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MECHANISMS OF MOLECULAR BIOLOGY OF TUBULAR TRANSPORT

Potassium transport: From clearance to channels and pumps

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Potassium transport: From clearance to channels and pumps. Potassium (K) homeostasis depends on the separate and interrelated regulation of K distribution between the intra- and extra-cellular fluid compartments and adequate renal excretion. This brief review focuses on the regulation of internal K distribution and the renal mechanisms of K handling. Based on clearance, micropuncture, and microperfusion studies, a large body of evidence supports the view that normally, renal secretion of K determines excretion and that the principal tubule cells in the initial and cortical collecting tubule secrete K, whereas K reabsorption may occur in intercalated cells. Studies of the electrochemical driving forces, of intracellular ion activities, the characterization of several ATPases, and patch clamp investigations have provided insight into the role of pumps and channels in those tubule cells that regulate K secretion and reabsorption.

The challenge of potassium homeostasis

Potassium (K) homeostasis poses two problems for the organism. First, high intracellular K concentrations safeguard cell volume and cell growth, the activity of many enzymes and the cell's acid-base equilibrium [1]. Second, low extracellular concentrations of K are necessary for normal muscle and nerve excitability because they depend critically on steep transmembrane concentration gradients and low extracellular concentrations of K. Accordingly, homeostatic demands can only be fulfilled if the concentration of K is regulated within normal limits in the extracellular *and* intracellular fluid.

Regulation of internal potassium balance

Figure 1 provides an overview of the distribution of K between intra- and extracellular fluid [2]. It is apparent that the vast majority of K resides within cells. The very small amount of extracellular K, some 1 to 2% of total K, can be drastically increased from two sources: external intake via the gastrointestinal tract, and internal redistribution. Consumption of the amounts of K in a normal meal would lead to a threatening increase of plasma K if several mechanisms were not activated to provide effective protection from such acute hyperkalemia [3].

Table 1 lists the factors controlling K uptake into cells. Acute effects on the distribution of K involve changes in activity of membrane Na,K-ATPase that occur with activation of hormones and changes in acid-base balance that achieve rapid and effective redistribution of K into tissue stores, particularly those of muscle and liver. Long-term factors affecting uptake and tissue distribution of K involve the synthesis and insertion of ATP molecules that regulate Na-K pump density [3, 4].

Inspection of Figure 1 shows that the kidneys are the main route of K excretion. Since Smith's 1951 assessment of K handling, that *"the regulation of the excretion of K is, however, very obscure"* [5], considerable progress has been made in our understanding of renal K transport and its regulation by clearance experiments, micropuncture and microperfusion studies and exploration of K transport at the single cell or membrane level.

Clearance studies

Early clearance studies provided strong indirect evidence that an important element of the renal handling of K included secretion by the tubules [2, 5, 6]. When animals are challenged with K, particularly when their filtration rate is low, K excretion in the urine may exceed the amount filtered, strong evidence that even if reabsorption of K were totally absent, filtration must be insufficient to account for K excretion. Accepting the premise of K secretion, clearance studies in the fifties demonstrated that even at relatively low rates of excretion, secretion of K contributes to and is largely responsible for K excretion. Clearance studies also provided strong evidence for the dependence of K secretion on Na and for an important role of adrenal steroids and acid-base factors in the regulation of renal K excretion [6].

Micropuncture and microperfusion studies

Studies at the single nephron level have supported the importance of K secretion as an essential and highly variable element of K transport in the kidney. Figure 2 provides a summary of free-flow micropuncture data showing that most of the filtered K is reabsorbed along the proximal tubule and the loop of Henle, whereas secretion takes place in the initial and cortical collecting tubule. Thus, K secretion is the major source of K excretion, and changes in secretion regulate K excretion [2, 6]. However, when dietary input of K is reduced, urinary K excretion drops sharply and K reabsorption may replace secretion. Thus, net secretion or reabsorption of K occurs in those tubule segments that regulate K excretion [2].

An important feature of the K-regulatory segments is the heterogeneity of their cells, as depicted in Figure 2. In the initial and cortical collecting tubule, there are cells of two types, principal and intercalated cells. Not only are they distinguished by their morphology and specific abundance (principal cells outnumber intercalated cells by a factor of about three), but functional studies at the single cell level have also revealed clear-cut differences. There is now firm evidence that principal cells secrete and intercalated cells reabsorb K [2, 7].

