Renal Tubular Acidosis: A New Look at an Old Problem

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Summary: Although the definition of renal tubular acidosis (RTA) is simple, understanding the physiologic basis underlying the various types of this clinical entity is much more difficult. The pathophysiology of this disorder is reviewed using the normal acid-base functions of the involved segments of the nephron as a guide to understanding. Clinical and laboratory features of the subtypes of RTA are addressed, and diagnosis and treatment discussed. New developments in the knowledge and understanding of the associated growth disturbances, mineral metabolism, and molecular biology of RTA are also reviewed to provide the most current view of this relatively common pediatric entity. Clin Pediatr. 2001;40:533-543

Introduction

Maintenance of a normal pH of body fluids is of critical importance to virtually all cell processes. The ability of changes in hydrogen ion concentration to affect the physical conformation and thus the biologic function of protein molecules, is a familiar example of the key role of pH. Moreover, the human organism produces substantial quantities of anions, such as, sulfate, phosphate, and lactate. These materials are collectively termed "unmeasured anions," and they must be excreted by the kidney; accumulation of one or more causes an increased plasma anion gap ([Na\(^+\)]-|[Cl\(^-\)]+|[HCO\(_3\)\(^-\)]|). Generally, such accumulation results from increased production (e.g., inborn errors of metabolism), so that absent such conditions most patients with metabolic acidosis have an anion gap of less than 16. Although the gut makes a significant contribution to electrolyte and fluid reabsorption, it is the renal tubular epithelium that is responsible for defense against accumulation of hydrogen ion. Accordingly, when there is clinical evidence of metabolic acidosis with no increase in the anion gap, a search for renal disease is a priority.

Clinically, renal tubular acidosis (RTA) is characterized by a normal anion gap, hyperchloremic metabolic acidosis, and associated failure to thrive secondary to growth failure as well as anorexia. Polyuria and constipation can also be seen, although neither may be apparent in the neonatal period. Hyperchloremic metabolic acidosis in pediatric practice is most often associated with diarrheal disease. Both diarrhea and RTA result in hypokalemia; in a young infant with diarrhea and underlying RTA, the true diagnosis may be obscured. Thus, inordinately slow resolution of hyperchloremic metabolic acidosis following diarrheal disease should suggest the possibility of an underlying primary RTA.

Beyond the difficulties inherent in delineating RTA, RTA can be subcategorized into different disorders with distinctly different prognoses. The diagnostic cata-
loguing of RTA is important because of these varied outcomes and is based on the underlying pathophysiology. Thus, we begin with a review of the normal processes for renal handling of an acid load and progress from this to a discussion of the pathophysiology underlying the different types of RTA. Following this, we provide an updated review of mineral metabolism in RTA and end with a discussion of our current understanding of the molecular biology of the disorder.

Physiology and Pathophysiology

Proximal Tubule

In a functional sense, the nephron regulates acid-base homeostasis by simultaneous processes of bicarbonate reabsorption and hydrogen ion secretion. For purposes of simplification we have chosen to represent these as base reabsorption and acid secretion (Figure 1). Conceptually, the proximal tubule is charged with the task of reclaiming filtered base (~85% of the total); failure of this process leads to reduction in systemic base, resulting in metabolic acidosis. Isolated proximal RTA of genetic origin is uncommon and is generally seen in association with other aspects of tubular dysfunction. The normal process of base salvage proceeds in the proximal tubule without generation of a significant pH gradient. The threshold for bicarbonate reabsorption in neonates is reduced, despite an eventual normal adult reabsorptive capacity.\(^1,2\) The threshold is increased gradually during maturation, which is reflected in increasing serum bicarbonate concentrations with age. In the normal adult, the proximal tubular system results in recovery of >6000 mEq of bicarbonate/day. Filtered sodium is actively transported across the luminal membrane using a Na\(^+\)-H\(^+\) carrier molecule (NHE-3) driven by the concentration gradient for sodium generated by Na\(^+\)-K\(^+\) ATPase located at the antiluminal surface of the cell (Figure 2). The expelled H\(^+\) rapidly associates with filtered luminal bicarbonate to form H\(_2\)CO\(_3\) (membrane-bound carbonic anhydrase, CA IV), which just as rapidly dissociates and liberates CO\(_2\) and water. The CO\(_2\) diffuses into the cell, where it is enzymatically (carbonic anhydrase, CA II) rehydrated to form carbonic acid, which again dissociates with the formation of H\(^+\) and HCO\(_3^-\). CA II, or cytosolic carbonic anhydrase, is the predominant (95%) renal isozyme and is found in large pro-
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Portion in the proximal tubules. Bicarbonate exits across the antiluminal membrane for two reasons: 1) mass action, because the bicarbonate concentration is lower in the interstitial space than in the cytosol; and 2) carrier-mediated cotransport (NBC-1) along an electrochemical gradient, generated by expulsion of the positively-charged Na⁺ cation into this space by the ion pump. While the economy of the system is marvelous, the net result is sodium and bicarbonate reabsorption but no net elimination of H⁺.

