Chapter 4
Etiologic Causes of Metabolic Acidosis II: Normal Anion Gap Acidoses

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Non-Anion Gap (Hyperchloremic) Metabolic Acidoses

Metabolic acidosis with a normal AG (hyperchloremic or non-AG acidosis) indicates that HCO_3^- in the plasma has been effectively replaced by Cl^-, and therefore, the AG does not change. The majority of disorders in this category can be attributed to either: (1) loss of bicarbonate from the gastrointestinal tract (diarrhea) or from the kidney (proximal RTA), or (2) inappropriately low kidney acid excretion (classical distal RTA [cDRTA], generalized distal RTA [type 4 RTA], or acute and chronic kidney disease). Hypokalemia may accompany gastrointestinal loss of HCO_3^-, proximal RTA, and cDRTA. Therefore, the major challenge in distinguishing these causes is to be able to define whether the response of kidney tubular function to the prevailing acidosis is appropriate acid excretion in the urine (consistent with gastrointestinal origin) or inappropriately low urine acid excretion (consistent with a kidney origin). The differential diagnosis of the non-gap acidoses is summarized in Table 4.1.

Diarrhea results in the loss of large quantities of HCO_3^- decomposed by reaction with organic acids. Because diarrheal stools contain a higher concentration of HCO_3^- and decomposed HCO_3^- than plasma, volume depletion and metabolic acidosis develop. Hypokalemia occurs because large quantities of K^+ are lost from stool and because volume depletion causes secondary hyperaldosteronism, which enhances K^+ secretion by the kidney collecting duct. Instead of an acid urine pH as might be anticipated with chronic diarrhea, a pH of 6.0 or more might be found. This occurs because chronic metabolic acidosis and hypokalemia each increases kidney ammonia (NH_3) buffer production that combines with protons (H^+) to form

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Table 4.1 Differential diagnosis of non-gap acidosis

Extra kidney causes
Diarrhea or other GI losses of bicarbonate (e.g., tube drainage)
Posttreatment of ketoacidosis (dilutional) (occasional: initial DKA)
Kidney causes not due to renal tubular acidosis
Ureteral diversion (e.g., ileal loop, ureterosigmoidostomy)
Progressive chronic kidney disease
Toluene ingestion (excretion of hippurate)
Drugs
With associated hypokalemia
Carbonic anhydrase inhibitors (acetazolamide and topiramate)
Amphotericin B
With associated hyperkalemia
Amiloride,
Triamterene,
Spironolactone,
Trimethoprim
With normal potassium
$CaCl_2$, $MgSO_4$
Cholestyramine
Exogenous acid loads (NH_4Cl, acidic amino acids—total parenteral nutrition, sulfur)
Post-hypocapnic state
Renal tubular acidosis
Low $[K^+]_p$
Type 1 (classical distal) RTA
Type 2 (proximal) RTA
Type 3 (mixed proximal and distal) RTA (carbonic anhydrase II deficiency)
High $[K^+]_p$
Type 4 (generalized distal RTA)
Hypoaldosteronism (hyporeninemic and isolated)
Aldosterone resistance
Voltage defect in collecting duct

ammonium (NH_4^+) for urine excretion. The resulting increase in urine NH_3/NH_4^+ buffer can increase urine pH. In the setting described, a urine pH of 6.0 or higher might erroneously suggest a non-kidney cause. Because urinary NH_4^+ excretion is typically low in patients with RTA and high in patients with diarrhea [1, 2], the level of urinary NH_4^+ excretion (not usually measured by clinical laboratories) in metabolic acidosis can be assessed indirectly [3] by calculating the urine anion gap (UAG), using the following equation [2]:

$$\mathrm{UAG} = [\mathrm{Na}^+ + \mathrm{K}^+]_\mathrm{U} - [\mathrm{Cl}^-]_\mathrm{U} \tag{4.1}$$

where U denotes the urine concentration of these electrolytes. The rationale for using the UAG as a surrogate for ammonium excretion is that in chronic metabolic acidosis ammonium excretion should be elevated if kidney tubular function is intact. Therefore, the UAG should become progressively negative as the rate of ammonium excretion increases in response to acidosis or to acid loading [3, 4]. A negative UAG (more than −20 mEq/L) implies that sufficient NH_4^+ is present in the urine, as might occur with an extra kidney origin of the hyperchloremic acidosis. Conversely, urine estimated to contain little or no NH_4^+ has more $Na^+ + K^+$ than Cl^- (UAG is positive) [2–4], which indicates a kidney mechanism for the hyperchloremic acidosis, such as in cDRTA (with hypokalemia) or hypoaldosteronism with hyperkalemia. If a patient has ketonuria, drug anions (penicillins or aspirin), or toluene metabolites in the urine, this test is not reliable and should not be used.

