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Need to quickly excrete K^+? Turn off NCC

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Abstract

Renal K^+ excretion is increased rapidly following dietary K^+ intake, but the underlying molecular mechanisms are largely unknown. Sorensen and colleagues show that K^+ intake in mice provoked rapid and near complete dephosphorylation of the renal distal convoluted tubule NaCl cotransporter, temporally associated with increases in both Na^+ and K^+ excretion. This response was independent of aldosterone and may be a crucial component of the acute homeostatic adaptation of the kidney to K^+ intake.

Commentary

The kidneys play a crucial role in extracellular K^+ homeostasis by regulating K^+ excretion to match K^+ intake. Long-term effects of altered K^+ intake on renal K^+ transport and excretion have been extensively studied and reviewed [1, 2]. Less attention has been focused on *acute* effects of K^+ intake on renal K^+ excretion. This may be due in part to the persistence of the classic concept that renal K^+ excretion during dietary K^+ intake is stimulated by a rise in plasma [K^+] and aldosterone. However, over two decades ago, Rabinowitz and colleagues provided evidence that meal-induced kaliuresis cannot be fully accounted for by increases in plasma [K^+] or aldosterone [3]. They proposed that in response to a K^+ containing meal, a kaliuretic reflex, arising from K^+ sensing in the splanchnic bed, stimulates renal K^+ excretion. Consistent with this idea, our more recent studies [4, 5] also provided evidence for a "gut factor" that is activated during dietary K^+ intake to increase renal K^+ excretion independent of changes in plasma K^+ or aldosterone. The mechanism by which the signal of K^+ intake is conveyed from the gut to the kidney is largely unknown.

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Disclosure

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Sorensen and colleagues (6) worked on the output end of the homeostatic response to define where along the nephron transporters were acutely regulated in response to K^+ intake in a manner that would rapidly increase K^+ excretion. They found that delivering oral K^+ plus 2% sucrose to mice by gavage provoked very rapid (within minutes) and near complete dephosphorylation of the renal distal convoluted tubule (DCT) NaCl cotransporter (NCC), temporally associated with increases in both Na^+ and K^+ excretion. Since NCC phosphorylation stimulates NCC transport activity across the apical membranes, dephosphorylation is predicted to decrease NCC activity in this region. Less Na^+ reabsorbed in the DCT leads to more Na^+ delivered downstream to the cortical connecting and collecting ducts (CCD) where reabsorption through epithelial Na^+ channels (ENaC) generates a lumen negative potential. This downstream shift in Na^+ reabsorption from DCT to CCD can rapidly increase the driving force for K^+ secretion. Since the kaliuresis and the NCC dephosphorylation occurred within 15 min of oral K^+ delivery, the authors conclude that depressing NCC activity in the DCT may be a key component of the acute homeostatic adaptation of the kidney to K^+ intake. The response was independent of aldosterone, as it occurred prior to the rise in plasma aldosterone, and was still present in aldosterone synthase deficient mice. The authors also suggest that the response may be independent of a rise in extracellular $[K^+]$, as incubating freshly prepared tubules *ex vivo* in media with elevated $[K^+]$ did not significantly decrease NCC phosphorylation.

Identification of the renal target would help elucidate the mechanisms underlying the signaling of K^+ intake from the gut to the kidney. Since the response involves a rapid decrease in NCC phosphorylation but not NCC abundance, it is possible that the target is a phosphatase or a kinase in the distal nephron, rather than the NCC itself. The Sorensen study convincingly demonstrates that the rapid dephosphorylation was independent of plasma aldosterone, but whether this effect was also independent of plasma $[K^+]$ remains an open question as $[K^+]$ increased substantially (to 7–10 mM) whether the K^+ was delivered orally by gavage or in a K^+ containing meal. Even though the authors show that NCC phosphorylation was not directly affected by extracellular $[K^+]$ in isolated renal tubules, the results cannot rule out a role for elevation in plasma $[K^+]$ on NCC dephosphorylation in intact animals, e.g., a humoral factor could be released or a neuro-humoral response stimulated in response to an increase in plasma $[K^+]$, analogous (but distinct) from K^+ stimulation of aldosterone release. Further investigations will have to be conducted to determine: the molecular mechanisms responsible for the decrease in NCC phosphorylation, whether plasma $[K^+]$ plays a role in driving NCC dephosphorylation, and whether a mechanism (e.g., gut factor) independent of plasma K^+ and aldosterone levels drives the response.

It is well established that inhibition of NCC increases sodium excretion, that thiazides diuretics work by inhibiting NCC, and that these diuretics increase K^+ excretion. The study of Sorensen and colleagues (6) provides a mechanistic explanation for the long-recognized effect of K^+ intake to increase Na^+ excretion, which may contribute to the beneficial blood pressure-lowering effects of a high K^+ diet, i.e. by suppressing NCC activity, analogous to a thiazide diuretic. The authors demonstrate that within minutes of ingesting K^+, a natriuresis

ensues that accompanies the NCC dephosphorylation. This natriuresis is blunted in $NCC^{-/-}$ mice, implicating NCC dephosphorylation (inactivation) as driving most of the response.

