Medicinski podmladak

Medical Youth

MINI REVIEW ARTICLE

POTASSIUM CHANNELS IN RENAL PROXIMAL TUBULE

KALIJUMSKI KANALI U PROKSIMALNOM TUBULU BUBREGA

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ABSTRACT

Potassium channels are a diverse family of membrane proteins which are present within all cells of the body. They contain two subunits α, which determine the structure of the channel, and β, which can modify the properties of the channel. Those transmembrane proteins take part in K^+ movement across cell membranes, via a highly selective pore. The kidneys have crucial role in maintaining total body potassium content, by matching its intake and excretion. K^+ absorption in the proximal tubule is primarily passive and proportional to Na^+ and water, so that changes in fluid and potassium transport are closely coupled. Proximal tubular K^+ channels are crucial for the maintenance of a hyperpolarized membrane voltage. In leaky epithelia, such as the proximal tubule, the hyperpolarization of the basolateral membrane also results in the hyperpolarization of the apical membrane, due to increase in the K^+ conductance of that barrier. They are also involved in regulating cell volume and in recycling potassium across the basolateral membrane. K^+ channels of the KCNK and KCNJ gene families have been discovered in the basolateral membrane cell of various species. One of the primary functions of basolateral K^+ channels is to recycle K^+ across the basolateral membrane for proper function of the Na^+-K^+-ATPase. Activation by extracellular alkalinization has been associated with a role of TASK-2 in kidney proximal tubule bicarbonate reabsorption. In renal proximal tubules, luminal K^+ channels play an important role for restoring the driving force of Na^+-coupled transport systems (amino acids, glucose), which depolarize the luminal membrane. Some of these luminal K^+ channels are activated directly by the transport-associated depolarization; others are regulated by mediators, second messenger pathways and cell volume.

Key words:
Proximal tubule,
Potassium,
Channels

doi: 10.5937/mp68-14259
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SAŽETAK

Kalijumski kanali predstavljaju raznoliku familiju membranskih proteina, prisutnih u svim ćelijama. Ovi transmembranski proteini posreduju u pasivnom kretanju kalijumovih jona kroz ćelijsku membranu putem visokoselektivnih pora. Regulacija kalijumske ravnoteže u organizmu zavisi od održavanja jedinstvenog raspoređivanja kalijuma između intra- i ekstraćelijskog odeljka i adekvatne ekskrecije putem bubrega. Apsorpcija kalijuma u proksimalnom tubulu prvenstveno je pasivna i proporcionalna apsorpciji natrijuma i vode. Kalijumski kanali u ćelijama proksimalnog tubula imaju ključnu ulogu u stvaranju negativnog membranskog potencijala ćelije. U propustljivim epitelima, kao što je epitel proksimalnog tubula, hiperpolarizacija bazolateralne membrane, usled povećanja provodljivosti kalijuma (K^+), takođe rezultira hiperpolarizacijom apikalne membrane. Kalijumski kanali proksimalnih tubula su uključeni u regulaciju ćelijskog volumena, kao i u kruženje kalijuma kroz bazolateralnu membranu. Različiti jonski kanali i transporteri odgovorni su za transcelularni transport jona i drugih supstanci kroz proksimalne tubule. Kalijumski kanali iz KCNK i KCNJ genske familije pronađeni su na bazolateralnoj membrani ćelija proksimalnih tubula. Kalijumski bazolateralni kanali su značajni u procesima metaboličkog povezivanja različitih transportnih procesa, regulaciji intraćelijskog pH, kao i intra- i ekstraćelijskom kruženju kalijuma. Na aktivaciju TASK-2 kanala direktno utiče ekstracelularna alkalinizacija, a ovaj mehanizam aktivacije kanala preovlađuje u procesu reapsorpcije bikarbonatnih jona u proksimalnim tubulima bubrega. Kalijumski kanali na luminalnoj membrani ćelija proksimalnih tubula imaju ulogu u stabilizaciji luminalnog membranskog potencijala nakon stimulisanja Na+ zavisnog kotransporta glukoze i aminokiselina, koji dovodi do depolarizacije luminalne membrane. Neki od ovih kanala su direktno aktivirani depolarizacijom luminalne membrane, dok su drugi regulisani medijatorima, sekundarnim glasnicima ili promenom volumena ćelije.

