Hyperkalemic forms of renal tubular acidosis: clinical and pathophysiological aspects

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ABSTRACT
In contrast to distal type 1 or classic RTA which is associated with hypokalemia, hyperkalemic forms of RTA also occur usually in the setting of mild to moderate CKD. Two pathogenic types of hyperkalemic metabolic acidosis are frequently encountered in adults with underlying CKD. One type, which corresponds to some extent to the animal model of selective aldosterone deficiency (SAD) created experimentally by adrenalectomy and glucocorticoid replacement, is manifested in humans by low plasma and urinary aldosterone levels, reduced ammonium excretion, and preserved ability to lower urine pH below 5.5. This type of hyperkalemic RTA is also referred to as type IV RTA. It should be noted that the mere deficiency of aldosterone when GFR is completely normal only causes a modest decline in plasma bicarbonate which emphasizes the importance of reduced GFR in the development of the hyperchloremic metabolic acidosis associated with SAD. Another type of hyperkalemic RTA distinctive from SAD in that plasma aldosterone is not reduced is referred to hyperkalemic DRTA because urine pH cannot be reduced despite acidemia or after provocative tests aimed at increasing sodium dependent distal acidification such as the administration of sodium sulfate or loop diuretics with or without concurrent mineralocorticoid administration. This type of hyperkalemic RTA (also referred to as voltage dependent DRTA) has been best described in patients with obstructive uropathy and resembles the impairment in both hydrogen ion and potassium secretion induced experimentally by urinary tract obstruction and when sodium transport in the cortical collecting tubule is blocked by amiloride.
Introduction

Distal renal tubular acidosis (DRTA) was initially considered a single entity characterized by several findings including the inability to maximally acidify the urine during systemic acidosis, hypokalemia and nephrocalcinosis [1-5]. The mechanism proposed for DRTA initially was an inability of the distal nephron to generate and maintain a steep hydrogen ion gradient [6]. A certain degree of associated sodium wastage would cause volume contraction which then would activate the renin-angiotensin system and aldosterone. This secondary hyperaldosteronism then would promote increased potassium excretion and hypokalemia [7]. Indeed, many patients with DRTA may first present with muscle weakness and even paralysis due to hypokalemia [7,8]. The other consequences of DRTA (i.e., stunted growth in children osteomalacia, rickets, and nephrocalcinosis) also thought to result from the persistent metabolic acidosis which results in increased titration of the bone buffers and the consequent release of bone calcium, which is excreted in the urine leading to hypercalcuiuria [9,10]. The nephrocalcinosis is the result of both hypercalcuiuria and decreased citrate excretion. The decrease in citrate excretion has been attributed to the decrease in intracellular pH in proximal tubular cells. The fact that correction of the metabolic acidosis by the administration of sodium bicarbonate results in the resolution of most of the manifestations of DRTA lends support to the suggestion that the main abnormality in DRTA is the chronic metabolic acidosis that ensues from failure to secrete hydrogen ions by intercalated cells of the collecting tubule.

Over the last three decades experimental, clinical, physiologic and genetic studies have shown that DRTA encompasses complex mechanisms that are now reasonably well understood [11-34]. Some of these disorders are accompanied by hyperkalemia as opposed to the classic finding of hypokalemia in distal or classic RTA [35-52]. Hyperkalemia with varying degrees of metabolic acidosis develops in syndromes in which the primary disturbance is either deficiency of aldosterone, resistance to the action of aldosterone, or a more diffuse tubular derangement of electrolyte transport causing hyperkalemic renal tubular acidosis. These syndromes span from rare genetic defects at the level of one transporter (mutations in the epithelial renal sodium channel, the mineralocorticoid receptor) or name WNK mutations to overlapping syndromes associated with chronic kidney disease in which "relative" aldosterone deficiency may coexist with "relative" tubular resistance or with a distinct form of hyperkalemic dRTA [41-44]. Notwithstanding this overlap, two pathogenic types of hyperkalemic metabolic acidosis are frequently encountered in adults with underlying chronic kidney disease. One type, which
corresponds to some extent to the animal model of selective aldosterone deficiency (SAD) created experimentally by adrenalectomy and glucocorticoid replacement, is manifested in humans by low plasma and urinary aldosterone levels, reduced ammonium excretion, and preserved ability to lower urine pH below 5.5. This clinical entity also referred to as type IV RTA or selective aldosterone deficiency is usually associated with low levels of plasma renin activity [37 - 59]. In the other type of hyperkalemic metabolic acidosis, ammonium excretion is also reduced and there is a tubular defect in distal hydrogen ion (H⁺) secretion, as evidenced by the finding that urine pH cannot be lowered below 5.5 not only during acidemia but also after stimulation of sodium-dependent distal H⁺ secretion by the administration of either sodium sulfate or loop diuretics such as furosemide or bumetanide [41-43]. The term hyperkalemic dRTA is used to designate the latter syndrome, regardless of whether plasma aldosterone levels are normal, low, or elevated. In this review article these hyperkalemic forms of RTA will be discussed.

Distal Acidification: Cell Types and Transepithelial Potential Difference (Voltage).

The α-intercalated cell constitutes 40% of the cells in the distal nephron and has the apical H⁺-ATPase pumps which are responsible for most H⁺ secretion and acidification in this segment [60-64]. The other 60% of cells in the distal tubule are the principal cells which contain ENaC and ROMK, the apical transporters involved in reabsorption of sodium and secretion of potassium, respectively [65-67]. Indirectly, however, the principal cells contribute to H⁺ secretion as a result of sodium transport via ENaC. This generates a transepithelial electrical (voltage) gradient that affects H⁺ secretion by the intercalated cells (figure 1). A decrease in transepithelial voltage might impair H⁺ secretion and also K⁺ secretion. The decreased voltage could be secondary to a process that decreases sodium transport through the apical channels for instance when blocked by drugs such as amiloride, triamterene, lithium, and trimethoprim. Although inhibition of sodium reabsorption can only occur at the level of the principal cells that have the ENaC, the decreased transtubular voltage secondarily reduces hydrogen secretion by the neighboring α-intercalated cells which have the acid-base transporters (figure 1).

The H⁺-ATPase in the α-intercalated cell is an electrogenic pump that transports positively charged protons out of the cell into the tubule lumen [68-70]. Clearly, if the tubular lumen has a negative voltage relative to the cell interior, H⁺ ions will be secreted with less effort, and
excretion of acid in the urine will increase accordingly in a buffer form (as NH₄⁺ or titratable acid). Such a negative lumen voltage is generated by the principal cells during Na⁺ transport via apical Na⁺ channels (ENaC). In addition, the cytosol of the principal cell (all kidney cells in fact) has a low concentration of Na⁺ relative to that in the tubule fluid of the collecting duct. In combination, these factors influence Na⁺ to move readily down its concentration gradient into the cell. Since there is no directly coupled anion transport, in the principal cells these Na⁺ channels produce an increasingly negative lumen voltage as the positively charged Na⁺ ions move into the cell (the favorable concentration gradient overpowers the induced negative voltage).