In such circumstances the urinary ammonium concentration ($U_{NH_4^+}$) may be estimated more reliably from the urine osmolal gap, which is the difference in measured urine osmolality (U_{osm}), and the urine osmolality calculated from the urine $[Na^+ + K^+]$ and the urine urea and glucose (all expressed in mmol/L) [3]:

$$U_{NH_4^+} = 0.5(U_{Osm} - [2(Na^+ + K^+) + \text{Urea} + \text{Glucose}]_U \quad (4.2)$$

Calculated urinary ammonium concentrations of 75 mEq/L or more would be anticipated if kidney tubular function is intact and the kidney is responding to the prevailing metabolic acidosis by increasing ammonium production and excretion. Values below 25 mEq/L denote inappropriately low urinary ammonium concentrations, suggesting the diagnosis of RTA.

Severe non-AG or hyperchloremic metabolic acidosis with hypokalemia may also occur in patients with ureteral diversion procedures. Because the ileum and the colon are both endowed with Cl^-/HCO_3^- exchangers, when the Cl^- from the urine enters the gut or pouch, the HCO_3^- concentration increases as a result of the exchange process and HCO_3^- is excreted [4]. Moreover, K^+ secretion is stimulated, which, together with HCO_3^- loss, can result in a non-AG (hyperchloremic) hypokalemic metabolic acidosis.

Loss of functioning kidney parenchyma in progressive kidney disease is associated with metabolic acidosis. Typically, the acidosis is a non-AG type when the GFR is between 20 and 50 mL/min but may convert to the typical high AG acidosis of uremia with more advanced chronic kidney disease, that is, when the GFR is less than 15–20 mL/min [5]. The principal defect in acidification of stage 3–4 CKD is that ammoniagenesis is reduced in proportion to the loss of functional kidney mass. Medullary NH_4^+ accumulation and trapping in the outer medullary collecting tubule may also be impaired [5]. Because of adaptive increases in K^+ secretion by the collecting duct and colon, the acidosis of chronic kidney disease is typically normokalemic [5]. Non-AG metabolic acidosis accompanied by hyperkalemia is almost always associated with a generalized dysfunction of the distal nephron [1, 2]. However, K^+-sparing diuretics (amiloride, triamterene), as well as pentamidine, cyclosporine, tacrolimus, nonsteroidal antiinflammatory drugs (NSAIDs), angio-

tensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), β-blockers, and heparin may cause hyperkalemia and a non-gap metabolic acidosis [1, 2]. Because hyperkalemia augments the development of acidosis by suppressing urinary net acid excretion, discontinuing these agents while reducing the serum K^+ allows ammonium production and excretion to increase, which will help repair the acidosis.

Disorders of Impaired Kidney Bicarbonate Reclamation: Proximal Renal Tubular Acidosis

Pathophysiology

The first phase of acidification by the nephron involves reabsorption of the filtered HCO_3^- so that 80 % of the filtered HCO_3^- is normally returned to the blood by the proximal convoluted tubule [1–3]. If the capacity of the proximal tubule is reduced, less of the filtered HCO_3^- is reabsorbed in this segment and more is delivered to the more distal segments (see Fig. 4.1). This increase in HCO_3^- delivery overwhelms the limited capacity for bicarbonate reabsorption by the distal nephron, and bicarbonaturia ensues, net acid excretion ceases, and metabolic acidosis follows. Enhanced Cl^- reabsorption, stimulated by ECF volume contraction, leading to replacement of lost $NaHCO_3$ with NaCl causes hyperchloremic (non-AG) chronic metabolic acidosis. With progressive metabolic acidosis and decreased serum HCO_3^- levels, the filtered HCO_3^- load declines progressively. As plasma HCO_3^- concentration decreases, the defective HCO_3^- reabsorption more completely absorbs the lower filtered load of HCO_3^- so that the absolute amount of HCO_3^- entering the distal nephron eventually reaches the level approximating the distal HCO_3^- delivery in normal individuals (at the normal threshold). At this point the reduced quantity of HCO_3^- entering the distal nephron can be reabsorbed completely, so urine pH declines. As a consequence, the serum HCO_3^- concentration usually reaches a nadir of 15–18 mEq/L, and the systemic acidosis no longer progresses. Therefore, in proximal RTA, in the steady state, the serum HCO_3^- is usually about 15–18 mEq/L and the urine pH acid (<5.5). With bicarbonate administration, the amount of bicarbonate in the urine increases the fractional excretion of bicarbonate ($FE_{HCO_3^-}$) to 15 % or more, and the urine pH becomes alkaline [1], and the diagnosis of proximal RTA can be made.