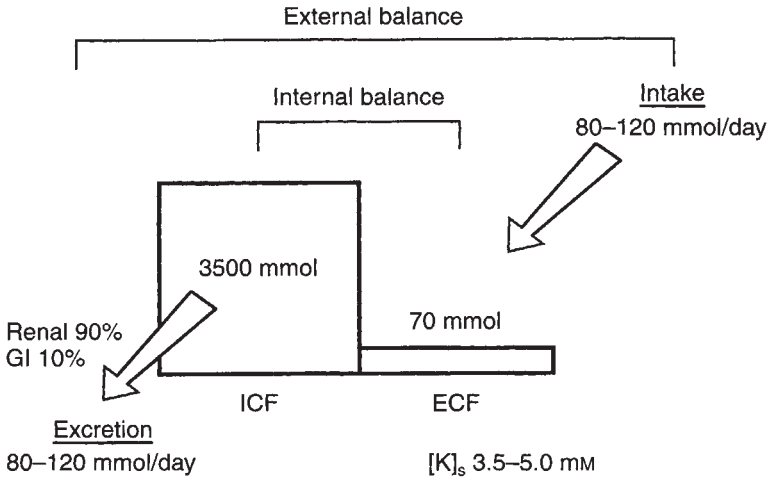

Fig. 1. *Potassium homeostasis depends on the balance between intake and excretion of K.* Most of body K resides within cells (ICF). The kidney is largely responsible for matching excretion to intake, whereas gastrointestinal excretion (GI), largely colonic, plays only a minor role. K is maintained in the extracellular fluid (ECF) at low concentrations. (Used with permission from [2].)

Table 1. Factors affecting internal potassium homeostasis

Acute	
Factor	Effect on potassium
Insulin	Enhanced cell uptake
β-Catecholamines	Enhanced cell uptake
α-Catecholamines	Impaired cell uptake
Acidosis	Impaired cell uptake
Alkalosis	Enhanced cell uptake
External potassium balance	Loose correlation
Cell damage	Impaired cell uptake
Hyperosmolality	Enhanced cell efflux
Chronic	
Factor	Effect on ATP pump density
Thyroid	Enhanced
Adrenal steroids	Enhanced
Exercise (training)	Enhanced
Growth	Enhanced
Diabetes	Impaired
Potassium deficiency	Impaired
Chronic renal failure	Impaired

Data are from [3, 4].

Cell models of potassium transport

Direction and magnitude of K transport across renal tubules depend on the distribution of specific ion transport mechanisms in apical and basolateral membranes; besides transcellular routes, paracellular movement of K between cells must also be considered. In the following, a brief survey of K transport mechanisms at the major nephron sites is presented. Knowledge of specific active and passive transport routes is based on microperfusion and electrophysiological studies, including measurements of transepithelial and transmembrane potentials and ion activities [2].

Proximal tubule

Figure 3 includes a model of K transport across the proximal tubule, the main site of K reabsorption in the nephron [2]. The transepithelial voltage is lumen-negative in the early proximal tubule and lumen-positive in late proximal convolutions. In addition to the Na,K-ATPase in the basolateral membrane–a feature that is shared by *all* tubule cells–K conductances are present in both cell membranes, but that of the apical membrane is small compared to that in the basolateral cell membrane. The presence of K channels in the apical membrane appears somewhat paradoxical. Although the electrochemical gradient for K favors its diffusion from cell to lumen, K is extensively reabsorbed along the proximal tubule. However, it appears that apical K channels are normally almost completely closed and open only under special conditions, particularly cell swelling [2, 8]. Accordingly, most of the K taken up by the Na,K-ATPase recycles across the basolateral membrane. Basolateral K channels are also important because they generate a K diffusion potential and thus contribute to the cell-negative potential. The cell-negative potential is a major driving force for apical electrogenic transport mechanisms, including both sodium-dependent and sodium-independent solute absorption.

How are K ions reabsorbed? Strong evidence supports the view that K reabsorption is closely coupled to proximal water and sodium transport [2]. Specifically, solvent drag and diffusion have been suggested to account for K reabsorption. With respect to solvent drag, active movement of sodium is thought to move water osmotically across the proximal tubule; K, entrained in the reabsorbate, follows along. Moreover, the lumen of the proximal tubule is electrically positive with respect to the interstitium over a significant fraction of its length. This electrical potential, and the fact that the K concentration in the lumen may slightly exceed that in the blood, provides a favorable diffusion gradient for the positively charged K ion. According to this view, a large fraction of the filtered K is reabsorbed, rather indiscriminately, across the proximal tubule. K transport is not specifically regulated in this part of the nephron.

Thick ascending limb of Henle

The thick ascending limb of the loop of Henle (TAL) is another important site of K reabsorption, but the mechanism of apical K transport differs significantly from that in the proximal tubule (Fig. 3). In the basolateral membrane K enters via the Na,K-ATPase and exits through K channels [2]. The lumen-positive