Ključne reči:
proksimalni tubul,
kalijum,
kanali

Introduction

The major function of epithelial tissues is to keep up the proper ion, solute and water homeostasis. Transepithelial transport is a well-organized physiological process that involves many membrane transport proteins (1). Potassium channels are a diverse family of membrane proteins, which are present within all cells of the body, in both excitable and non-excitable tissues (1, 2). They contain two subunits α, which determine the structure of the channel, and β, which can modify the properties of the channel (2). Those transmembrane proteins take part in K^+ movement across cell membranes via a highly selective pore. Potassium channels constitute the largest and the most various class of ion channels, which was confirmed in molecular studies carried out over the past decade. They are unique among cation channels since, unlike Na^+ and Ca^{2+} channels, they are found in nearly all living organisms and are widely distributed among all cells, within each organism. It is likely, therefore, that the other channels evolved from K^+ channels and that ionic specificity for Ca^{2+} or Na^+ was achieved by modifying the pore region (3).

The kidneys have crucial role in maintaining total body potassium content, by matching its intake and excretion. Under physiological conditions, potassium is normally filtered by the glomerulus. Approximately, more than 90% of filtered K^+ is reabsorbed in the proximal tubule and loop of Henle. Potassium absorption in the proximal tubule is primarily passive and proportional to Na^+ and water (4, 5). Fractional rates of reabsorption of potassium, sodium and water are similar to each other along the proximal tubule and concentration of potassium differs little along this part of nephron. Also, transepithelial voltage is lumen negative in early loops, and lumen positive further down the proximal tubule (5). Two mechanisms have been proposed - diffusion and solvent drag. Diffusion of K^+ from lumen to peritubular fluid can be driven by the lumen-possitive potential, along the second half of the proximal tubule and the modest increase in lumen K^+ concentration, that has been occasionally observed. Solvent drg depends on Na^+ transport which is responsible for local hypertonicity in the paracellular compartment. Furthermore, this process drives water reabsorption that entrains K^+ and at the same time decreases the intracellular concentration of K^+. Potassium diffusion from the lumen into the interspaces is also stimulated by this process, and may even explain possible rising transport of K^+ across the proximal tubule epithelium (**Figure 1**) (4, 6).

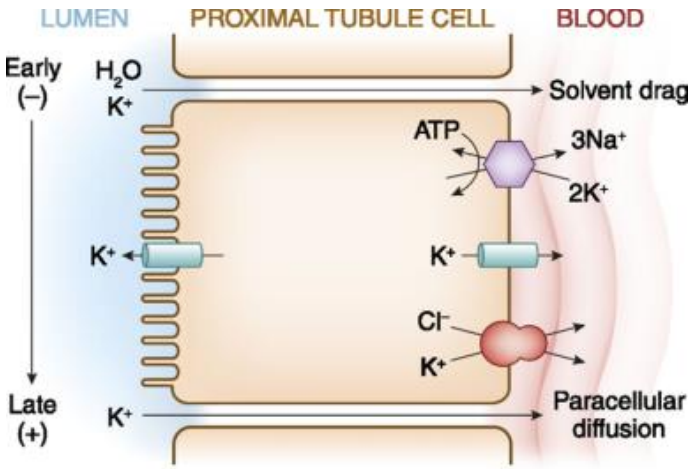

Figure 1. K^+ transport in the proximal tubule (Reprinted from: Palmer BF. Regulation of potassium homeostasis. Clin J Am Soc Nephrol. 2015 Jun; 10(6):1050-60).

Reabsorption in the thick ascedenting limb of Henle, occurs through both transcellular and paracellular pathways. The transcellular transport is mediated by K^+ movement on the apical membrane Na^+-K^+-$2Cl^-$ co-transporter. Potassium secretion begins in the early distal convoluted tubule and progressively increases along the distal nephron into the cortical collecting duct. Most urinary K^+ can be accounted for by electrogenic K^+ secretion, mediated by principal cells in the initial collecting duct and the cortical collecting duct. An electroneutral K^+ and Cl^- co-transport mechanism is also present on the apical surface of the distal nephron. Under conditions of K^+ reduction, reabsorption of K^+ occurs in the collecting duct. This process is controlled by up regulation in the apically located H^+-K^+-ATPase on α-intercalated cells (4). Potassium excretion in the proximal tubule is not specifically affected by regulation of its reabsorption, along the proximal tubule, and transport inhibitors of K^+-H^+ exchange do not reduce reabsorption. For instance, decreased reabsorption of fluid along the proximal tubule, following an increase in glucose load, administration of osmotic diuretics such as mannitol, or reduction of bicarbonate reabsorption by carbonic-anhydrase inhibitors, can lead to increased sodium, as well as fluid delivery into the distal tubule, and enhanced potassium secretion. Distal potassium secretion may be suppressed when excessive reabsorption of sodium, along the proximal tubule, lowers distal sodium and fluid delivery (5, 6).