A number of factors may in this way enhance or diminish this negative voltage, and therefore enhancing or diminishing acid excretion. Aldosterone increases the voltage by stimulating Na⁺ reabsorption by the principal cells. Similarly, infusion of salts containing readily absorbable cations associated with poorly absorbable anions, e.g., sodium sulfate, causes the voltage of the lumen to become increasingly negative after absorption of sodium. Both of these factors would then tend to enhance acid excretion. Conversely, a decrease in the negativity of the lumen and therefore acid excretion can result from factors that diminish Na⁺ reabsorption from the tubule. Such a diminution would be seen when the delivery of Na⁺ to the distal tubule is decreased, as would occur with volume contraction. In a similar fashion, the direct Na⁺ channel inhibitor amiloride or a decrease in mineralocorticoid activity such as occurs with aldosterone deficiency or the aldosterone receptor antagonist spironolactone would also diminish the negative lumen voltage and thereby urinary acid excretion.

The foregoing discussion has focused on the ability of the transepithelial voltage to influence active H⁺ secretion. It is important, however, to note that in isolated epithelium and perfused tubule segments, H⁺ secretion in the distal nephron can take place in the absence of Na⁺ reabsorption or when the voltage gradient created by Na⁺ absorption is nullified, albeit at a diminished pace. This independence is not surprising since active H⁺ secretion by H⁺-ATPase and Na⁺ reabsorption through the Na⁺ channel, (ENaC) although electrically coupled, are biochemically distinct events that occur in distinct cell populations. New experimental data on the role of the mTOR pathway in the regulation of ENaC and ROMK that may be relevant to altered potassium excretion in patients with hyperkalemic RTA is discussed later.
Aldosterone

Aldosterone has long been known to significantly influence sodium transport and urinary acidification in several important ways. [51,71-78]. By increasing the activity of the basolateral Na⁺-K⁺-ATPase of the principal cell, aldosterone reduces the intracellular concentration of Na⁺, thereby promoting the influx of Na⁺ through its apical channel. Aldosterone also influences the transepithelial voltage by increasing the number of Na⁺ channels on the principal cell. Aldosterone has an additional direct effect on the intercalated cell, that of redistributing vacuolar H⁺-ATPase to the apical membrane, thereby increasing the quantity of H⁺-ATPase in the CCD. Other effects of aldosterone on urinary acidification are mediated by its effect on K⁺. An increase in urinary K⁺ and subsequent K⁺ depletion are well-known consequences of hyperaldosteronism [78]. Potassium depletion, in turn, causes a marked increase in renal ammonia production [79-81]. The increased ammonia production facilitates urinary acid excretion by increasing the buffering capacity of the urine. Deficiency of aldosterone by decreasing Na⁺ reabsorption, results in a diminished transepithelial voltage in the CCT and thereby decreases K⁺ and acid excretion. The resulting increase in serum K⁺ decreases ammoniagenesis further impairing acid excretion. In addition, aldosterone stimulates ammonia formation and its deficiency further contributes to the decrease attributable to the associated hyperkalemia [78].

Deficiency of aldosterone also causes some degree of Na⁺ wastage with volume contraction and consequently a decrease in distal Na⁺ delivery, which would further inhibit acid and potassium secretion. Of interest is the observation that even when the effects on K⁺ and volume homeostasis are prevented, aldosterone deficiency still decreases net acid excretion and has a small but demonstrable effect on plasma HCO₃⁻ in adrenalectomized humans. [40]. That the effect on plasma bicarbonate is so small in people with normal GFR emphasizes the importance of reduced GFR for the development of acidosis and hyperkalemia with SAD, a situation that usually occurs in the setting of CKD.
Clinical and pathophysiologic findings attributable to aldosterone deficiency

In contrast to patients with hypokalemic DRTA who present with a rich clinical phenotype that includes hypokalemia and alterations in calcium metabolism, those with hyperkalemic RTA primarily attributable to aldosterone deficiency are commonly asymptomatic and are identified only when laboratory studies, reveal hyperkalemia. Occasionally, muscle weakness or cardiac arrhythmias may be present. Early observations were made by Lathem in a group of patients in which the renal disease was attributed to "chronic pyelonephritis" [35]. These patients had hyperchloremic acidosis, CKD, and hyperkalemia out of proportion to the degree of renal insufficiency; subsequent investigations disclosed several other groups of patients with similar metabolic abnormalities and deficiency of aldosterone was later documented as a key finding [36-47]. Diabetes accounts for approximately half of those patients; the remainder have a variety of chronic interstitial nephritides, but not all patients have aldosterone deficiency as the main cause of the hyperkalemic RTA (see below). That clinically diverse causes of CKD are associated with hyperkalemic RTA related to aldosterone deficiency suggests that a common pathophysiologic mechanism that hampers the formation of aldosterone, a hormone that is critically needed to prevent the development of hyperkalemia and metabolic acidosis in CKD. The simplest explanation is deficiency of renin by juxtaglomerular cells which may be suppressed by the chronic interstitial fibrosis commonly seen with CKD particularly in the setting of diabetic kidney disease. [78]. Low aldosterone production in patients with SAD is indeed often associated with low plasma renin activity but it can also be associated with normal or even high levels of plasma renin activity. [56-59] For instance, heparin causes a decrease in aldosterone synthesis and is thus associated with a reactive increase in plasma renin activity [82]. In critically ill patients, plasma renin levels are very high, yet aldosterone deficiency is present. [reviewed in 78]

The clinical features associated with SAD are typified by the syndrome of hyporeninemic hypoaldosteronism, which accounts for the majority of cases of SAD [36-56]. The syndrome has been the subject of extensive investigation. Patients present with moderate hyperkalemia, which is usually not associated with electrocardiographic abnormalities. In some cases, hyperkalemia may be intermittent Most patients are middle-aged or elderly, have cardiovascular disease, and have moderate CKD usually stages 3 and 4. The existence of these comorbid conditions may explain the lack of renal salt wasting, which would otherwise be expected in
someone with aldosterone deficiency. Salt wasting may occur if the levels of aldosterone are vanishingly low, and when the glomerular filtration rate (GFR) is normal or near normal. The development of hyperkalemic hyperchloremic metabolic acidosis in patients with SAD is common and is present in about 75% of cases [39-44]. The term type IV RTA was coined to designate this entity by Sebastian [37] and is still often used. Whereas most patients with adrenal insufficiency are hypotensive or exhibit postural hypotension, patients with SAD have normal or elevated arterial blood pressure owing to their underlying CKD. Postural hypotension, however, can be seen in patients with selective aldosterone deficiency, usually in diabetic subjects, who have severe autonomic dysfunction.