While the K^+ intake-provoked natriuresis was blunted in the $NCC^{-/-}$ mice, their pattern of K^+ excretion was indistinguishable from that observed in $NCC^{+/+}$ mice. This finding raises two questions. First, what drives K^+ excretion in response to K^+ intake in the $NCC^{-/-}$ mice (or patients taking thiazide diuretics)? An increase in ENaC abundance is reported in both this $NCC^{-/-}$ model as well as in a mouse knockin model recapitulating Gitelman's syndrome (GS) and in GS patients[7,8]. Thus, in GS, the CCD is optimized to secrete K^+, despite lower plasma [K^+]. While the thick ascending limb sodium potassium 2 chloride transporter (NKCC2) abundance was not altered in the $NCC^{-/-}$ or the GS knockin models[7,8], it remains to be determined whether acute K^+ intake depresses NKCC2 activity or phosphorylation, which would also shift more Na^+ to the CCD to drive K^+ secretion, analogous to a loop diuretic or Bartter's syndrome. The second question is whether the kaliuresis in response to K^+ intake is blunted in animal models of constitutively active NCC. NCC phosphorylation is doubled in a WNK4 knockin mouse model of pseudohypoaldosteronism type II (PHAII) [9]. The PHAII model also exhibits significantly elevated plasma [K^+] levels along with depressed fractional excretion of K^+ [9], both suggesting that K^+ excretion in response to acute K^+ intake would be blunted; this has not, to our knowledge, been tested. Their hyperkalemia was attributed to the over-reabsorption of Na^+ in the DCT via constitutively activated NCC decreasing Na^+ delivery to ENaC in the CCD [9]. From these mouse models it appears that the transporters driving K^+ secretion include the DCT NCC which meters Na^+ to the CCD, ENaC which provides the driving force for K^+ secretion and, ultimately, the apical K^+ channels. A role for more upstream transporters such as NKCC2 or proximal tubule Na^+/H^+ exchanger (NHE3) remains to be investigated. Any of these transporters would be logical targets for a "gut factor" released in response to K^+ intake.

There is a noteworthy dissociation between NCC dephosphorylation and the pattern of K^+ excretion when K^+ is given by oral gavage (with 2% sucrose) vs. in a 2% K containing meal: both protocols elevated plasma [K^+] and stimulated near complete NCC dephosphorylation by 60 min, and while urinary K^+ excretion peaked at 30 min after oral gavage, the peak was delayed to 6 hrs after the K^+ containing meal. Why there is not an earlier kaliuretic peak in the meal fed rats remains to be determined. One hypothesis is that the meal (vs. gavage) stimulates the release of a factor that acts to delay K^+ excretion in an NCC-independent manner, e.g., by stimulating cellular K^+ uptake. Both K^+ delivery protocols would be expected to increase insulin, known to increase cellular K^+ uptake, and perhaps the magnitude is greater or more prolonged after meal feeding. The release of K^+ from the cellular compartment to the plasma after a delay would allow time for aldosterone to increase ENaC, culminating in a peak of excretion at 6 hrs. Further studies are warranted to understand the interactions between gut factor(s), insulin and aldosterone in the coordinated extra- and intrarenal responses to a K^+ load.

Compared to other major electrolytes, K^+ has a very high ratio of dietary intake to extracellular pool size (only ~2% of the total body K^+ pool), representing a significant homeostatic challenge. Thus, without appropriate regulation, a K^+-rich meal runs the risk of

substantially increasing extracellular [K^+](hyperkalemia). In this study, plasma [K^+] rose to 10 mM in mice given K^+ orally and the level remained elevated at ~ 7 mM for 6 hr. One hr. after meal feeding 2% K^+ chow, plasma [K^+] was elevated to 7 mM. The authors report that the mice did not exhibit signs of hyperkalemia, and discuss the K^+ homeostatic challenge in mice: because of their high caloric needs relative to their body size, the ratio of dietary K^+ intake to extracellular pool size in mice is 40, compared to a ratio of 1 in humans. This high ratio in mice is consistent with well-established allometric scaling laws, specifically, that biological rates (including metabolism and turnover rates) are higher in smaller animals than in larger animals [10]. Thus, the homeostatic challenge appears to be much greater in mice than in humans. To prevent the life threatening sequelae of hyperkalemia in mice facing this high intake, either the K^+ homeostatic system is far more efficient at clearing plasma K^+, or the cardiac and nervous systems of mice are far more tolerant to elevated plasma [K^+] than those in humans. The molecular mechanisms underlying this apparent tolerance warrant further study as they might reveal additional strategies that could be used to treat hyperkalemia in patients. One strategy that this study supports is inhibition of the NCC, e.g. with a thiazide diuretic, to drive Na^+ downstream where its absorption via ENaC stimulates K^+ secretion and excretion.

