive of renal involvement in patients with primary Sjogren's syndrome. Clin Nephrol 56:10-18, 2001

22. LoSpalluto J, Dorward B, Biller W: Cryoglobulinemia based on interaction between a gammamacroglobulin and 7S gamma globulin. Am J Med 32:142, 1962

23. Mason AMS, McIllmur MB, Golding PL, et al: Fibrosing alveolitis associated with renal tubular acidosis. BMJ 4:596-599, 1970

24. Mason AMS, Golding PL: Renal tubular acidosis and autoimmune thyroid disease. Lancet 2:1104-1107, 1970

25. Jessop S, Eales L, Mumford G, et al: Renal tubular function in systemic lupus erythematosis. S Afr Med J 46:848, 1972

26. Tu WH, Shearn MA: Systemic lupus erythematosus and latent renal tubular dysfunction. Ann Intern Med 67:100-109, 1967

27. Golding PL: Renal tubular acidosis in chronic liver disease. Postgrad Med J 51:550-556, 1975

28. Golding PL, Smith M, Williams R: Multisystem involvement in chronic liver disease—studies on incidence and pathogenesis. Am J Med 55:772-782, 1973

29. Reade AE, Sherlock S, Harrison CV: Active "juvenile" cirrhosis considered as part of a systemic disease. Gut 4:378, 1963

30. Seedat YK, Raine ER: Active chronic hepatitis associated with renal tubular acidosis and successful pregnancy. S Afr Med J 39:595-597, 1965

31. Lazar GS, Feinstein DI: Distal renal tubular acidosis in multiple myeloma. Arch Intern Med 141:655-657, 1981

32. Batlle DC, Mozes MF, Manaligod J, et al: The pathogenesis of hyperchloremic metabolic acidosis associated with kidney transplantation. Am J Med 70:786-796, 1981

33. Jordan M, Cohen EP, Roza A, et al: An immunocytochemical study of Hþ ATPase in kidney transplant rejection. J Lab Clin Med 127:310-314, 1996

34. Cohen SI, Fitzgerald MG, Fourman P: Polyuria in hyperparathyroidism. QJM 26:423, 1957

35. Reynolds TB, Bethune JE: Renal tubular acidosis secondary to hyperparathyroidism. Clin Res 17:169, 1966

36. Huth EJ, Mayock RL, Kerr RM: Hyperthyroidism associated with renal tubular acidosis. Am J Med 26:818, 1959

37. Ferris T, Kashgarian M, Levitin H: Renal tubular acidosis and renal potassium wasting acquired as a result of hypercalcemic nephropathy. N Engl J Med 265:924-928, 1961

38. Parfitt AM, Higgins BA, Nassim JR: Metabolic studies in patients with hypercalciuria. Clin Sci Mol Med 27:463-482, 1964

39. Deck MDF: Medullary sponge kidney with renal tubular acidosis: A report of 3 cases. J Urol 94:330-335, 1965

40. Morris RCJ, Yamauchi H, Palubinskas AJ: Medullary sponge kidney. Am J Med 38:883-892, 1965

41. Yeoh SA: Fabry's disease with renal tubular acidosis. Singapore Med J 8:275-279, 1967

42. Preminger GM, Sakhaee K, Skurla C, et al: Prevention of recurrent calcium stone formation with potassium citrate therapy in patients with distal renal tubular acidosis. J Urol 134:20-23, 1985

43. Buckalew VM Jr, Purvis ML, Shulman MG, et al: Hereditary renal tubular acidosisReport of a 64 member kindred with variable clinical expression including idiopathic hypercalciuria. Medicine (Baltimore) 53:229-254, 1974

44. Reynolds TB: Observations on the pathogenesis of renal tubular acidosis. Am J Med 25:503-515, 1958

45. Batlle DC: Renal tubular acidosis, in Seldin DW, Giebisch G (eds): The Regulation of Acid–Base Balance. New York, 1989, 353-390

46. Tannen RL, Falls WFJ, Brackett NCJ: Incomplete renal tubular acidosis: Some clinical and physiological features. Nephron 15:111-123, 1975

47. Bruce LJ, Cope DL, Jones GK, et al: Familial distal renal tubular acidosis is associated with mutations in the red cell anion exchanger (Band 3, AE1) gene. J Clin Invest 100:1693-1707, 1997

48. Batlle D, Gaviria M, Grupp M, et al: Distal nephron function in patients receiving chronic lithium therapy. Kidney Int 21:477-485, 1982

49. Alper SL, Natale J, Gluck S, et al: Subtypes of intercalated cells in rat kidney collecting duct defined by antibodies against erythroid band 3 and renal vacuolar H+þ ATPase. Proc Natl Acad Sci U S A 86:5429-5433, 1989

