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Molecular Diversity and Regulation of Renal Potassium Channels

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Abstract

K⁺ channels are widely distributed in both plant and animal cells where they serve many distinct functions. K⁺ channels set the membrane potential, generate electrical signals in excitable cells, and regulate cell volume and cell movement. In renal tubule epithelial cells, K⁺ channels are not only involved in basic functions such as the generation of the cell-negative potential and the control of cell volume, but also play a uniquely important role in K⁺ secretion. Moreover, K⁺ channels participate in the regulation of vascular tone in the glomerular circulation, and they are involved in the mechanisms mediating tubuloglomerular feedback. Significant progress has been made in defining the properties of renal K⁺ channels, including their location within tubule cells, their biophysical properties, regulation, and molecular structure. Such progress has been made possible by the application of single-channel analysis and the successful cloning of K⁺ channels of renal origin.

I. INTRODUCTION

A. Physiological Roles for K⁺ Channels in Kidney

1. Overview of renal K⁺ transport in K⁺ homeostasis—The physiological regulation of the body's internal and external K⁺ balance depends on maintenance of unequal distribution between the intra- and extracellular fluid compartments and on effective renal excretion. Constancy of the small extracellular pool of K⁺ and its low extracellular concentration depend ultimately on effective mechanisms of regulated renal K⁺ excretion. Renal K⁺ excretion is the result of three mechanisms: free filtration in the glomerulus, extensive reabsorption in the proximal nephron segments, and controlled net K⁺ secretion in distal nephron largely determining K⁺ excretion (164,165,169,593). K⁺ reabsorption in certain distal nephron segments has also been observed in states of K⁺ deficiency.

Figure 1 provides an overview of K⁺ transport along the nephron. The bulk of filtered K⁺ is reabsorbed as tubule fluid passes through the proximal convoluted tubule. Some K⁺ enters the descending segments of the loop of Henle passively because of the increasing K⁺ concentration along the corticomedullary axis (15). K⁺ leaves the ascending limb of Henle, again passively, as K⁺ declines in the interstitium towards the corticomedullary region. K⁺ is further reabsorbed in the thick ascending limb of Henle (TAL) by a specific cotransporter (Na⁺-K⁺-2Cl⁻). Modest K⁺ secretion takes place in the distal convoluted tubule and is followed by regulated, more extensive secretion in the initial and cortical collecting ducts. The connecting tubule of deep juxtamedullary nephrons has also been shown to secrete K⁺ (227). The direction of K⁺ transport reverses as fluid passes the outer medullary and terminal papillary collecting duct. Variable

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net reabsorption has been demonstrated in these nephron segments (111). K^+ reabsorption in the terminal segments of the nephron, together with passive entry of K^+ into the descending limb of Henle, constitutes the pathways of K^+ recycling in the renal medulla (15).

2. Other physiological roles for K^+ channels in kidney—Figure 2 shows the basic functions of K^+ channels in various tubule cells along the nephron in the mammalian kidney. In addition to the roles of K^+ channels in mediating net K^+ secretion or absorption, these channels serve to 1) maintain the cell-negative potential at rest providing a driving force for electrogenic transport processes and stabilizing the membrane potential during large fluxes of cations into, or anions out of, tubule cells; 2) help in recovery of cell volume after swelling; 3) recycle K^+ back to tubule fluid in the TAL where K^+ entered cells via the $Na^+-K^+-2Cl^-$ cotransporter; and 4) recycle K^+ across basolateral membranes in conjunction with $Na^+-K^+-ATPase$ turnover. Detailed descriptions of these functions for the various cells along the nephron are given in section II.

B. Overview of Renal K^+ Channel Diversity and Structure

Although the molecular structure of many K^+ channels has been defined, our knowledge of their location along the nephron and their polarized expression and functions in native renal epithelial cells is incomplete. The current state of our understanding of the distribution of specific K^+ channel types along the nephron is shown in Figure 3. While the assignment of cloned K^+ channels to specific functions in tubule cells remains a major problem, the exceptions are as follows. ROMK, an inwardly rectifying K^+ channel with two membrane-spanning domains, has been identified as one of the main secretory K^+ channels; Ca^{2+} -activated maxi- K^+ channels are involved in volume control and flow-dependent K^+ secretion in the collecting duct; and voltage-sensitive K^+ channels play a role in the stabilization of the membrane potential in the face of electrogenic transport processes.

1. Evolution and diversity— K^+ channels are transmembrane proteins that mediate passive K^+ movement across cell membranes via a highly selective, aqueous pore. Molecular studies carried out over the past decade have firmly established that K^+ channels constitute the largest and most diverse class of ion channels. These data are in agreement with numerous electrophysiological studies documenting the existence of a wide variety of K^+ currents in virtually all cells examined to date. They are unique among cation channels since, unlike Na^+ and Ca^{2+} channels, they are found in virtually all living organisms and are widely distributed among cells within each organism. It is likely, therefore, that other cation channels evolved from K^+ channels and that ionic specificity for Ca^{2+} or Na^+ was achieved by modifying the pore region (235).

In spite of an extensive knowledge of the cellular and tissue distribution of K^+ currents and a rapidly growing understanding of the cellular physiology of K^+ channels, biochemical and structural information lagged behind until 1987. The structure of the Na^+ channel of excitable tissues had been determined more than 3 years previously (404,406) using Na^+ channel protein purified from the eel's electric organ, which expresses a large quantity of the protein. Conventional biochemical approaches failed to elucidate the structure of K^+ channels, in large part because these proteins are expressed in very low amounts and are not readily amenable to large-scale purification, and high-affinity probes had not been yet developed.

A major breakthrough in understanding the molecular structure of K^+ channels was achieved in 1987. Electrophysiological studies of *Drosophila melanogaster* mutants (*Shaker*) that exhibited leg shaking when exposed to ether, a volatile anesthetic, indicated the *Shaker* locus might encode a structural component of a voltage-dependent K^+ (K_v) channel. A combination of mutation mapping and chromosome walking was used to successfully identify the *Shaker*

gene (254,441,498,551). Expression of the *Shaker* gene product in *Xenopus* oocytes confirmed it mediated Kv currents (553). Subsequently, several other *Drosophila* K⁺ channel genes (*Shal*, *Shaw*, and *Shab*) were isolated by homology cloning (71). These four proteins had a close evolutionary relationship as evidenced by a high degree of identity (40%) at the amino acid level in pairwise comparisons. The first mammalian K⁺ channel was isolated by homology cloning in 1988 and noted to be most closely related to *Shaker* (70% amino acid identity; Ref. 550). Subsequently, homologs of each *Drosophila* gene have been identified in mammals either by homology or expression cloning (190).

Although *Shaker*-related Kv channels were the first to be identified, they are by no means the only class of K⁺ channels and may not even be the most diverse group of K⁺ channels. Indeed, as will be discussed in more detail, three other major classes of K⁺ channels have been isolated, namely, the calcium-activated K⁺ channels (124,274,562), the inward rectifiers (213,285), and the two-pore (2P) channels (174, 176, 309, 312, 415; see Fig. 4). The 2P channels appear to be the most diverse group of K⁺ channels with more than 50 members identified to date. Phylogenetic tree reconstruction, using deduced amino acid sequences of the various known classes of K⁺ channels, suggests that all known K⁺ channels arose from a common ancestor (101,107,237–239,347). It is also noteworthy that the 2P channels are predicted to be more closely related to the small-conductance calcium-activated K⁺ channel (SK) family in spite of very different secondary structures: 2 pores and 4 transmembrane segments (TM) for TWIK and 1 pore and 6 TM for SK (101,174,312).

Several mechanisms contribute to the observed complexity and diversity of K⁺ channels. Sequence information and chromosomal mapping studies indicate Kv gene clustering at chromosomal loci in both mouse and human, suggesting that Kv channel gene subfamilies arose through duplication of a primordial K⁺ channel gene, with subsequent chromosomal duplications and rearrangements (329). Candidates for ancestral K⁺ channel genes are present in a very wide range of organisms including plants, bacteria, ciliate protists, worms, squid, flies, and vertebrates. It is also likely that most K⁺ channels came into existence via primordial gene duplication. For instance, Kv and cyclic nucleotide-gated channels exhibit readily detectable homologies at the amino acid and functional domain levels (191,239).

2. Structural classification and functional domains—Since a very large number of K⁺ channel genes have already been identified, deduced amino acid sequences and secondary structure information can be used to generate a structural classification. Three broad classes emerge from such analysis. The first consists of channels with six or seven transmembrane segments and one pore region (6-TM) including the *Shaker*-related Kv channels (190), KvLQT1 and Ca²⁺-activated K⁺ channels (KCa). A schematic representation of a prototypic 6-TM channel is shown in Figure 4A. The deduced amino acid sequences range from 450–900 amino acids in length (see Table 1). Hydrophathy analysis indicates that they all contain six transmembrane segments. Because the proteins lack signal peptides, the amino and carboxy termini are both predicted to be located intracellularly. Figure 4B depicts the large-conductance voltage-gated K⁺ channel (hSlo), which unlike Kv has seven transmembrane segments and an extracellular amino terminus (138). Figure 4C shows the inward rectifiers (inward rectifier family; Kir1–7) that have two transmembrane segments and one pore (2-TM; Ref. 398). The amino and carboxy termini are both predicted to be located intracellularly and provide regulatory domains for modification by nucleotide, pH, phosphorylation, and phosphatidylinositol phosphates [e.g., phosphatidylinositol 4,5-bisphosphate (PIP₂)] and βγ from heterotrimeric G protein-coupled receptors. This group includes ATP-sensitive channels and ATP-regulated channels such as ROMK (213). The most recently discovered group (Fig. 4D), and likely the most diverse subfamily, consists of K⁺ channels with four transmembrane segments and two pores (2-P; Refs. 309,415). These channels appear to mediate background leak K⁺ currents in a variety of cells, and some currents are regulated by pH and membrane

stretch. MinK or KCNE1 is single transmembrane subunit (Fig. 4E) that was the first “K⁺ channel” found in kidney but has subsequently been shown to function as a subunit of the Kv channel, KCNQ1.

3. The pore region: an essential feature of K⁺ channels—All K⁺ channels mediate the rapid (>1 million ions/s) and selective transport of potassium. Before the cloning of the first K⁺ channel, a fairly comprehensive view of the pore and the selectivity filter was constructed based on electrophysiological data (203). It was envisioned that K⁺ entered the channel via a water-filled pore, wide on the outside but narrower as it reached the intracellular face of the membrane. The narrow passage facilitated interactions with stabilizing charges and conferred the high selectivity for K⁺. It was also predicted that the pore could accommodate several K⁺ lined in single file. These predictions proved to be remarkably accurate. Recent data, obtained from site-directed mutagenesis experiments of known K⁺ channels proteins (7,8,199,263,354,355), have confirmed the model. Moreover, direct structural data not only validated the proposed structure but also provided an exquisitely detailed view of the pore (119,189,460). The 6-TM K⁺ channels contain a large hydrophobic core that thwarted repeated attempts at obtaining protein crystals suitable for high-resolution X-ray crystallographic studies. A bacterial channel, KcsA, of the 2-TM class was subsequently used to successfully generate protein crystals for high-resolution studies (119,460). It is assumed that the model derived from these data is relevant to all known K⁺ channel pores. X-ray analysis of KcsA crystals revealed that K⁺ channels are tetramers. The four subunits interact to form a symmetrical structure at the center of which lies an aqueous pore. The critical structural elements of the pore consist of two membrane segments linked by a stretch of ~25 amino acids, hydrophobic enough to partly penetrate the lipid bilayer, and also containing a highly conserved signature sequence: TxGYG. This latter sequence along with the last membrane segment (M2 and S6 for the 2-TM and 6-TM class) form the lining of the pore and determine permeation and selectivity. The pore is asymmetric and has a wide extracellular vestibule that narrows abruptly to ~3 Å. This narrowing represents the selectivity filter and measures ~15 Å in length. The pore then widens briefly, about halfway into the bilayer, to form a water-filled cavity 10 Å wide. The selectivity filter provides a binding pocket, lined by negatively charged backbone carbonyl groups of the signature sequence, which provides a better fit for a dehydrated K⁺ than for a Na⁺. The pore contains three of these K⁺ binding sites arranged in single file and in close enough proximity for electrostatic repulsion.

Crystallization of the KcsA pore under high and low K⁺ conditions indicates that the selectivity filter also functions as an outer gate for the channel (657). High K⁺ maintains the filter in an open configuration, and all four binding sites have similar electron density. Low K⁺ alters the structure of the filter and causes the two binding sites at opposite ends of the filter to have the highest electron density. K⁺ cannot move easily, and channel conductance is low. It has been proposed that K⁺ channels also possess an inner gate, formed by hinging of the inner transmembrane helix at a conserved glycine residue, and that sensors (such as voltage, nucleotides, calcium, and pH) may interact with the inner gate and regulate channel function (244). The KcsA pore and selectivity filter are similar to those recently shown for a bacterial Kir homolog Kirbac1.1 (296). This model also appears to provide a reasonable approximation of accurately the more complex pore/selectivity filter structures of the voltage-gated (Kv) 6-TM K⁺ channels based on the recent X-ray structure of a voltage-dependent K⁺ channel (KvAP) from *Aeropyrum pernix* (245). The selectivity filter of KvAP resembles that of KcsA. However, the structures diverge within the intracellular membrane leaflet, and in contrast to KcsA, KvAP has an opened pore. In addition, KvAP's pore is flanked by voltage “sensor paddles,” which are postulated to move across the membrane and modulate the opening and closing of the pore.

Most K⁺ channels do not remain open indefinitely but alternate between open and closed states. The movement of K⁺ through these channels is governed by conformational changes resulting

in channel opening or closing, also referred to as gating. K^+ channels have evolved an array of gating sensors that respond to membrane voltage and/or a variety of extra- and intracellular molecules or ligands including protons, Ca^{2+} , mono- and dinucleotides, cyclic nucleotides, and membrane phospholipids. For example, Kv channels have the ability to respond to membrane voltage. The fourth membrane domain is a critical part of a complex that participates in sensing changes in membrane voltage. The S4 segment stands out by virtue of having 6–9 positively charged amino acids (either lysine or arginine) out of ~20. Membrane depolarization is believed to open the channel through an S4-mediated conformational change (256,302,318,364,425, 434,514). The recent X-ray structure of the voltage-gated K^+ channel has shown that S1-S4 helices are attached to the pore region and the latter half of S3 and S4 form the voltage sensor (245,246).

It should be noted that there is at least one other mechanism for conferring voltage dependence. The 2-P channels, which lack an S4 segment, are thought to mediate background leak current. Recently, it was demonstrated that phosphorylation of a single amino acid of the 2-P channel, KCNK2 (expressed in the hippocampus), allows the channel to sense changes in membrane voltage (52). Furthermore, some 6-TM channels with conserved S4 segments lack voltage sensitivity (32,46), consistent with voltage sensitivity depending on the complex interaction of S3-S4 and other membrane segments.

In the case of Kv channels, the activation process is complex and often facilitates transition into an inactivated state. Inactivated channels are not closed but do not carry any current due to a segment of the cytosolic region of the channel “plugging” the inner vestibule of the pore. The first 20 amino acids of the amino terminus form the inactivation gate for fast inactivation (215,248). The positively charged inactivation gate swings toward the cytoplasmic face of the pore and binds to a negatively charged receptor region in the S4-S5 loop which occludes the pore and prevents K^+ permeation. Interestingly, the inactivation ball can also be formed by soluble cytosolic accessory (β) subunits (454).

