Mechanisms in Hyperkalemic Renal Tubular Acidosis

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ABSTRACT

The form of renal tubular acidosis associated with hyperkalemia is usually attributable to real or apparent hypoaldosteronism. It is therefore a common feature in diabetes and a number of other conditions associated with underproduction of renin or aldosterone. In addition, the close relationship between potassium levels and ammonia production dictates that hyperkalemia *per se* can lead to acidosis. Here I describe the modern relationship between molecular function of the distal portion of the nephron, pathways of ammoniagenesis, and hyperkalemia.

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To begin, we need a definition and differential diagnosis for hyperkalemic (type IV) renal tubular acidosis (RTA). Inability of the kidney either to excrete sufficient net acid or to retain sufficient bicarbonate results in a group of disorders known as RTAs.[1] These all are normal anion gap hyperchloremic acidoses; in their traditional classification, type IV refers to the only variant associated with hyperkalemia. Unlike other distal RTAs, the collecting duct here fails to excrete both protons and potassium. Such a situation arises when aldosterone is insufficient in either quantity or activity and/or because of some intrinsic (genetic) or acquired molecular defect in relevant transporters. Sufficiency of aldosterone is both quantitatively and functionally necessary for adequate sodium reabsorption by the epithelial sodium channel (ENaC) located on the luminal surface of principal cells in the terminal portions of the nephron, which under normal conditions leads to the lumen-negative potential essential for potassium and proton secretion (Figure 1A). In addition, aldosterone has a direct, Na-independent, nongenomic effect on proton secretion through upregulation of apical proton pumps on intercalated cells, in rodents at least.[2,3]

TRUE HYPOALDOSTERONISM

Low levels of aldosterone or tubular unresponsiveness to this hormone are present in the majority of patients with hyperkalemia and impaired renal function before end stage.[4,5] The most common medical conditions associated with hyporeninemic hypoaldosteronism include diabetes and various forms of interstitial disease, including amyloid, monoclonal gammopathies, and particularly the interstitial nephritis associated with nonsteroidal anti-inflammatory agents. In the last case, renin levels may be normal, and some patients with diabetes fail to respond with aldosterone synthesis or release despite hyperkalemia. Other situations in which hypoaldosteronism is present but not matched by hyporeninism include adrenal destruction (whether surgical, malignant, or hemorrhagic), Addison disease, angiotensin-converting enzyme inhibitor therapy or angiotensin receptor blockade, critical illness (because of direct adrenal suppression), and inhibition of aldosterone synthesis by heparin.[6,7] Hyporeninemic hypoaldosteronism is also predictable with β blockade.[8]

APPARENT OR FUNCTIONAL HYPOALDOSTERONISM

Functional hypoaldosteronism occurs in the context either of various inherited disorders (see next section) or of a number of drugs that affect aldosterone activity, either directly by interference with its receptor or by affecting its target pathway.[9] For example, mineralocorticoid receptors on the basolateral surface of distal nephron epithelia (Figure 1A) are antagonized by spironolactone and eplerenone, whereas the ENaC itself is blocked not only by amiloride and triamterene but also by trimethoprim and pentamidine.[10,11] Cyclosporine therapy interferes with the sodium gradient in the collecting duct by interference with the basolateral Na/K-ATPase and possibly NKCC2 and/or distal K^+ channels.[12]

WHAT CAN WE LEARN FROM MENDELIAN DISORDERS?

Single-gene disorders that affect the renal transporters mentioned in the previ-

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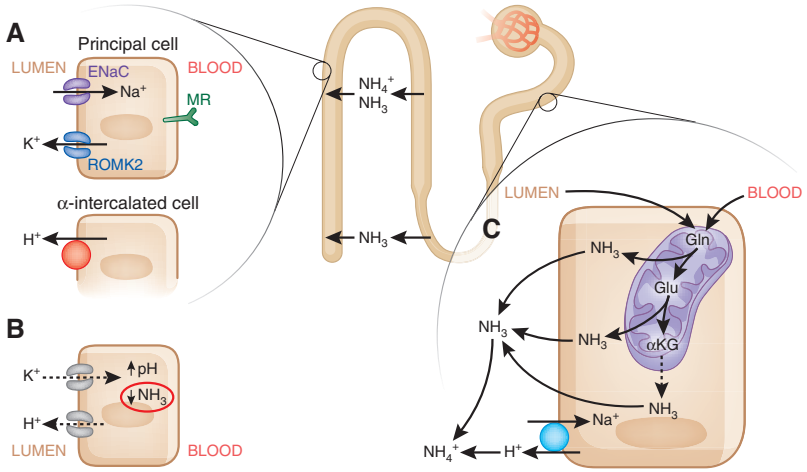