Function and regulation of potassium channels in the proximal tubule

There are several important functions of potassium channels in the proximal tubule (3). Proximal tubular K^+ channels are crucial for the maintenance of a hyperpolarized membrane voltage (7). In leaky epithelia, such as the proximal tubule, the hyperpolarization of the basolateral membrane also results in the hyperpolarization of the apical membrane, due to increase in the K^+ conductance of that barrier (8). Changes in cell membrane potential can affect Na+-coupled transport of molecules including glucose, phosphate, amino acids and bicarbonate, because these transports are electrogenic. Cl^- diffusion, Na^+-coupled HCO^-_3 co-transporter and Na^+-Ca^{2+} exchanger can also be affected by changes in basolateral membrane potential (3).

Potassium channels are responsible for regulation of cell volume (3). In all epithelia, interplay between Na^+-K^+ pump and basolateral K^+ channels are important to prevent excessive fluctuations in intracellular K^+ content, when pump activity changes. If pump activity is increased, in the absence of a parallel increase in K^+ conductance, one might expect an increase in cell K^+ content, which must be accompanied by an increase in the content of some anion, most likely Cl^-, an increase in cell water content and cell swelling (8). In renal proximal tubule cells, stimulation of Na^+-dependent carriers, such as Na^+-glucose co-transporters, is expected to increase intracellular sodium and cell volume. This cell swelling activates both apical and basolateral potassium channels and increases its efflux, restoring the cell volume (3). It has been demonstrated that the increase in basolateral membrane K^+ conductance, that is associated with Na^+-coupled glucose absorption, could be prevented by preventing or reversing cell swelling by exposure to a hypertonic solution (8).

Important role of potassium channels is in recycling potassium across the basolateral membrane, required for maintaining electro neutrality. Basolateral K^+ current is coupled with the Na^+-K^+-ATPase current, in order to balance the charge movement across the apical membrane for Na^+ reabsorption (1).
Basolateral potassium channels

Potassium channels of the KCNK and KCNJ gene families have been discovered in the basolateral membrane cell of various species (1). It is found that there are three types of K^+ channels in the basolateral membrane of the rabbit proximal tubule, with different single-channel conductance (12 pS, 36-41 pS and 50-60 pS). Basolateral K^+ channel with 50-60 pS conductance indicates sensitivity to inhibition by micromolar concentrations of ATP. This feature can associate the function of this K^+ channel to changes in basolateral Na^+-K^+-ATPase activity. Stimulating

the apical Na^+-glucose co-transporter enhances Na+ influx, which increases Na^+-K^+-ATPase activity in the basolateral membrane, all leading to increased hydrolysis of ATP and lower ATP concentrations. With the decrease in intracellular ATP, ATP-sensitive K^+ channels are relived from ATP block, resulting in an increase in efflux K^+ to extracellular space (3). ATP sensitivity, together with the ability for taurine inhibition, favored KCNJ8 (Kir 6.1), together with the regulatory subunit SUR2A/B to be the ATP-regulated K^+ channel (7, 9). KCNJ8 expression has been reported in a variety of cells and tissues, with multitude functions including: shortening of the action potential, cellular loss of potassium during metabolic complications of the hearth, insulin secretion, regulation of smooth muscle function, regulation of skeletal muscle excitability and release of neurotransmitters (10). Activation of ATP-sensitive K^+ channels during renal ischemia can contribute to hypoxic injury in renal epithelial cells. Measurement of passive K^+ leak from hypoxic proximal tubules revealed an increased rate of leak, at a time when Na^+-K^+-ATPase activity was still normal (11). During ischemia, ATP levels fall - due to decreased production and the opening of ATP-inhibited K^+ channels provides additional driving force for luminal Na^+ uptake. From this perspective, K^+ depletion would lead to a reduced pump rate, to an increase in cytosolic Na^+ concentration, and to cell swelling, causing cell damage (7). Blockade of those ATP sensitive K^+ is protective against cellular injury (11).

The maintenance of unidirectional Na^+ transport across epithelia requires K^+ recycling across the membrane, in which the Na^+-K^+-ATPase is localized (12). One of the channels that have been detected in the proximal tubule is KCNJ13 (Kir7.1), which might be particularly suited for this recycling. KCNJ13 (Kir7.1) has been shown to be very powerful against a reduction in extracellular K^+ concentration and is expressed in close association with the Na^+-K^+-ATPase (7). This channel is very unique, and it shows different characteristics from most KCNJ K^+ channels. It has a very small conductance, low sensitivity to barium, and the inward rectification is independent of extracellular K^+. Also, this channel is not sensitive to ATP concentrations. It maintains a high efflux of K^+ at low interstitial K^+ concentrations (1).