4. K^+ channels are heteromultimeric complexes—The basic structure of all K^+ channels is a tetramer of membrane-spanning subunits with a central pore. The subunits forming the tetramer may be the same protein (homotetramer) or two different proteins (heterotetramer) (see Table 1). For example, certain Kir channels consist of identical pore-forming subunits (Kir1.1 or ROMK) while others contain two different proteins (e.g., Kir4.1 and Kir5.1). In addition, many K^+ channels exist as heteromeric assemblies of the pore tetramers with accessory proteins. Kv channels are complexes consisting of four α -subunits that form the pore and cytosolic β -subunits that modulate channel inactivation or other channel functions. In addition, calmodulin is complexed with the Ca^{2+} -activated small-conductance K^+ (SK) channel and through this interaction mediates calcium sensing (493). Moreover, some Kir channel tetramers may form heteromeric complexes with an ATP binding cassette (ABC) protein, like the cystic fibrosis transmembrane conductance regulator (CFTR), or the glibenclamide (sulfonylurea)-binding protein SUR2A/B.

The tetrameric nature of the K^+ channel pore has been demonstrated using site-directed mutagenesis and X-ray crystallography (70,233,319,447,464,502). α -Subunits can coassemble to form either homo- or heteromultimers. Some of the structural elements that control tetrameric assembly have been identified in both Kv (628) and Kir (634) channels. At the amino terminus of Kv channels, the T1 domain is a conserved region ~110 amino acid long proximal to S1 that mediates heteromultimeric interactions of Kv channels. The structure of T1 from Kv1.1 channels has been elucidated (189,382). It is believed that active channels have four T1 domains that hang directly under the cytoplasmic mouth of the pore. They form a sort of platform, 20 Å away from the pore, connected to S1 by thin protein bands. K^+ may access or leave the channel pore sideways, through 20-Å-long openings defined by that T1 domain.

The electrophysiological properties of cloned subunits forming the tetrameric pore may not always match those known for these channels in native tissues (see Table 2). In general, this is due to pore-forming subunits interacting with accessory proteins in native cells that modify their kinetic and pharmacological properties. Furthermore, accessory proteins often modulate the levels of expression of pore-forming tetramers. These latter interactions with β -subunits have been well-studied for Kv channels. For example, the Kv β genes encode soluble proteins (367–404 amino acids), related to the NAD(P)H-dependent oxidoreductase superfamily, that interact with many Kv α -subunits (442). The KChIP genes encode calcium sensors that modify the expression level and kinetic properties of Kv4.2 and Kv4.3 (297). The KChAP proteins act as chaperone for Kv proteins such as Kv1.3, Kv2.1, Kv2.2, and Kv4.3 (297,617). The MinK-related proteins (MiRPs) also interact with Kv channels (1–3,27,471). KCNA4B encodes a soluble protein (141 amino acids) with limited similarity to the NAD(P)H-dependent oxidoreductase superfamily (552). KCNA4B binds to the carboxy terminus of KCNA10, increases KCNA10 current expression by almost threefold, and also alters its sensitivity to cAMP.

II. FUNCTION AND REGULATION OF POTASSIUM CHANNELS IN THE KIDNEY

A. Epithelial K⁺ Channels

1. K⁺ channels along the nephron

A) FUNCTION OF K⁺ CHANNELS IN PROXIMAL TUBULE: The vast majority of filtered K⁺ is reabsorbed passively along the proximal tubule (164). Two mechanisms, passive diffusion and Na⁺-dependent solvent drag of tubule fluid, have been shown to mediate K⁺ retrieval from the filtrate. There is at present no convincing evidence that K⁺ reabsorption involves transcellular movement or K⁺ channels; rather, the bulk of K⁺ reabsorption is thought to proceed via paracellular pathways (612).

K⁺ channels in the proximal tubule serve at least three important functions (Fig. 2; Refs. 164,168,498). First, they participate in generating the cell negative membrane potential. Since several membrane transport processes are electrogenic, alteration in cell membrane potential can affect the Na⁺-coupled transport of molecules including glucose, phosphate, amino acids, and bicarbonate. Relevant examples include Na⁺-coupled phosphate, sulfate, and glucose entry into cells, transport processes which have been shown to be sensitive to membrane depolarization. In the basolateral membrane, Cl⁻ diffusion, Na⁺-coupled HCO₃⁻ cotransporter, and Na⁺/Ca²⁺ exchanger are affected by changes in basolateral membrane potential. Second, K⁺ channels in the proximal tubule are involved in regulating cell volume. For instance, stimulation of Na⁺-dependent carriers such as Na⁺-glucose cotransporters is expected to increase intracellular Na⁺ and cell volume. Such cell swelling activates both apical and basolateral K⁺ channels and increases K⁺ loss, restoring the cell volume. Third, K⁺ channels are responsible for K⁺ recycling across the basolateral membranes where they prevent K⁺ depletion in unstirred fluid layers in the complex system of interstitial spaces adjacent to the basolateral membrane.

In addition to the above-mentioned physiological function, ATP-sensitive K⁺ channels may be involved in hypoxic-induced renal injury (452). It was demonstrated in this latter study that inhibition of K⁺ channels in the proximal tubule by the sulfonylurea glibenclamide attenuates hypoxic injury.

I) K⁺ channels in the basolateral membrane of mammalian proximal tubule: Figure 5 and Table 2 summarize the biophysical properties of, and factors known to regulate, K⁺ channels in the basolateral membrane of the proximal tubule. Three types of K⁺ channels with single-

channel conductances of 12 pS (405), 36–41 pS (171,172), and 50–60 pS (35,94,172,426,⁴⁴¹, 451,498,529,563) have been observed in the basolateral membrane of the rabbit proximal tubule. An important feature of the 50- to 60-pS K⁺ channel is its sensitivity to inhibition by millimolar concentrations of ATP (35,221). This may link (356) the function of this K⁺ channel to changes in basolateral Na⁺-K⁺-ATPase activity (also see Fig. 2). Stimulating the apical Na⁺-glucose cotransporter augments Na⁺ influx, which subsequently causes increased Na⁺-K⁺-ATPase activity in the basolateral membrane. Such enhanced Na⁺-K⁺-ATPase activity is expected to increase the hydrolysis of ATP and to lower intracellular ATP concentrations. With the decrease in intracellular ATP, ATP-sensitive K⁺ channels are relieved from ATP block, resulting in an increase in K⁺ recycling. In this way, the turnover rate of Na⁺-K⁺-ATPase can be tightly linked to the activity of basolateral K⁺ channels. This hypothesis is supported by several observations: 1) adding luminal glucose and alanine decreases the intracellular ATP concentrations and simultaneously increases basolateral K⁺ channel activity (563); 2) sulfonylurea agents, inhibitors of the ATP-sensitive K⁺ channels, also abolish the effect of stimulating Na⁺ transport on channel activity (563); and 3) inhibition of Na⁺-K⁺-ATPase increases intracellular ATP concentrations and inhibits basolateral K⁺ channel activity in proximal tubule cell (221).

Basolateral ATP-sensitive K⁺ channels have also been shown to be sensitive to changes in cell pH: acidic pH inhibits the activity of these K⁺ channels (35). Moreover, it has been reported that the activity of the basolateral 50- to 60-pS K⁺ channel decreases upon exposure to high extracellular taurine (405). Since cell swelling, as accompanying increased apical Na⁺ entry, is expected to reduce the concentration of taurine, it has been proposed that changes in taurine concentration could mediate the swelling-induced increase in the basolateral K⁺ channel activity and play a role in volume regulation (63,405).

The molecular nature of the ATP-sensitive K⁺ channel in the proximal tubule has been explored. Kir6.1 mRNA is expressed in the proximal tubule (405; see Fig. 3 and Table 1). Moreover, coexpressing Kir6.1 with a sulfonylurea receptor (SUR2A/2B) in oocytes results in an ATP-sensitive K⁺ channel that shares with the native basolateral K⁺ channels inhibition by taurine and glibenclamide (405). Therefore, it has been suggested that Kir6.1 is an important part of the basolateral 50- to 60-pS K⁺ channel. More discussion regarding the molecular nature of renal ATP-sensitive K⁺ channels can be found in section IVB3.

II) K⁺ channels in the apical membrane of the mammalian proximal tubule: Ca²⁺-activated large-conductance (200–300 pS; see Figs. 3, 4B, and 5; Table 2) or maxi-K⁺ channels have been identified in the apical membrane of cultured proximal tubule cells (42,204,205,262, 380,548) and in the brush border of rabbit proximal tubules (666). These channels are activated by mechanical stretch and membrane depolarization. However, since the channel open probability is very low, it is unlikely that these maxi-K⁺ channels contribute significantly to the apical K⁺ conductance under normal circumstances in native cells. However, it may play a role in stabilization of the apical membrane potential following stimulation of Na⁺-coupled glucose and amino acid transporters, which tend to depolarize the apical membrane. 33- and 63-pS K⁺ channels have also been found in the apical membrane of the proximal tubule (171; see Figs. 3 and 5; Table 2), although their physiological roles are unknown. A 42-pS ATP-regulated and pH-sensitive inwardly rectifying K⁺ channel has also been identified in the apical membrane of human cultured proximal tubule cells (395).

Molecular cloning has identified several types of voltage-gated K⁺ channels (638) and Ca²⁺-dependent maxi-K⁺ channels (193,388) expressed in proximal tubules. Two voltage-gated K⁺ channels (e.g., KCNQ1, KCNE1, and KCNA10) have been localized to the apical membrane of proximal tubules (Fig. 3; Table 1; Ref. 569). These voltage-gated K⁺ channels may also be involved in stabilization of the apical membrane potential. The properties and

potential roles of these voltage-gated K^+ channels in the regulation of proximal tubule epithelial transport are discussed in section IV. The Ca^{2+} -dependent maxi- K^+ channel *rbslo1* was cloned from rabbit renal cells and has homology to *mslo*; however, it is not clear whether *rbslo1* transcripts are expressed in the rabbit proximal tubule (1 of 8 tubules gave a PCR signal; Ref. 388).

III) K^+ channels in the basolateral membrane of the amphibian proximal tubule: At least two inward-rectifying K^+ channels (27–30 pS, 47–50 pS) have been identified in the basolateral membrane of the proximal tubule of the amphibian kidney (Fig. 5 and Table 2; Refs. 218, 261, 367, 397, 397, 468, 566). The activity of the 27- to 30-pS K^+ channel is increased by depolarization and membrane stretch (218, 260) and inhibited by ATP (367). In contrast, the activity of the 47- to 50-pS K^+ channel is stimulated by hyperpolarization (261, 468). This feature suggests the possibility of metabolic coupling of the activity of Na^+ - K^+ -ATPase to that of basolateral K^+ channels.

IV) K^+ channels in the apical membrane of amphibian proximal tubule: A Ca^{2+} -activated maxi- K^+ channel has been identified in the apical membrane of the amphibian proximal tubule (147) and found to be activated by depolarization and membrane stretch. In contrast to the behavior of the basolateral stretch-activated K^+ channels, the effect of mechanical stimulation on channel activity may be indirect and mediated by an increase in intracellular Ca^{2+} . This view is based on the observation that membrane stretch activates a Ca^{2+} -permeant nonselective cation channel in the apical membrane of proximal tubules (147, 260, 466, 467).

B) FUNCTION OF K^+ CHANNELS IN THE TAL: The TAL reabsorbs not only 20–25% of the filtered Na^+ load but also plays an important role in reabsorption of divalent cations such as Mg^{2+} and Ca^{2+} . K^+ channels in the TAL are important in generating the cell membrane potential, apical K^+ recycling coupled to K^+ entry via Na^+ - K^+ - $2Cl^-$ cotransport, regulating cell volume, and basolateral K^+ recycling coupled to the activity of Na^+ - K^+ -ATPase (see Figs. 2 and 6).

I) K^+ channels in the basolateral membrane of mammalian TAL: Cl^- efflux across the basolateral membrane of the TAL via Cl^- channels is crucial to net Cl^- reabsorption (see Fig. 6). Basolateral K^+ channels are involved in generating and maintaining the membrane potential which provides an important driving force for this passive Cl^- exit across the basolateral membrane. Regulation of the basolateral K^+ channel has not been extensively explored due to technical difficulties in accessing the basolateral membrane using intracellular microelectrodes or patch clamp. However, an inward-rectifying K^+ channel with a slope conductance between 41 and 43 pS has been detected in the basolateral membrane of the mouse TAL (222) (Fig. 6 and Table 2). This K^+ channel is inhibited by reductions in cytosolic pH (431) and cytochrome *P*-450-dependent metabolites of arachidonic acid (183). The activity of the 41- to 43-pS K^+ channel increases with depolarization (183). The voltage dependence of this 41- to 43-pS K^+ channel would help maintain the driving force for passive Cl^- movement across the basolateral membrane during periods of increased transcellular Cl^- flux.

II) K^+ channels in the apical membrane of mammalian TAL: K^+ channels play a key role in K^+ recycling across the apical membrane of the TAL. Their importance is underscored by the observation that inhibition of apical K^+ recycling impairs $NaCl$ reabsorption in the loop of Henle (164, 180, 195, 593). Several functions are served by K^+ recycling (see Fig. 6). First, K^+ recycling hyperpolarizes the cell membrane potential, which is an essential factor for Cl^- diffusion across the basolateral membrane. Second, K^+ recycling across the apical membrane, coupled to Cl^- exit across basolateral membranes, generates the lumen-positive transepithelial potential that is the main driving force for paracellular Na^+ , Ca^{2+} , and Mg^{2+} transport. Third,

K⁺ recycling maintains an adequate supply of K⁺ for the Na⁺-K⁺-2Cl⁻ cotransporter in the cortical TAL.

Three types of K⁺ channels, a low-conductance (30–35 pS), an intermediate-conductance (70–72 pS), and a large-conductance (140–200 pS) maxi-K⁺ channel, have been observed in the apical membrane of the TAL (Fig. 6 and Table 2; Refs. 49,94,188,589,599). Patch-clamp studies have demonstrated that both the low- and intermediate-conductance K⁺ channels contribute to the apical K⁺ conductance and to K⁺ recycling. Both the large apical membrane conductance and K⁺ recycling can be accounted for by the high open probabilities and channel densities (593). For example, the 70-pS K⁺ channel has been estimated to contribute up to 75% of the total apical K⁺ conductance of the TAL in rat maintained on a high-K⁺ diet (604). In contrast, the open probability of the maxi-K⁺ channel is very low under normal conditions in native cells and therefore is unlikely to play a significant role in apical K⁺ recycling (188, 545). However, the maxi-K⁺ channel in TAL cell culture can be activated by membrane stretch (545) and thus may be involved in regulating cell volume. It has not been explored whether increased flow rate in the TAL could stimulate maxi-K⁺ channels as has been described for principal cells in the cortical collecting duct (CCD) (620). Such a mechanism has been implicated in the CCD (546,620) and, therefore, could provide an additional K⁺ recycling mechanism in the TAL.

The molecular nature of the low-conductance, 35-pS K⁺ channel is established to be ROMK (Kir1.1; Fig. 2 and Table 1; see sect. III; Refs. 342,593). The ROMK-knockout mouse exhibits a Bartter's-like phenotype (333,342), and these mice lack expression of both the 35- and 70-pS K⁺ channels in the TAL (342). Thus it is possible that ROMK may also be involved in forming the 70-pS K⁺ channel.

III) Regulation of K⁺ channels in the TAL: Figure 6 provides a summary of the factors regulating apical and basolateral K⁺ channels in the mammalian TAL (166,593).

