Regulation of Potassium Excretion in the Kidney

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The maintenance of potassium balance depends primarily on excretion by the kidney. The regulated secretion of potassium normally accounts for most of urinary potassium excretion. Potassium transport along the nephron has two main features : the ubiquitous Na,K-ATPase defines basolateral membranes, whereas site-specific potassium transporters are responsible for the apical transport. Two different cell types mediate secretion and reabsorption of potassium. Principal cells secrete potassium, whereas intercalated cells, especially those belonging to the subfamily of β-intercalated cells, reabsorb potassium. The factors that stimulate potassium secretion by the principal cells include (1) increased extracellular fluid potassium concentration (2) increased aldosterone and (3) increased tubular flow rate. One factor that decreases potassium secretion is increased hydrogen concentration (acidosis). In situations associated with severe potassium depletion, there is a cessation of potassium secretion and net reabsorption of potassium. It is believed that H,K-ATPase transport mechanism located in the luminal membrane of the cortical and outer medullary collecting duct cells reabsorb potassium in exchange for hydrogen secreted into the tubular lumen.

Key Words : Potassium balance, Principal cells, Intercalated cells, Aldosterone, Acidosis, Na,K-ATPase, H,K-ATPase

Dietary potassium intake is 70-100 mmoles per day for a 70 kg man. The maintenance of potassium balance depends primarily on excretion by the kidney, because the amount excreted in the feces is only about 5-10% of the intake. The renal handling of potassium is similar to sodium in many ways, except there is secretion in addition to filtration and reabsorption. The regulated secretion of potassium normally accounts for most of urinary potassium excretion.

Sites and mechanisms of potassium transport along the nephron

In the glomerulus, potassium is freely filtered. Proximal nephron segments between the glomerulus and the distal convoluted tubule reabsorb the filtered potassium, like sodium, in a rather fixed fraction (80-90%). Most of the day-to-day variation of potassium excretion is not due to changes in reabsorption in the proximal tubule or loop of Henle, although changes in potassium reabsorption in these segments can influence potassium excretion.

Potassium can be either reabsorbed from or secreted into the urine depending on the needs of the body. Two different cell types mediate secretion and reabsorption of potassium. Principal cells secrete potassium, whereas intercalated cells, especially those belonging to the subfamily of β-intercalated cells, reabsorb potassium.

The secretion into the collecting duct occurs throughout the cortex and probably in the outer stripe of the outer medulla as well. In the inner stripe of the outer medulla, potassium reabsorption appears once again and contributes to potassium accumulation in the medullary interstitium. Both secretion and reabsorption of potassium have been de-

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scribed along the terminal portions of the inner medullary collecting duct.

Potassium transport along the nephron has two main features : the ubiquitous Na,K-ATPase defines basolateral membranes, whereas site-specific potassium transporters are responsible for the apical transport. Apical transport mechanisms include (1) reabsorptive cotransport of NaCl with potassium in the thick ascending limb of Henle, (2) secretory potassium channels and KCl cotransport in principal cells, and (3) ATPase-dependent K/H exchange in intercalated cells.

Most of potassium is secreted by diffusion through a well-defined small-conductance potassium channel with high open probability. This channel responds to changes in potassium intake and cellular pH and is modulated by external and cytosolic ATP, phosphatidylinositol phosphates and several specific phosphorylation processes. A second secretory pathway involves another potassium channel distinguished by its much higher single-channel conductance, low open probability and sensitivity to cell calcium and changes in membrane potential. Although this channel does not significantly contribute to potassium secretion under physiological conditions, it may participate in potassium secretion during high rates of flow and tubule distension. A third mechanism of apical potassium secretion involves KCl cotransport. This channel mediates only a modest fraction of potassium secretion at physiological concentrations of chloride in the lumen, and may become activated during conditions such as metabolic alkalosis when the bicarbonate concentration in the tubule lumen rises.

Potassium channels may play an important role in coordinating apical and basolateral transit of potassium during net reabsorption and secretion. In the potassium-replete state, most of potassium taken up from the lumen diffuses back through barium-sensitive potassium channels. In potassium depletion, however, apical potassium channel activity is suppressed and accompanied by activation of a barium-sensitive potassium transport pathway in the basolateral membrane. This transport mechanism may involve either potassium channels or KCl cotransport.

There is no evidence that the mechanism of reabsorption of the bulk of filtered potassium along the proximal tubule involves specific apical transport mechanisms. However, it is generally accepted that diffusion along a favorable electrochemical gradient (lumen positive potential in the second half of the proximal tubule) and solvent drag (dependent on active Na transport and a high potassium permeability of the paracellular shunt pathway) are responsible for potassium retrieval from the filtrate. The function of potassium channels in the apical membrane is thought to be that of stabilizing the membrane potential during transport of electrically charged cotransporters that tend to depolarize the brush border membrane.

Secretory process of potassium in principal cells

The principal cells make up about 90 per cent of the epithelial cells in the late distal and cortical collecting tubules. The urinary potassium excretion is largely the result of its secretion in these cells. The secretion of potassium into the tubular lumen is a two-step process, beginning with uptake from the interstitium into the cell by Na,K-ATPase pump in the basolateral membrane. The Na,K-ATPase pump creates a high intracellular potassium concentration. The second step is thus passive diffusion of potassium from the interior of the cell into the tubular fluid.

The luminal membrane of the principal cells is highly permeable to potassium. There are special channels that are specifically permeable to potassium ions, thus allowing these ions to diffuse across the membrane. Under physiological conditions, only a small amount of potassium recycles across the basolateral membrane back into the blood because the membrane potential of principal cells approaches

potassium equilibrium potential.