Proximal RTA can present in one of three ways (summarized in Fig. 4.1): one in which acidification is the only defective function, one in which there is a more generalized proximal tubule dysfunction with multi-transporter abnormalities (most common), and as a part of a mixed variety of RTA (type 3). Inheritance patterns for isolated proximal RTA include autosomal recessive and autosomal dominant. Isolated pure bicarbonate wasting is typical of autosomal recessive proximal RTA with accompanying ocular abnormalities and has been defined as a number of mis-

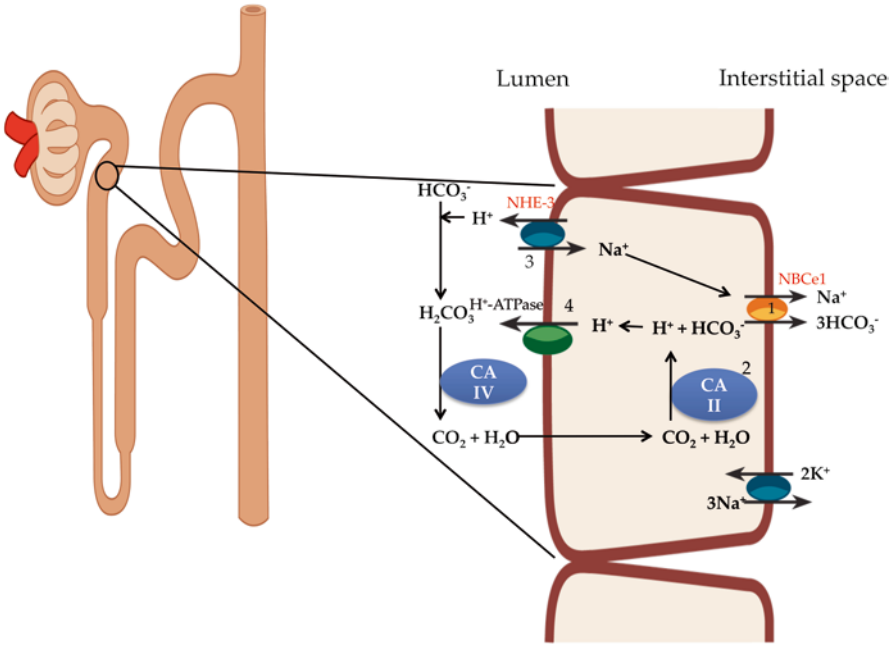

Fig. 4.1 Model of acidification in the proximal convoluted tubule. Numbers refer to unique defects in specific transporters responsible for defective bicarbonate absorption and bicarbonaturia typical of proximal RTA: 1. Autosomal recessive mutation of NBCe1/*SLC4A4* located on B-L membrane. 2. Carbonic anhydrase II deficiency causing osteopetrosis, mixed proximal/distal RTA (Type III RTA). 3. Autosomal dominant mutation of NHE-3. 4. Inherited defect of the H^+-ATPase (has not been described in association with proximal RTA)

sense mutations of the gene *SLCA4* that encodes for the basolateral transporter, NBCe1. A rare variant, inherited as an autosomal dominant trait, has been described and appears to be a mutation of the gene that encodes the apical Na^+/H^+ exchanger, NHE-3, and has been reported to be associated with short stature. Familial disorders associated with proximal RTA include: cystinosis, tyrosinemia, hereditary fructose intolerance, galactosemia, glycogen storage disease type 1, Wilson's disease, and Lowe's syndrome.