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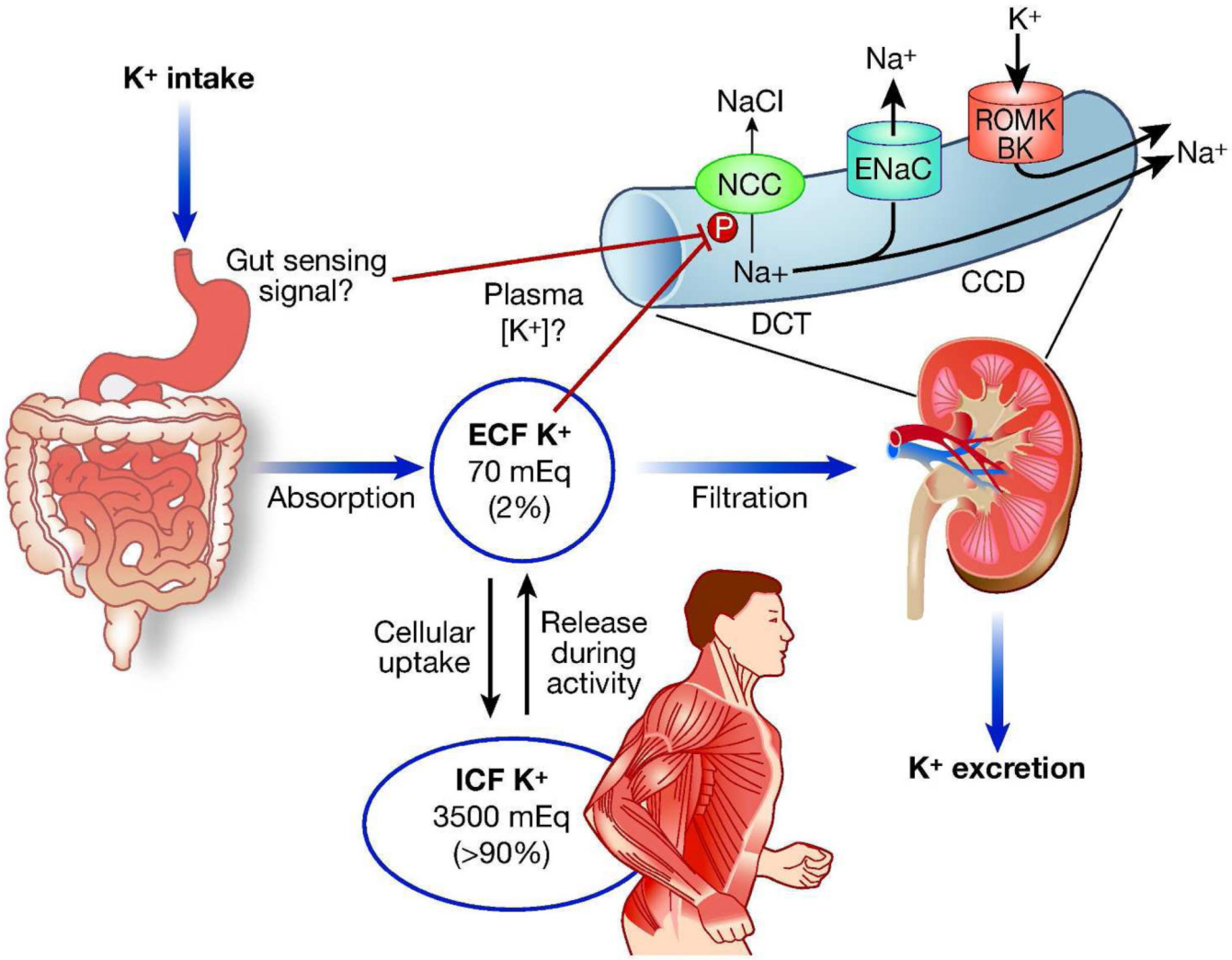

Figure 1. Overview of homeostasic responses to acute K^+ intake

Upon ingestion, K^+ is absorbed across the gut into the small extracellular fluid (ECF) pool of K^+ and a fraction is taken up into the large pool of intracellular fluid(ICF) K^+, for example, secondary to insulin stimulation of Na, K-ATPase. This ICF K^+ is presumably released back into the ECF during muscle activity and then filtered into the kidney. K^+ excretion by the kidney may be stimulated after acute K^+ ingestion by either a rise in plasma [K^+] (feedback regulation) or a signal initiated by the gut sensing of K^+ independent of plasma [K^+] (feedforward regulation); critical involvement of aldosterone stimulation of K^+ secretion was ruled out in studies in aldosterone synthase knockout mice. Sorensen and colleagues, in this issue, show that acute K^+ intake provokes rapid and near complete dephosphorylation of the renal distal convoluted tubule NaCl cotransporter (NCC), temporally associated with increases in both Na^+ and K^+ excretion. Specifically, they postulate that NCC dephosphorylation inactivates the transporter and provokes a downstream shift in Na^+ to the CCD where reabsorption through epithelial Na^+ channels (ENaC) generates a lumen negative potential which increases the driving force for K^+ secretion through the ROMK and BK K^+ channels. In addition, the NCC dephosphorylation

and inactivation provokes a natriuresis and diuresis which may help explain the blood pressure lowering effects of a high K^+ intake, analogous to a thiazide diuretic.