A) The apical 35-pS K⁺ channel: Vasopressin increases the activity of this K⁺ channel via a cAMP-dependent pathway, and the channel can be directly stimulated by cAMP-dependent protein kinase (PKA) in the absence of hormone (451,589). Since vasopressin also stimulates Na⁺ reabsorption in the TAL (180,196,197), it is possible that at least part of the vasopressin effect is mediated by increasing apical K⁺ recycling. Consistent with this notion, the arginine vasopressin analog 1-deamino-(8-D-arginine)-vasopressin (DDAVP) increases Kir1.1 (ROMK) abundance in the TAL of the Brattleboro rat (125).

The 35-pS K⁺ channels are inhibited by millimolar intracellular ATP and by acidic pH (48, 589). The former may be involved in metabolic sensing to coordinate apical and basolateral potassium fluxes as demonstrated in proximal tubule (563,613) and collecting duct principal cells (602). pH sensing by the 35-pS K⁺ channel may serve to modulate apical K⁺ conductance during acid-base disturbances (pH reductions are inhibitory) and also may be involved in the altering of channel activity by other factors [e.g., phosphatidylinositol 4,5-bisphosphate (PIP₂); see sect. III]. In addition, modulating the activity of the Na⁺-K⁺-2Cl⁻ cotransporter may alter intracellular pH and affect apical K⁺ conductance as in the amphibian diluting segment (93).

Since ROMK encodes the 35-pS K⁺ channel, modulation of its expression by hormones or dietary factors provides information about regulation of this low-conductance channel. Increase in glucocorticoids, protein, or sodium intake enhances ROMK expression in the TAL while low sodium intake reduces channel expression (125,158). In addition, increases in osmolality also enhance ROMK expression in the medullary TAL (158).

B) The apical 70-pS K⁺ channel: The 70-pS K⁺ channel is also stimulated by PKA and inhibited by millimolar intracellular ATP (49,589,599). Moreover, two eicosanoids, 20-hydroxyeicosatetraenoic acid (20-HETE) and PGE₂, play important roles in regulating the activity of this K⁺ channel. In the medullary TAL (mTAL), 20-HETE is the major metabolite of cytochrome *P*-450 ω -oxidation of arachidonic acid, whereas PGE₂ is the major product of cyclooxygenase-dependent metabolism of arachidonic acid in the mTAL (75,76,369). Addition of arachidonic acid inhibits the 70-pS K⁺ channel (596), and this effect can be mimicked by 20-HETE. The latter eicosanoid has also been shown to inhibit the Na⁺-K⁺-2Cl⁻ cotransporter (134). Reduction in the activity of the 70-pS K⁺ channel may be an additional mechanism by which 20-HETE lowers the activity of the Na⁺-K⁺-2Cl⁻ cotransporter via a decrease in apical K⁺ recycling. At low concentrations, PGE₂ inhibits the 70-pS K⁺ channels by reducing cAMP level, whereas high concentrations of PGE₂ directly inhibit the channel activity by stimulating protein kinase C (PKC) (328).

It has been suggested that extracellular Ca²⁺-mediated stimulation of the basolateral G protein-coupled Ca²⁺-sensing receptor (CaSR) provides a major mechanism for regulation of NaCl and Ca²⁺/Mg²⁺ transport by the TAL (66). Increased blood/interstitial concentrations of Ca²⁺, Mg²⁺, or aminoglycoside antibiotics (e.g., neomycin) activates the CaSR resulting in reductions in both divalent mineral and NaCl reabsorption (99,241,242,446,537,538). As a consequence, divalent mineral excretion is enhanced, and countercurrent multiplication and urinary concentrating ability are reduced. Ca²⁺-mediated activation of the CaSR in the TAL reduces cAMP production by adenylate cyclase (probably type 6) and enhances cAMP destruction by phosphodiesterases (PDE) (241,242). This CaSR-mediated reduction in cAMP generation would reduce the activity of both the 70- and 35-pS K⁺ channels (Fig. 6). In addition, stimulating the CaSR in the TAL significantly increases 20-HETE production, which inhibits the 70-pS K⁺ channel (604). Since the CaSR is half-maximally activated at the normal plasma concentration of Ca²⁺, the CaSR could account for the basal production of 20-HETE. Thus CaSR activation can inhibit both types of K⁺ channels involved in apical K⁺ recycling, consistent with reduction in NaCl and Ca²⁺/Mg²⁺ transport by the TAL. The potent effect of CaSR activation on apical K⁺ channels in the TAL has been recently supported by the observations that certain activating (gain-of-function) mutations of the human CaSR gene produce a Bartter's-like phenotype (573,609).

It has also been suggested that 20-HETE may mediate the low K⁺ intake-induced decrease in the activity of the 70-pS K⁺ channel, since the concentration of this eicosanoid is four times higher in the mTAL from rats on a K⁺-deficient diet than in those from animals on a high-K⁺ diet (185). Channel open probability is significantly diminished in mTAL harvested from rats on a K⁺-deficient diet (185). In contrast, inhibiting cytochrome *P*-450 ω -oxidation increases channel activity to an extent similar to that observed in the high K⁺ adapted animals (185).

The apical 70-pS K⁺ channel is activated by two gases, nitric oxide (NO) and carbon monoxide (CO) (327,346). Inhibition of NO synthase (NOS) attenuates, whereas addition of NO donors increases, the activity of the 70-pS K⁺ channel. The effect of NO is mediated by a cGMP-dependent pathway because the effect of NOS inhibitors can be reversed by membrane-permeant cGMP analogs (346). The mechanism by which CO regulates the 70-pS K⁺ channel is unlikely to involve cGMP because CO effects can also be observed in excised patches (327).

C) The basolateral K⁺ channel: Application of arachidonic acid (AA) reduces the activity of the 41-pS K⁺ channel, and this effect of AA is abolished by blocking the cytochrome *P*-450 metabolic pathway (see Fig. 6). Thus the effect of AA may also be mediated by 20-HETE (183). Given that basolateral K⁺ channels play an important role in maintaining the driving

force for Cl^- exit across the basolateral membrane, inhibition of basolateral K^+ channels is expected to decrease Cl^- transport.

IV) K^+ channels in the amphibian diluting segment: An inward-rectifying K^+ channel with a conductance of 25–31 pS has been identified in the apical membrane of the frog diluting segment which shares the properties of the TAL (223–225). This channel is activated by increasing cell pH from 7.4 to 8.2 and inhibited by acidic pH (6.6). Furosemide, which inhibits Na^+ - K^+ - 2Cl^- cotransport and increases intracellular pH, activates the apical K^+ channel (93). With the use of isolated cells from the frog diluting segment, three types of K^+ channels with differing conductances have been found (24, 45, and 59 pS; Ref. 594). However, their membrane location is not known. Of interest is the finding that aldosterone stimulates the 45-pS K^+ channel that is sensitive to changes in intracellular pH (594). Because aldosterone raises the cell pH in frog diluting segment, it is possible that the effect of aldosterone on the 45-pS K^+ channel results from increasing cell pH (594).

C) FUNCTION OF K^+ CHANNELS IN THE MAMMALIAN DISTAL CONVOLUTED TUBULE: The distal convoluted tubule (DCT) plays an important role in the regulation of Na^+ , Mg^{2+} , and Ca^{2+} transport (26,95,98). However, only a few studies have assessed the properties of K^+ channels in this nephron segment. A 48- to 60-pS K^+ channel has been observed in the basolateral membrane of the rabbit distal tubule (547). In addition, an inwardly rectifying K^+ channel with inward slope conductance of 37 pS has been observed in the cultured mouse distal tubule cells, and this channel is inhibited by acidic pH (337). Specific roles of these channels in distal tubule function are unknown.

D) FUNCTION OF K^+ CHANNELS IN THE COLLECTING DUCT: The CCD plays a key role in the regulated secretion of K^+ (164, 168; see Figs. 1, 2, and 7). K^+ secretion occurs in principal cells by a two-step process: active entry of K^+ across the basolateral membrane mediated by Na^+ - K^+ -ATPase, followed by passive diffusion across the luminal membrane via apical K^+ channels along a favorable electrochemical gradient (164). In addition to playing an important role in the secretion of K^+ , it has been suggested that apical K^+ channels are also involved in modulating the process of reabsorption of K^+ that occurs in cells of the outer medullary collecting duct (OMCD). In these cells, K^+ channels are coupled to the activity of K^+/H^+ exchange (H^+ - K^+ -ATPase); channel activity is high during K^+ repletion but decreases sharply during K^+ depletion (653,654). Thus variable apical recycling of K^+ , in concert with regulated basolateral K^+ channel activity, could be an important mechanism modulating the efficacy of active K^+/H^+ exchange.

Basolateral K^+ channels are responsible for generating the basolateral membrane potential that determines the magnitude and direction of K^+ diffusion from cell to peritubular fluid. K^+ channels also mediate K^+ recycling coupled to K^+ entry into cells by the Na^+ - K^+ -ATPase. Recycling of K^+ across the basolateral membrane is modest under physiological conditions because of the similar magnitude of the K^+ equilibrium potential and membrane potential. Accordingly, most of K^+ entering principal cells exits through the apical membrane. However, stimulation of Na^+ - K^+ -ATPase by mineralocorticoids can hyperpolarize the basolateral membrane and result in a reversal of the electrochemical potential for K^+ . As a consequence, K^+ now enters the cell across the basolateral membrane in parallel with active K^+ transport by Na^+ - K^+ -ATPase (436).

I) K^+ channels in the apical membrane of mammalian CCD: Low-conductance (35 pS), maxi- K^+ (140 pS), and voltage-gated (10–16 pS) channels have been identified in the apical membrane of the CCD (Fig. 7; Refs. 152,153,209,220,324,478,483,525,598). The low-conductance and voltage-gated channels are restricted to principal cells (153,598). However,

the maxi-K⁺ channel has been observed in both principal and intercalated cells, although it is mostly expressed in intercalated cells (152,219,220,418).

The 35-pS K⁺ channel mediates the bulk of K⁺ secretion in the CCD under normal conditions when distal flow is not high (152,153). The 35-pS K⁺ channel is encoded by Kir1.1 (ROMK; Refs. 168,213,342,652). This was demonstrated by the absence of this 35-pS K⁺ channel in principal cells in the ROMK knockout mouse (342). The structure, function, and regulation of the ROMK channel are discussed in section III. With high luminal flow rates, the maxi-K⁺ channel may contribute significantly to net K⁺ secretion (546,620). Moreover, maxi-K⁺ channels do not contribute significantly to the apical K⁺ conductance under normal physiological conditions because its open probability is very low (152). The maxi-K⁺ channel is encoded by *rbsoll*, a *mslo* homolog (388). It is of interest that maxi-K⁺ channels in the perfused Ambystoma collecting duct appear to mediate K⁺ secretion during exposure to high concentrations of KCl (526,527). Activity of the voltage-gated channels has been shown to be increased by membrane depolarization and may be encoded by Kv1.3, although the membrane localization of this channel is unclear. The voltage-gated K⁺ channel may stabilize the membrane potential whenever high rates of luminal Na⁺ tend to depolarize this membrane (106).

II) Regulation of apical K⁺ channels: Figure 7 illustrates the known mechanisms by which the apical 35-pS, maxi-K⁺, and voltage-gated K⁺ channels are regulated in the CCD.

A) The maxi-K⁺ channel: The Ca²⁺-activated maxi-K⁺ channel is sensitive to TEA, ATP, and acidic pH (152,207,209,219). The sensitivity to ATP and pH depends on the cell Ca²⁺; in the presence of 1 mM Ca²⁺, neither ATP nor acidic pH can inhibit the channel activity, whereas 1 mM ATP and acidic pH decrease the K⁺ channel activity in the presence of 1 μM Ca²⁺ (207). The maxi-K⁺ channels are also activated by hypotonic cell swelling (209). In addition, increases in flow rate stimulate K⁺ secretion (131,359,360), which is associated with an increase in intracellular Ca²⁺ (621). It has been suggested that maxi-K⁺ channels mediate this Ca²⁺-associated, flow-dependent K⁺ secretion. This is based on the observation that TEA (152) or charybdotoxin (546) inhibits K⁺ secretion with high luminal flow rates. TEA does not alter K⁺ secretion during low flow rates. Moreover, deletion of the gene encoding the β₁-accessory subunit of maxi-K⁺ channels impairs K⁺ excretion following acute volume expansion, an effect consistent with a role for these channels in K⁺ excretion during high rates of distal tubule flow rate (440). The mechanism, by which a high flow rate increases intracellular Ca²⁺ and presumably maxi-K⁺ channel activity, is not completely understood but may be related to an increase in cell Ca²⁺ (546). One hypothesis for coupling flow to increases in intracellular Ca²⁺ in principal cells involves flow-dependent deformations of the central cilium (443,620). Deformation of the cilium increases intracellular Ca²⁺ through opening of mechanically sensitive channels that probably reside in the cilium or its base. This influx of Ca²⁺ is followed by Ca²⁺ release from inositol 1,4,5-trisphosphate (IP₃)-sensitive stores. Therefore, increase in intracellular Ca²⁺ would activate maxi-K⁺ channels and increase in K⁺ secretion. Intercalated cells in the CCD lack a central cilium; however, increases in flow rate still raise intracellular Ca²⁺ in these cells. Therefore, a mechanism other than cilium deformation is likely to be involved in mediating the effect of increasing flow rate on intracellular Ca²⁺ in intercalated cells.

B) The 35-pS K⁺ channel: The activity of the 35-pS K⁺ channel is regulated by a large number of factors including nucleotides, phosphatidylinositol phosphates, cytosolic pH, kinases, phosphatases, and arachidonic acid. These factors regulate both channel gating and density in the membrane (see Fig. 7). The activity state of the channel is complexly determined not only by these individual factors but also by the interplay of multiple factors that influence each other.

The 35-pS K⁺ channel is regulated by both cytosolic and extracellular ATP. The channel is inhibited by millimolar concentrations of cytosolic Mg-ATP (592,598), and channel sensitivity to ATP could play a role in linking its activity to Na⁺-K⁺-ATPase (221,563). External ATP has also been shown to inhibit the 35-pS K⁺ channel via purinergic receptor-mediated effects (340). P2 type purinergic receptors are present on both apical and basolateral membranes of principal cells (304). Stimulating P2Y2 purinergic receptors increases cytosolic Ca²⁺ (340) which, in turn, enhances cGMP generation by activating Ca²⁺-regulated NOS (338). Increasing cGMP activates protein phosphatases and facilitates the dephosphorylation of K⁺ channels. Because the phosphorylation state of the channel in principal cells is an important determinant of its activity (350,630), enhancing dephosphorylation would be expected to lower channel activity.

The 35-pS K⁺ channel in principal, as in TAL, cells is sensitive to changes in cell pH in the physiological range. Decreasing pH from 7.4 to 7.2 reduces channel activity by 50% (482, 598). K⁺ secretion is inhibited during acidosis and likely contributes to the effect of acidosis on K⁺ excretion (164).

Arachidonic acid inhibits the 35-pS K⁺ channel in the CCD (591). The effect of arachidonic acid is specific because other fatty acids such as lenoleic or palmic acid cannot mimic its effect. Moreover, the effect of arachidonic acid is not mediated by its metabolites since inhibiting cyclooxygenase, lipoxygenase, and cytochrome *P*-450 monooxygenase does not block the effect of arachidonic acid.

Ca²⁺-dependent signal transduction pathway kinases, such as PKC and calmodulin-dependent kinase II (CaMKII), inhibit the 35-pS K⁺ channel (290). Increasing intracellular Ca²⁺ reduces the activity of the 35-pS K⁺ channel, and this effect is blocked by inhibiting PKC or CaMKII and mimicked by adding the catalytic subunits of PKC and CaMKII (602).