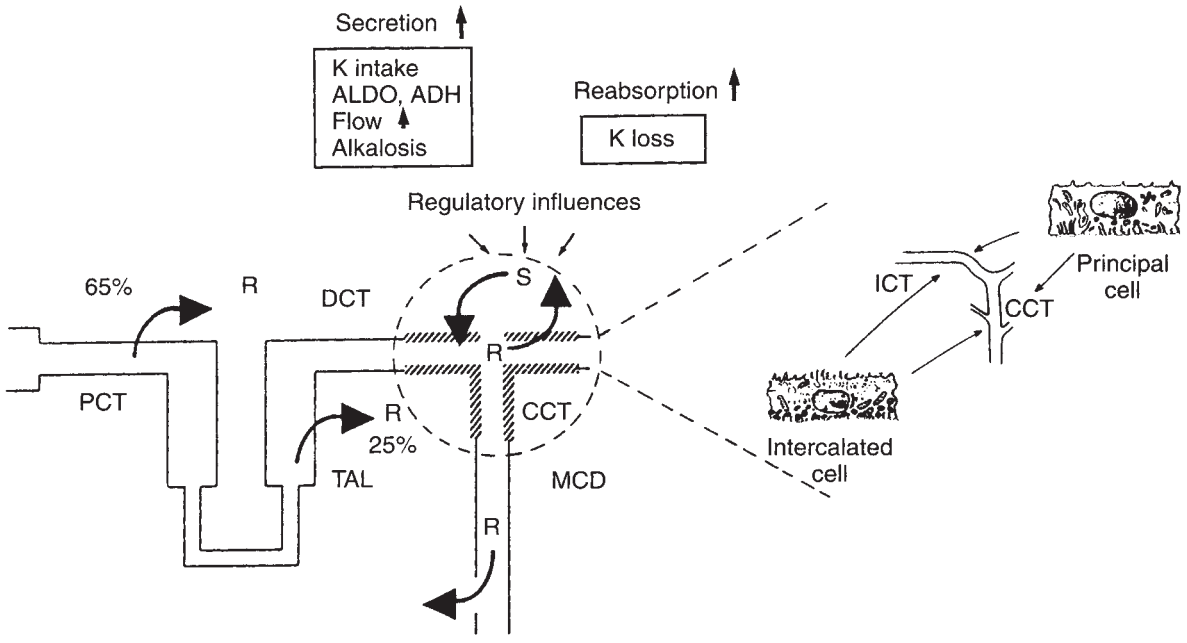

Fig. 2. *Summary of K transport along the nephron.* After free filtration, most K is reabsorbed along the proximal tubule and the loop of Henle. K is normally secreted along the initial and cortical collecting tubule, but secretion can be diminished or abolished and replaced by reabsorption in states of K depletion. Also shown are the cell types lining the distal tubule and cortical collecting tubule.

potential drives a significant fraction of K from lumen to blood through the paracellular pathway [2].

Two transporters are shown in the apical cell membrane. K reabsorption proceeds by Na-2Cl-K cotransport [2, 9]. Since this is an electroneutral transporter, both low cell Na and Cl concentrations generate an ample driving force for downhill movement; only K ions move against a chemical gradient. The cotransport's sensitivity to agents such as furosemide and bumetanide makes the TAL an important site of action of powerful diuretics. Additional transporters include an apical Na/H exchanger (not shown in Fig. 3) and ATP-inhibitable K channels that share important properties with similar channels in the apical membrane of principal cells in the initial and cortical collecting tubule [2, 10].

The K conductive pathway in the apical membrane has important functional implications. First, it serves as an important pathway for apical K recycling which is essential for safeguarding the turnover of the Na-2Cl-K cotransporter. Inhibition of apical K channels reduces net sodium absorption. The apical K conductance is also responsible for the steep membrane potential across the apical membrane and for the lumen-positive potential, which is an important driving force for Na and K reabsorption via the paracellular pathway. Thus, apical K channels play an important role in NaCl reabsorption [2].

Second, net K secretion via apical K channels may occur when Na-2Cl-K cotransport is inhibited by loop diuretics because K diffusion from cell to lumen is no longer opposed by cotransport-mediated reabsorption of K [2]. Third, ATP-sensitive K channels can be activated by an increase in cytosolic pH [2, 10]. Accordingly, stimulation of Na/H exchange, for instance by adrenal steroids [2], favors K movement into the lumen. Fourth, microperfusion experiments of the loop of Henle *in vivo* have demonstrated that adrenal steroids stimulate K absorption [2]. Reabsorption of K along the loop of Henle declines in the absence of mineralocorticoids and results in greater delivery of K into the distal nephron, perhaps a mechanism that could compensate, partially at least, for the failure of K secretion that typically accompanies adrenal failure. Finally, in amphibian nephrons in which distal K secretion is less well developed than in mammals, the diluting segment, sharing many functional properties with the TAL, emerges as an important site of regulation of K excretion [2].

The initial and cortical collecting tubule

The initial and cortical collecting tubule are the main sites of regulation of K secretion [2]. These tubule segments are lined by two cell populations, principal and intercalated cells, and the pathways mediating K transport are also summarized in Figure 3.