50. Alper SL, Darman RB, Chernova MN, et al: The AE gene family of Cl-/HCO$_3$-exchangers. J Nephrol 15:S41-S53, 2002 (suppl 5)

51. Alper SL, Natale J, Gluck S, et al: Subtypes of intercalated cells in rat kidney collecting duct by antibodies against erythroid band 3 and renal vacuolar Hþ ATPase. Proc Natl Acad Sci U S A 86:5429-5433, 1989

52. Brown D, Hirsch S, Gluck S: An H+ ATPase in opposite plasma membrane domains in kidney epithelial cell subpopulations. Nature 331:622-624, 1988

53. Gluck SL, Underhill DM, Iyori M: Biochemical regulation of proton secretion by the vacuolar Hþ ATPase of renal epithelial cells, in Santo NG, Capasso G (eds): Acid–Base and Electrolyte Imbalance, Molecular, Cellular, and Clinical Aspects. Annual Reviews. Naples, Italy, 2002, 30-42

54. Nelson RD, Guo XL, Masood K, et al: Selectively amplified expression of an isoform of the vacuolar H+ ATPase 56 kilodalton subunit in renal intercalated cells. Proc Natl Acad Sci U S A 89:3541-3545, 1992

55. Ko SB, Luo X, Hager H, et al: AE4 is a DIDS-sensitive Cl+/HCO3- exchanger in the basolateral membrane of the renal CCD and the SMG duct. Am J Physiol 283:C1206-C1218, 2002

56. Soleimani M, Greeley T, Petrovic S, et al: Pendrin: An apical Cl+/HCO3- exchanger in the kidney cortex. Am J Physiol 280:F356-F364, 2001

57. Kopp P: Perspective: Genetic defects in the etiology of congenital hypothyroidism. Endocrinology 143:2019-2024, 2002

58. Koeppen BM: Electrophysiological identification of principal and intercalated cells in the rabbit outer medullary collecting duct. Pflugers Arch 409:138-141, 1987

59. Kumpulainen T: Immunohistochemical localization of human carbonic anhydrase isozymes. Ann N Y Acad Sci 429:359-368, 1984

60. Sato S, Zhu XL, Sly WS: Carbonic anhydrase isozymes IV and II in urinary membranes from carbonic anhydrase II-deficient patients. Proc Natl Acad Sci U S A 87:6073-6076, 1990

61. Cohen EP, Bastani B, Cohen MR, et al: Absence of Hþ ATPase in cortical collecting tubules of a patient with Sjogren's syndrome and distal renal tubular acidosis. J Am Soc Nephrol 3:264-271, 1992

62. Defranco PE, Haragsim L, Schmitz PG, et al: Absence of vacuolar H+ ATPase pump in the collecting duct of a patient with hypokalemic distal renal tubular acidosis and Sjogren's syndrome. J Am Soc Nephrol 6:295-301, 1995

63. Karet FE, Finberg KE, Nelson RD, et al: Mutations in the gene encoding B1 subunit of Hþ ATPase cause renal tubular acidosis with sensorineural deafness. Nat Genet 21:84-90, 1999

64. Smith AN, Skaug J, Choate KA, et al: Mutations in ATP6N1B, encoding a new kidney vacuolar proton pump 116-kD subunit, cause autosomal-recessive distal renal tubular acidosis with preserved hearing. Nat Genet 26:71-75, 2000

65. Stover EH, Borthwick KJ, Bavalia C, et al: Novel ATP6V1B1 and ATP6V0A4 mutations in autosomal-recessive distal renal tubular acidosis with new evidence for hearing loss. J Med Genet 39:796-803, 2002

66. Steinmetz PR, Lawson LR: Defect in acidification induced in vitro by amphotericin B. J Clin Invest 49:596-601, 1970

67. Rosen S: Turtle bladder. II. Observations on epithelial cytotoxic effect of amphotericin B. Exp Mol Pathol 12:297-305, 1970

68. Batlle DC, Sabatini S, Kurtzman NA: On the mechanism of toluene induced renal tubular acidosis. Nephron 49:210-218, 1988

69. Inaba M, Yawata A, Koshino I, et al: Defective anion transport and marked spherocytosis with membrane instability caused by hereditary total deficiency of red cell band 3 in cattle due to a nonsense mutation. J Clin Invest 97:1804-1817, 1996

70. Jarolim P, Shayakul C, Prabakaran D, et al: Autosomal dominant distal renal tubular acidosis is associated in three families with heterozygosity for the R589H mutation in the AE1 (band 3)gene. J Biol Chem 273: 6380-6388, 1998