Although initially considered a rare entity, SAD is observed frequently. Failure to recognize it in the past was probably due to the fact that most patients with SAD have asymptomatic hyperkalemia. Classically, these patients are admitted for other problems, and serum potassium levels are usually in the range of 5 to 6 mEq/L but at times may be much higher. Also common in 50% to 60% of these patients is the presence of a mild hyperchloremic metabolic acidosis. The diagnosis of SAD is easily made by excluding other causes of hyperkalemia namely of iatrogenic origin (potassium chloride administration, potassium sparing diuretics, RAS blockers, heparin, etc) (see table 1). Demonstration of a relatively low aldosterone level relative to the level of plasma potassium is essential to the diagnosis of SAD. The diagnosis of SAD is suggested the finding of hyperkalemia with a plasma aldosterone-to-plasma potassium ratio of less than 3.0. [44, 46]. The levels of plasma cortisol, by definition, need to be normal.

**Studies in patients with SAD**

Schambelan and coworkers [39] prospectively studied patients with hyperkalemia and varying degrees of CKD. Increased serum potassium levels could not be attributed to any common factors capable of causing hyperkalemia. The authors showed that urinary aldosterone secretion was low when corrected for serum potassium in most of their patients [39]. Plasma renin activity was low and failed to rise during volume contraction, and plasma cortisol levels were normal [39]. Therefore, these patients were classified as having hyporeninemic hypoaldosteronism. A study by Arruda and coworkers [44] confirmed these observations by showing that hyperkalemia due to aldosterone deficiency was found in 80% of patients with CKD. A small group of patients studied by Schambelan and coworkers had increased levels of plasma potassium and the urinary aldosterone levels corrected by plasma potassium were within the normal range [39]. Despite
these findings, the authors classified this group of patients as having selective aldosterone
deficiency. One could argue that it is difficult to accept the diagnosis of selective SAD in the
presence of normal urinary aldosterone levels. Although one could take the position that the
levels of aldosterone, while in the normal range, can still be considered inappropriately low in
the face of hyperkalemia. To support this contention, it would be necessary to measure urinary
aldosterone in patients with CKD and normal serum potassium levels. Potassium chloride should
then be given and the measurement of aldosterone repeated. This would permit the determination
of the normal level of urinary aldosterone in a patient with CKD and hyperkalemia. In other
words, how much aldosterone is necessary in renal insufficiency to allow normal potassium
excretion? Arruda and coworkers [44] also noted that 20% of patients studied with CKD had a
normal plasma aldosterone-to-plasma potassium ratio, and classified these patients as having
tubular unresponsiveness to aldosterone. This study suffers from the same criticism applied to
Schambelan's et al study; namely that aldosterone levels were measured only when plasma
potassium was in the normal range [39]. In both studies, however, a renal defect for potassium
excretion was evident in that potassium excretion, corrected for glomerular filtration rate (GFR)
and serum potassium, was lower than that of controls with comparable GFR. It will seem logical
to anticipate that with chronic reductions in GFR, an increased amount of aldosterone would be
required to maintain potassium homeostasis. Indeed, there are data showing that aldosterone
increases with progressive loss of GFR [83] Such an increase in aldosterone would help facilitate
the adaptive increase in potassium secretion and acid excretion per remaining nephron, which is
characteristic of CKD [78].

The mechanism of metabolic acidosis in selective aldosterone deficiency is not
completely understood. The metabolic acidosis has been attributed to several factors. These
include a direct effect of aldosterone on the hydrogen ion pump. This contention is supported by
the experimental studies showing that aldosterone increases urinary acidification in isolated
bladders of epithelial analogues of the mammalian collecting tubule [75] and in perfused
collecting tubules [51]. In bladder membranes, aldosterone increases the rate at which the pump
operates without affecting the force of the pump [75]. This explains in part why patients with
selective, aldosterone deficiency are capable of lowering the urine pH maximally in response to
acidosis. This ability to lower the urine pH maximally would be the in vivo functional equivalent
of the force of the hydrogen ion pump but, of course, in vivo the lack of urinary ammonia buffer
associated with CKD and aldosterone deficiency also explains the low pH. [84] Aldosterone
deficiency can also lead to sodium wastage, volume contraction, and decreased distal sodium delivery. This decreased distal delivery can impair acid excretion. The role of decreased distal sodium delivery in mediating the suppressed acid secretion and potassium in selective aldosterone deficiency is controversial and has not been adequately studied. It should be noted that the experimental model of selective aldosterone deficiency (bilateral adrenalectomy with replacement of glucocorticoids) may not replicate the clinical counterpart of selective aldosterone deficiency. In the experimental model, the adrenal medulla is removed, and this may contribute to the alteration in GFR seen in these animals. Also patients with SAD have a decreased GFR, not because of volume contraction but rather because of renal disease. Animals with selective aldosterone deficiency are volume contracted, whereas, most patients with selective aldosteronism are volume expanded. Thus, any extrapolation from the experimental model to the clinical counterpart must be made with caution.

The administration of fludrocortisone to patients with selective hypoaldosteronism increases net acid excretion [37]. This finding has been used to support the theory that aldosterone deficiency plays a major role in the decrease in net acid excretion. It should be emphasized, however, that fludrocortisone administration to these patients also corrects serum potassium, and an inverse correlation between potassium and ammonium excretion has been observed [37]. Since hyperkalemia is well known to decrease ammonium production, it is possible that fludrocortisone administration increases net acid excretion at least in part by normalizing serum potassium and thus increasing ammonium production [53].

To further investigate the role of mineralocorticoid replacement on acid-base homeostasis, Sebastian and coworkers [40] studied adrenalectomized patients with normal GFR. Patients who had undergone bilateral adrenalectomy usually for breast cancer (cancer of the breast, Cushing's disease, and primary hyperaldosteronism) were replaced with glucocorticoid and were studied during discontinuation of mineralocorticoid replacement or during the initiation of mineralocorticoid replacement. All patients had normal GFRs, thus eliminating the presence of renal failure as a variable capable of influencing net acid excretion. The authors observed that net acid excretion and plasma bicarbonate concentration levels decreased in patients in whom mineralocorticoid replacement was discontinued [40]. Conversely, they observed that net acid excretion and plasma bicarbonate concentration increased in patients in whom mineralocorticoid therapy was instituted. There was a significant correlation between the change in net acid excretion and the change in plasma bicarbonate concentration. Absence of mineralocorticoids
decreased plasma bicarbonate concentration by only 1.1 mEq/L, and maximum mineralocorticoid replacement increased plasma bicarbonate concentration from 0.7 to 2.6 mEq/L. It was concluded that in the presence of a normal GFR, plasma aldosterone plays only a permissive role on net acid excretion [40]. It should be emphasized that the small decrease in plasma bicarbonate concentration observed during mineralocorticoid deficiency parallels the increase in plasma bicarbonate concentration observed during the administration of supraphysiological amounts of mineralcorticoids. Therefore, the lower level in plasma bicarbonate concentration in patients with SAD in the setting of CKD must be attributed to factors other than aldosterone alone. CKD in itself results in a marked reduction in ammonium excretion [85, 86].