Principal cells

Regulated secretion of K in principal cells occurs in two steps: active uptake across the basolateral membrane by Na,K-ATPase, and passive diffusion from cell into the lumen along a favorable electrochemical gradient through K-selective channels and via a K-Cl cotransport mechanism [2]. Under normal conditions, K also recycles across the basolateral membrane through another K-conductive pathway. It is, however, the K channel in the apical membrane that ultimately determines how much K enters the lumen by secretion. The cell model also includes a "secondary" regulator of K secretion, the apical Na channel. Na channels play a key role in regulating K secretion through their ability to depolarize the membrane and thus to modulate the electrochemical driving force of K diffusion from cell to lumen. Optimal conditions for K secretion depend on parallel activation of K and Na channels. Were only K channels stimulated, the resulting increase of apical K conductance would tend to hyperpolarize the

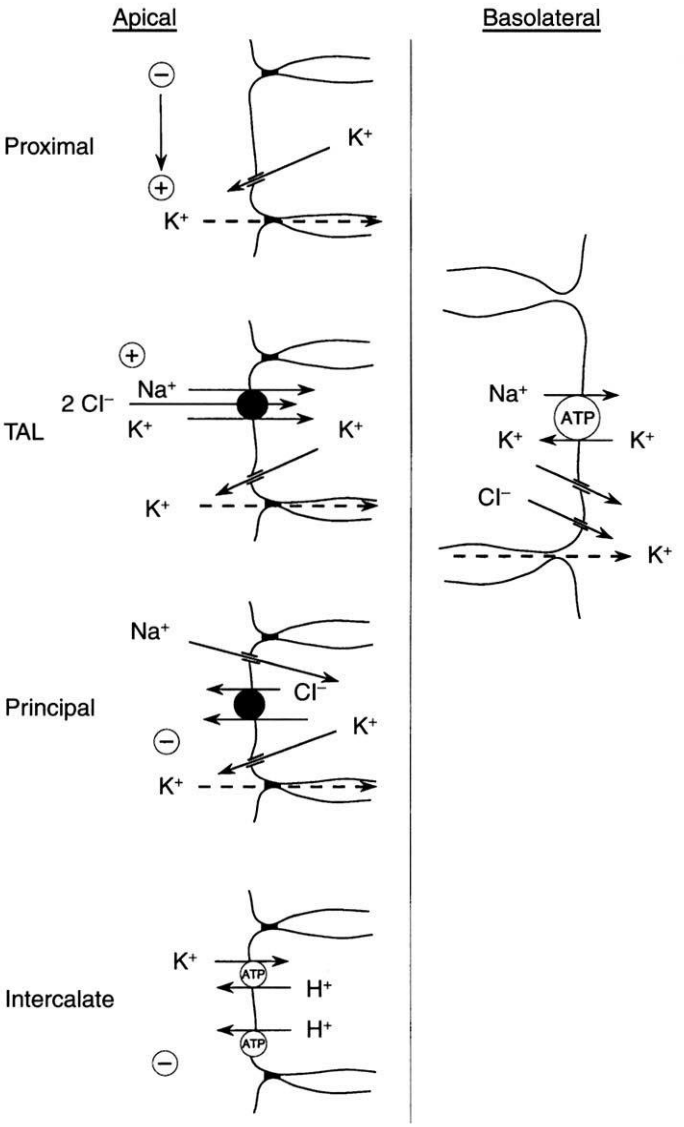

Fig. 3. *Cell models of K transport along the nephron.* Note that the transporters in the basolateral membrane are similar whereas different mechanisms mediate K transport along the nephron across the apical membrane. (Modified from [2], with permission.)