PKA and Mg-ATP play important roles in regulating the activity of the 35-pS K⁺ channel. Modulation of kinases by application of cAMP or inhibition of phosphatases stimulates the channel phosphorylation and increases the number of the functional 35-pS K⁺ channel in the cell membrane (77,287). PIP₂ increases the activity of the 35-pS K⁺ channel in the rat CCD (339) as well as ROMK expressed in *Xenopus laevis* oocytes (217). The stimulatory effect of PKA and Mg-ATP on channel activity involves both a potentiation of the PIP₂ effect (294, 339) and modulation of cytosolic pH sensitivity (305).

Dietary K⁺ intake is also an important regulator of the 35-pS K⁺ channel. Low K⁺ intake decreases, whereas a high K⁺ intake increases, the number of K⁺ channels in principal cells (421,423). Several lines of evidence indicate that protein tyrosine kinase (PTK) mediates the effect of low K⁺ intake on the 35-pS K⁺ channel (595, 610, 611; see Figs. 8–10). First, the kidney expression of *c-Src* and *c-yes*, members of Src family of tyrosine kinases, increases significantly in rats on a K⁺-deficient diet. Second, inhibiting PTK increases the number of the 35-pS K⁺ channels to the same extent as that observed in CCD segments harvested from rats on a high-K⁺ diet. Third, in rats on a high-K⁺ diet, inhibiting protein tyrosine phosphatase (PTP) decreases channel activity in principal cells from the CCD. The effect of PTK does not result from direct inhibition of channel activity since adding exogenous *c-Src* does not affect channel activity in excised membrane patches. Moreover, the effect of inhibiting PTP on the 35-pS K⁺ channel is completely blocked by 20% sucrose, which blocks endocytosis of membrane proteins. Studies performed in oocytes expressing ROMK1 and *c-Src* further support the thesis that stimulation of PTK-induced phosphorylation enhances channel endocytosis, whereas suppressing PTK-induced phosphorylation facilitates the exocytosis of the 35-pS K⁺ channel (see Figs. 9 and 10; Refs. 610,611).

III) K^+ channels in the basolateral membrane of mammalian principal cells in the CCD:

Basolateral K^+ channels in principal cells participate in generating the cell membrane potential and are involved in recycling of K^+ entering via $Na^+-K^+-ATPase$ across the basolateral cell membrane (Figs. 2 and 7; Ref. 164). Patch-clamp studies using the cell-attached configuration have identified three types of K^+ channels in the basolateral membrane: small- (28 pS), intermediate- (63 pS), and large-conductance (145 pS) channels (Fig. 7 and Table 2; Refs. 208,209,605). In cell-detached, inside-out patches with symmetrical KCl solutions, the channel conductances of these channels are 18 pS (small), 28 pS (intermediate) and 85 pS (large), respectively.

IV) Regulation of basolateral K^+ channels in the CCD: The factors regulating the three types of basolateral K^+ channels are shown in Figure 7. All channels are stimulated by protein kinase G (PKG) and inhibited by acidic pH (208,344,601). The 28-pS K^+ and 85-pS K^+ channels are also activated directly by NO (210). Ca^{2+} has been shown to inhibit the basolateral K^+ channels (345). The mechanism by which Ca^{2+} inhibits the small-conductance K^+ (18 pS) channel depends on the formation of peroxynitrite, a product of interaction between superoxide (O_2^-) and NO (345). The basolateral K^+ channels play an important role in K^+ recycling, which is coupled to the $Na^+-K^+-ATPase$ activity. Stimulation of apical Na^+ transport increases the activity of the $Na^+-K^+-ATPase$ and augments the basolateral K^+ channel conductance (338). However, it is unlikely that ATP could be a mediator for coupling the basolateral K^+ conductance to $Na^+-K^+-ATPase$ because basolateral K^+ channels are not inhibited by ATP. It has been suggested that the NO-dependent cGMP pathway is responsible for linking the activity of $Na^+-K^+-ATPase$ to the basolateral K^+ conductance (270). Stimulation of Na^+ transport has been shown to increase the intracellular Ca^{2+} , which stimulates NO and cGMP production in principal cells. An increase in cGMP concentration stimulates PKG, which activates basolateral K^+ channels.

2. K^+ channels in cultured renal epithelial cells

A) PROXIMAL TUBULE CELL CULTURE: Several investigators have reported the presence of an inward-rectifying K^+ channel with inward conductance of 90 pS in OK proximal tubule cells (288,409). The channel is inhibited by ATP and acidic pH (288,409,568) and stimulated by PKG (289). Natriuretic peptides (atrial natriuretic peptide, brain natriuretic peptide, and urodilatin) regulate this K^+ channel in immortalized human proximal tubule cells by cGMP-dependent and independent pathways (211).

B) DISTAL TUBULE CELL CULTURE: A Ca^{2+} -activated 95- to 127-pS K^+ channel and a 18-pS K^+ channel have been identified in the apical membrane of TAL cells cultured from rabbit (94,188,381). Several K^+ channels have also been detected in the apical membrane of Madin-Darby canine kidney (MDCK) cells: a small- (31 pS), two intermediate- (89 pS, 109 pS) and a large-conductance (220 pS) K^+ channel (299). A Ca^{2+} -activated 53- to 60-pS K^+ channel in the basolateral membrane of MDCK cells is thought to be involved in cell migration (494–496).

Two types of apical K^+ channels, a Ca^{2+} -activated maxi- K^+ channel and an ATP-sensitive 35-pS K^+ channel, are expressed in CCD cells cultured from rabbit (324,475,534). The Ca^{2+} -activated maxi- K^+ channel is activated by both arachidonic acid and PGE_2 (325), and these effects may be mediated by stimulating Ca^{2+} release. The maxi- K^+ channel is also inhibited by ATP and GTP (475,534). Cyclosporin A, an immunosuppressive agent, has been demonstrated to inhibit the 35-pS K^+ channel (323). This finding may have clinical relevance since the drug has been reported to decrease kaliuresis (4,255). In cultured A6 kidney cells, cAMP has been shown to activate a 13-pS K^+ channel (192).

B. Nonepithelial K⁺ Channels

1. Mesangial K⁺ channels—Mesangial cells are smooth muscle-like pericytes and form a biomechanical unit involved in regulating glomerular filtration rate. Mesangial cell excitability is modulated by a variety of vasoactive hormones such as angiotensin II, which increases intracellular Ca²⁺ (522). K⁺ channels are responsible not only for the resting cell membrane potential but are also involved in regulating excitability of mesangial cells (see Ref. 522 for a review). A Ca²⁺-activated and scorpion toxin-sensitive large-conductance K⁺ channel (205 pS) and an ATP-sensitive K⁺ channel have been identified in glomerular mesangial cells (366,474,476,522). Inhibition of ATP-sensitive K⁺ channels with sulfonylurea agents leads to contraction of mesangial cells (476), whereas an inhibitor (iberiotoxin) of Ca²⁺-activated maxi-K⁺ channels was not effective. These results suggest that ATP-sensitive K⁺ channels are active under resting conditions (476). However, the Ca²⁺-activated maxi-K⁺ channel may regulate mesangial cell contraction by another mechanism. Angiotensin II induces contraction of mesangial cells by raising intracellular Ca²⁺. Repolarization of the cell membrane by Ca²⁺-activated maxi-K⁺ channels would inactivate Ca²⁺ channels and reduce Ca²⁺ influx (522). This effect of maxi-K⁺ channels would act as a brake on the contracting effect of angiotensin II. The maxi-K⁺ channel is stimulated by cGMP-dependent protein kinase and inhibited by protein phosphatase 2A-induced dephosphorylation (474,522).

In addition to the Ca²⁺-activated and ATP-sensitive K⁺ channels, an intermediate-conductance (40-pS) K⁺ channel has also been found in cultured rat mesangial cells (365). This channel is also activated by Ca²⁺, vasopressin, and angiotensin II. In cultured human mesangial cells, a 9-pS K⁺ channel has also been observed in inside-out patches (476). Functional roles of these channels remain unclear.

2. K⁺ channels in juxtaglomerular apparatus—Macula densa cells are a component of the juxtaglomerular apparatus (JGA) that plays a key role in glomerulotubular feedback (41, 484). Macula densa cells located at the junction between the TAL and the DCT can sense changes in luminal fluid Na⁺ and Cl⁻ concentrations, and its basolateral membranes are in close contact with the glomerulus. The properties of the macula densa are very similar to those of the cortical TAL including luminal Na⁺-K⁺-2Cl⁻ cotransporters (301). Similar to the TAL, apical K⁺ channels play an important role in K⁺ recycling (301). Patch-clamp studies have demonstrated that the biophysical properties of the apical K⁺ channel in the macula densa are similar to those in the TAL (226). The channel conductance is 41 pS, and the channel is inhibited by acidic pH and high concentrations of Ca²⁺. In contrast to the 35-pS channel in apical membranes of the TAL, the 41-pS channel in macular dense cells is not blocked by Na-ATP. The physiological role of the apical K⁺ channels in mediating tubuloglomerular feedback is demonstrated by experiments in which inhibition of the K⁺ channel with U37883A, an inhibitor of the ATP-sensitive K⁺ channel (587), attenuated tubuloglomerular feedback (570). It is likely that the 41-pS channel in macula densa cells is encoded by ROMK, since mice lacking the ROMK gene exhibit severely impaired glomerulotubular feedback (333).

3. Vascular K⁺ channels—K⁺ channels in smooth muscle cells of renal arteriole determine not only the cell membrane potential but also are involved in mediating the effects of vasoactive substances such as eicosanoids and adenosine on myogenic tone of blood vessels (160,252, 444,531,660). Several types of K⁺ channels including ATP-sensitive K⁺, voltage-gated K⁺, and delayed-rectifier K⁺ channels have been identified in the renal vascular smooth muscles by molecular biological methods (362,445). Only a Ca²⁺-dependent K⁺ channel and a 4-aminopyridine (4-AP)-sensitive delayed rectifier K⁺ channel has been directly identified by electrophysiological techniques. Evidence in support of ATP-sensitive K⁺ channels is indirect and based on the use of pharmacological blockers. In contrast, the role of Ca²⁺-dependent K⁺ channels in regulating the vasoactivity has been well established. Three types of Ca²⁺-

dependent K^+ channels, with channel conductance of 68, 105, and 195–251 pS, have been identified in the renal vascular smooth muscle (252,531,645,660). TEA blocks all three types of Ca^{2+} -sensitive K^+ channels (252,660). Furthermore, apamin inhibits the 68-pS K^+ channel but had no effect on the 252-pS K^+ channel (160). 20-HETE inhibits the 105- and 251-pS K^+ channels (252,660), whereas 11,12-epoxyeicosatrienoic acid (EET) specifically activates the 251-pS K^+ channel (665). The regulation of K^+ channels by eicosanoids may have an important role in modulating renal blood flow. It has been reported that 11,12-EET dilates the small renal vessels, whereas 20-HETE induces vasoconstriction (660,665). NO also stimulates the 251-pS K^+ channel, and this effect results from suppressing cytochrome *P*-450 metabolism of arachidonic acid (531). In addition, CO activates the 105-pS K^+ channel and causes vasodilation. The action of CO does not depend on cGMP formation because cyclase inhibitors do not abrogate this response (252).

The delayed rectifier K^+ channels are open at physiological membrane potentials. Angiotensin II or caffeine inhibits these channels in canine renal artery (162). The effect of angiotensin II on channel activity may be mediated by the associated rise in intracellular Ca^{2+} because the delayed rectifier K^+ channel can be directly inhibited by increasing Ca^{2+} in excised patches.

C. Major Physiological Role of K^+ Channels in Renal Epithelial Function

1. K^+ secretion—Micropuncture and microperfusion experiments have shown that segments beyond the thick ascending limb are the main sites of K^+ secretion (see Fig. 1; Refs. ^{130,266,358,360,439,519,520,576}). In superficial nephrons, the primary sites for K^+ secretion are the DCT, connecting tubule, and initial collecting duct. In juxtamedullary nephrons, the connecting tubule directly drains into the CCD, and both of these segments contribute to the K^+ secretory process. Many factors regulate K^+ secretion including dietary K^+ intake, distal flow rate, and Na^+ delivery (177,266,576), mineralocorticoids (146), vasopressin (275), changes in acid base balance, and diuretics (56,358). K^+ channels play an important role in mediating such functional modifications.

A) EFFECT OF K^+ DIET: K^+ secretion in the initial cortical and outer medullary collecting ducts responds promptly to changes in dietary K^+ intake: an increase in K^+ intake stimulates whereas a decrease in K^+ intake reduces K^+ secretion (322,359,360). The augmentation of K^+ secretion includes changes in apical K^+ channel activity in distal nephron segments. Augmentation in dietary K^+ intake increases aldosterone secretion from the zona glomerulosa of the adrenal gland. However, both aldosterone-dependent and -independent pathways contribute to stimulation of K^+ secretion by a high- K^+ diet.

At least three factors contribute to the kaliuresis following an increase in K^+ intake. Both aldosterone-dependent and -independent mechanisms are involved stimulating K^+ secretion (595,611). First, high plasma K^+ reduces proximal tubule fluid and Na^+ reabsorption, and the subsequent increase in distal fluid and salt delivery promotes K^+ secretion (61,164). Second, the early phase of altered K^+ secretion occurs at a time when distal K^+ channel activity is unaltered (421) and appears to be due to mineralocorticoid-mediated stimulation of both basolateral Na^+ - K^+ -ATPase and apical Na^+ channels which would promote K^+ secretion. This leads to increased K^+ secretion by augmenting the driving force for K^+ exit across the apical membrane and may, additionally, stimulate apical K^+ channel activity by a “cross-talk” mechanism that depends on increased basolateral Na^+ - K^+ -ATPase (see Fig. 8; Refs. 391, 602). Such a mechanism has also been identified in the proximal tubule (34,36,563). Third, a sustained increase in the K^+ content of the diet leads to an augmentation of apical K^+ conductance in principal cells (420,421,598) due to an increase in the number of apical small-conductance, 35-pS K^+ channels. While the maxi- K^+ channel could be activated by the high distal flow that may occur with K^+ adaptation, direct evidence for this channel playing a

significant role in K^+ secretion has not yet been obtained in this condition. The high K^+ intake-induced increase in small-conductance channel number is neither related to enhanced transcription of channel protein (154) nor to direct stimulation by aldosterone (421).

High dietary K^+ intake can increase plasma K^+ , and this, in turn, can increase aldosterone. Several attempts have been made to separate the independent effects of aldosterone and high plasma K^+ (392,393). When the level of circulating aldosterone is clamped in adrenalectomized rats, K^+ secretion along the perfused initial collecting tubule rises sharply in response to high K^+ intake (97,393). Simultaneously, both apical K^+ and Na^+ conductances rise in principal cells (393). This indicates that an increase in plasma K^+ per se stimulates K^+ secretion. Patch-clamp studies confirm these conclusions by showing enhanced 35-pS K^+ channel activity in excised non-perfused CCD.

Changes in dietary K^+ intake can modulate PTK activity in the CCD. PTK activity is increased in low- K^+ and reduced in high- K^+ conditions. A series of approaches, including patch-clamp experiments, confocal microscopy, and biochemical studies (321,385,595,611), demonstrated that stimulation of PTK enhances endocytosis of ROMK1 in the CCD. In contrast, inhibition of PTK has the opposite effect and leads to increased channel activity associated with insertion of ROMK1 channels into oocyte cell membranes (385). Moreover, it has also been shown that tyrosine phosphorylation of 35-pS channels is markedly enhanced in the renal cortex and outer medulla harvested from rats on a K^+ -deficient diet (321). Figures 9 and 10 illustrate the mechanism by which a low dietary K^+ intake decreases the apical K^+ conductance and K^+ secretion. Reduced dietary K^+ intake increases the PTK levels and the tyrosine phosphorylation of ROMK channels, which further initiates endocytosis of ROMK.