As renal function declines, aldosterone levels are expected to increase despite volume expansion. There are data, albeit limited, that supports this concept [83]. This increase in aldosterone plays a pivotal role in the adaptive increase of potassium excretion seen with CKD. The levels of ammonium in the urine in CKD fall as GFR declines low [85, 86]. Accordingly, any associated deficiencies in aldosterone would aggravate the metabolic acidosis by further decreasing ammonium excretion. In aldosterone deficiency, failure of the adaptive increase leads to hyperkalemic hyperchloremic acidosis at relatively high levels of the glomerular filtration rate. In the diseased kidney, aldosterone deficiency further contributes to the defect in renal sodium conservation. Yet, patients with SAD seldom present with sodium wastage. Indeed, because associated CKD, CHF and normal or excessive salt intake edema may be present. Sodium wastage may manifest itself clinically only when intercurrent illness results in decreased dietary salt intake to a level below the capacity of the diseased kidney to conserve sodium.

The diagnosis of SAD is easily made by excluding other causes of hyperkalemia (e.g., potassium chloride administration, potassium-sparing diuretics, transcellular shifts, RAS blockers [table 1]. In the absence of these medications a finding of a low aldosterone level after correcting for the serum potassium suggest aldosterone deficiency. Plasma renin activity is reduced in the majority of cases. A urinary potassium level of less than 40 mEq/L or a fractional potassium excretion of less than 20% in a patient with overt hyperkalemia suggests a defect in renal potassium excretion. An elevated serum potassium and abnormal renal function invariably indicate either the presence of SAD or defects in hydrogen ion and potassium secretion not primarily caused aldosterone deficiency as occurs in obstructive uropathy or sickle cell nephropathy (discussed below).
Studies in patients with Hyperkalemic dRTA.

Patients with hyperkalemic dRTA present with clinical findings that are often indistinguishable from those of patients with hyperkalemic RTA due to SAD. In both entities the main finding is hyperkalemic hyperchloremic metabolic acidosis, usually in the setting of preexisting chronic renal disease of mild to moderate severity (GFR 25 to 90 mL/min). Aldosterone levels are usually normal, or high in patients with hyperkalemic dRTA whereas they are, by definition, low in SAD. In addition to the aldosterone level the distinguishing feature of this entity is that urine pH cannot be lowered below 5.5 despite acidemia and other provocative tests that stimulate distal urinary acidification [41-44]. This is in contrast to patients with SAD, whose urine pH is typically below 5.5 [37, 40 -46]. Patients with hyperkalemic dRTA and normal plasma aldosterone levels have a rate of ammonium excretion higher than that of patients with pure SAD which supports the concept of an effect of aldosterone independent of potassium, in suppressing urinary ammonium excretion [41]. Hyperkalemic dRTA was best characterized in some patients with obstructive uropathy as discussed below.

Hyperkalemic Distal RTA associated with Obstructive Uropathy

In adults with chronic obstructive uropathy a syndrome of hyperkalemic RTA may be associated with high or low levels of aldosterone suggesting a mechanism distinctive from selective aldosterone deficiency [41]. We studied a group of 13 patients with obstructive uropathy and hyperkalemic hyperchloremic metabolic acidosis and divided into two main groups based on their urine during academia [41]. One group lowered the urine pH below 5.5 and had reduced ammonium excretion. These patients were found to have reduced plasma aldosterone levels, and therefore, fulfilled the criteria for the syndrome of SAD as described above. The other group was of interest because patients were not able to lower their urine pH below 5.5 and plasma aldosterone levels were not reduced and, in fact, were increased in some cases which is appropriate for the concurrent presence of hyperkalemia. Therefore rather than SAD these patients had a distinctive tubular defect that involves both acid and potassium excretion. To investigate the mechanism of such defect the patients were given 1mg of fludrocortisone 24 hours prior to the intravenous administration of sodium sulfate. [41] Normally, in a mineralocorticoid replete state, the infusion of sodium sulfate allows for an amplification of the voltage gradient usually found in the cortical collecting tubule. This occurs because
mineralocorticoid activity increases the reabsorption of sodium via ENaC, leaving an increased amount of poorly reabsorbable anion (sulfate, in this case) in the lumen of the distal tubule/CCT. As noted before, this increase in lumen negativity in the CCT enhances the secretion of hydrogen and by α intercalated cells and potassium by principal cell (Figure 1). In patients who did not acidify their urine or increase potassium excretion with the infusion of sodium sulfate ammonium, titratable acidity, and net acid excretion also did not increase significantly. The abnormal response of patients with obstructive uropathy to sodium sulfate infusion in the face of mineralocorticoid administration was attributed to a defect in sodium transport in the CCD i.e a voltage dependent type of DRTA [41]. This would prevent the generation of the lumen negative potential difference and secondarily impair both hydrogen and potassium secretion. Alternatively, there could be a generalized defect in hydrogen ion and potassium ion secretion due to the direct effect of obstructive damage to the cells of the distal nephron. Finally, obstructive uropathy could damage the deep nephrons more severely than the superficial nephrons, and nephron heterogeneity could be responsible in part for the defect in potassium and hydrogen ion secretion.

In the cortical collecting tubule, potassium is secreted mainly by a passive process Sodium reabsorption occurs in this segment as an active process leaving the lumen negatively charged because the permeability to chloride ion is much less than that sodium reabsorption via ENaC. Chloride movement therefore lags behind the movement of sodium and the negative voltage results. Since the concentration of potassium is high in the tubular cells in comparison to the concentration in the tubular fluid, potassium moves from the principal cell into the tubular lumen down both an electrical and concentration gradient. It can be readily seen that factors that affect sodium reabsorption also clearly affect potassium secretion via this mechanism in the same way they affect hydrogen ion secretion. Furthermore, if reabsorption of sodium is decreased, sodium wastage results and leads to intravascular volume contraction and decreased distal delivery of sodium. If sodium is not delivered distally to be reabsorbed and to generate lumen negativity, hydrogen ion and potassium ion secretion could be hampered as well. It should be emphasized, however, that in this study a defect of sodium reabsorption was not examined by performing balance studies while on a low salt diet. The concept of a defect in sodium reabsorption was based on animal studies where the post obstructed kidney which displays a mineralocorticoid-resistant defect in sodium reabsorption [87]. Hyperkalemic hyperchloremic metabolic acidosis has also been described in children with obstructive uropathy [88].
children had salt wastage and high levels of plasma renin activity and plasma aldosterone. Fractional K excretion was not different from controls but, considering the serum K levels, it is reasonable to attribute the hyperkalemia to a defect in K excretion. After correction of obstructive uropathy, the hyperkalemic hyperchloremic acidosis and other biochemical abnormalities resolved, except for a mild decrease in the urine Na/K ratio, thus indicating the persistence of some defect in K and Na transport [88]. These authors concluded appropriately that hyperkalemia and salt wastage due to obstructive uropathy in children must be ruled out before the diagnosis of primary pseudohypoaldosteronism can be established.