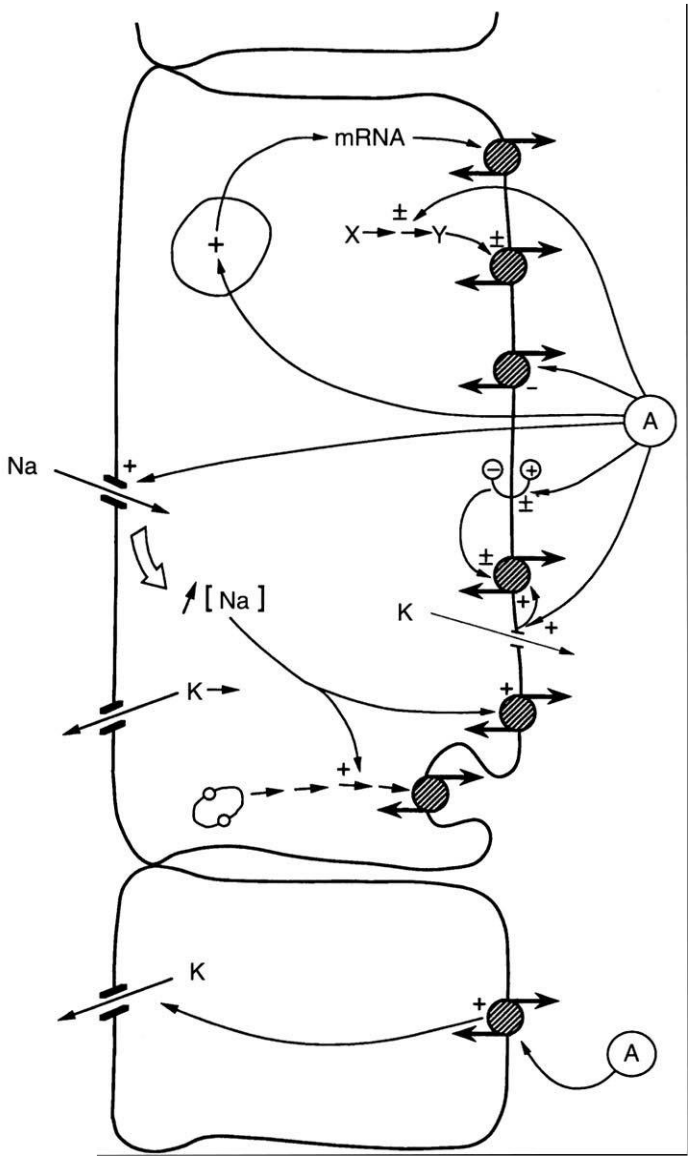

Fig. 4. *Summary of mechanisms involved in modulation of basolateral Na,K-ATPase by aldosterone (A).* Changes in Na,K-ATPase activity in the basolateral membrane may be mediated by genomic factors leading to alteration in pump synthesis, effects on the pump turnover rate by mediators, substrate-related effects of cell Na concentration by primary effects of aldosterone on apical Na channels, or recruitment by Na concentration changes of latent pump units through exocytosis. Additional factors may involve changes in pump activity secondary to alterations in basolateral K conductance (recycling of K and effects of membrane voltage changes on electrogenic pump activity). Shown in the lower cell model is the effect of changes in basolateral ATPase activity on apical K conductance. (Modified from [14] with permission.)

membrane potential and diminish the electrochemical potential for K diffusion from cell to lumen.

Frequently, changes in net secretion of K are achieved by tightly correlated changes of apical and basolateral transport mechanisms of K. The most carefully explored example is that of the action of adrenal mineralocorticoids on principal tubule cells [2, 11]. Stimulation of K transport following administration of aldosterone or desoxycorticosterone (DOCA) involves a complex pattern of transport adjustments involving not only rapid activation of basolateral Na,K-ATPase (turnover) but also delayed activation of genomic pump expression that involves increasing the rate of synthesis, basolateral targeting and membrane insertion of ATPase [11]. Closely associated with these basolateral events are apical effects of mineralocorticoids that involve a significant enhancement of K and Na channel activity [2, 11]. As a consequence of such basolateral and apical transport adjustments, changes in cell K and Na concentrations and cell volume are minimized. K intake, acid-base disturbances and vasopressin are known to modulate K secretion in principal tubule cells [2]. Emerging evidence suggests that their effects on K transport are also mediated by coordinated changes of basolateral pump and apical K and Na channel activity [2].

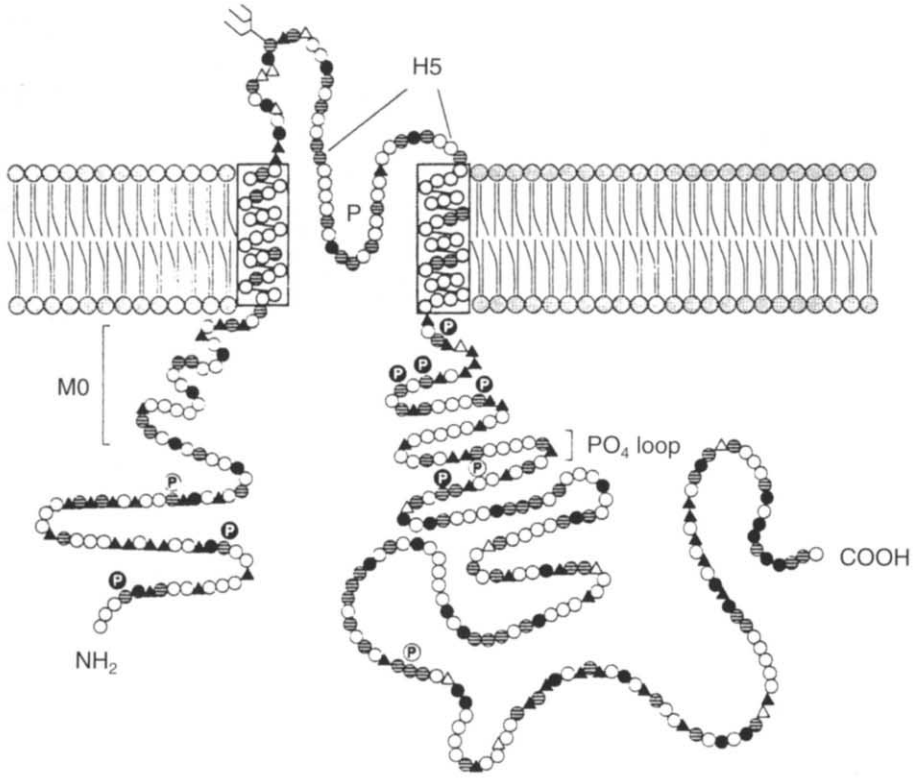

Fig. 5. *Model of ROMK1 channel protein.* Note that the pore-forming P segment is located between the membrane-spanning segments. A single ATP-binding site (Walker-type A motif), PO_4^- is associated with several phosphorylation sites and is likely to be involved in channel regulation. A glycosylation site and potential phosphorylation sites for protein kinase C (PKC) and cAMP-dependent protein kinase A (PKA) are also shown. ROMK2 is identical to ROMK1 with the exception that its amino acid terminus is shorter by 19 amino acids. (From [15]; used with permission.)

