Renal potassium physiology: integration of the renal response to dietary potassium depletion

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We summarize the current understanding of the physiology of the renal handling of potassium (K^+), and present an integrative view of the renal response to K^+ depletion caused by dietary K^+ restriction. This renal response involves contributions from different nephron segments, and aims to diminish the rate of excretion of K^+ as a result of: decreasing the rate of electrogenic (and increasing the rate of electroneutral) reabsorption of sodium in the aldosterone-sensitive distal nephron (ASDN), decreasing the abundance of renal outer medullary K^+ channels in the luminal membrane of principal cells in the ASDN, decreasing the flow rate in the ASDN, and increasing the reabsorption of K^+ in the cortical and medullary collecting ducts. The implications of this physiology for the association between K^+ depletion and hypertension, and K^+ depletion and formation of calcium kidney stones are discussed.

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The physiology of the renal regulation of potassium (K^+) homeostasis has been summarized in a number of reviews.[1–6] In this paper, we emphasize recent advances and provide an integrative view of the renal response to dietary K^+ depletion.

We acknowledge, and point out in the discussion, that some of the proposed mechanisms are speculative or are based on data from studies in cell models or from animals with genetic manipulations and therefore that there may be limitations in their application to human physiology.

Although the degree of hypokalemia from K^+ depletion induced by restricting dietary K^+ intake is usually modest, this setting has the advantage of avoiding confounding factors that may alter the renal response to K^+ depletion in other settings: for instance, aldosterone release in response to a low effective arterial blood volume in a patient taking diuretics or changes in acid-base status (metabolic alkalemia in patients with chronic vomiting, metabolic acidemia in patients with chronic diarrhea).

Control of K^+ secretion occurs in the aldosterone-sensitive distal nephron (ASDN), which includes the second portion of the distal convoluted tubule (DCT2), the connecting tubule (CNT) and the cortical collecting duct (CCD).[7] The DCT2 and the CNT play the major role; the CCD is involved when a high rate of K^+ secretion is needed to dispose of a very large K^+ load.[8–11] Two factors affect the rate of excretion of K^+: *net* K^+ secretion rate (secretion minus reabsorption) in the ASDN and flow rate in the ASDN.[12] Two elements are required for K^+ secretion in the ASDN: the generation of a transepithelial lumen-negative voltage via electrogenic reabsorption of sodium (Na^+) and the presence of a sufficient number of open K^+ channels in the luminal membranes of principal cells in the ASDN. Under conditions of K^+ depletion, K^+ reabsorption is stimulated in the CCD and in the outer medullary collecting duct (MCD). In the following, we discuss the physiology of each of these components, and at the end of each section, we discuss how the kidney decreases the rate of K^+ excretion in response to dietary K^+ depletion.

ELECTROGENIC REABSORPTION OF Na^+ IN THE ASDN

K^+ ions are actively transported from the interstitial fluid across the basolateral membrane of cells in the ASDN via the sodium-potassium-ATPase pump (Na-K-ATPase). K^+ preferentially leaves principal cells in the CNT and CCD and principal-like cells in DCT2 through K^+ channels in the

apical rather than the basolateral membrane of these cells. This is because a more favorable electrochemical gradient for the movement of K^+ across the apical membrane is generated by the electrogenic reabsorption of Na^+ through the amiloride-sensitive epithelial sodium channel (ENaC), which depolarizes the apical membrane and creates a lumen-negative transepithelial electrical potential.

Effects of aldosterone

An increase in plasma K^+ concentration stimulates the secretion of aldosterone from the zona glomerulosa of the adrenal cortex.[13] Aldosterone actions lead to an increase in Na-K-ATPase activity in the basolateral membrane[14] and the abundance of open ENaC units in the luminal membrane of principal cells in the ASDN.[4] Aldosterone binds to the mineralocorticoid receptor in the cytoplasm of principal cells and the hormone-receptor complex translocates to the nucleus and activates the transcription of its target genes, including the gene encoding for serum and glucocorticoid regulated kinase 1 (SGK1).[15–18] Aldosterone (together with insulin) also stimulates mTOR complex 2 to activate SGK1 by phosphorylating its hydrophobic motif at Ser422, which subsequently enables 3-phosphoinositide–dependent kinase 1 to bind SGK1 and activate its kinase domain by phosphorylating Thr256.[19–22] SGK1 increases the number of ENaC units in the luminal membrane of principal cells by phosphorylating and inactivating the ubiquitin ligase NEDD4-2.[23–25] Other proteins are also likely involved in the processing and trafficking of the ENaC when aldosterone levels are high. A study in SGK1 knockout mice showed that ENaC activity in principal cells in CCD and CNT was minimal under control conditions, but was increased to a similar extent to that in wild-type animals when they were fed a high K^+ diet and hyperkalemia and elevated aldosterone levels developed.[26]