Of potential interest to the mechanism of decreased K+ secretion as a cause of hyperkalemic DRTA is recent work showing that the mammalian target of rapamycin (mTOR) pathway has been implied in the regulation of renal potassium excretion [89-91]. mTOR has two distinct functional complexes termed mTOR complex 1 (mTORC1) and mTORC2. Chen et al [89] showed that mice with collecting duct specific ablation of TSC1 (tuberous sclerosis complex protein) (CDTsc1KO) had greater mTORC1 activation in the collecting duct. This model had features of pseudohypoaldosteronism, including hyperkalemia, hyperaldosteronism and metabolic acidosis. Interestingly, mTORC1 activation also reduced the expression of serum and glucocorticoid-inducible kinase 1, a crucial regulator of potassium homeostasis in the kidney and decreased the expression and / or activity of ENaC and ROMK and Na\(^+\), K\(^+\) -ATPase in the CD [89]. In this regard mTORC1 activation could be another mechanism that could explain the diffuse defect in collecting tubule function with hyperkalemic metabolic acidosis that we reported in patients with obstructive uropathy and normal aldosterone levels [41].

Recent work also has shown that pharmacologic inhibition of mTORC2 regulates tubular sodium uptake by promoting ENaC activity [90], Grahammer et al [91] generated a mouse model lacking mTORC2 in the distal tubule (Rictor fl/fl Ksp-Cre mice). Interestingly while on a high potassium diet they developed hyperkalemia despite an increase in serum aldosterone levels. They attributed the hyperkalemia to reduced potassium excretion owing to diminished secretion because of failure to activate ROMK channels. Patch clamp experiments on split open tubular segments from the transition zone of the late connecting tubule and early cortical collecting duct demonstrated that Ba-sensitive apical K currents were barely detectable in the majority of Rictor fl/fl Ksp-Cre mice. Conversely, epithelial sodium channel (ENaC) activity was largely preserved suggesting that the reduced ability to maintain K homeostasis is the result of impaired apical K conductance and not a reduced electrical driving force for K secretion. These findings show that
upregulation of mTORC2 is an important regulator of potassium excretion when the levels of potassium increase. mTORC2 phosphorylates PKC alpha and SGK1 thereby regulating ROMK abundance and current at the plasma membrane. These mice also had an increase in aldosterone levels and when challenged with a low sodium diet they were able to reduce sodium excretion suggesting appropriate collecting tubule sodium reabsorption of sodium [91]. This mice model shows that hyperkalemia can develop without an associated decrease in sodium transport via ENaC but no data was provided on the renal handling of acid or the presence or absence of metabolic acidosis. Therefore, we think that mTORC2 is an important pathway for collecting tubule potassium secretion but alterations in this pathway are not likely to account for the development of hyperkalemic DRTA.

Studies of urinary obstruction in the postobstructed kidney

A detailed analysis of potassium handling in experimental models of obstructive uropathy has only been partially completed [87]. Following the release of unilateral ureteral obstruction, the postobstructed kidney had significantly lower potassium excretion (corrected for GFR) than the contralateral kidney during maneuvers that increase potassium excretion, such as bicarbonate loading or volume expansion. These results suggested a defect in the ability of the postobstructed kidney to increase potassium excretion in response to kaliuretic stimuli. The defect in potassium excretion in the postobstructed kidney was further investigated by giving dogs pharmacological doses of mineralocorticoid and Na₂SO₄. Infusion of Na₂SO₄ into animals or patients treated with mineralocorticoids usually results in increased potassium excretion as explained above. In the postobstructive kidney, Na₂SO₄ infusion not only failed to increase potassium excretion, but also failed to decrease urine pH normally [87]. This response is similar to that observed in patients with obstructive uropathy as described above.

Under baseline conditions the postobstructed kidney had a higher urine pH than did the control kidney. The postobstructed kidney also failed to increase the U-B PCO₂ gradient in response to HCO₃ loading, further indicating a defect in hydrogen ion secretion [87]. The postobstructed kidney failed not only to lower urine pH with sodium sulfate but also to increase urine PCO₂ in response to phosphate infusion [87]. These results were interpreted as indicating a defect in distal nephron hydrogen ion secretion. By analogy to studies utilizing amiloride, a hypothesis explaining the nature of the acidification defect in the post obstructed kidney was proposed by Arruda and Kurtzman [12,14]. Amiloride, a diuretic that blocks sodium channels in
the distal nephron, decreases sodium transport and thus decreases or abolishes the negative lumen potential difference. The latter phenomenon results in a decrease in hydrogen and sodium ion secretion due to the removal of the favorable electric gradient (voltage-dependent) for secretion of these ions. In the turtle bladder, amiloride (in small concentrations) caused a significant decrease in sodium transport and in the negative lumen potential difference, but it failed to decrease hydrogen ion secretion under short circuit conditions (the potential difference was clamped at 0 mV) [14]. Under open circuit conditions, amiloride decreased hydrogen ion secretion and the potential difference. Return of the potential difference to baseline values (with an external source of current) returned hydrogen ion secretion to control values despite the presence of amiloride [14]. Thus, the effect of amiloride on hydrogen ion secretion was interpreted as being solely the result of the removal of the favorable electric gradient (voltage-dependent). The post obstructed kidney also had a defect in sodium transport unresponsive to mineralocorticoid administration and defects in potassium ion and hydrogen ion secretion [87]. It was hypothesized that, if the defect in sodium transport occurred at the level of the collecting duct, the failure to reabsorb sodium would prevent the generation of a favorable electrical gradient for the secretion of potassium and hydrogen ions; this would result in a defect in potassium ion and hydrogen ion secretion much like the effect of amiloride. Experiments with monoclonal antibodies to H⁺-ATPase later showed a striking decrease in α-intercalated cell H⁺-ATPase staining in the collecting duct of animals with obstructive uropathy [92]. A reduction in numbers of vacuolar hydrogen pumps also plays a role in the acidification defect of obstructive uropathy whereas diminished sodium transport by the principal cells may cause a voltage defect. It could be interesting to study the mTOR pathway in the post obstructed kidney looking for alterations that may also account for the defect in potassium secretion observed in this model.