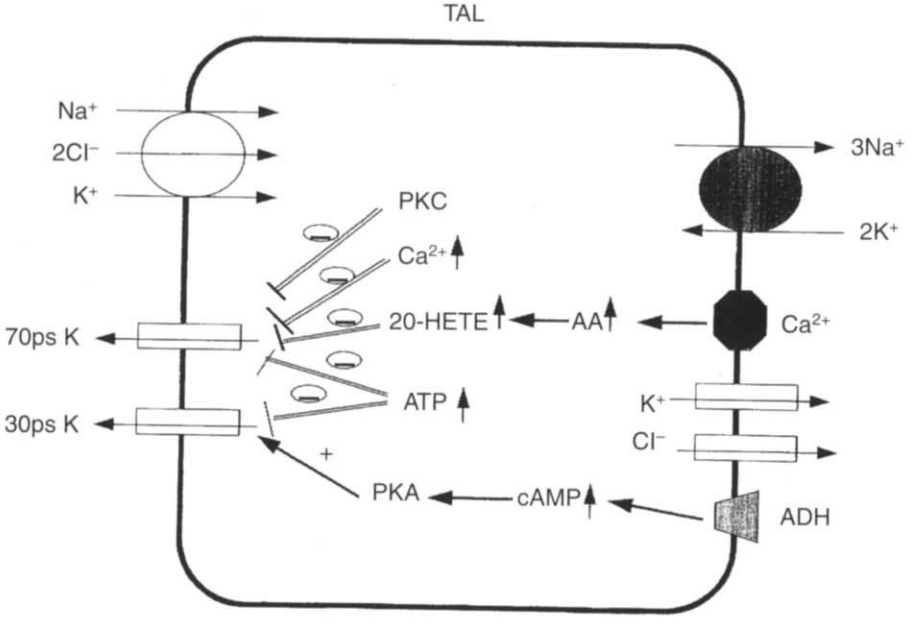

Fig. 6. *Cell models of the thick ascending limb (TAL).* Note two apical K channels and the effects of several cell messengers. Shown also are Ca and ADH receptors and the effects of cAMP and arachidonic acid (AA) on apical K^+ channels. Volume-sensitive, Ca-stimulated maxi-K channels have been described in cell cultures of TAL [2] but have not been observed in intact mammalian TAL. (Based on data from [27–29]; used with permission.)

Intercalated tubule cells

Reabsorption of K is a process that is limited to intercalated tubule cells. Morphological evidence, such as selective hypertrophy of the apical membrane and an increase of the number of rod-shaped intramembraneous particles in a subgroup of intercalated cells suggests insertion of K-absorbing transport proteins [2]. Our knowledge has been greatly advanced by the discovery of K-activated ATPase in isolated collecting ducts, and its increase following K-depletion [2, 12]. Apparently, this active transporter reabsorbs K in exchange for H, is not inhibited by ouabain and regulated by K intake. It is responsible for net K reabsorption and