Additionally, features of both proximal RTA (bicarbonate wasting), and distal acidification abnormalities are evident in patients with autosomal recessive RTA (mixed proximal and distal, or type 3 RTA) that has been attributed to a defect in the *CA2* gene that encodes for carbonic anhydrase II (CAII), an intracellular form of the enzyme distributed to the proximal tubule and other distal tubule segments [1]. The phenotype includes osteopetrosis, and ocular abnormalities.

The majority of cases of proximal RTA fit into the category of generalized proximal tubule dysfunction with multi-transport abnormalities manifest as glycosuria, aminoaciduria, hypercitraturia, and phosphaturia, and referred to as *Fanconi's syndrome.*

Although proximal RTA is more common in children, the most common causes of acquired proximal RTA in adults are multiple myeloma, in which increased excretion of immunoglobulin light chains injures the proximal tubule epithelium, and chemotherapeutic drug injury of the proximal tubule (e.g., ifosfamide). RTA due to ifosfamide toxicity, lead intoxication, and cystinosis is more common in children. Carbonic anhydrase inhibitors cause pure bicarbonate wasting but not Fanconi's syndrome. Topiramate, widely used in the prevention of migraine headaches, or for treatment of a seizure disorder is a potent carbonic anhydrase inhibitor, and is an important cause of non-AG metabolic acidosis. Approximately 15–25 % of patients on topiramate will manifest a stable non-gap metabolic acidosis due to a mixed form of RTA with features of both proximal and distal RTA (type 3). This phenotype occurs because the enzyme carbonic anhydrase II is present in both the proximal and distal tubules, and subsides when topiramate is discontinued.

Disorders of Impaired Net Acid Excretion with Hypokalemia: Classical Distal Renal Tubule Acidosis

Pathophysiology

The mechanisms involved in the pathogenesis of hypokalemic cDRTA (type 1 RTA) have been more clearly elucidated by appreciation of the genetic and molecular bases of the inherited forms of this disease in the last two decades. Most studies suggest that the inherited forms of cDRTA are due to inherited defects in either the basolateral HCO_3^-/Cl^- exchanger (encoded by the gene *SLC4A1*), or subunits of the H^+-ATPase (encoded by the *ATP6V1B1 or ATP6V0A4 genes, respectively*) localized to the Type A intercalated cell of the collecting duct (Fig. 4.2).

While the classical finding is an inability to acidify the urine maximally (to a pH of <5.5) in the face of systemic acidosis, attention to urine ammonium excretion rather than urine pH alone is necessary to diagnose this disorder [1, 2]. The pathogenesis of the acidification defect in most patients is evident by the response of the urine PCO_2 to sodium bicarbonate infusion. When normal subjects are given large infusions of sodium bicarbonate to produce a high HCO_3^- excretion, distal nephron H^+ secretion leads to the generation of a high PCO_2 in the kidney medulla and final urine [8, 9]. The magnitude of the urinary PCO_2 (often referred to as the *urine minus blood* PCO_2 or $U-B$ PCO_2) can be used as an index of distal nephron H^+ secretory capacity [6–9]. The U – B PCO_2 is generally subnormal in classical hypokalemic distal RTA, with the notable exception of amphotericin B-induced distal RTA, which remains the most common example of the "gradient" defect [7, 9, 10].

Patients with impaired collecting duct H^+ secretion and cDRTA exhibit uniformly low excretory rates of NH_4^+ when the degree of systemic acidosis is taken into