A traditional view of proximal renal tubular acidosis holds that the tubular maximum (Tm) for bicarbonate is reduced, thus lowering the plasma concentration and permitting a greater proportion than normal of the filtered HCO₃⁻ to escape into the urine. At first glance, this is an adequate explanation for the clinical observations; a closer look leaves us with the difficulty of explaining how the tubular maximum (Tm) is physically lowered and why patients with type 2 RTA often can produce an acid urine. Modern molecular biology has helped us to address the central issue of reduction in the Tm.

Contrary to the natural tendency to conceive a reduced Tm as impairment of transport across the brushborder surface, the real defect is almost certainly located in the carrier for Na⁺-HCO₃⁻ co-transport across the antiluminal or basolateral surface. This molecule, NBC-1 (Na⁺-bicarbonate co-transporter), is a protein consisting of approximately 1000 amino acid residues and undergoes functional changes with varying pH conditions. Human gene cloning experiments have revealed the existence of three molecular isoforms in kidney (NBC-1, NBC-2, and NBC-3); it is unclear at present what the precise functional distinctions are between each of the three isoforms. It is also not yet apparent whether the cause(s) for the varying clinical severity of type 2 RTA can be attributed to mixed heterozygosity of mutations in these three isoforms because of limited access to tissue for study. Nonetheless, it appears that the mechanism underlying the reduced tubular maximum for bicarbonate is actually reduced transport out of the proximal tubular cell with increased backflow (efflux) of cytosolic bicarbonate into the tubular lumen.

The inability of the proximal tubule to achieve net hydrogen ion elimination renders the bicarbonate buffer system vulnerable to an impairment in the process of bicarbonate reclamation. In such circumstances, the result is a non-anion gap metabolic acidosis. This is because the body's metabolic processes generate nonvolatile, or fixed acids, which must be buffered by the blood and eliminated through the kidneys. The laws of electrical neutrality also demand that each mole of bicarbonate that is lost be accompanied by a mole of cation, usually potassium and, to a lesser extent, sodium. The sodium loss provokes a blood volume contraction and a secondary release of al-
dosterone, which exacerbates the urinary potassium loss and creates a significant hypokalemia, although this is generally mild and does not require treatment. These are the phenomena underlying the clinical entity termed proximal or type 2 RTA, defined as a systemic acidosis deriving from a relative decrease in the ability of the tubule to reclaim base.

Finally, while bicarbonaturia may be expected to produce alkaline urine, this is not necessarily the case in clinical practice. Although the ability of the proximal tubule to reclaim base is impaired in proximal RTA, the ability of the nephron to eliminate H⁺ remains unaffected. Thus, patients with type 2 RTA and systemic acidosis may produce urine with an acid pH, rendering urine pH alone an inaccurate diagnostic test for distinction between types I and II RTA. Since the bicarbonate threshold increases with age, the relative reduction in bicarbonate Tₘ in the neonate often contributes to a picture of hyperchloremic metabolic acidosis and acid urine pH, which disappears as the infant develops. Notwithstanding its disappearance, however, this situation may require alkali therapy in early life to avoid anorexia and permit normal growth.