K^+ channels have been shown to modulate the effect of H^+ - K^+ -ATPase on K^+ absorption in the OMCD and IMCD (see Fig. 2; Ref. 619). The net function of H^+ - K^+ -ATPase is to secrete protons and reabsorb K^+ . In K^+ -repleted rabbits, Ba^{2+} -sensitive K^+ recycling across the apical membrane is required to maintain the function of H^+ - K^+ -ATPase in the OMCD and IMCD. This minimizes the effect of H^+ secretion by H^+ - K^+ -ATPase on net K^+ reabsorption in K^+ -repleted animals. In contrast, proton secretion is not altered by luminal Ba^{2+} in K^+ -depleted animals. The elimination of apical K^+ recycling permits net K^+ reabsorption in this condition. Although the molecular nature of the apical K^+ recycling channel is not known, ROMK1 is expressed in OMCD and IMCD and is a potential candidate for this function. In K^+ depletion, K^+ reabsorption is inhibited by basolateral Ba^{2+} , suggesting that K^+ entering across the apical membrane by H^+ - K^+ -ATPase may leave the cell across the basolateral membrane by K^+ channels. The molecular identity of this basolateral K^+ exit mechanism is not known.

B) EFFECT OF ACID AND BASE BALANCE: Acidosis reduces and alkalosis increases renal K^+ excretion and secretion in the initial collecting duct and CCD under conditions of constant flow (56,358,358,519,557). Acid-base disturbances can alter intracellular pH which in turns affects the activity of the 35-pS K^+ channel in the CCD (482,598). Its activity is reduced by 50% with a decrease in cell pH from 7.4 to 7.2. A similar, albeit slightly more acidic, EC_{50} has been observed with ROMK, the channel protein forming the 35-pS K^+ channel (84, 140,371,627).

C) HUMORAL REGULATION: Basolateral vasopressin stimulates K^+ secretion in the distal tubule and CCD (129,145,480) via V_2 -receptor mediated increases in cAMP (77). Moreover, luminal vasopressin has also been shown to stimulate K^+ secretion; however, this effect appears to be mediated by V_1 receptors (12). Although changes in K^+ balance do not evoke alterations in vasopressin release, this hormone, nevertheless, is thought to play a role in K^+ homeostasis by affecting K^+ channel activity and K^+ secretion in principal cells (129, 145,480). Thus alterations in K^+ secretion that might occur with changes in sodium and fluid

delivery into the distal tubule and CCD may be minimized by alterations in vasopressin (518). For example, expansion of the extracellular fluid inhibits proximal tubule fluid absorption, increases flow rate, and should enhance K^+ secretion in view of the well-established flow dependence of K^+ secretion (518). Similarly, a positive water balance is associated with excretion of hypotonic urine associated with enhanced fluid delivery into collecting ducts (518). Accordingly, changes in extracellular fluid and plasma osmolality could alter K^+ excretion through coupling of K^+ secretion to distal flow rate and sodium delivery. However, expansion of the extracellular volume also lowers vasopressin release in experimental animals (but not humans and other primates; Ref. 173), which would decrease K^+ channel activity. Accordingly, changes in K^+ excretion would be minimized in experimental animals. In contrast, K^+ excretion is maintained by an increase in vasopressin levels when either a decline in extracellular fluid volume or dehydration lowers distal flow rate. Taken together, vasopressin thus appears to play a role, not as a primary regulator of excretion, but as a hormone that tends to stabilize K^+ secretion during changes in Na^+ and water balance.

Aldosterone increases K^+ secretion in the distal tubule and CCD (473,479,518). This action is unlikely to involve a direct effect on apical K^+ channels. On the one hand, it has been reported that administration of miner-alcorticoids significantly increase the apical K^+ conductance in rabbit CCD (412,473). On the other hand, such an effect was not observed in the rat CCD (421,480), and it was suggested that the mechanism of stimulation of K^+ secretion in this species was mediated by a primary increase of apical Na^+ conductance and increased driving force resulting from depolarization of the apical membrane potential (480). It should also be noted that acute infusions of aldosterone do not increase apical ROMK-like 35-pS K^+ channel activity in principal cells (421), but the increase in K^+ channel density observed during prolonged administration of a high- K^+ diet is blunted by adrenalectomy (421). It is possible that the permissive effects on apical K^+ channels by mineralocorticoids are secondary to stimulation of Na^+ - K^+ -ATPase activity.

D) PATTERN OF MATURATION: Although the CCD plays a key role in K^+ secretion in the adult mammalian kidney, K^+ secretion is absent during the first 2 wk of postnatal rabbit kidney (477). Thus the CCD has a limited capability for K^+ secretion in the neonatal kidney. This hypothesis has been supported by the patch-clamp experiments in which ROMK-like 35-pS K^+ channels can be detected only in the CCD isolated from 2-wk-old rabbits (478). With the use of ROMK-specific primers, RT-PCR of the CCD failed to detect mRNA encoding ROMK in 1-wk-old rabbits. In contrast, RT-PCR can detect ROMK in CCD segments dissected from 3-wk-old rabbits (43). A similar temporal pattern of ROMK protein expression has been reported with immunocytochemical staining (659). In addition, maxi- K^+ channels that may be involved in TEA-inhibitable K^+ secretion in the CCD during states of high tubular flow are also absent in the kidney of newborn rabbits (622). TEA-sensitive secretion by maxi- K^+ channels is observed only after 5 wk of postnatal rabbit kidney development (622). The absence of K^+ channels in the early postnatal period may be important to limit renal K^+ losses during this period of rapid body growth.

2. Volume regulation—Cell swelling is known to activate K^+ channels in a wide variety of cells (33). Mechanical distortion of cell membranes (“stretch activation”) as well as exposure to hypotonic media are effective stimuli of both stretch-activated K^+ channels and of Ca^{2+} -permeant channels that secondarily activate K^+ channels (262,525,545,568). Stimulation of volume-sensitive K^+ channels expedites the loss of K^+ along a favorable electrochemical gradient and tends to restore cell volume (regulatory volume decrease, RVD). Such volume regulatory decrease involving activation of K^+ channels has been observed in both proximal (260,466) and principal cells (528). The mechanisms involve either direct effects of volume change or activation of Ca^{2+} -permeant cation channels that secondarily stimulate K^+ channels

(467). The physiological role of this RVD mechanism is incompletely understood but may be involved in cell volume regulation during enhanced entry of solute into renal epithelial cells.

D. Pattern of Regulation of K⁺ Channels

1. Pattern of regulation of apical K⁺ channels in principal cells—Three mechanisms mediate changes of apical K⁺ channel activity in response to a wide variety of physiological stimuli. These are shown in Figure 8 and involve 1) alterations in the number of active channels (channel density), modulated by varying insertion into or removal from the membrane; 2) gating of channels in the membrane by factors related to metabolism, protein phosphorylation, lipids and second messengers, and voltage and tubule fluid conditions such as flow rate and K⁺ concentration; and 3) responses to stimuli originating from changes in transport activity in the basolateral membrane (“cross-talk”). Changes in the cytosolic concentrations of ATP, Ca²⁺, and pH initiated by changes in basolateral Na⁺-K⁺-ATPase turnover have been proposed as possible mediators of basolateral-apical cross-talk.

An example of the first mechanism is the modulation of apical channels by protein tyrosine phosphorylation in response to altered K⁺ balance (385,595,611), a process involving changes in endocytosis. Relevant to the second mechanism are a wide variety of stimuli, for example, changes in cytosolic ATP concentration or PIP₂ in regulating the 35-pS channels, tubule flow, or cytosolic Ca²⁺ activating the maxi-K⁺ channels, and membrane potential altering the voltage-dependent K⁺ channels (166,593). An example of “cross-talk” is the tight coupling between basolateral Na⁺-K⁺-ATPase activity and apical K⁺ channels that has been observed in principal cells. Inhibition of Na⁺-K⁺-ATPase initiates a prompt reduction in apical K⁺ channel activity (602).

2. Pattern of regulation of basolateral K⁺ channels—Figure 11 shows a cell model incorporating known factors modulating basolateral K⁺ channels in principal cells. In view of the technical difficulty of carrying out patch-clamp studies on basolateral membranes of isolated CCD, information of the factors regulating channel activity is modest. These channels are gated by factors such as cytosolic pH and PKA, both also modulating apical K⁺ channels (208, 209, 218, 605). In addition, membrane voltage and, importantly, PKG also alter channel activity (600, 601).

Interaction between Na⁺-K⁺-ATPase and basolateral K⁺ channels (K⁺ recycling; Fig. 11) has also been postulated and may involve changes in the concentration of ATP. Evidence for a role of ATP in mediating pump-related changes in basolateral K⁺ channels has been obtained in studies on proximal tubules (34,36,563) but not yet demonstrated in principal cells. Changes in NO are also involved in coupling pump activity and basolateral K⁺ channels (338). An example is the sequence of events following an increase in apical Na⁺ entry which initiates a rise in cell Na⁺ concentration and basolateral pump stimulation (338). Increased apical influx of Na⁺ also augments cell Ca²⁺ levels by slowing basolateral Na⁺/Ca²⁺ exchange. This rise in cytosolic Ca²⁺, in turn, activates Ca²⁺-dependent NOS and the subsequent rise in NO stimulates basolateral K⁺ channels (338).

III. MOLECULAR PHYSIOLOGY OF ROMK CHANNELS

A. ROMK Channel Structure and Function

1. ROMK channel structure—ROMK (Kir1.1; Refs. 53,213,398,652) is the pore-forming protein of the 35-pS K⁺ channel expressed in apical membranes of TAL and principal cells (333, 342; Figs. 3, 6, and 7; Table 1). Far more is known about the structure, localization, and function of this channel than any other K⁺ channel in the kidney. Like all Kir channels, ROMK expressed in *Xenopus laevis* oocytes exhibits inward rectification, although weak, like that of

the 35-pS channel in renal tubules. While inward rectification would not seemingly be ideal for K^+ secretion, the outward conductance of ROMK is significant and together with its high open probability (>0.9) would favor K^+ secretion.

Recent studies support a tetrameric model for Kir channels (66,89,139,623,634). The X-ray structures of two inward rectifiers have recently been elucidated [GIRK1 or Kir3.1 (400) and the bacterial KirBac1.1 (296)]. The KirBac1.1 channel tetramer forms five regions (see Fig. 12:) 1) an outer selectivity filter, containing the Gly-Tyr-Gly triplet that is conserved in channels with high K^+ selectivity (198,236), that discriminates between K^+ and other cations (657); 2) a pore cavity within the membrane; 3) a channel gate at the membrane-cytosol interface; 4) flexible linkers connecting the gate to the fifth region; and 5) carboxy-terminal β -strands forming a cytoplasmic vestibule or pore. The membrane helices form an “inverted teepee” originally identified in the bacterial *KcsA* channel (119) that come close together at the cytosolic interface to form a gate. The bending of helices at conserved glycine residues in the second membrane helix of each subunit allows the helices to move apart and open the gate (244,296). The initial amino terminus is cytosolic with the distal amino terminus forming a “slide” helix in KirBac1.1 that interacts with the membrane (296; we called this “M0” in the original cloning paper, Ref. 213). This slide helix has been proposed to move laterally in order for M2 to kink and open the channel gate (296).

The carboxy terminus is completely cytosolic and forms the cytoplasmic pore. Acidic residues lining the cytoplasmic pore may interact with positively charged polyamines and divalent minerals (e.g., Mg^{2+}), which provides the basis of inward rectification (296,400). Both the amino and carboxy termini provide regulatory domains that can be phosphorylated by kinases (320,385,630,644) and that interact with protons (84,140,371), nucleotides (114,374,572), and phosphatidylinositol phosphates (201,217,315,326,331,351). While specific amino acid residues involved in assembly of ROMK subunits into tetramers have not been identified, multiple interactions in amino and carboxy termini, and in the transmembrane spanning segments (M1 and M2; Ref. 281) and with potassium ions in the selectivity filter (H5 region; Ref. 656) appear to be needed, and this would be consistent with the X-ray structure of the prokaryotic KirBac1.1 (296). In addition, the amino terminus of one KirBac1.1 subunit interacts with the distal carboxy terminus of the adjacent subunit forming another interface that could be involved in subunit assembly (296). Similar interactions between amino- and carboxy-terminal segments have been observed in other Kir channels (250).

Although the X-ray structure of ROMK is unknown, the structure of this channel has been probed using other methodologies. Brazier et al. (62) have analyzed the secondary structure of a synthetic peptide containing the two membrane-spanning segments and the selectivity filter regions of ROMK1 using Fourier transform infrared (FTIR) and CD spectroscopy (62). Their analyses indicate that both membrane segments adopt an α -helical structure in phospholipids, consistent with the original model for ROMK (213) and the X-ray crystal structures of the KirBac1.1 channel (296). Moreover, Minor et al. (383) have analyzed the packing structure of the two membrane helices using a yeast genetic screening technique. Their analysis suggests that the second membrane helix of each subunit lines the pore and is surrounded by the first membrane helix that also participates in subunit-subunit interactions in the tetrameric channel (see Figs. 12 and 13; Ref. 87). Consistent with this view, both the second membrane helix and the proximal carboxy terminus determine both homo- and heteromultimerization on other Kir channels (79,348,536,555,633). Height fluctuations of ROMK protein have also been observed using the atomic force microscope and the molecular sandwich technique when the channel is exposed to gating agents (e.g., pH and PKA phosphorylation; Ref. 407). Because these molecular fluctuations occurred under conditions that activate ROMK channel, ROMK tetramers appear to change shape with channel gating. Finally, while ROMK permits rapid permeation of K^+ , net H_2O movement through the pore is negligible (465). Although water

may move through the selectivity filter at a rate equal to that of K^+ , the net volume flux would be small. This is consistent with the high expression of ROMK in K^+ secretion and low water permeability epithelia in the loop of Henle, distal tubule, and collecting duct.

2. ROMK channel isoforms—The ROMK gene contains several exons producing alternatively spliced transcripts (Fig. 14) and named ROMK1 ($K_{IR}1.1$), ROMK2 ($K_{IR}1.1b$), and ROMK3 ($K_{IR}1.1c$) and ROMK6 ($K_{IR}1.1d$) (53,213,276,652). ROMK proteins differ at the beginning of the amino terminus with ROMK2 having the shortest amino terminus (rat ROMK6 has the same amino acid sequence as ROMK2; Fig. 14; Ref. 276). ROMK2 and ROMK3 have either 19- or 26-amino acid extensions at the beginning of the amino terminus, respectively (see Fig. 14; mouse ROMK1 has a 20-residue extension). Relative ROMK mRNA abundance assessed by competitive PCR indicates that ROMK2 and ROMK3 are much more abundant than ROMK1 or ROMK6 in rat kidney (37). Moreover, novel ROMK proteins, about one-third the size of native ROMK, may be formed by alternative splicing of the ROMK core exon (38); however, their significance remains unclear. The human ROMK gene, *KCNJI*, located on chromosome 11q24 produces six splice variants (51,506,637) that encode only three distinct polypeptides, two of which are similar to rat ROMK1 and ROMK2 (51). A rat homolog of the third human ROMK isoform has not been identified.