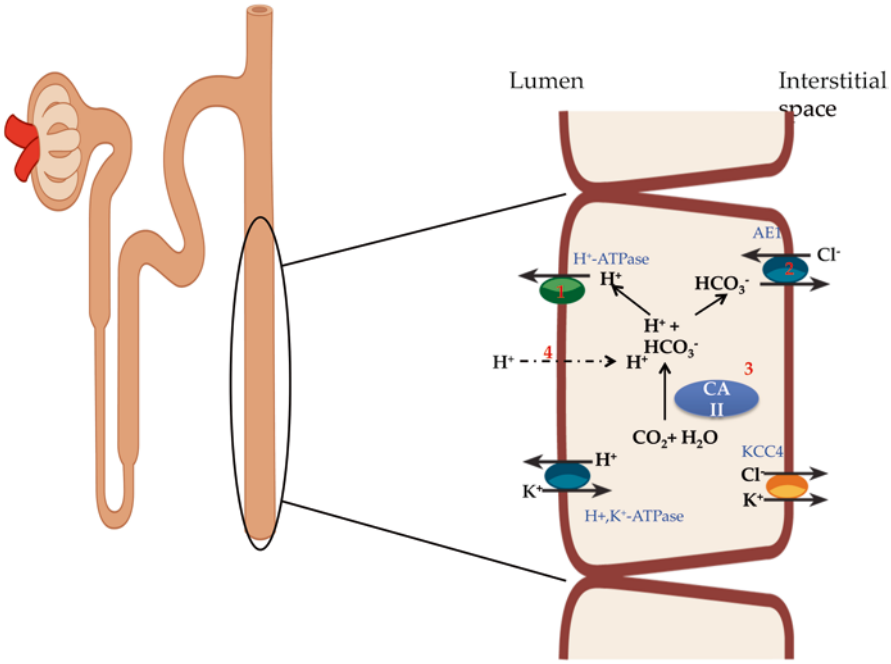

Fig. 4.2 Type A intercalated cell of cortical collecting duct and reported causes of distal renal tubular acidosis. 1. Inherited or acquired defect of the H^+-ATPase. Autosomal recessive mutations of *ATP6V1B1* with deafness and of *ATP6V04* without deafness have been reported. Defects in the H^+-ATPase may be acquired in Sjögren's syndrome. 2. Autosomal dominant mutations of *SLC4A1* cause an abnormality of the basolateral HCO_3^-/Cl^- exchanger. 3. Carbonic anhydrase II deficiency is associated with mixed (Type III) proximal and distal RTA. 4. Inherited or acquired disorders resulting in backleak of H^+ have been reported. The acquired defect best described is that caused by the antibiotic amphotericin B

account [1, 2, 11]. Low NH_4^+ excretion equates with inappropriately low regeneration of HCO_3^- by the kidney, which indicates that the kidney is responsible for causing or perpetuating the chronic metabolic acidosis. Low NH_4^+ excretion in classical hypokalemic distal RTA occurs because of the failure to trap NH_4^+ in the medullary collecting duct as a result of higher than normal tubule fluid pH in this segment and loss of the disequilibrium pH (pH > 6.0) [12].

Medullary interstitial disease, which commonly occurs in conjunction with distal RTA, may impair NH_4^+ excretion by interrupting the medullary countercurrent system for NH_4^+ [1, 2, 13, 14]. The complete form of classical distal RTA is manifest by a non-AG acidosis without treatment. The clinical spectrum of complete cDRTA may include stunted growth, hypercalciuria, hypocitraturia, osteopenia, nephrolithiasis, and nephrocalcinosis, all a direct consequence of the chronic non-AG metabolic acidosis. The dissolution of bone is due to calcium resorption and mobilization from bone in response to the acidosis [1] and through activation of the pH sensitive

G-protein coupled receptor, OGR1, which resides in bone [15]. Other common electrolyte abnormalities, not due to acidosis include hypokalemia, hypernatremia and salt wasting, and polyuria due to nephrogenic diabetes insipidus. The hypokalemia may be due to a signaling pathway involving activation and release of PGE2 by β-intercalated cells that directly communicate to enhance sodium absorption and potassium secretion by activation of the epithelial sodium channel (ENaC) and BK channels in collecting duct principal cells. Because chronic metabolic acidosis also decreases kidney production of citrate [1, 2, 11], the resulting hypocitraturia in combination with hypercalciuria increases urinary stone formation and nephrocalcinosis. Distal RTA occurs frequently in patients with Sjögren's syndrome and because of autoantibodies and infiltration of lymphocytes, is due to the inability to traffic and insert the H^+-ATPase into the apical membrane properly [16]. The numerous causes of both inherited and acquired defects resulting in classical distal RTA are summarized in Table 4.2.