Distal Tubule

As noted, base reabsorption is handled primarily in the proximal tubule, which is physiologically unequipped to form a hydrogen ion gradient between the blood and the tubular lumen with which to regulate blood pH. This task falls to the distal tubule, where hydrogen ion is secreted with the generation of a steep H⁺ gradient. Thus, the role of the distal tubule in acid-base homeostasis may be conceptualized as one of acid secretion, in contrast to the proximal tubule, which serves as a major site for reabsorption of base. It is this difference in roles that also accounts for the differences in clinical severity between disturbances of proximal and distal tubular functions. Hence, although increased loss of base from the proximal tubule causes development of a systemic acidosis, the degree of the acidosis is mitigated considerably by the ability of the distal tubule to eliminate hydrogen ion. In contrast, however, when the distal tubule is not capable of normal H⁺ elimination, there is a major acid-base disequilibrium resulting in severe acidosis.

The key to the ability of the distal tubule to cause net acid secretion is the capacity to directly secrete H⁺ into the tubular lumen independent of sodium, using a H⁺-ATPase pump. Other features distinct to the distal tubule include the following: nonleaky tight junctions permitting generation of very steep concentration gradients, and the generation of ammonia (Figure 3). It is important to understand that the hydrogen ion that is expelled is generated by the action of carbonic anhydrase on water and CO₂, so that the remaining HCO₃⁻ can be exchanged at the basal surface for a chloride ion. The deficit left by expulsion of the hydrogen ion is addressed by diffusion of a sodium ion, which exits with the bicarbonate in exchange for a K⁺. The simultaneous production of NH₃ from glutamine and its diffusion into the lumen captures the hydrogen ion by formation of ammonium radical and combination with filtered phosphate. It is the formation of these acid salts that comprises titratable acid and renders the ability of the distal tubule to produce an acid urine.

Remarkably, there is a direct similarity between the molecular defects in proximal and distal RTA. As in type 2 RTA, the defect in type 1 RTA lies not in the brushborder H⁺-ATPase, which might be an intuitive assumption, but rather in the Cl⁻-HCO₃⁻ exchanger at the antiluminal surface (see Figure 3). This has been definitively demonstrated in those individuals showing an autosomal dominant transmission pattern, but is less clear in those with the autosomal recessive variety, in which some patients are thought to have a defect in the brushborder H⁺-ATPase. The failure of chloride-bicarbonate exchange leads to accumulation of intracellular carbonic acid that impedes further synthesis as well as dissociation into hydrogen ion and bicarbonate. Sodium-potassium exchange will be adversely affected as well, since sodium normally exits into the pericapillary space along with bicarbonate. Since less hydrogen ion is formed by dissociation, there is less expelled into the lumen to form acid salts and the urine pH tends toward the neutral range.

As in proximal RTA, the diminished sodium reabsorption causes a volume contraction, reduced body sodium, and a secondary hyperaldosteronism. The resulting potassium loss leads to hypokalemia, often of a rather severe degree. However, there is a divergent response of the hypokalemia to therapy between the two forms of RTA; with volume and pH correction there is a decrease in aldosterone and a correction of potassium wasting in distal RTA. By contrast, in proximal RTA the potassium wasting increases with volume correction, because there is increased delivery of sodium bicarbonate to the distal tubule, which is charged
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A final pathogenic issue in both forms of RTA is that of calcium-phosphorus metabolism and secondary effects on the kidney. Common to both proximal and distal RTA is a state of chronic metabolic acidosis, requiring that H+ be both buffered and excreted by alternative means. The most direct effect of acidosis is the displacement of protein-bound calcium by hydrogen in the blood, thereby increasing both the amount of ionized calcium and its filtration by the glomerulus. However, chronic acidosis provokes divergent responses to this increased calcium load in the proximal and distal segments, increasing reabsorption in the former and inhibiting it in the latter. The net effect is to cause hypercalciuria, which can reach striking proportions in the distal RTA form but usually remains of no consequence in isolated type 2 disease. Type 1 RTA is due to failure to eliminate hydrogen ion, while type 2 is a consequence of diminished base reabsorption; thus, the marked difference in degree of systemic acidosis may also play a role.