3. ROMK channel localization—ROMK transcripts are widely expressed in the cortex and outer medulla (Fig. 15A). The differential expression of ROMK1–3 transcripts along the nephron from the TAL to the OMCD is shown in Figure 16 (53,303). The TAL and DCT express ROMK2 and ROMK3 transcripts while principal cells in the CCD express ROMK1 and ROMK2 transcripts (see Fig. 16). The OMCD cells express only ROMK1 transcripts. While the single-channel conductances and open probabilities of ROMK1, -2, and -3 isoforms are similar, the amino-terminal extensions (Fig. 14) add distinct regulatory characteristics to ROMK channels (352,353). Whether tetrameric ROMK channels are composed of different subunits (e.g., heterotetramers of ROMK2 and ROMK1 in the cortical collecting duct; Figs. 12 and 13) or exist only as homotetramers is not known (unfortunately, isoform-specific antibodies are not available). Finally, ROMK transcripts are present in some other tissues (213), including the brain and the early gravid uterus (349). Roles for ROMK in these tissues have not been determined.

Antibody generated to sequences of ROMK shared by all isoforms has demonstrated an apical pattern of channel protein expression, consistent with the ROMK channel providing a K^+ secretory pathway in renal epithelia. Specific apical staining has been observed in rat TAL (including macula densa cells), DCT and early connecting tubule cells, and principal cells of the CCD and OMCD (see example in Fig. 15B of staining in the rat TAL; Refs. 273,379, 629).

4. Characteristics of the ROMK channel—The general properties of ROMK channels expressed in *Xenopus* oocytes include 1) weak inward rectification (80,213,651,652); 2) activation by PKA-dependent phosphorylation processes (350,373,630); 3) inhibition by high concentrations of Mg-ATP (374,462); 4) regulation of channel trafficking by protein tyrosine kinase and phosphatase (321,385), as well as by PKC (320); 5) inhibition by slight reductions in cytosolic pH (112,140,305,371,463,486,487,561); and 6) inhibition by arachidonic acid and PKC (352,353).

A) CHANNEL KINETICS: The single-channel permeation, gating, and regulatory properties of ROMK expressed in oocytes are similar to those of the native 35-pS K^+ channels in TAL cells (49,589,599) and principal cells in the CCD (153,161,167,384,⁴⁸³,592,593,597,603). For example, the ionic dependence of gating kinetics is similar in the native 35-pS K^+ channel in the rat CCD and ROMK2 channels expressed in *X. laevis* oocytes (80,422). Moreover, ROMK,

like the native 35-pS K^+ channel in principal cells (152,153,161,597,598), lacks sensitivity to external TEA^+ (213).

All ROMK channel isoforms have high open probabilities (P_o) of >0.9 (80,83,213,350). There are two closed states, but one is very short (~ 1 ms; 99% frequency) and the other, while longer (~ 40 ms), is very infrequent (83,350). The latter is due to block by divalent cations as it can be abolished by EDTA (83). Choe et al. (83) have also suggested that the closed state of ROMK results from K^+ transiently blocking its own pathway.

B) CHANNEL RECTIFICATION: Inward rectification of Kir channels, including ROMK, is due to blocking of the cytosolic vestibule or pore of the channel (see Fig. 17A) by Mg^{2+} (296,348,397,400) or cytosolic polyamines like spermine or spermidine (144,330). Variations in the cytosolic concentrations of these cations provide a mechanism for regulating outward (i.e., K^+ secretory) current. Kinetic studies of inward rectification by Mg^{2+} and polyamines indicate that the effect is voltage dependent, depends on the concentration of K^+ on both sides of the membrane, and varies with the K^+ reversal potential (83,397,410,515).

The M2 segment and carboxy terminus determine the inward rectifying characteristics of Kir channels (348,536,616,633). Differences in second membrane helix and the loop between the first and second membrane helices account for the distinct channel kinetics of weak (ROMK2; Kir1.1) versus strong (IRK1; Kir2.1) inward rectifier channels (82). Two negatively charged residues are crucial for strong inward rectification (like in IRK1 or Kir2.1): aspartic acid (D172 in IRK1) in the second membrane helix (285) and glutamate (E224) in the carboxy terminus (348,616). In ROMK, the aspartate is replaced by asparagine (N171) and the glutamate by glycine (G223) residues, accounting for the weak rectification (see Fig. 17A). Both exchange of the ROMK carboxy terminus with that on IRK1 and exchange of ROMK1 N171 for Asp produces strong rectification (536,616). Residues lining the cytoplasmic pore are depicted in the structural model of ROMK shown in Figure 17A (31,144,286,296,^{348,400},535,536,616,633). In general, the density of negative charges in this cytoplasmic pore-lining region correlates with the affinity of polycationic blockers (e.g., spermine) and the “strength” of inward rectification.

C) INHIBITORS OF ROMK: Two different extracts of venoms have been shown to inhibit ROMK channels (228,247). Both the snake toxin δ -dendrotoxin (228) and the honey bee venom extract teriapiin (247) appear to block ROMK activity by binding to the external vestibule of the channel pore. The ability of the honey bee toxin to inhibit ROMK is sensitive to pH with alkaline pH values diminishing the dissociation constant for binding to ROMK1 (450). Replacing histidine-12 with alanine eliminates pH sensitivity of the bee toxin while preserving its affinity for ROMK (450).

B. Regulation of the ROMK Channel Is Similar to the Distal Small-Conductance (35-pS) K^+ Secretory Channel

ROMK channel activity, like that of the native 35-pS K^+ channel in TAL and principal cells, is regulated by a variety of factors that either activate or inhibit the activity of channels in the membrane or modify membrane expression (Fig. 18). The molecular mechanisms for these alterations in channel function are rapidly being identified.

1. Protein kinases and phosphatases—ROMK channel activity and the number of active channels in the plasma membrane can be modulated by both serine-threonine (PKA and SGK) and tyrosine kinases and phosphatases. These processes involve, but are not limited to, direct phosphorylation of the channel protein at specific sites on either the amino or carboxy terminus.

A) PKA: Maintenance of ROMK channel activity in excised inside-out patches of oocytes requires activation by PKA-dependent phosphorylation processes (373). Rundown or loss of ROMK channel activity occurs whenever phosphatase-mediated dephosphorylation activity is greater than PKA-mediated phosphorylation (373). Phosphopeptide analysis and mapping have identified three PKA phosphorylation sites on the ROMK channel protein (in ROMK1, Ser-44 on the amino terminus and Ser-219 and Ser-313 on the carboxy terminus; Figs. 14 and 17B; Ref. 630). Mutation of any single PKA phosphorylation site on ROMK2 reduces whole cell K^+ currents by 35–40% in oocytes; mutation of two or more of the three sites produces nonfunctional channels (630). None of the serine mutations alters the single-channel conductance. Each of the carboxy-terminal PKA phosphorylation site mutations, however, reduces P_o by ~30–40% (350), which is sufficient to account for the observed reduction in whole oocyte currents (630). The mechanism by which phosphorylation modifies P_o is due, at least in part, to lowering the membrane concentration of PIP_2 that is required to activate ROMK (326; see sect. IIIB2B) and a right shift in the pK_a for cytosolic pH to more alkaline values (305). Alanine mutation of the amino-terminal Ser-44 does not change P_o but reduces the probability of finding functioning channels by ~60%. Thus phosphorylation of Ser-44 by PKA is thought to increase the number of functional channels in the plasma membrane. This possibility is supported by observations using another serine-threonine kinase, serum and glucocorticoid regulated kinase (SGK), that phosphorylates Ser-44 leading to increased surface expression of ROMK channels (644). Taken together, these results show that S44 regulates surface expression of ROMK, while S219 and S313 modulate P_o .

These studies of the influences of PKA phosphorylation on ROMK channels activity explain the activation of the 35-pS K^+ channel in principal cells by G_s -coupled receptors or by the addition of cAMP, one of the fundamental characteristics of the native K^+ channel (593). In addition, activation of ROMK1 channels in *X. laevis* oocytes by cAMP requires a kinase anchoring protein, like AKAP79 (10). AKAPs are A-kinase-anchoring proteins that bind kinases and maintain the PKA enzyme at specific intracellular sites (142,432), and thus an AKAP appears to be required to direct the PKA to the plasma membrane (432). Several novel AKAPs have recently been cloned from mouse (113), and one of these, AKAP-KL, is expressed in kidney tubules at apical borders.

B) SGK: Aldosterone stimulates SGK1 transcription and has been suggested to regulate the activity of the Na^+ channel, ENaC, and ROMK in collecting duct principal cells (see Ref. 298 for a review), although this view has been recently challenged (11). Nevertheless, in *X. laevis* oocytes SGK1 phosphorylates Ser-44 (the same site that is phosphorylated by PKA; see Fig. 14) on ROMK shifting the pK_a for pH sensitivity of the channel to more acid values, thereby enhancing ROMK activity. The Na^+/H^+ exchanger regulatory factor NHERF-2 (a.k.a. E3KARP) is a scaffolding protein that synergizes with SGK1 to further stimulate ROMK by enhancing trafficking to the oocyte plasma membrane (646). NHERF-1/2 have two PDZ domains that differ in protein binding specificities (586), allowing for interaction with multiple proteins, and thereby organization of multiprotein complexes at the plasma membrane. NHERF-2 is expressed in principal cells, colocalizes with ROMK in apical borders of these cells (580), and regulates the trafficking and targeting of proteins to plasma membranes (see Fig. 14; Ref. 503).

C) PKC: PKC phosphorylation processes inhibit the 35-pS K^+ channel in CCD cells (603). ROMK1, which is exclusively expressed in collecting ducts, has three potential PKC phosphorylation sites involving serine residues: one on the amino terminus (S4) and two on the carboxy-terminal end (S1863 and S201). ROMK2 and ROMK3 only have the two carboxy-terminal PKC phosphorylation sites (see Fig. 14). PKC, like PKA, influences many proteins by direct phosphorylation. Indeed, ROMK1 has been shown to be a PKC phosphoprotein with the major phosphorylation sites being S4 and S201 (320). PKC phosphorylation is essential

for trafficking of ROMK1 to the plasma membrane in oocytes and HEK293 cells (320). This could not account, however, for the reduction in channel activity observed in CCD cells. A mechanism for PKC-mediated reduction in activity was recently suggested (648). PKC decreases plasma membrane PIP₂ content in *X. laevis* oocytes and could account for a lower channel activity. However, the PKC activator phorbol 12-myristate 13-acetate (PMA) only reduced ROMK1 whole cell current when the R219 PKA phosphorylation site was mutated (recall that this mutant has a higher requirement for membrane PIP₂; Ref. 326). Thus an effect of PKC to reduce ROMK1 channel activity in CCD cells would require that the plasma membrane content of PIP₂ is lower in oocytes and/or that the channel is in a partially PKA phosphorylated state (648).

D) WNK: Pseudohypoaldosteronism type II (PHAII; Gordon's syndrome) is an autosomal dominant form of hypertension with hyperkalemia that is sensitive to Cl⁻ intake and is ameliorated by thiazide diuretics (178). PHAII is caused by mutations in either of two serine-threonine kinases [WNK1 and WNK4 (577); with no lysine (K); (317)] and these kinases regulate the surface expression of the thiazide-sensitive Na⁺-Cl⁻ cotransporter (NCC) mediating salt reabsorption in the DCT (618,632). Wild-type WNK4 reduces the plasma membrane expression of NCC and thus diminishes salt transport by the DCT, while PHAII mutations of WNK4 relieve this inhibition. The modulation of NCC activity by WNK is dependent on the kinase activity of these proteins (618,632). WNK kinases are also expressed in the collecting duct, and a recent study has shown that WNK4 regulates the plasma membrane expression of ROMK in *X. laevis* oocytes by enhancing clathrin-dependent endocytosis (251). In contrast to the mechanism of action of WNK kinases on NCC, the effect of WNK4 on ROMK expression is not dependent on kinase activity. The same WNK4 mutations that relieve NCC inhibition significantly increase inhibition of ROMK (251). Thus WNK kinases join a growing list of kinases that have been postulated (or shown) to regulate K⁺ secretion in the CCD by modulating 35-pS K⁺ channel density in the apical plasma membrane. Moreover, WNK kinases could provide a molecular switch that can vary the balance between salt reabsorption in the DCT and K⁺ secretion in the CCD.

E) PTK-PTP: Dietary K⁺ restriction reduces the number of functioning 35-pS K⁺ channels in the apical membrane of principal cells, thereby limiting secretion of K⁺ into the urine (166, 590). This regulatory process is mediated by increasing PTK/PTP-stimulated endocytosis of the K⁺ channel (85,595,610,611). Only the ROMK1 isoform, which is exclusively expressed in the collecting duct principal cells, is regulated by PTK/PTP (385). The reason for this isoform specificity is unknown but likely involves the unique ROMK1 amino terminus. Thus the 35-pS K⁺ channel formed by ROMK2 and ROMK3 in TAL cells is not regulated by this kinase (184). In the TAL, however, increases in PTK/PTP with dietary K⁺ restriction regulate the 70-pS K⁺ channel. The mechanism of regulation of ROMK1 by PTK/PTP involves channel phosphorylation on Tyr-337 (see Fig. 14; ROMK1; Ref. 321) via a dynamin-dependent process (647) using clathrin-coated pits (647). The specificity of the PTK/PTP regulation to ROMK1 is even more intriguing since all ROMK isoforms contain the carboxy-terminal Tyr residue critical to this regulation.

2. Lipids and products of lipid metabolism

A) ARACHIDONIC ACID: Like the native 35-pS K⁺ channel in the CCD (591), ROMK1 channels are sensitive to arachidonic acid (AA) (352,353). The effect of AA is specific, since other fatty acids fail to mimic the effect (352). However, AA has little-to-no effect on the other two ROMK isoforms (353). Ser-4 in the unique ROMK1 amino terminus is critical to regulation by AA (Fig. 14; Ref. 353), and this action may involve AA stimulation of PKC and phosphorylation of this serine residue (320).

B) PHOSPHATIDYLINOSITOL PHOSPHATES (PIP₂): A growing number of ion channel and transporters are being recognized to be regulated by PIP₂ (202). Phospholipids, particularly PIP₂, have been shown to modulate K_{ATP} channels including ROMK1 (30,201, 217). In general, PIP₂ functions as a K⁺ channel activator by increasing channel *P*_o. ROMK, like many K_{IR} channels (271,458,459,509,650), contains a high density of positively charged (basic) amino acids in the carboxy terminus that interact with the negatively charged head groups of phosphatidylinositol phosphates. PIP₂-containing liposomes bind to a recombinant ROMK1 carboxy-terminal fusion protein (217,351), and Lys-181, Lys-186, Arg-188, Arg-217, Lys-218, and R311 have been implicated in the interaction of ROMK and PIP₂ (217,331, 649). Mutation of one of these PIP₂-interacting sites, R188, in ROMK1 gives rise to a subconductance state with a lower *P*_o and an increased sensitivity to intracellular protons (315). The low *P*_o of the R188Q mutant channel can be increased by alkalization, but this is not associated with a change in PIP₂-channel interaction. Thus PIP₂ and cytosolic pH modulate ROMK channel activity by independent but interacting mechanisms. The mechanism of pH-mediated inhibition of ROMK channel activity is discussed in the next section.

Since PIP₂ and phosphatidylinositol trisphosphate (PIP₃) are generated by ATP-dependent lipid kinases [e.g., phosphoinositide (PI) 3-kinase (13)], the stimulatory effect of low concentrations of cytosolic ATP are due, in part, to the generation of PIP₂ (217). In addition, receptor-mediated hydrolysis of PIP₂ by phospholipases (e.g., phospholipase A₂) can dramatically alter membrane phospholipids content, and thereby modulate the activity of ROMK channels (271). The latter can be illustrated by the effects of the membrane PIP₂ content on modulation of ROMK activity by serine-threonine kinases, like PKA and PKC (326,648). Thus changes in the membrane content of PIP₂ contribute to the inhibition of ROMK activity by PKC and its activation by PKA. In addition, PIP₂ dramatically modulates the ATP sensitivity of K_{ATP} channels (508,510), and this is due to competition of nucleotide binding by PIP₂ (351). This latter mechanism likely accounts for the abrogation of ATP-mediated inhibition of 35-pS K⁺ channels in principal cells by phosphatidylinositol phosphates (339). Finally, modulation of PIP₂ effects on ROMK has been implicated as a potential mechanism for reduction in channel activity associated with mutations of basic residues in type II Bartter's syndrome (331).