Disorders of Impaired Net Acid Excretion with Hyperkalemia: Generalized Distal Nephron Dysfunction (Type 4 Renal Tubular Acidosis)

The coexistence of hyperkalemia and a non-gap metabolic acidosis indicates a generalized dysfunction in the cortical and medullary collecting tubules [1, 2]. Hyperkalemia is an important mediator of the kidney response to acid–base balance, because it independently reduces ammonium production and excretion. Chronic hyperkalemia decreases ammonium production in the proximal tubule and whole kidney, inhibits absorption of NH_4^+ in the mTAL, reduces medullary interstitial concentrations of NH_4^+ and NH_3, and decreases entry of NH_4^+ and NH_3 into the medullary collecting duct, all leading to a marked reduction in urinary ammonium excretion [1, 2]. The potential for development of a hyperchloremic metabolic acidosis is greatly augmented when a reduction in functional kidney mass (GFR of <60 mL/min) coexists with hyperkalemia or when aldosterone deficiency or resistance is present.

Drug-Induced Kidney Tub ular Secretory Defects

Impaired Renin–Aldosterone Elaboration

Drugs may impair renin or aldosterone elaboration or cause mineralocorticoid resistance in patients with CKD, and produce effects that mimic the clinical manifestations of the acidification defect seen in the generalized form of distal RTA with hyperkalemia. Examples include NSAIDs or COX-2 inhibitors [17], spironolactone and eplerenone, β-adrenergic antagonists, heparin, and ACE inhibitors and ARBs.

Table 4.2 Disorders associated with classical hypokalemic distal RTA primary

Familial	
1. Autosomal dominant	
a. Abnormality of the basolateral HCO_3^-/Cl^- exchanger (AE-1) due to *SLC4A1* mutation	
2. Autosomal recessive	
a. Deficiency or abnormality of the H^+-ATPase Autosomal recessive *ATP6V1B1* mutation with deafness Autosomal recessive *ATP6V0A4* mutation with or without deafness b. Carbonic anhydrase II deficiency—mixed PRTA–DRTA	
Endemic	
Northeastern Thailand	
Acquired defect of the H^+-ATPase	
Sjögren's syndrome	
Secondary to systemic disorders	
Autoimmune diseases	
Hyperglobulinemic purpura	Fibrosing alveolitis
Cryoglobulinemia	Chronic active hepatitis
Sjögren's syndrome	Primary biliary cirrhosis
Thyroiditis	Polyarthritis nodosa
HIV nephropathy	
Hypercalciuria and nephrocalcinosis	
Primary hyperparathyroidism	Vitamin D intoxication
Hyperthyroidism	Idiopathic hypercalciuria
Medullary sponge kidney	Wilson disease
Fabry disease	Hereditary fructose intolerance
X-linked hypophosphatemia	Hereditary sensorineural deafness
Drug and toxin induced disease	
Amphotericin B	Cyclamate
Mercury	
Vanadate	Lithium
Hepatic cirrhosis	Classic analgesic nephropathy
Ifosfamide	Foscarnet
Topiramate	Acetazolamide
Tubulointerstitial diseases	
Balkan nephropathy	Kidney transplantation
Chronic pyelonephritis	Leprosy
Obstructive uropathy	Jejunoileal bypass with hyperoxaluria
Vesicoureteral reflux	
Associated with genetically transmitted diseases	
Ehlers–Danlos syndrome	Hereditary elliptocytosis
Sickle cell anemia	Marfan syndrome
Medullary cystic disease	Jejunal bypass with hyperoxaluria
Hereditary sensorineural deafness	Carnitine palmitoyltransferase I
Osteopetrosis with carbonic anhydrase II deficiency	

Voltage Defect of Collecting Duct

Autosomal recessive PHA-1. This disorder is the result of a loss-of-function mutation of the gene that encodes one of the α-, β-, or γ-subunits of the ENaC [18–22]. Typically, children with PHA-1 also manifest vomiting, hyponatremia, failure to thrive, and respiratory distress [21, 23], and respond to a high salt intake and correction of the hyperkalemia.

Amiloride and triamterene may be associated with hyperkalemia, because these potassium-sparing diuretics occupy and thus block the apical Na^+-selective channel (ENaC) in the collecting duct principal cell. Occupation of ENaC inhibits Na^+ absorption and reduces the negative transepithelial voltage, which alters the driving force for K^+ secretion (Fig. 4.3 displays the pathophysiology of a prototypical voltage defect in the CCT).