The severe acidosis of type 1 disease also inhibits production and release of mitochondrial citrate, which is normally present to react with calcium and enhance its solubility. Increased filtered load and inhibited reabsorption causes severe hypercalciuria, while the reduction in solubility leads to a marked tendency toward nephrocalcinosis. Moreover, the need to maintain serum calcium necessitates increased turnover of bone matrix and results in osteomalacia. In contrast, bone disease in type 2 RTA is relatively mild, generally resulting from phosphate loss and secondary hyperparathyroidism. Phosphate, a major urinary buffer, is filtered by the glomerulus and enters the proximal tubular lumen where it becomes available to buffer hydrogen ions. However, ammoniagenesis is submaximal in chronic acidosis, which restricts the usefulness of NH3 as a urinary buffer, especially in an alkaline urine such as that produced in type 1 RTA. In addition, this reduced synthetic rate limits cations required for fixed acid excretion and obligates other cations, such as Ca++, to act in its place.

Rate-Dependent Distal RTA

Conditions that alter transepithelial voltage in the distal seg-
Diagnostic Approach

Identification and appropriate categorization of patients with RTA require consideration of an extensive list of differential diagnoses (Figure 4). The initial task is to determine the presence of a hyperchloremic metabolic acidosis and absence of any significant plasma anion gap ([sodium] – [bicarbonate] + [chloride]). The differential list of entities fitting this description is presented in Table 1.

The most common cause of this situation in pediatrics is acute diarrheal disease. Potassium losses can be substantial enough in either RTA or diarrheal disease to cause hypokalemia, making the two difficult to distinguish from each other when they coexist in the infant. The most direct means to approach a differential in suspected RTA is by determination of the urinary anion gap, defined somewhat differently from the serum anion gap, as the sum of (urine [Na⁺] + urine [K⁺]) – urine [Cl⁻]. Ammonium excretion is usually increased as acidosis develops, most commonly in the form of chloride salts, although urinary ammonium is considered an unmeasured cation. Thus, in a state of acidosis, the urinary anion gap should decrease as the chloride excretion increases in concert with ammonium. The utility of this calculation reflects the fact that ammonium generation by the kidney occurs in the distal tubule, so that in all forms of distal RTA it would be anticipated that no decrease in urine anion gap would be seen. In contrast, a normal renal response to gastrointestinal bicarbonate losses, or in a kidney affected by Type II RTA, would be increased ammonium production, increased chloride excretion, and hence, a decreased value of the urinary anion gap.
Renal Tubular Acidosis

Table 1

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<tr>
<th>METABOLIC ACIDOSIS WITH NORMAL ANION GAP (HYPERCHLOREMIA)</th>
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<tbody>
<tr>
<td>Renal bicarbonate wasting</td>
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<td>Renal tubular acidosis</td>
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<td>Early uremic acidosis</td>
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<td>Hyperparathyroidism</td>
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<td>Hypoaldosteronism</td>
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<td>Carbonic anhydrase inhibitor</td>
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<tr>
<td>Gastrointestinal bicarbonate wasting</td>
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<td>Diarrhea</td>
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<td>Ureterosigmoidostomy</td>
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<td>Intestinal fistulas</td>
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<td>Calcium chloride</td>
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<td>Magnesium sulfate</td>
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<td>Cholestyramine</td>
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<td>Anion exchange resins</td>
</tr>
<tr>
<td>Miscellaneous</td>
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<tr>
<td>Dilutional acidosis</td>
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<tr>
<td>Acid loads</td>
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Examples