71. Karet FE, Gainza FJ, Gyory AZ, et al: Mutations in the chloride bicarbonate exchanger gene AE1 cause autosomal dominant but not autosomal-recessive distal renal tubular acidosis. Proc Natl Acad Sci U S A 95:6337-6342, 1998

72. Vasuvattakul S, Yenchitsomanus PT, Vachuanichsanong P, et al: Autosomal-recessive distal renal tubular acidosis associated with Southeast Asian ovalocytosis. Kidney Int 56:1674-1682, 1999

73. Peters LL, Jindel HK, Gwynn B, et al: Mild spherocytosis and altered red cell ion transport in protein 4.2 null mice. J Clin Invest 103:1527-1537, 1999

74. Brosius FC III, Alper SL, Garcia AM, et al: The major kidney band 3 gene transcript predicts an amino terminal truncated band 3 polypeptide. J Biol Chem 264:7784-7787, 1989

75. DuBose TD Jr: Autosomal dominant distal renal tubular acidosis and the AE1 gene. J Am Kidney Dis 33:1190-1197, 1999

76. Fathallah DM, Bejaoui M, Lepaslier D, et al: Carbonic anhydrase II (CA II) deficiency in Maghrebian patients: Evidence for founder effect and genomic recombination at the CA II locus. Hum Genet 99:634-637, 1997

77. Aramaki S, Yoshida I, Yoshino M, et al: Carbonic anhydrase II deficiency in three unrelated Japanese patients. J Inherit Metab Dis 16:982-990, 1993

78. Hu PY, Ernst AR, Sly WS, et al: Carbonic anhydrase II deficiency: Single base deletion in exon 7 is the predominant mutation in Caribbean Hispanic patients. Am J Hum Genet 54:602-608, 1994

79. Hu PY, Lim EJ, Ciccolella J, et al: Seven novel mutations in carbonic anhydrase II deficiency syndrome identified by SSCP and direct sequencing analysis. Hum Mutat 9:383-387, 1997

80. Karet FE, Finberg KE, Nayir A, et al: Localization of a gene for autosomal-recessive distal renal tubular acidosis with normal hearing (rdistal RTA2) to 7q33–34. Am J Hum Genet 65:16, 1999

81. Wagner CA, Finberg KE, Stehberger PA, et al: Regulation of the expression of the Cl-/anion exchanger pendrin in mouse kidney by acid-base status. Kidney Int 62:2109-2117, 2002

82. Kovacikova J, Winter C, Loffing-Cueni D, et al: The connecting tubule is the main site of the furosemide-induced urinary acidification by vacuolar H+-ATPase. Kidney Int 90(10):1706-1716, 2006

83. Valles P, Lapointe MS, Wysocki J, et al: Kidney vacuolar H+ATPase: Physiology and regulation. Semin Nephrol 26:361-374, 2006

84. Sebastian A, McSherry E, Morris RC Jr: Renal potassium wasting in renal tubular acidosis (RTA). J Clin Invest 50:667, 1971

85. Sebastian A, McSherry E, Morris RC Jr: Impaired renal conservation of sodium and chloride during sustained correction of systemic acidosis in patients with type I, classic renal tubular acidosis. J Clin Invest 58:454-469, 1976

86. Dafnis E, Spohn M, Lonis B, et al: Vanadate causes hypokalemic distal RTA. Am J Physiol 262(3 Pt 2):F449-453, 1992

87. Wingo CS, Straub SC: Active proton secretion and potassium absorption in the rabbit outer medullary collecting duct. J Clin Invest 84:361-365, 1989

88. Codina J, DuBose TD Jr: Molecular regulation and physiology of the H+ K+-ATPases in kidney. Semin Nephrol 26:345-351, 2006

89. Sitprija V, Eiam-Ong S, Suvanapha R, et al: Gastric hypoactivity in distal RTA. Nephron 50:395-396, 1988

90. Phakdeekitcharoen B, Ruangraska C, Radinahamed P: Hypokalemia and paralysis in Thai population. Nephrol Dial Transplant 19:2013-2018, 2004

91. Simpson AM, Schwartz GJ: Distal renal tubular acidosis with severe hypokalemia probably caused by colonic H+/K+ ATPase deficiency. Arch Dis Child 84:504-507, 2001

92. Mujais SSK, Chen Y, Batlle D: Profile of H+/K+ ATPase along the collecting duct: Effect of K+ depletion. Clin Res 39:F709A, 1991

93. Meneton P, Schultheis PJ, Greeb J, et al: Increased sensitivity to K+ deprivation in colonic H+ K+ ATPase-deficient mice. Clin Invest 101: 536-542, 1998

94. Ruf R, Rensing R, Topaloglu R, et al: Confirmation of the ATP6B1 gene as responsible for distal RTA. Pediatr Nephrol 18(2):105-109, 2004