Activation of the ENaC at the cell surface requires proteolytic cleavage by serine proteases at specific sites within the extracellular loops of the α and γ subunits.[27,28] Aldosterone induces the production of the channel-activating protease prostatin, which is anchored to the apical membrane by glycosyl-phosphatidylinositol and mediates extracellular cleavage of the ENaC.[27,29]

Aldosterone plays a permissive role in K^+ homeostasis under physiological conditions, but is required to achieve maximal rates of K^+ secretion in response to a large K^+ load.[30,31] Increased apical Na^+ and K^+ conductances were observed in the CCD from adenalectomized animals with increased dietary K^+ intake.[31,32] Aldosterone synthase knockout mice, which lack aldosterone altogether, maintained normokalemia on a K^+-rich diet, as the increase in dietary K^+ intake was associated with upregulation of the renal outer medullary potassium (ROMK) channel and of the ENaC. However, when given a large supraphysiological dietary K^+ load, hyperkalemia developed in these mice, as upregulation of the ENaC was insufficient to achieve the needed increase in the electrochemical force required for high rates of K^+ secretion.[33] The nature of the non-aldosterone kaliuretic factor(s) remains undetermined. An unknown "gut factor" that is activated by dietary K^+ intake, independent of changes in aldosterone or the plasma K^+, is suggested from studies in animals[34–36] and recently in humans.[37] The mechanisms by which this message is sensed in the gut and conveyed to the kidney remain unknown.

Effects of with no lysine kinases

Modulating the rate of NaCl reabsorption by the thiazide-sensitive, sodium chloride cotransporter (NCC) (the product of the *SCL12A3* gene) in the DCT plays an essential role in adjusting the rate of K^+ excretion in the urine. Inactivating mutations in the NCC, as occurs in patients with Gitelman syndrome, cause renal K^+ wasting and hypokalemia.[38] On the other hand, activation of the NCC, as occurs in patients with the syndrome of familial hyperkalemic hypertension (also known as pseudohypoaldosteronism type 2 or Gordon syndrome), is associated with hyperkalemia due to decreased renal K^+ excretion.[39]

Cells in the proximal portion of the DCT (DCT1) express NCC, but not the ENaC, in their luminal membrane.[40–42] Increased reabsorption of NaCl in the DCT1 diminishes the rate of its delivery to the ASDN, which may decrease the rate of electrogenic reabsorption of Na^+ and limit the ability to generate a lumen-negative voltage for K^+ secretion and also may decrease the flow rate in the ASDN.

The term *aldosterone paradox* is used to describe aldosterone's ability to function as a NaCl-retaining hormone under conditions of low NaCl intake or intravascular volume depletion without inducing kaliuresis and as a kaliuretic hormone during K^+ excess without inducing Na^+ retention.[43] A complex network of serine-threonine kinases seem to function as a molecular "switch" to appropriately change the renal response to aldosterone either to conserve Na^+ or excrete K^+, depending on the stimulus for aldosterone release. These kinases achieve this by modulating the rate of reabsorption of NaCl in the DCT and the abundance of ROMK in the luminal membrane of principal cells in the ASDN. These kinases lack the amino acid lysine (abbreviated as K) in their subdomain II, so they are named "with-no-lysine" (WNK) kinases. The WNK family has 4 members (WNK1–WNK4) in mammals; WNK2 is not expressed in the kidney.

Extensive studies on the function of WNK kinases[44–48] followed the discovery that mutations in *PRKWNK1* and *PRKWNK4* genes, encoding for WNK1 and WNK4, respectively, cause familial hyperkalemic hypertension.[49] WNK kinases exert their effect on the NCC by phosphorylating members of the Sterile (STE)-20 superfamily of serine/threonine kinases, specifically, the STE20-related proline-alanine–rich kinase (SPAK) and the oxidative stress response kinase type 1 (OSR1), and they in turn phosphorylate and activate the NCC.[50,51]

Studies in *in vitro* systems suggested that WNK4 *inhibits* NCC,[52] by forming heteromultimers with WNK1 and WNK3, thereby diminishing their ability to activate the