<table>
<thead>
<tr>
<th>Normal</th>
<th>Type I RTA</th>
<th>Type II RTA</th>
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<tbody>
<tr>
<td>Cl⁻&gt;Na⁺K⁺</td>
<td>Cl⁻&gt;Na⁺K⁺</td>
<td>Cl⁻&gt;Na⁺K⁺</td>
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<td>100±5-150–45</td>
<td>100±5-150–45</td>
<td>100±5-200–95</td>
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The use of this parameter in children has been discussed,

\[ \text{load of NH}_4\text{Cl; recently, the intravenous arginine hydrochloride infusion test (100–150 mEq H}^+\text{/m}^2\text{ body surface area) has been used.} \]

The overall purpose of these tests is to create systemic conditions that will maximize renal hydrogen ion excretion, and to determine systemic and urine pH under these circumstances. If urine pH falls below 5.5, the patient can be assumed not to have distal RTA. Some patients with proximal RTA can achieve a normal urine pH response under these circumstances, so that type II RTA cannot be ruled out by this technique.

Another test of the ability of the distal tubule to secrete H⁺ is to alkalinate the urine and measure the secretory capacity along a hydrogen ion gradient where blood pH should be less than urine pH. Classically this was achieved using an oral sodium bicarbonate dose, but oral acetazolamide as a urinary alkalinizing agent (17 mg/Kg) has been found to be more efficient. Distally secreted hydrogen ions enter the tubular lumen and combine with bicarbonate ions to form carbonic acid, which slowly dehydrates into water and CO₂ because of the absence of luminal membrane carbonic anhydrase in distal tubular cells. Accumulation of luminal CO₂ because of delayed dehydration of carbonic acid is further enhanced by diminished diffusion due to an unfavorable volume to surface area relationship in the medullary collecting duct. As a result of these two factors, the pCO₂ of the urine increases and, measured in sufficiently alkaline urine, it can be used as a reliable index of distal hydrogen ion secretion. Under these conditions, normal individuals are capable of increasing urine pCO₂ above 70 mm Hg and achieving a pCO₂ difference between urine and blood of 25 to 30 mm Hg. Given the same conditions, a difference of less than 20 mm Hg strongly suggests diminished H⁺ secretory capacity, which is characteristic of distal RTA.

Normal individuals given furosemide (1–2 mg/kg) generate a markedly acid urine and a significant increase in net acid excretion within 2 to 3 hours. This effect is based on furosemide-induced increased sodium delivery to and inhibition of chloride reabsorption in the distal tubule. As a consequence, the increased sodium load results in greater exchange for H⁺ and the greater presence of chloride induces a
higher degree of luminal electronegativity. Thus, patients with RTA should show concordant responses to a furosemide test. In patients suspected of having type 4 RTA in whom hyperkalemia could become hazardous with acid loading, furosemide can provide a useful and safe alternative.

Growth Failure in RTA

Disturbances of growth are typically associated with RTA of all types and with chronic metabolic acidosis in general. The effects of acidosis appear to fall into two separate categories: direct (by committing calcium as a buffer for H+) and indirect (through the growth hormone-IGF axis). In the classical view, the pathophysiologic response to chronic acidosis leads to increase in the ionized fraction in serum, a resultant increase in glomerular filtration and a consequent enhanced urinary loss as calcium salts. The net result of this is osteomalacia with bowing of the long bones, particularly those in the lower extremities, and growth failure. We have already examined the tubular processes leading to these effects, so that this mechanism for the adverse impact of acidosis upon growth should be clear.

In 1981, McSherry and associates reported a blunted growth hormone release in children with RTA, although no data were included on frequency, quantity, or other aspects of growth hormone secretion. To update this report, Challal and co-workers recently demonstrated that pulse amplitude and area, as well as total growth hormone secretion were diminished in acidic rats, compared to control and pair-fed animals, while the pulse frequency remained unaffected in the acidotic animals. Other findings included suppressed serum IGF, hepatic IGF-1 mRNA and hepatic growth hormone receptor mRNA, as well as gene expression of IGF at the growth plate of the long bones in these animals. The changes in IGF-1 mRNA and growth hormone receptors seem to be specific to the cellular effects of acidosis. Taken together, these findings are representative of an additional mechanism for the adverse impact of chronic acidosis upon growth, although they will need confirmation in humans.