**Sickle Cell trait and sickle cell disease**

Patients with sickle cell anemia may have an incomplete form of distal acidification defect. De Jong et al. [93] evaluated urinary acidification before and after indomethacin administration in control subjects and in patients with sickle cell anemia. Urinary acidification was tested with the short NH₄Cl loading test. Urine pH after NH₄Cl was higher in sickle cell anemia patients than in controls, indicating the presence of a distal acidification defect. Administration of indomethacin failed to change urine pH in both groups. However, it increased
titratable acid in both groups; ammonia excretion was unchanged in controls and decreased in SCA patients. Net acid excretion was unchanged in sickle cell anemia patients and increased in the controls. The authors concluded that the inability of patients with SCA to lower urine pH is not corrected by indomethacin, indirectly suggesting that prostaglandins was not involved in the acidification defect.

De Fronzo and coworkers [94] studied patients with sickle cell disease. These patients had impaired potassium excretion when challenged with an acute potassium load. This defect could not be reversed by the administration of mineralocorticoids and sodium sulfate. Despite the defect of potassium excretion, none of the patients studied by DeFronzo were hyperkalemic. It should be noted, however, that the failure to disclose hyperkalemia in these patients could be due to the fact that they had normal GFR. We studied 6 patients with hemoglobinopathy (3 with sickle cell anemia, 2 with sickle cell trait, and 1 with sickle cell disease) [43]. Of note these patients had developed a hyperkalemic, hyperchloremic metabolic acidosis in the face of only mild to moderate CKD. The decreased GFR was attributed to the underlying disease process in the SS hemoglobin patients. The cause of decreased GFR in the patients with SA hemoglobin was unclear. As in the study of obstructive uropathy patients, some of these patients had normal aldosterone levels, whereas others had subnormal levels of aldosterone for the degree of hyperkalemia. It was found that fractional potassium excretion in these patients was lower than that of controls with comparable GFR and normal serum potassium [43]. The finding of a low baseline fractional excretion of potassium in the presence of hyperkalemia that persisted after sodium sulfate infusion after mineralocorticoid administration indicates the presence of a defect in potassium excretion.

We attributed the presence of hyperkalemia in our patients with sickle cell disease and trait to a defect in collecting tubule potassium excretion which was unmasked by the presence of CKD. In CKD there is an adaptive increase in potassium excretion which prevents the occurrence of hyperkalemia until the GFR is below 20-25ml/min. The mechanism of this adaptive increase include: overperfusion of the nephrons with poorly reabsorbable anions, hypertrophy of the remaining nephrons with amplification of the surface area of cells in the collecting tubule, increased aldosterone, increased sodium potassium adenosinetriphosphatase (ATPase) activity, and the increased capacity of the juxtamedullary nephrons to secrete potassium. In sickle cell nephropathy, the presence of a defect of potassium excretion in the presence of a normal GFR would hamper the normal adaptive increase in potassium excretion as CKD supervenes. All 6
patients that were studied by us had metabolic acidosis [43]. Despite the presence metabolic acidosis, 4 patients were unable to lower the urine pH below 5.5, indicating a distal acidification defect similar to that described above for patients with obstructive uropathy.

**Hyperkalemic RTA associated with other conditions**

Hyperkalemic renal tubular acidosis (RTA) is a common disorder in adult patients, particularly in the elderly. Cyclosporine A and tacrolimus administration are a well-recognized cause of hyperkalemic RTA. The early study of Adu et al.[95] suggested that the mechanism responsible for RTA in patients treated with Cyclosporine A is hyporeninemic hypoaldosteronism. Other mechanisms, however, are likely involved because some patients have normal aldosterone levels. Stahl et al. [96] described four (out of 23) renal transplant patients treated with Cy A who had hyperkalemic hyperchloremic metabolic acidosis and normal aldosterone levels. Although one could argue that the aldosterone levels may still be relatively low in the face of hyperkalemia, it is reasonable to assume that these patients had sufficient mineralocorticoid activity to acidify their urine and excrete potassium. A direct role of Cy A is suggested by showing that reduction of the dose of Cy A improved both the acidosis and the hyperkalemia [96].

Experimental studies showed that high-dose cyclosporine A administration for eight days to rats results in mild acidification defect as well as a defect in potassium excretion [97]. The mechanism responsible for these abnormalities was attributed to a voltage defect [97]. Consistent with this mechanism a transplant patient studied by Kamel et al [98] increased potassium excretion when distal sodium delivery was increased by bicarbonate administration but not after mineralocorticoid administration but to date the mechanism of calcineuric induced hyperkalemic RTA is not completely understood.

Kushner and Sitrin described two patients treated with triamterene (200 mg twice a day) or amiloride (10 mg/day) who developed hyperchloremic metabolic acidosis while on hyperalimentation [99]. The occurrence of hyperchloremic acidosis during the concomitant diuretic administration and hyperalimentation would be explained by the acid load provided by hyperalimentation in presence of impaired acid excretion by diuretics that are sodium channel antagonists. In essence, these human studies reproduce animal studies in which high doses of amiloride alone failed to induce acidosis, but when an acid load is given, a significant acidification defect was disclosed.

The occurrence of renal tubular acidosis with hyperkalemia in patients with systemic lupus erythematosus (SLE) has been well recognized. The prevalence of this disorder in SLE is unknown and also unclear is the possible correlation between tubular defects and histologic abnormalities. Kozeny et al. [100] reported 30 patients with SLE studied for the presence of an acidification defect. 18 patients showed some form of defect for H+, K, or Na transport. Of the patients with tubular defect, 16 had systemic acidosis. In some patients, the tubular defect disappeared during remission of the disease. Kozeny et al. used several tests of acidification including urine pH during acidosis, urine pH during administration of Na₂SO₄ and urine-blood pCO₂ gradient during
NaHCO3 infusion to characterize the acidification defect. In addition, they measured serum potassium, fractional potassium, and Na excretions. Five patients had an acidification defect associated with hyperkalemia. Of these, one patient clearly fulfilled the criteria for hyporeninemic hypoaldosteronism while the remaining four patients had a “voltage-dependent defect”. The remaining 13 patients were normokalemic, and eight of these patients could not lower the urine pH maximally in response to acidosis or to Na2SO4 infusion. In summary, one group of patients with SLE had an acidification defect and hyperkalemia while the other group had only an acidification defect. The patients with tubular defect appeared to have more severe interstitial disease as inferred by the finding that 75% of the patients appeared to more severe histologic abnormalities. This study indicates that tubular defects are common in patients with SLE who have tubule interstitial involvement. The failure to find a significant correlation between the tubular defect and histologic changes may be due to the relatively small number of patients studied.