3. Cytosolic pH—Cytosolic, but not extracellular, protons gate ROMK (561). Acidification closes channels while alkalization opens channels (84,112,140,371,561). Similar responses to cytosolic protons are observed in the 35-pS K⁺ channel in TAL and CCD (481,597). Mutation of Lys-80 on the amino terminus of ROMK1 (Lys-61 on ROMK2; see Figs. 14 and 17C) abolishes or severely reduces the pH sensitivity of ROMK (84,140,371). Other residues on the amino and carboxy termini of ROMK also modulate pH sensitivity: Thr-51 (84) and Arg-41 (486) in the amino terminus (ROMK2; Thr-70 in ROMK1); Arg-311 in the carboxy terminus (ROMK1; Ref. 486). It has been suggested that electrostatic interactions in the Arg-41-Lys-80-Arg-311 triad of basic residues form the pH sensor and provides a basis for understanding some of the channel abnormalities in ROMK (type II) Bartter's syndrome (463,485,486). pH-dependent closure of ROMK channels is associated with conformational changes in both amino and carboxy termini involving formation of disulfide binds (Cys-49 and Cys-308) that require reducing agents for channel opening with reversal of pH (487). Cytosolic pH gating can also be observed when CO₂ is increased (hypercapnia; Ref. 658). Modulation of either Lys-53 and one or more of several carboxy-terminal histidine residues (His-225, His-274, His-342, and His-354) alter the inhibitory effect of raising CO₂ (78,627).

The sensitivity to cytosolic protons is allosterically linked to the concentration of external K⁺ (112,463). With low external K⁺ concentrations ≤1 mM, outward ROMK currents slowly decrease and become undetectable but return to control values when K⁺ (or other permeable cation) is increased (112,488). This is due to an alkaline shift in pH sensitivity or IC₅₀ (112,

469,470). This interaction between external permeant cations and cytosolic protons does not occur at a single site but depends on different domains. The ability of external permeant cations to gate ROMK depends on an intact pH sensor (e.g., is abolished by mutating Lys-80 in ROMK1 or Lys 61 in ROMK2; Refs. 470,488). In addition, removal of K^+ from both sides of an excised patch does not inactivate ROMK when internal pH is held at pH 8 (488). Mutation of external residues involving the pore helix can also disrupt the ability of ROMK to be gated by lowering external K^+ . However, these mutations do not abolish the gating by cytosolic pH. Thus ROMK has been modeled as having two gates: an external gate sensing cations and an inner gate sensing protons. Mutations in either gate can disrupt communication between these two gates. The physiological role of this interaction between external K^+ and internal H^+ may be a positive feedback where a rise in luminal K^+ leads to an increase in K^+ channel activity at a time when the electrochemical driving force for K^+ secretion is reduced. In this way, K^+ secretion is maintained.

Other factors can modulate cytosolic pH sensing. As discussed in the previous section, there is a link between phosphorylation of amino- and carboxy-terminal serine residues by PKA (and SGK for the amino-terminal Ser-44) and the IC_{50} for cytosolic protons (305,419,492). In addition, PIP_2 interaction with the channel can modulate pH sensing (315). The $K_{1/2}$ for nucleotide inhibition of ROMK channel activity is not fixed but can be modulated by altering cytosolic side pH. Finally, decreasing the pH from 7.4 to 7.2 on the cytosolic face of excised patches from oocytes expressing ROMK2 reduced the $K_{1/2}$ for Mg-ATP inhibition from ~2.5 to <0.5 mM, almost a 10-fold increase in affinity with this small acidification (371). This effect appears to be independent of the lysine residue implicated in pH-dependent regulation of ROMK channel activity.

4. Nucleotide sensitivity and CFTR—Exposure of ROMK (as well as native 35-pS K^+) channels to Mg-ATP activates both stimulatory and inhibitory processes with the net affect on channel function being the complex (and often difficult to sort out) integrated effect of these modulations. Micromolar concentrations of Mg-ATP support kinases that regulate ROMK activity by phosphorylation of the channel and associated molecules (e.g., phosphatidylinositol; see sect. IIIB2; Refs. 166,167,590). These phosphorylation processes either modulate channel gating or trafficking of the channel to or from the plasma membrane (see sect. III, B1–B3). With inside-out patches of ROMK expressed in *X. laevis* oocytes or of the native 35-pS K^+ channel in TAL or CCD, addition of micromolar Mg-ATP usually activates the channel by PKA- and lipid kinase-dependent mechanisms (339,373,592).

In contrast, exposure of the renal 35-pS K^+ channel to millimolar concentrations Mg-ATP reproducibly leads to inhibition (592,603). This sensitivity to intracellular nucleotides indicates that ROMK belongs to a functional subgroup of Kir channels referred to as ATP-sensitive or K_{ATP} channels (18,384). K_{ATP} channels formed by Kir6.x are found in both renal and a number of nonrenal cells including pancreatic β -cells, cardiac muscle, vascular smooth muscle, and certain neurons. The classic K_{ATP} channel (5,24,68,121,229,500,558,564) is a heterooctamer formed by four pore-forming Kir6.x subunits and four regulatory SUR1 (sulfonyleurea-binding protein) subunits, (6,24,68). The 4:4 stoichiometry for functional K_{ATP} channels in plasma membranes is fixed by subunit interactions necessary for shielding ER retention signals on both the Kir and SUR subunits (89,231,332). Kir6.2 channels can be trafficked to the plasma membrane in the absence of SUR when the ER retention signal is removed (e.g., Kir6.2 Δ 36 with truncation of 36 residues from the end of the carboxy terminus), and these channels can be inhibited by ATP (566). The responses of K_{ATP} channels to nucleotides, and models derived from this kinetic behavior, suggest that ATP-mediated inhibition requires binding of the nucleotide to the pore-forming (Kir6.x) subunits (see Ref. 132 for a recent review). Nucleotide binding leads to longer closed states resulting in channel inhibition. The direct binding of ATP to Kir6.x is supported by cross-linking of azido-ATP compounds (541,542) and by interaction

with fluorescent ATP analogs (572). Nucleotides also interact with the SUR subunits via classical (Walker A and B) nucleotide-binding folds and mediate ADP-dependent increases in K_{ATP} channel activity.

Interestingly, it has been more difficult to identify the mechanism for ATP inhibition of the 35-pS K^+ channel. Despite the ability of the ROMK carboxy terminus to bind fluorescent analogs of ATP (572), only a few studies have found that ATP can inhibit ROMK expressed in *X. laevis* oocytes (371,374,462). The EC_{50} for ATP-mediated inhibition of ROMK channel activity in *X. laevis* oocytes is reduced by cytosolic acidification (371). This could provide one mechanism for reducing channel activity during cellular acidosis resulting from disturbances in cellular metabolism or during systemic acidosis. As observed with other K_{ATP} channels (18,253,253), addition of ADP to ATP inhibited ROMK channels relieved the ATP block (374). These factors (i.e., pH and ADP) may allow the K^+ channel to be open at cytosolic ATP concentrations, although other mechanisms may contribute (e.g., channel phosphorylation and PIP_2).

Several significant differences, however, exist in the nucleotide sensitivities between the renal 35-pS K^+ and the pancreatic β -cell K_{ATP} channels (384,593). First, inhibition of the renal K_{ATP} channel requires hydrolyzable ATP (i.e., Mg-ATP; Ref. 592), while the β -cell channel can be inhibited by nonhydrolyzable nucleotides like Na-ATP (18). Second, near-millimolar ATP concentrations are required to inhibit the renal K_{ATP} channel while low micromolar ATP can inhibit the β -cell channel. Third, despite the robust trafficking of ROMK to the *X. laevis* oocyte plasma membrane in the absence of a SUR (or other ABC protein), a direct inhibitory effect of Mg-ATP on channel activity has been difficult to reproduce. This contrasts with the ability of ATP to reproducibly inhibit Kir6.2C Δ 36 in this same oocyte expression system.

A) EVIDENCE THAT AN ABC PROTEIN FORMS A SUBUNIT OF THE 35-pS K^+ CHANNEL: Another characteristic of K_{ATP} channels, including the renal 35-pS K^+ channel, is sensitivity to inhibition by sulfonylureas like glibenclamide (Glyburide; Refs. 18,19,384). Glibenclamide reduces NaCl absorption from the loop of Henle in *in vivo* microperfusion experiments (588), and in conscious rats induces natriuresis without attendant K^+ loss (88). While the effects of glibenclamide on vascular tone or other targets may contribute to the lack of urinary K^+ loss with sulfonylureas (267), patch-clamp experiments have confirmed that glibenclamide inhibits the 35-pS K^+ channel in the rat TAL (588,589). The sensitivity of the native K^+ channel in TAL to sulfonylureas is, however, much less than in other K_{ATP} channels (384).

In K_{ATP} channels, the ABC protein subunit, SUR, and not the pore-forming Kir subunit, provides the receptor for sulfonylurea drugs (6). Thus the ability of glibenclamide to inhibit the renal K^+ secretory channel suggests that an SUR (or SUR-like) protein is associated with this channel and mediates the effect of glibenclamide. What is the nature of the SUR-like protein that interacts with ROMK? Both SUR2b (115,544) and the CFTR (370,462,544) have been proposed to be the ABC partner of ROMK in PC and TAL cells. SUR2B is a subunit of the cardiac K_{ATP} channel (230), and CFTR is known to regulate the activities of other ion channels (200,499), and Cl^- currents mediated by CFTR can be inhibited by sulfonylureas like glibenclamide (491). Furthermore, CFTR mRNA and protein are expressed in the same apical regions as ROMK channels in the CTAL and CCD (96,363,386,556), and a functional truncated hemi-CFTR is also expressed in the mTAL (386). CFTR transcripts are also expressed in distal nephron segments in fetal human kidney (109). Consistent with ROMK-ABC protein interactions, ROMK K^+ currents in oocytes are significantly inhibited by glibenclamide only when ROMK is coexpressed with CFTR (72, 370, 372, 462; EC_{50} ~1–30 μ M) or SUR2B (544), although this view has been challenged (278). Moreover, this effect of CFTR on ROMK requires a low external K^+ concentration (generally ≤ 1 mM; Ref. 370), is abrogated by

increasing PKA phosphorylation processes using forskolin (370), and requires a functional nucleotide binding domain, NBD1, on CFTR (372).

Fewer data are available concerning the physical and functional interactions of ROMK and SUR2B. Immunostaining with anti-SUR2B antibody in mouse kidney detected SUR2B in distal nephron segments that express ROMK (i.e., TAL and CCD), although the precise apical versus basolateral pattern could not be discerned (39). In rat kidney, SUR2B transcripts are expressed in cortical TAL and CCD, but not in the medullary TAL (544). With the use of an in vitro antibody-based “pull-down” approach, ROMK2, but not ROMK1 or ROMK3, directly interacts with SUR2B (544). An amino acid triplet “IRA” in the amino-terminal extensions of ROMK1 and ROMK3 prevented the direct interaction of ROMK1/3 with SUR2B and the resultant glibenclamide sensitivity (115). The EC₅₀ (150–200 μM) for glibenclamide inhibition of ROMK2-SUR2b K⁺ currents in oocytes (544) was much higher than that with CFTR (372,544). While it is possible that ROMK2 could be interacting either with CFTR or SUR2B under certain circumstances, ROMK1 (specific for principal cells) and ROMK3 (specific for TAL cells) cannot interact with SUR2B (115,544). Thus it is likely that CFTR is the major ABC protein subunit of ROMK in TAL and principal cells.

B) FUNCTIONAL CONSEQUENCES OF ABC PROTEIN-ROMK INTERACTIONS:

What roles could CFTR play in ROMK function? Based on the Kir6.x-SUR model of a K_{ATP} channel (17,69), interaction of ROMK with an ABC protein (CFTR and/or SUR2b) is likely to alter metabolic (ATP/ADP) sensing by ROMK. Increasing intracellular ATP inhibits the activity of ATP-sensitive K⁺ channels (K_{ATP}) by direct interaction with the pore-forming (Kir) subunits (120,282,374,509,542,559,565,566), while activation of K_{ATP} channels by ADP and modulation by sulfonylureas (e.g., glibenclamide) or K⁺ channel opening agents (e.g., minoxidil) requires the associated SUR or CFTR (17). Thus the ATP/ADP ratio is thought to be the important link between metabolism and K_{ATP} channel activity. When ROMK is expressed alone in oocytes, high millimolar concentrations (>2 mM) of Mg-ATP are required to inhibit partially the K⁺ current (374). Coexpression of ROMK1 with CFTR dramatically increases the sensitivity of ROMK1 K⁺ currents to Mg-ATP (462) with an EC₅₀ of ~0.6 mM, an affinity that is similar to that for 35-pS K⁺ channel in principal cells (592). In fact, coexpression of CFTR with ROMK1 was required for significant inhibition of ROMK1 currents by Mg-ATP in oocytes. Because NHERF-1/2 can bind to CFTR (503) and ROMK (643) and can increase surface expression of ROMK (643), it seems likely that the 35-pS K_{ATP} channel in TAL and principal cells is formed by ROMK-NHERF-2-CFTR interactions (212,643). Consistent with this notion, NHERF-2 has two PDZ domains, the first domain interacting with ROMK (643) and the second domain binding to CFTR (532). The observation that CFTR and ROMK can interact in *X. laevis* oocytes in the absence of NHERF (643) and that ROMK coimmunoprecipitates with CFTR in the absence of NHERF (643) suggests that ROMK and CFTR may directly interact with NHERF, enhancing this interaction by bringing the proteins together. Moreover, the interaction between NHERF and CFTR is regulated by serine-threonine kinases (448). Thus the modulation of K⁺ channel glibenclamide sensitivity (due to interacting with CFTR) by activating PKA observed in ROMK2-CFTR coexpressing oocytes may have been due to disruption of CFTR interaction with ROMK (in this case with a *Xenopus* NHERF-like scaffolding protein).

C) CFTR, ROMK, AND THE EPITHELIAL SODIUM CHANNEL INTERACTIONS:

The epithelial Na⁺ channel (ENaC) forms the Na⁺ channel in apical membranes of principal cells where it mediates Na⁺ absorption. Sodium entry through ENaC makes the CCD lumen electrically negative compared with the interstitium, providing a favorable electrical gradient for K⁺ secretion through 35-pS K⁺ (i.e., ROMK) channels. Recombinant expression studies have suggested that CFTR also interacts with ENaC (291) and that cAMP-mediated activation of CFTR inhibits ENaC (295), although this issue is controversial (394). A similar observation

has been made in mouse CCD cells in culture (314). The inhibition of ENaC activity by CFTR activation may be mediated by a rise in cell Cl^- (277,292,294), although the specific mechanism is unclear. CFTR has been suggested to be a regulatory link between ENaC and ROMK (279) such that ENaC upregulates the surface expression of ROMK in a CFTR-dependent manner (279).