Genetics and Molecular Genetics

Until recently, elucidation of the genetic aspects of types 1 and 2 RTA was hampered by confusing clinical associations (e.g., deafness, Fanconi syndrome) and familial, inherited, and sporadic patterns of occurrence for each. However, with the advent of molecular genetics, many of the previously puzzling aspects of these disorders are now coming into sharper focus. The transient, neonatal form of RTA may be caused by relative immaturity of the apical Na+-H+ exchanger molecule (NHE-3), which is known to undergo postnatal development in animals. The gene for NHE-3 has been mapped to 5p15.3. With respect to genetic type 2 RTA, the molecular basis for an inherited defect is now in hand with the cloning of the two human genes for the Na+−HCO3− cotransporter (NBC) protein molecules. The gene for NBC-1 has been mapped to 4p21. However, it may require development of diagnostic technology to ascertain the presence of an abnormal NBC-1 transporter gene in nonrenal tissue from affected individuals, since renal biopsy in type 2 RTA is difficult to rationalize. The vast majority of cases of proximal RTA are seen in association with other genetic disorders, in which the acid-base disturbance is simply a part of a generalized proximal tubular dysfunction called the renal Fanconi syndrome. In these individuals, the genetics of the RTA follows the pattern of the underlying disorder, almost always an autosomal recessive trait. It is worth noting that type 2 RTA due to a carbonic anhydrase (CA II) deficiency occurs in association with osteopetrosis and cerebral calcification as an autosomal recessive trait, as well. CA II deficiency may also cause a mixed type 1-type 2 RTA, originally designated type III, a term no longer in use. CA II has been mapped to 8q22; use of a CA II-deficient mouse model has provided the basis for successful, but temporary gene therapy.

In contrast, distal RTA occurs with the greatest frequency as an isolated defect, often transmitted as an autosomal dominant trait due to a mutation at 17q21-q22. The molecular abnormality in these cases is an impaired Cl−-HCO3− exchanger within the cell at the antiluminal surface, as previously discussed. Norman and associates studied two pedigrees in which clinically affected individuals were shown to be hypocitraturic; other, asymptomatic members of the pedigree with incomplete distal RTA were found to be hypocitraturic and were also shown to have an abnormal response to acid loading. These observations are entirely consistent with an autosomal dominant trait. In addition, distal RTA can be inherited as an autosomal recessive trait, with or without associated sensorineural hearing loss. Those individuals without hearing de-
fects carry mutations at 7q33-q34. Distal RTA in association with hearing loss has been shown to involve the gene (ATP6B1) coding for the B-subunit of the H^+ATPase, which is normally responsible for the secretion of hydrogen ion into the lumen. Significantly, neither of the two recessive forms of distal RTA involves a locus even remotely connected with that which determines the chloride-bicarbonate exchanger defect in the dominant trait. Thus, there are clearly at least three distinct abnormalities of the genome which can adversely affect urinary acidification in the distal tubule. While a good deal of work remains to be done on the molecular biology of RTA, the data are already beginning to help us to understand the clinical genetics as well as the pathophysiology to a degree not possible 20 years ago.

**Variation on the Theme**

In past literature on the subject, RTA nomenclature had evolved to a degree of confusion vastly out of proportion to its underlying pathophysiologic complexity. The more recent literature on the subject deals essentially with three types: 1, 2, and 4. It is now clearly recognized that type 4, also called hyperkalemic distal RTA to distinguish it from classical type 1, is an acquired defect generally due to either aldosterone deficiency or relative aldosterone resistance. The first situation often pertains in cases of congenital adrenogenital syndrome, while the second may be seen whenever renal mass is diminished (e.g., obstructive uropathy, diabetic nephropathy). Although chronic renal failure is a prominent cause of type 4 RTA in adults, it is rarely seen in children. The mechanism behind the hyperkalemia is plainly an impaired or inhibited exchange of potassium for sodium, a process regulated in the distal tubule by aldosterone. The same applies to the systemic accumulation of H^+, since secretion of hydrogen ion is linked to the same process that is impaired in the absence of normal aldosterone regulation.

