Potassium deprivation: a systems approach

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THE AMMONIA CONTINGENT WITHIN the renal research community has always faced a challenge of scholarship in discussing the significance of their results. The context of any particular observation easily includes the entire nephron, proximal tubule, loop of Henle, and most distal segments, the pathophysiological conditions of acidosis, hyper- and hypokalemia, and all of the various K⁺ transporters on or through which NH₄⁺ can ride. In brief, ammonia is synthesized in proximal tubule and flows to the renal medulla, where it can short-circuit the return to the cortex by exiting Henle’s limb and entering the collecting duct, in a step facilitated by luminal proton secretion. Acidosis enhances ammonia synthesis, in conjunction with increases in proton secretion all along the nephron, and this coordinated response makes good sense. Ammoniagenesis also responds to serum K⁺ concentration, increasing with hypokalemia and decreasing with hyperkalemia, to an extent that is evident in everyday clinical medicine. The rationale of this reciprocal response to K⁺ has been murky. What Hossain et al. (6) show us in this issue of the American Journal of Physiology-Renal Physiology is that the response to K⁺ seems to be so important to the organism that changes in amioniagenesis occur with variations in dietary K⁺, well before there are any changes in serum electrolyte concentrations.

The basic experiment of Hossain et al. is to place rats on a K⁺-free diet for 2 or 6 days and measure the impact on blood composition, on renal K⁺ excretion and urinary acidification, and on the expression of proximal tubule machinery for ammonia generation and transport. Their key finding is that within the 2-day window, urinary K⁺ excretion falls by ~3.5 mmol/day and urinary NH₄⁺ (and net acid excretion) increases by ~1 mmol/day. The increase in urinary NH₄⁺ is coincident with increased proximal tubule mRNA for a glutamine transporter, and for several enzymes key to ammoniagenesis. After 6 days, the urine was virtually K⁺ free and net acid excretion increased nearly sixfold, all without altering blood composition, a finding that the authors emphasize in the title of their paper, which designates it as a study of “potassium deprivation” rather than “potassium depletion.” This study complements earlier findings of Amlal et al. (1) that K⁺ deprivation for 2 or 3 days (in the absence of decreased serum K⁺) triggered decreases in luminal Na⁺-Cl⁻ and Na⁺-K⁺-2Cl⁻ cotransporters of the distal nephron. The observations of Hossain et al. (6) appear to be the downside counterpart to the report by Lee et al. (7), who documented that gustic K⁺ loading provokes renal K⁺ excretion before serum K⁺ rises, and that this does not occur if the same K⁺ load is infused either systemically or into the portal vein. The work by Hossain et al. (6) also provides a larger context for the extensive work of Wang and collaborators (5), who have documented the impact of dietary K⁺ manipulations on distal nephron K⁺ channel density. Since their dietary protocols did impact serum K⁺ concentrations, the fact that a low-K⁺ diet decreased ascending Henle limb K⁺ channel activity, the primary signal could have been serum K⁺. The larger context of the Hossain study (6) is that it addresses the simultaneous impact of dietary K⁺ on acid-base transport.

Potassium balance intersects acid-base metabolism at the level of luminal acidification as well as buffer synthesis (ammoniagenesis). Frank K⁺ depletion enhances proton secretion, both proximally and distally, and the distal effect includes new luminal H⁺-ATPase (8) as well as H⁺-K⁺-ATPase (3). The effect of new H⁺-K⁺-ATPase is straightforward, retrieving K⁺ at the expense of H⁺ secretion. The effect of new H⁺-ATPase in α-intercalated cells is less direct, providing a secretory proton current that blunts the lumen negative electrical potential, established by principal cell Na⁺ reabsorption. Since the electroenergative proton potential difference drives K⁺ secretion, it is to be expected that for any level of Na⁺ reabsorption, increased proton secretion should decrease K⁺ secretion. The impact of amioniagenesis on K⁺ transport takes us from the likely to the conjectural. Basically, NH₄⁺ can do anything that K⁺ can do: it traverses ROMK channels about as well as K⁺ (2), it can substitute for K⁺ on the Na⁺-K⁺-2Cl⁻ cotransporter (13). In a mathematical model of thick ascending Henle limb function, with fidelity to observed affinities and concentrations, luminal NH₄⁺ was as effective in driving Na⁺ reabsorption as luminal K⁺, so that one might imagine the importance of NH₄⁺ as a stand-in to guarantee Na⁺ reabsorption in times of K⁺ scarcity (14). The interstitial medullary NH₂⁺ gradient is about an order of magnitude greater than proximal NH₂⁺, although the impact of K⁺ depletion on this gradient has not been examined. Wall (10) demonstrated that medullary interstitial NH₂⁺ can substitute for K⁺ on inner medullary collecting duct (IMCD) Na⁺-K⁺-ATPase to drive Na⁺ reabsorption. In so doing, it acidifies the IMCD cell and increases flux through the luminal membrane H⁺-K⁺-ATPase (12). In brief, this is a plausible scheme in which K⁺ depletion increases medullary NH₂⁺, and thus drives IMCD K⁺ reabsorption.

The paper of Hossain et al. (6) provokes a number of natural next questions. Does dietary K⁺ deprivation act on the same “gut factor” hypothesized by Lee et al. (7)? If so, then it would seem that this putative substance is not only triggered by K⁺ loads, but is tonic and suppressible by dietary K⁺ absence. It is immediately clear from Hossain et al. (6) that dietary K⁺ impacts the proximal tubule with a number of molecular targets during K⁺ deprivation. We do know that with frank K⁺ depletion, there is enhanced proximal NHE3, the key NH₂⁺ secretory transporter (1, 4); however, the timing of this increase and its impact on distal Na⁺ delivery have not been studied. The data of Hossain et al. (6) also indicate that the
increase in net acid excretion on day 6 is threefold greater than the increase in NH₄⁺ excretion. This suggests distal nephron targets of K⁺ deprivation, and specifically an impact on distal nephron proton ATPases, and this remains to be examined. At this time, it is difficult to fathom the physiological significance of the prior observations of decreased distal chloride cotransporters during K⁺ deprivation. To secure a coherent picture of renal transport during K⁺ deprivation, it would be necessary to determine luminal Na⁺,K⁺, and net acid flow, both proximally and distally, as well as medullary interstitial composition, well in advance of frank K⁺ depletion. From a translational perspective, there are times when blunting renal ammoniagenesis might prevent the deterioration from a neurologically intact individual to an encephalopathic patient. The work of Hossain et al. points to the existence of signals that we don’t yet appreciate.

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REFERENCES