The calcineurin inhibitors cyclosporine A and tacrolimus may be associated with hyperkalemia in the transplant recipient as a result of inhibition of the basolateral Na^+-K^+-ATPase and the consequent decrease in intracellular [K^+] and the transepithelial potential, which together reduce the driving force for K^+ secretion (see Fig. 4.3) [17]. Calcineurin inhibitors may also inhibit K^+ secretion by directly interfering

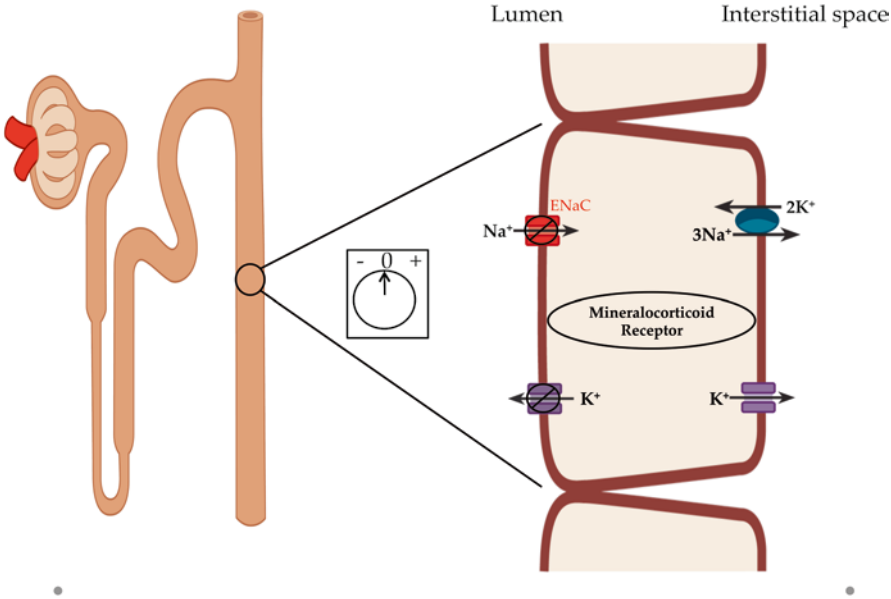

Fig. 4.3 Definition of voltage defect in the cortical collecting duct principal cell. Loss of function of the Na^+ channel, ENaC, prevents the generation of a lumen-negative transepithelial potential, therefore, negating the favorable voltage for K^+ secretion into the lumen (similarly, H^+ secretion by the neighboring Type A intercalated cell is also impaired). Calcineurin inhibitors may cause a voltage defect by inhibition of the B-L Na^+,K^+-ATPase or by inhibition of the ROMK channel on the apical membrane. Most voltage defects cause hyperkalemic non-gap metabolic acidosis, therefore

with the K channel, ROMK [24]. An additional explanation for the association of hyperkalemia, volume expansion and hypertension, a syndrome that resembles the phenotype of familial hyperkalemic hypertension or PHA-2, is enhanced activity of NCC in the DCT [25].

Disorders of Impaired Net Acid Excretion and Impaired Bicarbonate Reclamation with Normokalemia: Acidosis of Progressive Kidney Failure

The metabolic acidosis of CKD associated with chronically reduced GFR is initially hyperchloremic (GFR in the range of 20–30 mL/min) but may convert to the high AG variety as kidney insufficiency progresses and GFR falls below 15 mL/min [2, 5]. Unlike patients with classical distal RTA, patients with primary kidney disease have a normal ability to lower the urine pH during acidosis [5]. The net distal H^+ secretory capacity is qualitatively normal and can be increased by buffer availability in the form of PO_4^{3-} or by nonreabsorbable anions. Thus, the principal defect is an inability to produce or to excrete NH_4^+ sufficient to match net endogenous acid production. Consequently, the kidneys cannot quantitatively excrete all the metabolic acids produced daily, and net positive acid balance supervenes [5].

Evidence continues to indicate that chronic acidosis in patients with CKD is deleterious and accelerates CKD progression [26, 27] and augments dissolution of bone [2], and impaired hydroxylation of 25-hydroxycholecalciferol [2, 5], causing kidney osteodystrophy. Furthermore, the chronic acidosis also causes sarcopenia from enhanced skeletal muscle protein degradation with subsequent loss of muscle strength.

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