In addition to pseudohypoaldosteronism discussed below, the clinician should suspect other adrenal disorders and tubular defects in young patients with hyperkalemic RTA. In this context it should be remembered that moderate hyperkalemia with appropriately higher levels of aldosterone may be present in children who have undergone successful correction of congenital hydronephrosis. Rodriguez-Soriano et al. [101] described hyperkalemic RTA in two infants with salt-losing congenital adrenal hyperplasia (CAH). The diagnosis was established by the finding of elevated levels of 17-hydroxyprogesterone, normal aldosterone levels, high plasma renin activity, and the presence of hyponatremia, hyperkalemia, and metabolic acidosis. The acidification defect was corrected by chronic administration of hydrocortisone or by acute administration of fludrocortisone. This finding strongly suggests that resistance to adrenal steroids was responsible for the acidification defect and that replacement in pharmacologic doses corrected the defect. Even though aldosterone levels were normal, the acidification defect seems related to mineralocorticoids because pharmacologic doses of fludrocortisone corrected the acidification defect. This apparent paradox can be explained by the fact that in congenital adrenal hyperplasia there are adrenal steroids that are mineralocorticoid antagonists and compete for the mineralocorticoid receptor. These antagonists would displace aldosterone from the receptor and thus prevent the action of aldosterone. The acute administration of fludrocortisone would displace these antagonists for the receptor and result in normal acidification. In addition, chronic administration of hydrocortisone corrected the acidification defect, presumably by suppressing the production of adrenal steroids, which were antagonizing the action of aldosterone.

**Genetic causes of Pseudohypoaldosteronism**
The syndromes of pseudohypoaldosteronism are characterized by features of hyperkalemia, hyperchloremic metabolic acidosis with normal or high aldosterone levels in presence of normal GFR [102-113]. These syndromes can be subdivided in two categories. Type I pseudohypoaldosteronism or pseudohypoaldosteronism of infancy which was described by Chuck and Perry in 1958 and is manifested by salt wasting and failure to thrive [102]. The spectrum of clinical manifestations varies from severely affected patients who die in infancy to asymptomatic carriers. Typically infants present with weight loss, dehydration, hypotension, failure to thrive, high urinary sodium despite volume depletion and hypotension, a non-anion gap metabolic acidosis, and hyperkalemia. Plasma and urine aldosterone levels are elevated, and plasma renin activity is increased. More recently, this syndrome has been designated as primary pseudohypoaldosteronism type I (PHA I). Many but not all of the patients have mineralocorticoid receptor mutations (MLR) transmitted in an autosomal dominant fashion. Mutations of ENaC have also been identified and associated with pseudohypoaldosteronism type I. In general, the phenotype is less severe in the one caused by the mineralocorticoid receptor MLR mutations (reviewed in reference [78]).

Gordon syndrome, also known as pseudohypoaldosteronism type II (PHAII), is a familial disorder characterized by hypertension, hyperkalemia, and normal renal function. The syndrome is associated with hyperchloremic metabolic acidosis and suppressed renin activity. Paver and Pauline first described a patient with hypertension, normal glomerular filtration rate (GFR), persistent hyperkalemia, and normal aldosterone levels [107]. This patient had low urinary potassium excretion and persistently positive potassium balance, indicating that the hyperkalemia was due to a defect in renal potassium excretion. Studies of acid excretion during ammonium chloride administration showed a blunted increase in ammonium and titratable acid excretion. The plasma renin response to upright posture or to a low-sodium diet was blunted. Aldosterone levels varied from low to high, depending on the level of hyperkalemia. Other associated features included intellectual impairment, short stature, and unusual facial appearance. Later Gordon et al. [107] described a similar patient, but with low aldosterone levels. The disease is also characterized by a marked sensitivity to thiazide diuretics, with improvement in excretion of potassium and correction of the hyperkalemia. Gordon syndrome may be familial, in that 17 of 28 patients described by Gordon originated from four families [108]. Actually, hypertension is not uniformly present; a review of all reported cases showed a prevalence of only 68%. Other features, which may or may not be present, include short stature, intellectual impairment, and
unusual facial appearance. Virtually every patient has a normal glomerular filtration rate and hyperchloremic metabolic acidosis.

Gordon proposed that the primary abnormality was a natriuretic factor deficiency, which, coupled with high Na\(^+\) intake, would increase sodium reabsorption proximal to the site of Na\(^+\) reabsorption regulated by aldosterone [107]. Such increased Na\(^+\) retention would cause volume-dependent hypertension and chronic inhibition of the renin-angiotensin system, resulting in levels of aldosterone too low to maintain potassium homeostasis, despite the presence of hyperkalemia. The suppressed K\(^+\) and H\(^+\) secretion, which is dependent on distal Na\(^+\) delivery and aldosterone levels, would then result in hypertension, hyperkalemia, and hyperchloremic acidosis. This view was supported by the finding that a low-salt diet resulted in increased plasma renin levels and controlled the hypertension and hyperkalemia. A possible mechanism was later suggested by Shambelan et al [112] who proposed an abnormal increase in renal tubular chloride reabsorption (“chloride shunting”). Renal clearance of potassium was low, despite normal/high levels of serum and urinary aldosterone (after normal dietary intake of NaCl). Potassium clearance remained low, despite administration of supraphysiologic levels of mineralocorticoids or of the concomitant administration of mineralocorticoids with NaCl infusion, suggesting mineralocorticoid resistance. Renal clearance of potassium increased only with the administration of mineralocorticoid and sodium coupled with a poorly reabsorbable anion such as sulfate. It was therefore postulated that there was an abnormally increased rate of reabsorption of chloride in the distal tubule (chloride shunt), resulting in a decrease in the negative transtubular electric gradient and decreased K\(^+\) secretion [112].

Recently, it has been shown that mutations in WNK kinases have resulted in a clinical scenario similar to Gordon syndrome. WNK stands for “With No lysine Kinase” at a key catalytic kinase residue. Wilson et al. [114] identified two human genes associated with PHA II. New kindred with typical features of PHAII were studied, and it was found that inheritance of the trait was consistent with autosomal dominant transmission with high penetrance. Both genes encoded members of the WNK family, and were found to be homologous to the rat WNK1 and WNK4. WNK4 was localized almost exclusively in the kidney, whereas WNK1 was found in other tissues as well. Both WNK1 and WNK4 localize to the distal collecting tubule and cortical collecting tubule, adjacent to segments of the distal nephron that play key roles in salt, water, K\(^+\) and pH homeostasis. The putative relationship of WNK1 and WNK4 can be described as follows: normally WNK4 inhibits sodium chloride cotransporter (NCCT) expression in the distal
collecting tubule membrane. Loss of WNK4 activity would relieve this inhibition and therefore result in increased NCCT expression. WNK1 was found to inhibit WNK4. Mutations of WNK1 that result in increased WNK1 activity would cause further suppression of WNK4 activity, and therefore result in an increase in NCCT membrane expression. WNK4 also decreases paracellular Cl permeability and inhibits the renal K⁺ channel, ROMK. The inhibition of ROMK is independent of WNK4 kinase activity and mediated by a mechanism distinct from NCCT inhibition. WNK4 mutations that cause loss of inhibition of NCCT expression resulted in increased inhibition of ROMK. Mutant WNK4 found in Gordon Syndrome results in increased NCCT membrane expression, decreased ROMK function via inhibition, and increased paracellular chloride permeability, all of which explains the hypertension, hyperkalemia, and hyperchloremic acidosis seen in Gordon syndrome.