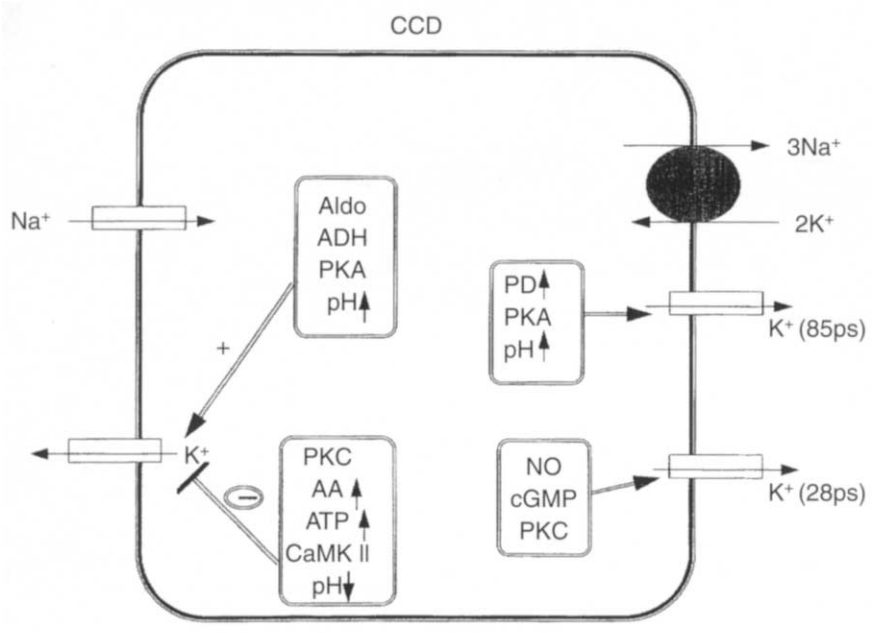

Fig. 7. *Cell model of principal cell of cortical collecting tubule.* Four different K channels are shown; the Ca-and depolarization-activated maxi-K channel in the apical membrane is not included. The apical K channel is not voltage-sensitive whereas the 85ps K channel in the basolateral membrane is activated by hyperpolarization so that basolateral K conductance increases with stimulation of electrogenic Na,K-ATPase activity. Regulation of renal ATP-sensitive K channels by membrane-bound protein phosphates has also been demonstrated. Whereas PKA-mediated phosphorylation induces channel opening, channel activity is inhibited by protein phosphatase PP-2A and Mg^{2+}-dependent protein phosphatase PP-2C, both of which dephosphorylate PKA-mediated phosphorylation sites [30]. (Based on data from [17, 18, 21, 23, 25, 26, 29]; used with permission.)

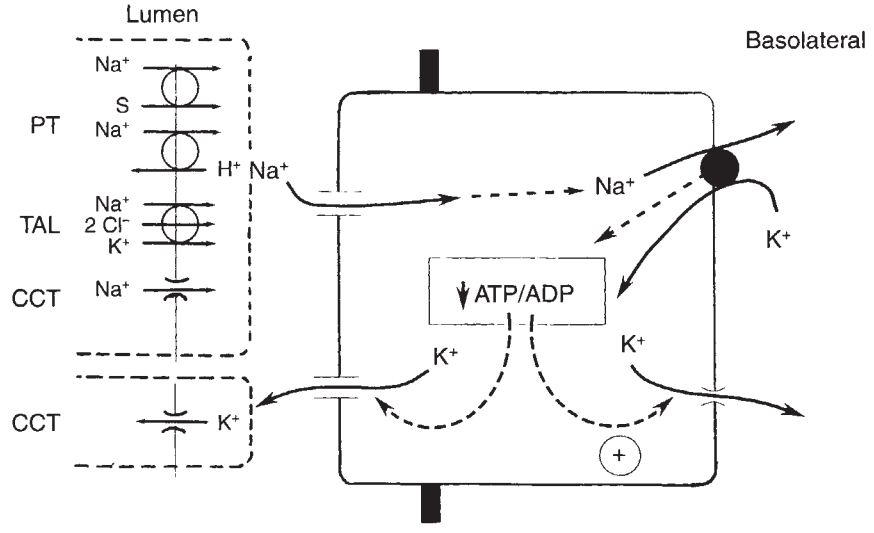

Fig. 8. *Cell model including mechanisms that couple sodium transport and basolateral Na,K-ATPase activity to basolateral K channels.* Shown on the left are several Na-entry mechanisms in the apical membrane of tubule cells. Abbreviations are: PT, proximal tubule; S, substrates like glucose, amino acids, etc.; TAL, thick ascending limb; CCT, cortical collecting tubule. ATP-related regulation of basolateral K channels following transport changes by Na-glucose cotransport has been observed in isolated proximal rabbit tubules [19, 20]. Transport-related changes in apical K channel activity in the TAL and CCT could also be mediated by alterations in cell ATP.

a significant fraction of distal H secretion in states of K depletion [2, 13].

Renal tubule Na,K-ATPase and K channels

Figure 4 provides an overview of the factors that regulate Na,K-ATPase activity in cortical collecting tubules [14]. A prominent feature is the redundancy of pump control as evidenced by several mechanisms that have been identified. First, hormones such as aldosterone stimulate pump genomic expression by increasing the rate of pump synthesis of Na,K-ATPase. Second, some stimuli, aldosterone and insulin for example, can also activate pump-turnover directly: in the early phase of pump stimulation these hormones affect pump rate directly and independently of pump synthesis. Third, an increase in apical sodium entry mediated by enhanced Na-channel activity can either directly stimulate pump units (a substrate effect), or increase the recruitment of latent pumps from a labile pool [14]. Aldosterone can also stimulate K secretion by activation of electrogenic Na-K pump activity. Driving the membrane potential above K equilibrium enhances passive uptake of K from the peritubular fluid and thus induces additional K uptake beyond that driven by Na,K-ATPase activity [2].