Heteromers of KCNJ10/KCNJ16 (Kir4.1/Kir5.1) have been expressed in the proximal tubule basolateral membrane, and they are mainly regulated by cytosolic pH. KCNJ16 (Kir5.1) also forms heteromers with KCNJ2 (Kir2.1), which is also expressed in the proximal tubule. In native tissue, where Kir5.1 is strongly co-expressed with Kir2.1, for example, in the pontine region of the brain or the proximal tubule of the kidney, it is quite likely that Kir5.1 subunits act as a negative regulator of the Kir2.1 conductance (7, 13). It was reported that two pro-inflammatory cytokines, INF-γ and IL-1β affected the activity of the 40 pS K+ channel in cultured human proximal tubule cells. INF-γ possesses a time dependent biphasic effect on this channel, a delayed suppressive and an acute stimulatory one. IL-1β also acutely affects the activity of channel, by suppressing it (14). This 40 pS K^+ channel conductance is most likely representing KCNJ10/KCNJ16 (Kir4.1/Kir5.1) (15).

Member of the KCNK gene family which can be found in the proximal tubule is KCNK 5 (TASK-2) potassium channel (1). TASK-2 expression has been reported in a variety of cells and tissues ranging from kidney to immune cells and including specific neurons, its proposed functions spanning from an involvement in the regulation of cell volume, to the control of excitability (16). In amphibians, TASK-2 channel is expressed predominantly on the luminal part of the proximal epithelial cell. One of the possibilities is that this channel in the proximal tubule of frog kidney functions instead of the KCNQ 1 K^+ channel (17, 18). Activation by extracellular alkalinization has been associated with a role of TASK-2 in kidney proximal tubule bicarbonate reabsorption. TASK-2 is highly sensitive to pH changes in the alkaline range; 50% activity is attained at pH 8.6 or 7.8. Functional experiments have clearly demonstrated that TASK-2 was indirectly engaged in the bicarbonate reabsorption and the accompanying Na^+ and water movements. Increased bicarbonate transport from the proximal tubule cells activated a potassium conductance, as a consequence of alkalinization of the basolateral compartment. Activation of TASK-2 by alkalinization of the extracellular space, during a hypotonic challenge, also contributes to the counter regulatory volume decrease of proximal tubular cells. Activation of TASK-2 is secondary to the swelling-activated Cl^- efflux, which accelerates Cl^--HCO^-_3 exchange and thereby alkalinizes the basolateral side of the proximal tubular cells (19).

Luminal potassium channels

In renal proximal tubules, luminal K^+ channels play an important role for restoring the driving force of Na^+-coupled transport systems (amino acids, glucose), which depolarize the luminal membrane. Some

of these luminal K^+ channels are activated directly by the transport-associated depolarization; others are regulated by mediators, second messenger pathways and cell volume. Since the epithelia of renal proximal tubules have a low paracellular resistance, basolateral K^+ channels interact with luminal channels and hyperpolarize both basolateral and luminal membranes. However, the direction of the paracellular short-circuit current differs, depending on luminal or basolateral K^+ channel activation (20). Ca^{2+}-activated large conductance (200-300 pS) or maxi-K^+ channels have been identified in the luminal membrane of the proximal tubule cells. These channels are activated by mechanical stretch and membrane depolarization. They have role in stabilization of the apical membrane potential following stimulation of Na^+ coupled transporters, which tend to depolarize the membrane (3).

For three of these K^+ channels, there is evidence for luminal presence from functional studies, as well as from molecular analysis. While KCNK1 (TWIK-1) provides an outward conductance at any membrane voltage, KCNQ1 (Kv7.1, KvLQT1) and KCNA10 (Kv1.8) with their β subunits KCNE1 and KCNA4B, open if the membrane is depolarized respectively. KCNA10 activates at voltages more positive than -60 mV. If the luminal membrane further depolarizes, KCNQ1 activates at about -40 mV. With this setting of channels in the luminal membrane, at least -40 mV of electrical driving force is secured, even at variable electrogenic substrate reabsorption. Any Na^+ ion entering the cell together with glucose induces an equivalent K^+ outward current across the luminal membrane. Thus, the role of KCNQ1/KCNE1 for Na^+ -coupled glucose transport is reflected by K^+ secretion as a result of the respective luminal K^+ currents (7).

Conclusion

Regulation of potassium transport in proximal tubule is complex and includes different transport mechanisms - that are active on both basolateral and apical membrane of these cells. Effective interaction of transport processes, between the basolateral and apical proximal tubule cell membrane, is important in maintaining normal intracellular potassium concentration and normal volume of tubule cells, despite large fluctuations of net transport of potassium and sodium ions. Many different types of potassium channels are involved in these transport mechanisms in proximal tubular cells. Further investigation is needed, in order to understand the detailed mechanisms of these processes.

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