Figure 1. Factors involved in hyperkalemic acidosis. (A) Proper function of the ENaC at the apical surface of principal cells is necessary for K^+ secretion by ROMK in these same cells and H^+ secretion by adjacent intercalated cells. Inherited or acquired loss of ENaC function or its regulation by aldosterone *via* the mineralocorticoid receptor (MR) gives rise to hyperkalemic acidosis. (B) Hyperkalemia raises intracellular pH by exchange with protons, impairing enzymes involved in ammoniagenesis. (C) Ammoniagenesis in the proximal tubule is chiefly by deamidation of filtered or secreted glutamine (Gln). Ammonia (NH_3) diffusing into the nascent urine assists in buffering H^+; both NH_3 and NH_4^+ undergo further reabsorption in the medullary loop followed by distal nephron movement into the final urine. Glu, glutamate; aKG, α-ketoglutarate.

ous section also contribute to knowledge of the complex interplay between salt handling and acid-base balance. A good example is pseudohypoaldosteronism type 1 (OMIM 264350, 177735). Here, despite activation of the renin-aldosterone axis, renal salt wasting is accompanied by hyperkalemia and hyperchloremic metabolic acidosis, all of which are due either to loss of function of ENaC because of mutations in one of the three genes encoding its subunits in the severe, recessive form of the disease[13,14] or to abnormalities in the mineralocorticoid receptor in the milder, dominant form.[15] These phenotypes are recapitulated in mouse models.[16,17]

Pseudohypoaldosteronism type 2 (OMIM 145260), also known as Gordon syndrome, represents a different problem: that of dominantly inherited hyperkalemic hypertension with an associated (usually mild) acidosis, in which either removal of the distal NaCl cotransporter from the distal convoluted tubule apical surface or insertion of ROMK into the collecting duct membrane is impaired because of mutation in one of their regulators, the WNK (with no lysine [K] kinases.[18] Both of these defects have the effect of impairing distal K^+ secretion—the former because distal sodium delivery falls and the latter because K^+ secretion fails.[19] In either case, the renin-aldosterone axis fails to compensate. Whether WNK kinases also regulate proton pumps in the collecting duct is unknown.

Rare nonrenal conditions that impair mineralocorticoid synthesis include inherited enzyme defects such as 21-hydroxylase, 3β-hydroxysteroid dehydrogenase, and corticosterone methyloxidase deficiency (OMIM 201910, 201810, 203400, 610600).

HOW DOES HYPERKALEMIA CAUSE ACIDOSIS?

Thirty-five years ago, normal men who were fed a high-K^+ diet were observed to decrease their urine pH, ammonium, and net acid excretion. This was interpreted as being due to decreased renal ammonia production.[20,21] In the presence of normal aldosterone production, however, a high intake of K^+ does not commonly lead to metabolic acidosis *per se* in humans compared with rodents, in which dietary manipulation results in a much bigger K^+ load. Reduction in ammonia production in humans is offset by an increase in distal sodium delivery and aldosterone upregulation, which promote K^+ and H^+ excretion as discussed already.

The roles of aldosterone and hyperkalemia in the physiology of human hyperkalemic acidosis were considered in a case report in the *New England Journal of Medicine*.[22] The case concerned a patient with hyperkalemic hypoaldosteronism but only moderate renal impairment. The authors demonstrated reduced urinary ammonium excretion that resolved with the use of ion exchange resins to correct the hyperkalemia, whereas replacing the mineralocorticoid only partly corrected the biochemical and acid-base disturbance. This finding implicated hyperkalemia itself in the pathophysiology.

The mechanism of this observation was not addressed in the article, and the vast majority both of *in vivo* and *in vitro* studies from which conventional wisdom is extracted concern the kidneys of experimental animals. Experiments in dogs were probably the first to reveal that mineralocorticoid deficiency led not only to hyperkalemia but also to diminished ammonia production and proton secretion[23,24] and revealed a species difference in that dogs are unable to lower urine pH in this context, whereas humans do. Kamm reported to the American Society of Nephrology in a 1971 abstract that chronic K^+ loading in rats reduced ammonium excretion.[25] A variety of studies thereafter agreed, albeit with differing percentage falls, DuBose and Good[26] reporting a 40% drop in urinary ammonium excretion with 50% fall in whole-kidney ammonium production; however, the fine details of how this happens mechanistically are still to some extent unclear, in part because of methodologic as well as species differences between studies. For example, rats fed a

high-K^+ diet for 1 wk showed diminished distal nephron ammonium secretion in the isolated perfused kidney, although this was not significantly different from control animals, whereas perfusing individual kidney tubules with K^+ led to a 30% fall in ammoniagenesis.[27] The finding was amiloride independent,[28] but the role of aldosterone was not addressed at that point.