**Incidence**

The relative incidence of the three types of RTA was reported by Brennen and associates shortly after the initial description of type 4 RTA. These workers suggested that type 1 was most common, followed by type 4, with type 2 the least common of all. This order is, however, unlikely because genetic defects rarely, if ever, outnumber acquired ones. Thus, the number of elderly males with prostatic hypertrophy and patients of all ages with obstructive uropathy who become relatively resistant to aldosterone and in whom type 4 RTA develops are clearly more numerous than individuals with mutations for a chloride-bicarbonate exchanger (type 1). Although it is certain that every infant is born with a lower bicarbonate threshold than its parents, most newborns do not develop systemic acidosis in relation to their age cohorts as a consequence. Nonetheless, it is at least arguable that type 2, due to a physiologic immaturity, appears in the general population more frequently than genetically determined type 1. However, it is certain that after infancy, isolated type 1 is seen far more commonly than isolated type 2.

**Treatment**

The basis for treatment of a patient with any form of RTA is the resulting metabolic acidosis, which all patients experience. In proximal RTA, where the fundamental physiologic abnormality, as we have defined it, is in base reabsorption, it stands to reason that base replacement would be therapeutic. Thus, base replacement as sodium bicarbonate or the more palatable alternative, citrate or Shohl’s solution (2-14 mEq/kg/day in divided doses) is utilized to maintain plasma bicarbonate higher than the reduced T_m and offset the increased urinary losses. In both forms of distal RTA, notwithstanding the different underlying mechanism compared to type 2 RTA, the clinical problem remains a systemic metabolic acidosis. Citrate replacement has been used as an effective mainstay of treatment in type 1 RTA. Finally, in treatment of type 4 RTA, it is essential to determine the underlying mechanism, whether hypoaldosteronism vs end-organ resistance. For the former state, mineralocorticoid replacement is effective, but the patient should be monitored for sodium retention and volume overload. For the latter, generally resulting from chronic renal disease, administration of furosemide (2 mg/kg/day) is highly effective and avoids the problem of volume overload by promoting sodium excretion.

**Conclusions**

We presented a conception of the two major types of RTA based on the characteristic functional deficit of each. In the case of type 2 (proximal) RTA, the underlying genetic defect in sodium-bicar-
bonate cotransporter molecule (NBC-1) results in a deficit in base reabsorption. Thus, proximal RTA results in reduced plasma bicarbonate and systemic metabolic acidosis on this basis. By contrast, type 1 (distal) RTA has been presented as a failure to eliminate hydrogen ion, a concept amply supported by the molecular definition of a genetic deficiency of the chloride-bicarbonate exchanger molecule impairing the distal tubule’s ability to secrete H+. The utility of this conceptualization lies primarily in the fact that it emphasizes both the normal and abnormal function of each of the two involved segments, while also helping to explain the physiologic basis for the clinical presentations.

The marked abnormalities of linear growth, particularly evident in distal RTA, are understood as the result of at least two separate sets of events: osteomalacia and bowing of the lower extremities due to calcium loss; and, the acidosis-induced changes in the growth hormone-IGF axis. Our knowledge of the latter influence is still in the most rudimentary stages, although techniques of molecular biology provide the promise of rapid advances in the near future. The molecular genetics of RTA has progressed dramatically in the past decade, providing evidence of the actual molecular defects in types 1 and 2 RTA and furthering our understanding of the underlying cellular events. These observations have also helped greatly in our delineation of the inheritance patterns of both proximal and distal RTA. Thus, the progress in the past two decades has been dramatic and holds direct implications for clinical care of patients affected by RTA.

REFERENCES