Reabsorption of potassium in intercalated cells during depletion

In situations associated with severe potassium depletion, there is a cessation of potassium secretion and net reabsorption of potassium. It is believed that H,K-ATPase transport mechanism located in the luminal membrane of the cortical and outer medullary collecting duct cells reabsorb potassium in exchange for hydrogen secreted into the tubular lumen. The potassium then diffuses through the basolateral membrane of the cell into the blood. This transporter is necessary to allow potassium reabsorption during extracellular fluid potassium depletion, while it plays a small role in controlling the excretion of potassium under normal conditions.

Factors regulating potassium secretion

Potassium secretion is regulated in principal cells by the supply of Na, the intake of potassium, by hormones such as mineralocorticoids and vasopressin, and by changes in blood pH. It is important to recognize that renal potassium excretion has multiple determinants so that it may not be responding only to changes in potassium balance. The factors that stimulate potassium secretion by the principal cells include (1) increased extracellular fluid potassium concentration (2) increased aldosterone and (3) increased tubular flow rate. One factor that decreases potassium secretion is increased hydrogen concentration (acidosis).

Increased ECF potassium concentration stimulates potassium secretion

High levels of potassium intake or progressive reduction of nephron numbers in renal disease lead to significant stimulation of potassium secretion in principal cells. In these situations, the increased plasma potassium leads to an increased rate of secretion presumably due to an increased cellular potassium concentration that creates a more favorable gradient for the passive secretion of potassium into the urine. In addition, increased potassium concentration stimulates aldosterone secretion from the adrenal cortex, which further stimulates potassium secretion. Increased plasma potassium concentration also inhibits sodium and fluid reabsorption by the proximal tubule and thus increases flow rate into the distal nephron.

Aldosterone stimulates potassium secretion

Aldosterone has important effects on both sodium and potassium in the late distal tubule. Aldosterone stimulates the secretion of potassium, which is related to the ability of aldosterone to stimulate the activity of basolateral Na,K-ATPase and to alter the apical membrane conductance of potassium. In addition to its apical effects, when administered chronically, aldosterone induces significant proliferation of the basolateral membrane area.

High peritubular levels of potassium and aldosterone synergistically stimulate apical sodium channels, leading to increased sodium entry, depolarization of the membrane potential and stimulation of basolateral pump-mediated Na-K exchange. In fact, a rise in plasma potassium level is a potent stimulus to release aldosterone from the adrenal cortex by a mechanism independent of the renin-angiotensin system. This aldosterone feedback mechanism acts synergistically with the direct effect of increased extracellular potassium concentration to elevate potassium excretion when potassium intake is raised. In the absence of aldosterone, both total body and plasma potassium are increased due to a decreased renal excretion. The same increase of potassium intake causes a much larger increase of potassium concentrations, when the aldosterone feedback system is blocked.

When vasopressin acts to increase the water permeability of the luminal membrane, it also increases the potassium permeability. When vasopressin stimulates NaCl absorption by the medullary thick ascending limb, it also increases potassium conductance.

Increased distal tubular flow rate stimulates potassium secretion

An increase in distal tubule flow rate increases urinary potassium excretion, presumably by maintaining chemical gradient for potassium that favors the passive secretion of potassium from the cell into the lumen. This effect of increased distal tubule flow rate explains the kaliuresis that occurs with extracellular fluid volume expansion, non-potassium sparing diuretics, and administration of salts of poorly reabsorbed anions. These conditions increase flow rates in the distal tubule. In the presence of significant potassium depletion, however, potassium secretion is not increased by an increase in flow rate, which is probably due to decreased peritubular uptake of potassium. Sodium delivery to distal nephron may promote potassium excretion (Na-K exchange), but it is not certain if this is independent of flow rate since in most instances increased urinary sodium is accompanied by increased urinary flow rate.

Acute acidosis decreases potassium secretion

Changes in acid-base balance have major effects on renal potassium excretion. In acute metabolic acidosis, decreased uptake of potassium by distal cells tends to reduce potassium secretion. The primary mechanism by which increased hydrogen ion concentration inhibits potassium secretion is by reducing the activity of Na,K-ATPase pump. This in turn decreases intracellular potassium concentration and subsequent passive diffusion of potassium across the luminal membrane into the tubule.

In metabolic alkalosis, plasma potassium concentration tends to be low; however, cell uptake of potassium is enhanced. Acute alkalosis causes an increase in the potassium concentration of the distal tubular cells, leading to a more favorable gradient that is associated with increased urinary secretion of potassium. Aldosterone levels are often elevated in alkalotic states to promote potassium secretion. High luminal bicarbonate concentration permits distal chloride concentration to fall to low levels and thus also favors potassium secretion.

The effects of acute and chronic acid-base disorders may differ. Chronic acid-base disorders, except respiratory alkalosis, all cause kaliuresis. For instance, with a prolonged acidosis lasting over a period of several days, there is an increase in urinary potassium excretion. Although the underlying mechanism is not clear, there may be changes in distal tubule flow rates. Chronic acidosis inhibits proximal tubular sodium chloride and water reabsorption to increase distal volume delivery, thereby stimulating the secretion of potassium. This effect overrides the inhibitory effect of hydrogen ions on the Na,K-ATPase pump. Thus, chronic acidosis leads to a loss of potassium, whereas acute acidosis leads to decreased potassium excretion.

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