Renal K channels

The application of patch-clamp techniques to apical and basolateral membranes of tubule cells [2, 10] and the successful cloning of renal K channels [15] provide new insights into the membrane mechanisms of K transport. The following discussion focuses on the properties of K channels that permit recycling in the TAL and secretion of K in principal tubule cells. The apical

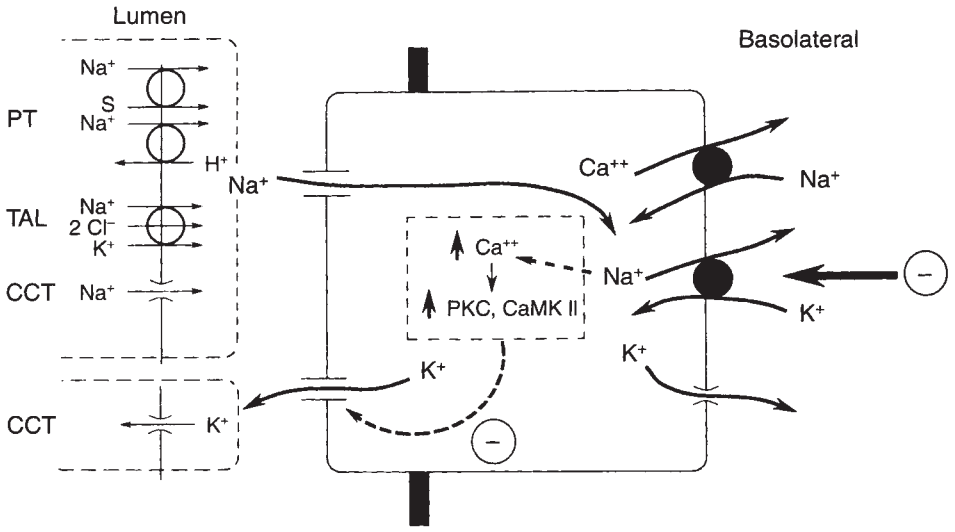

Fig. 9. *Cell model including mechanisms that couple sodium transport and basolateral Na,K-ATPase activity to apical K channels.* Down-regulation of apical K channels following inhibition of basolateral Na,K-ATPase activity involving changes in cell Ca and PKC have been observed in isolated rat CCT [23]; it is likely that CaMK kinase II) is also involved [24].

membrane of these cells also contains a second population of volume activated K channels that do not appear to contribute to K recycling or secretion [10].

Figure 5 shows the structure of a recently cloned inwardly rectifying K channel from the outer medulla of the kidney [15]. In contrast to the K channels of the Shaker family the renal channel (ROMK 1) contains only two membrane-spanning regions that flank the H 5 region assumed to be the channel pore. A splice variant with a shorter amino acid terminal (ROMK 2) has also been cloned, and the functional characteristics of ROMK channels resemble those of the low-conductance K channels observed in the apical membranes of TAL and principal tubule cells [2, 16]. These ROMK isoforms are differentially distributed along the nephron. Whereas ROMK2 is most widely distributed (TAL and collecting ducts), ROMK1 is limited to the TAL [16]. The structural model of both isoforms shows interesting sites that correspond to the functional properties of the secretory K channels *in vivo*. Noteworthy are an ATP-binding motif and phosphorylation sites for cyclic AMP-dependent protein kinases and protein kinase C, and sensitivity to changes of cytosolic pH and ATP [2, 17, 18]. Although not directly inhibited by Ca, low-conductance K channels are blocked indirectly by an increase in cell Ca via activation of PKC [18]. Figures 6 and 7 provide an overview of the most important factors that regulate K channel activity in cells of the TAL and cortical collecting duct.

An interesting relationship exists between the activity of both apical and basolateral K channels and basolateral Na,K-ATPase activity. This phenomenon is interesting because it limits changes in cell volume and cell composition with alterations in net sodium transport. Although not completely resolved, two mechanisms in tubule cells deserve consideration.

First, transport-related changes in cell ATP have been shown to be involved in the regulation of basolateral K channels of proximal tubule cells [2, 19, 20]. Pump stimulation lowers ATP and opens K channels, whereas pump inhibition, because it reduces ATP consumption, leads to increase in ATP with consequent channel blockade. Figure 8 shows a cell model incorporating the events thought to mediate coupling between pump and K channel activity. Whether a similar relationship exists between pump rate, cell ATP and apical channel activity in the TAL and in principal cells needs further exploration. If it were present it could explain that basolateral pump stimulation, for instance by high K intake, increases apical K channel activity [21, 22].

A second mechanism that has been identified to modulate apical K channels involves pump-related changes of cell Ca [23]. Figure 9 demonstrates how inhibition of basolateral Na,K-ATPase, by elevation of cell Na and interference with effective Ca extrusion, leads to activation of PKC and apical K channel blockade. Whereas changes of Na concentration play a key role in this proposed coupling mechanism, pump-related alteration in cell ATP levels could conceivably occur without fluctuation of cell Na, and thus complement the Ca-dependent coupling between pump and channel activities.

The challenge of future investigations will be the further in-depth characterization of K channel behavior in physiological and pathophysiological conditions, involving especially the role of a host of messenger molecules in modulating apical and basolateral channel populations. The recent successful cloning of renal K channels will also provide an unusually rich field for structure-function studies at the molecular level. Taken together, this combination of methods should provide us with a unique opportunity to apply powerful reductionist approaches in a physiological perspective and to advance our knowledge of the role of the kidney in K homeostasis.

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