Looking at the role of the proximal tubule at the level of the single nephron, both acute and chronic K^+ loading in rats diminishes proximal ammonia generation but does not affect the rate of its transport in easily accessible cortical nephrons,[26,29] leading to the suggestion that deeper nephrons contribute a greater net effect on ammonia physiology. Isolated perfused mouse nephrons yielded similar findings: a significant fall in proximal tubular ammonia production without affecting the rate of secretion.[30]

Despite agreement that proximal production is affected, how this is achieved is unclear. It probably involves potassium entry into cells, displacing protons and thereby raising intracellular pH,[31,32] which by extrapolation from the opposite effects of acidosis likely leads to reduced enzyme function (Figure 1B); however, a number of unresolved issues remain. First, it is not clear whether this would be an acute or a chronic adaptation: In an early study, long-term K^+ loading of rats led to drops in ammonia levels in kidney slices of 5% in cortex and 36% in medulla, whereas acutely treating kidney slices with K^+ solution *ex vivo* did not have the same effect[33] Conversely, another study showed rat cortical slices acutely exposed to K^+ up to 10 mmol/L inhibited ammonia formation.[34]

Second, there has been controversy as to the actual mechanism modulating ammonia production, a large proportion of which normally takes place through deamidation of glutamine within mitochondria in proximal tubular cells (Figure 1C). Although there is support in the literature for lower levels of glutamate deamination in cortical tissue in hyperkalemic rat and dog,[35] a study of isolated mitochondrial function *in vitro* concluded that overall glutamine metabolism was not greatly affected by high potassium.[36] These differing observations are in contrast to increased mitochondrial activity repeatedly observed in K^+ depletion. The differences may be accountable by *in vitro* experimental variations and/or effects of build-up of intermediate metabolites,[37] and it is notable that assessments of changes in systemic and/or intracellular pH have not in general been reported in dietary K^+ studies.

In addition, the reported effects of direct pH change on isolated mitochondria do not necessarily mirror those on intact cells, as exemplified by Tannen and Kunin's[36] finding that lowering medium pH seems to inhibit isolated mitochondrial ammonia production in rats, whereas, contrary to expectation, it was alkalosis that had this effect in a dog study.[38] Again, most studies are concerned with metabolic acidosis as the primary insult rather than hyperkalemia. Overall, however, there is agreement that ammonia production in the proximal tubule is indeed decreased by hyperkalemia, with the caveat that many studies have focused more on states of K^+ depletion.

Further down the nephron, interstitial accumulation of both ammonia and ammonium by their movement out of the loop of Henle and their subsequent reappearance in the final urine play important roles in normal acid-base and fluid balance that may be disturbed in hyperkalemia and therefore contribute to the acidosis. Because a proportion of proximally produced ammonia is protonated by the extruded H^+ ions exchanged for Na^+ by NHE3 (Figure 1C), both nonionic diffusion of ammonia and ionic transport of ammonium are required for transport from lumen to interstitium and back again. These have been the subject of large bodies of work that in normal animals together demonstrate relative predominance of ammonium transport in the loop but ammonia diffusion in the collecting duct, both of which are subject to alterations that depend on pH, lumen voltage, and electrolyte concentrations.

The transport of ammonium in both loop and collecting duct has been implicated in the acidosis of hyperkalemia.[39] In the loop, ammonium reabsorption is furosemide sensitive, suggesting a role for the apical Na/K/2Cl co-transporter.[40] Hyperkalemia diminishes this transcellular transport, probably by direct competition between elevated luminal K^+ and ammonium for the K^+ binding site on the co-transporter.[41,42] Similarly, in the inner medulla, failure of normal, transcellular ammonium secretion into urine in the context of hyperkalemia has been linked to impaired capacity of the collecting duct's basolateral sodium pump to carry the NH_4^+ ion.[43] In addition, reduced availability in the collecting duct lumen of ammonia will preclude buffering of directly secreted protons (Figure 1A).

Thus, interplay between renal potassium and acid-base homeostatic function is complex,[44] involving direct effects of one on the other through modulation of ion transport by aldosterone, lowering of ammonia formation, and defective medullary ammonium handling. In the clinical context, hypoaldosteronism is the dominant factor in human hyperkalemic RTA, and rodent studies of hyperkalemic metabolic alterations must be extrapolated with caution.

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DISCLOSURES

None.

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