To add to the extreme complexity of this syndrome involvement of two other genes kelch-like 3 (KLHL3) and cullin 3 (CUL3) have been described recently (115). It has been reported that these two genes form a RING-type E3-ubiquitin ligase complex that modulates WNK1 and WNK4 abundance. WNKs regulate the activity of the Na⁺:Cl⁻ cotransporter (NCCT), via the phosphorylation of other serine-threonine kinases known as SPAK-OSR1. The ubiquitous isoform of WNK 1 known as L-WNK 1 activates the kinase SPAK which in turn phosphorylates and activates NCCT (116).

**Treatment**

Although mineralocorticoid replacement should be considered in patients with SAD, the reality is that most patients with this syndrome have CKD with hypertension and often congestive heart failure. This greatly limits this form of therapy. In the absence of heart failure or uncontrolled hypertension a low dose of 0.1 gm of fludrocortisone can be considered. When this approach is not tolerated the administration of a loop diuretic helps control the hyperkalemia by increasing sodium delivery to the cortical collecting tubule. Education on avoiding potassium rich foods, of course, is part of the treatment strategy as well as avoiding drugs that can precipitate hyperkalemia, (table 1.)

The amount of alkali therapy is usually about 30 mEq/day as these patients are only moderately acidotic. Another approach that is already feasible is the use of potassium binders such as patiromer for the treatment of chronic hyperkalemia in CKD [117-121]. Potassium binders suitable for chronic use such as patiromer, by lowering plasma potassium, may increase ammonium excretion and help correct the metabolic acidosis. However, studies demonstrating
this expected beneficial effect of lowering plasma potassium on increasing ammonium and increasing plasma bicarbonate are not currently available.

With the expected introduction of novel therapies for treatment of CKD such as TRC101 [122], the treatment of SAD and hyperkalemic distal RTA may be further facilitated.
References

1. Albright F, Burnett CH, et al. Osteomalacia and late rickets; the various etiologies met in the United States with emphasis on that resulting from a specific form of renal acidosis, the therapeutic indications for each etiological sub-group, and the relationship between osteomalacia and Milkman's syndrome. Medicine (Baltimore). 1946;25:399-479.


24. Sly WS, Hewett-Emmet D, Whyte MP, Yu YS, Tashian RE. Carbonic anhydrase II deficiency identified as the primary defect in the autosomal recessive syndrome of


34. Norgett EE, Golder ZJ, Lorente-Canovas B, Ingham N, Steel KP, Karet Frankl FE. Atp6v0a4 knockout mouse is a model of distal renal tubular acidosis with hearing loss, with additional extrarenal phenotype. PNAS. 2012;109:13775-13780.


69. Lee HW, Verlander JW, Handlogten ME, Han KH, Weiner ID. Effect of collecting duct-specific deletion of both Rh B Glycoprotein (Rhbg) and Rh C Glycoprotein (Rhcg) on renal response to metabolic acidosis. Amer J Physiol Ren Physiol. 2014;306:F389-400.


78. Mitra A, Batlle D. Aldosterone deficiency and resistance in Acid-Base and Electrolyte Disorders A companion to Brenner and Rector’s The Kidney (Dubose and Hamm editors), Saunders 2002;413-433
82. Leehey D, Gantt C, Lim V: Heparin-induced hypoaldosteronism. JAMA 246:21B9-2190


Principal cell. This cell has a luminal membrane epithelial sodium channel, ENaC and the renal outer medullary small-conductance K channel (ROMK). A transtubular electrical gradient, lumen negative, is generated by sodium transport via ENaC that favors not only K secretion via ROMK by principal cells but also H+ secretion by neighboring α intercalated cell mainly via the V-type H⁺-ATPases, the voltage-dependent effect, see text.

Type α intercalated cell. Bicarbonate and proton generation is catalyzed by cytosolic CAII providing protons for luminal V-type H⁺-ATPases and bicarbonate for basolateral chloride/bicarbonate exchangers including AE1. Type α intercalated cells also express
basolateral KCC4 KCl-cotransporters that maintains low levels of intracellular chloride. Type α intercalated cells express also on their apical membrane H⁺/K⁺-ATPases that serve mostly preservation of potassium during potassium deficiency with a limited role of H⁺ secretion under normal conditions.

Table 1. Iatrogenic causes of Renal Hyperkalemia

<table>
<thead>
<tr>
<th>Aldosterone Deficiency</th>
<th>Aldosterone Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>Cyclosporine A</td>
</tr>
<tr>
<td>Angiotensin-converting Enzyme Inhibitors</td>
<td>FK506 (tacrolimus)</td>
</tr>
<tr>
<td>Angiotensin II blockers</td>
<td>Amiloride</td>
</tr>
<tr>
<td>Heparin</td>
<td>Triamterene</td>
</tr>
<tr>
<td>Cyclosporine A</td>
<td>Trimethoprim</td>
</tr>
<tr>
<td>FK506 (tacrolimus)</td>
<td>Pentamidine</td>
</tr>
</tbody>
</table>

Drug induced Hyperkalemia separated on causes of aldosterone deficiency and resistance. Cyclosporine A and tacrolimus are listed under both categories, see text. Adapted from Mitra A, Batlle D. Aldosterone deficiency and resistance in Acid-Base and Electrolyte Disorders A companion to Brenner and Rector’s The Kidney (Dubose and Hamm editors), Saunders 2002;413-433.
Table 2. Causes of Pseudohypoaldosteronism

<table>
<thead>
<tr>
<th>Mode of Inheritance</th>
<th>Gene</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudohypoaldosteronism Type IA</td>
<td>Dominant</td>
<td>Mineralocorticoid receptor</td>
</tr>
<tr>
<td>Pseudohypoaldosteronism Type IB</td>
<td>Recessive</td>
<td>Epithelial Sodium Channel</td>
</tr>
<tr>
<td>Pseudohypoaldosteronism Type II A</td>
<td>Dominant</td>
<td>WNK 1, WNK4, KLHL3, CUL 3</td>
</tr>
</tbody>
</table>

Adapted from Mitra A, Batlle D. Aldosterone deficiency and resistance in Acid-Base and Electrolyte Disorders A companion to Brenner and Rector’s The Kidney (Dubose and Hamm editors), Saunders 2002; 413-433.