Familial hyperkalemia and hypertension and a hypothesis to explain proximal renal tubular acidosis

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Familial hyperkalemia and hypertension (FHHt) is an inherited disease characterized by hyperkalemia, hypertension, and hyperchloremic acidosis (1, 2). The primary defect is a hyperactive sodium chloride cotransporter (NCC), expressed exclusively in renal distal convoluted tubule (DCT). FHHt is caused by a mutation in 1 of 4 genes, WNK1, WNK4, KLHL3, and Cul3, which leads to activation of NCC (2). A recent publication in PNAS (3) shows that a mutation of WNK4 prevents specific modulation by Cl^- ions, inhibits its activity, and produces a FHHt phenotype. This emphasizes the significant role of WNK4 in renal Cl^- handling in pathogenesis of FHHt and the question of the mechanism of hyperchloremic metabolic acidosis (4). Is hyperchloremia in FHHt a primary abnormality or a secondary consequence of activation of NCC? FHHt is most effectively treated with thiazide diuretics that specifically inhibit NCC, implying the primary role of this transporter. Activation of NCC should increase renal reabsorption of Cl^- as well as Na^+ ions in DCT. Increased Na^+ reabsorption leads indirectly to hyperkalemia and eventually hypertension (2).

One recent publication (5) described a mechanism of renal distal tubular acidosis in a transgenic mouse, involving WNK4-induced activation of pendrin, an electroneutral $2Cl^-/2HCO_3^-$ exchanger, expressed in collecting duct β-intercalated cells. However, the significance in humans is unproven since mutations in the pendrin gene, producing the "Pendred syndrome," do not display a renal phenotype. By contrast, a bicarbonate loading test in patients with FHHt displayed proximal renal tubular acidosis (pRTA), i.e., hyperbicarbonaturia (6). The proximal tubule (PT) is the major site of reabsorption of Cl^- and HCO_3^- ions. Thus, exchange of Cl^- with HCO_3^- is expected in this segment. Since direct exchange of Cl^- and HCO_3^- is not known for PT, indirect coupling must be invoked.

A molecular mechanism for indirect coupling between increased Cl^- and decreased bicarbonate reabsorption in PT is described in ref. 7. Eighty to 90% of HCO_3^- is reabsorbed in PT by a mechanism involving apical CO_2 diffusion, intracellular conversion to H_2CO_3 and $HCO_3^- + H^+$ catalyzed by carbonic anhydrase (CAII), removal of H^+ by the apical Na^+/H^+ exchanger, NHE-3, and $1Na^+$-$3HCO_3^-$ cotransport from the basolateral surface into the peritubular fluid on NBC-1, the $1Na^+/3HCO_3^-$ transporter (SLC4A4), expressed exclusively in PT. Dinour et al. (7) showed that, in subjects with familial pRTA, mutations in the NBC-1 transporter inhibit activity and the electrogenic current, resulting in hyperbicarbonaturia. Since the bulk of filtered Cl^- is reabsorbed in PT paracellularly, and the driving force is the transepithelial electrical potential (2 to 3 mV + basolateral), inhibition of the negative electrogenic current should increase the transepithelial potential that drives Cl^- reabsorption. In FHHt, we assume that hyperchloremia reflects increased Cl^- retention associated with increased NCC activity in DCT. The glomerular filtrate should have increased Cl^- and thus increased paracellular uptake compared with unaffected subjects. It has also been reported that disease-causing WNK4 mutations increase the paracellular Cl^- permeability (8). In principle, an increased paracellular Cl^- permeability and flow should reduce the transepithelial potential and thus the driving force for Na^+/HCO_3^- cotransport across the basolateral membrane. In conclusion, activation of NCC is the primary defect in FHHT and the hyperkalemia, hypertension, and hyperchloremic acidosis are all secondary consequences.

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