C. Regulation and Developmental Changes of ROMK Expression

1. Regulation—It is well established that dietary K^+ modulates renal K^+ secretion and excretion by altering the functional expression of 35-pS K^+ channels in the apical membrane of principal cells (359,420,424,590). ROMK mRNA expression is reduced in both cortex and medulla by K^+ deficiency, while K^+ loading increases ROMK transcript abundance slightly, but only in medulla (581). Moreover, neither ROMK transcript (154) nor protein (378) abundance in the CCD was altered by a high- K^+ diet. Thus the high- K^+ diet-induced increase in density of active 35-pS K^+ channels in principal cells in the CCD is not due to increased ROMK mRNA. Rather, changes in ROMK channel abundance in apical membranes due to regulated clathrin-dependent endocytosis have been identified as the major mechanism modulating K^+ secretion in the collecting duct by dietary K^+ (590).

Mineralocorticoids also regulate ROMK abundance. Adrenalectomy decreased ROMK mRNA abundance in cortex but increased transcript abundance in the medulla (581). In this latter study, K^+ deficiency in adrenalectomized rats reduced ROMK mRNA to control levels, suggesting that the hyperkalemia associated with adrenalectomy was the cause for the increased ROMK message in medulla. Aldosterone administration by minipump to adrenal intact rats also has been shown to increase ROMK2, -3, and -6 isoforms transcripts in whole kidney (37). The latter is consistent with mineralocorticoid-mediated regulation of ROMK mRNA abundance in cortex.

In the mTAL, ROMK protein abundance is increased by dDAVP in Brattleboro rats and by increasing NaCl intake in Sprague-Dawley rats (125). In contrast, a low NaCl intake reduced ROMK abundance in TAL (125). Thus chronic adaptive changes in ROMK abundance occur in the TAL with maneuvers that alter salt transport in this nephron segment.

2. Developmental expression of ROMK—Patch-clamp analysis in the maturing rabbit CCD demonstrated that the 35-pS K^+ increased only after the third week after birth (478). This increase in apical K^+ channel activity correlated with the ability of the CCD to secrete K^+ (477) and with ROMK mRNA abundance (43). Similar developmental increases in ROMK mRNA have been shown in the rat TAL and CCD (659). The low abundance of K^+ secretory capacity during the first few postnatal weeks is consistent with the necessity for K^+ conservation during this phase of cell proliferation associated with rapid body growth.

D. Lessons From Bartter's Syndrome

1. Bartter's syndrome: a TAL tubulopathy—The role of Kir1.1 (ROMK) in renal K^+ and NaCl handling was confirmed by finding *KCNJ1* mutations in antenatal Bartter's syndrome (143,259,513,579). Bartter's syndrome (29) comprises a set of autosomal recessive renal tubulopathies characterized by hypokalemic metabolic alkalosis, renal salt wasting, hyperreninemia, and hyperaldosteronism (21,187,258,438,457). Antenatal Bartter's syndrome is the most severe form of Bartter's syndrome and is genetically heterogeneous resulting from mutations in at least four additional genes expressed in the TAL (see Fig. 19; Ref. 194): *SLC12A1* encoding the apical $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter (512,574); *CLCKB* encoding the basolateral Cl^- channel (511); *BSND* encoding the β -subunit of CLCKB (47,136); and *CaSR* encoding the extracellular CaSR that regulates the apical intermediate conductance K^+ channel in TAL (573,609). The effect of loss-of-function mutations in *KCNJ1* (see Fig. 20) on salt

handling by the TAL can be understood, since apical K^+ recycling is crucial both to supplying K^+ to the $Na^+-K^+-2Cl^-$ cotransporter and to generation of the lumen-positive transepithelial voltage that drives 50% of the reabsorbed sodium paracellularly (49, 181; Fig. 6). Transient neonatal hyperkalemia with salt wasting, hyponatremia, and hyporeninemic hyperaldosteronism, mimicking pseudohypoaldosteronism type 1, has been seen in some individuals with ROMK Bartter's syndrome (81,148). This transient hyperkalemic phenotype is consistent with the role of ROMK in forming the 35-pS K^+ channels in both TAL and principal cells. These Bartter mutations in *KCNJ1* result in alterations in channel PKA phosphorylation, pH sensing, channel gating, proteolytic processing, or trafficking to the apical membrane (102,103,149,150,^{240,331},437,486,497,521).

2. The mouse ROMK knockout—Deletion of the *KCNJ1* gene in mice results in a severe renal $NaCl$ and K^+ wasting phenotype, confirming the importance of ROMK in salt handling by the TAL (333,342). Patch-clamp studies have shown that the small-conductance K^+ channel is absent in both TAL and principal cells (342), establishing that ROMK encodes the 35-pS K^+ channel (Figs. 6 and 7).

That loss-of-function mutations in ROMK (*Kir1.1*; *KCNJ1*) cause Bartter's syndrome raises some questions regarding the mechanism of K^+ handling by TAL and principal cells. First, the intermediate-conductance, 70-pS, K^+ channel forms the dominant apical K^+ conductance in rats and mice, at least under some conditions (343,589). Thus deletion of ROMK would be expected to have only a modest effect on the apical K^+ conductance of TAL cells unless ROMK is a subunit of the intermediate conductance K^+ channel or in some other manner regulates the functional expression of that channel. The absence of the 70-pS K^+ channel in TAL from ROMK-deficient mice has also established that ROMK is required for expression of the intermediate-conductance K^+ channel in this nephron segment (341). Second, ROMK forms the apical 35-pS K^+ channel in principal cells that mediates K^+ secretion in the collecting duct. Yet, most Bartter individuals with *KCNJ1* mutations are hypokalemic and have a high rate of urinary K^+ excretion. ROMK knockout mice also have a high rate of urinary K^+ excretion. Several factors may contribute to the K^+ loss seen in ROMK null mutant mice and in ROMK Bartter individuals. These include 1) diminished reabsorption of K^+ in the TAL due to reduction in $Na^+-K^+-2Cl^-$ function (216); 2) K^+ secretion due to flow-dependent, Ca^{2+} -activated K^+ channels in the CCD (546,620); 3) K^+ secretion by KCl cotransport in the CCD (575); and 4) augmented paracellular K^+ backleak into the CCD. Elucidation of these mechanisms will likely provide important insights to potassium handling by distal nephron segments including the collecting duct.

IV. OTHER POTASSIUM CHANNELS IN KIDNEY

A. 6-TM Renal K^+ Channels

Most Kv channels only open when the cell membrane depolarizes beyond -60 mV and therefore might not be expected to function in renal epithelial cells that have resting membrane potentials between -40 and -75 mV. However, proximal tubule and cortical and medullary collecting duct cells can have large enough depolarizations to activate Kv channels when transporting certain charged solutes.

1. Proximal tubule—Activation of electrogenic transporters in the proximal tubule results in significant cell membrane depolarization (45,73,155). For instance, Na^+ entry is facilitated by a favorable electrical chemical gradient, and the apical membrane depolarizes by 10–15 mV during sodium-coupled glucose and amino acid uptake. Sustaining such electrogenic transport requires mechanisms that maintain the membrane potential to preserve the favorable electrochemical gradient for sodium. Voltage-gated (Kv) K^+ channels are well suited for this task since their activation by membrane depolarization would result in repolarization. Several

Kv channels have been detected in the apical membrane of the proximal tubule by patch clamp and immunocytochemistry (see Table 1). For example, Ca²⁺-activated, maxi-K⁺ type have been observed in cultured proximal tubule cells (42,204,205,262,380,548) and in proximal tubule bush-border membranes (666). In addition, calcium-insensitive, voltage-gated K⁺ channels have also been detected. Moreover, two other types of voltage-gated K⁺ channels (KCNQ1 and KCNA10; see Table 1) have been detected using Northern blotting, in situ hybridization, and immunocytochemistry.

The 6-TM protein KCNQ1 forms a heteromultimeric complex with a single transmembrane segment subunit (KCNE1 or minK; Fig. 4E) to form a small-conductance (2–10 pS) voltage-gated K⁺ channel. KCNQ1 and KCNE1 are abundantly expressed in the proximal tubule (see Fig. 3). The KCNQ1-KCNE1 channel plays a crucial role in cardiac repolarization, and mutations of these genes cause long QT syndrome (27,471,585). In proximal tubule, the KCNQ1-KCNE1 channel may also prevent depolarization following stimulation of electrogenic Na⁺-coupled glucose or amino acid transport (Fig. 21; Ref. 569). KCNE1-deficient mice exhibit a reduction in glucose and amino acid uptake by the proximal tubule (569,608).

Other Kv channels, such as Ca²⁺-activated, maxi-K⁺, and KCNA10 (see below), may also participate in stabilizing proximal tubule membrane potential during electrogenic Na⁺ uptake (Fig. 21; Ref. 607). The 6-TM voltage-gated K⁺ channel KCNA10 (300) has 58% amino acid identity with Kv1.3 but also contains a putative cyclic nucleotide (CN) binding domain at the carboxy terminus, suggesting that channel function may be regulated by cyclic nucleotides. KCNA10 protein has been detected in the apical membrane of the proximal tubule (642). KCNA10 channels are closed at the holding potential of –80 mV but are progressively activated by depolarization more positive than –60 mV, with half-activation at –20 mV. The human KCNA10 channel is inhibited by the classical K⁺ channel blockers (Ba²⁺, TEA⁺, and 4-AP) as well as by inhibitors (verapamil and pimozide) of cyclic nucleotide-gated (CNG) cation channels. KCNA10 has five putative PKC phosphorylation consensus sites (300), and activation of PKC reduces whole cell current. Two PKC sites are located in the putative cyclic nucleotide-binding domain, suggesting that cyclic nucleotides might modulate the effect of PKC on channel current. A small soluble protein of 141 amino acids, KCNA4B, with limited structural similarity to the NAD(P)H-dependent oxidoreductase superfamily is a β -subunit of KCNA10 (552). K⁺ current increases nearly threefold when KCNA4B is coinjected with KCNA10 and becomes more sensitive to activation by cAMP.

2. Distal tubule—While several Kv, *Shaker*-related genes are detected in kidney (104), Kv1.2 and Kv1.3 appear to be preferentially localized in the distal tubule, although on which membrane is not known (106, 638; Fig. 3; Table 1). Kv1.3 channel activity is modulated by phosphorylation (PKA, PKC, tyrosine kinase). Insulin inhibits channel activity via tyrosine phosphorylation of multiple residues (58,92,137,214). The scorpion toxins, margatoxin and kaliotoxin, specifically inhibit Kv1.3 (159). PKC increases (86) and tyrosine kinase (TK) inhibits Kv1.3 channel activity (137). In the distal tubule and collecting duct, Kv1.3 could help stabilize the apical membrane potential closer to the K⁺ equilibrium potential during electrogenic Na⁺ entry via ENaC channels. Interestingly, Kv1.3 is activated by SGK that has been suggested to mediate the action of aldosterone in the distal tubule by stimulating the ENaC (606). SGK appears to mediate its effect on Kv1.3 by altering the rate of inactivation and by increasing the half-life of Kv1.3 protein in the plasma membrane. These observations suggest that Kv1.3 may link aldosterone-stimulated Na⁺ reabsorption and K⁺ secretion (Fig. 22) and probably contributes to the stabilization of the membrane potential under conditions of increased apical sodium entry. Finally, there are also functional data suggesting expression of Kv channels in the renal medulla (578). In the inner medulla, extracellular K⁺ can reach levels

greater than 40 mM as a result of K⁺ recycling. Membrane depolarization by this high extracellular K⁺ may be sufficient to activate these Kv channels.

Several recent findings support the notion that Kv1.3 channels participate in Na⁺ reabsorption and K⁺ transport in the IMCD (Fig. 3; Table 1). Kv1.3-like currents have been detected in primary cultures of ICMD cells using perforated patch and conventional whole cell methods (135). Immunofluorescence studies also show that Kv1.3 protein colocalizes with Na⁺-K⁺-ATPase at the basolateral membrane of IMCD cells. Kv1.3 may function in the reabsorption of K⁺ in this part of the nephron in low-K⁺ states (638). In addition, Kv1.3 may help stabilize the membrane potential during electrogenic Na⁺ reabsorption. The latter could be especially important for the IMCD, which can be exposed to high extracellular K⁺ concentrations (both luminal and interstitial) that would depolarize the cell and reduce the driving force for Na⁺ reabsorption. Finally, Kv1.3 channels could also play an important role in cell volume regulation (108).

Maxi-K⁺ channels are another type of 6-TM K⁺ channel thought to play a significant role in renal solute transport. Large Ca²⁺-activated K⁺ currents have been detected in the apical membranes of principal cells in the CCD and TAL cells. The maxi-K⁺ channel in the TAL is encoded by *rbsoll*, a *mslo* homolog (388) where it is thought to play a role in cell volume regulation. Maxi-K⁺ channels also are thought to mediate flow-dependent K⁺ secretion both in the connecting tubule and CCD. Support for the role of maxi-K⁺ channels in K⁺ excretion during high rates of distal tubule flow rate is that deletion of the gene encoding the β 1 accessory subunit of maxi-K⁺ channels impairs K⁺ excretion following acute volume expansion (440). While ROMK primarily mediates baseline K⁺ secretion, maxi-K⁺ channels and possibly other Kv channels could contribute to flow-dependent K⁺ secretion (Fig. 22).

B. 2-TM Renal K⁺ Channel (Non-ROMK)

1. Kir2.3 channel—In CCD principal cells, the maintenance of the negative membrane potential depends, at least in part, on the activity of an inwardly rectifying 18-pS K⁺ channel (Fig. 7). This basolateral K⁺ channel has been suggested to be the inwardly rectifying K⁺ channel, Kir2.3 (614; Table 1). The kidney Kir2.3 was cloned from a mouse CCD cell line and its expression in kidney confirmed by Northern analysis (614). When the MDCK cells were transfected with Kir2.3, the channel is expressed in the basolateral membrane (306) and a basolateral sorting signal was identified at the carboxy-terminal tail (307,411). Kir 2.3 shares some biophysical properties with the native 18-pS K⁺ channel such as high P_o and channel conductance, 14.5 pS (614).

2. Kir4.1/4.2 and Kir5.1 channels—Recent evidence suggests that heteromeric Kir4.0/Kir5.1 channels form the basolateral small-conductance K⁺ channel in distal nephron segments (337; Table 1; Figs. 3 and 7). The inward rectifier K⁺ channel, Kir4.1, was originally identified from rat brain and exhibits 53% amino acid identity to ROMK1 (a.k.a., BIR10, K_{AB}-2 and BIRK1; Table 1; Refs. 55,540). The kidney also expresses Kir4.1 mRNA, and the channel protein has been immunolocalized to the basolateral membrane of distal nephron segments (DCT, CNT and ICD; Ref. 234). Subsequently, Kir4.1 was cloned from human kidney (507). Kir4.1 K⁺ channels expressed in *X. laevis* oocytes exhibited Ba²⁺-sensitive K⁺ currents that are inhibited by internal (referred to as Kir1.2; Refs. 485,507,625,626), but not external (156), protons. Internal protons decrease Kir4.1 K⁺ current by reducing P_o ; however, internal protons also increase channel conductance (635). Mice with deletion of the Kir4.1 gene (KCNJ10; Table 1) have been generated (272), but a specific renal phenotype, to our knowledge, has not been identified.

Kir4.2 was originally cloned from human kidney and called Kir1.3 (507). While this study reported that Kir4.2 channels were not functional in *X. laevis* oocytes (507), subsequent studies

have shown that this protein forms inward rectifying K⁺ channels that are inhibited by PKC and internal protons (337,433). Kir4.2 mRNA is found in human (507) and mouse (337) kidney, and in the latter species, specifically in the DCT.

The inward rectifier K⁺ channel, Kir5.1, was also cloned from rat brain but does not form functional K⁺ channels by itself when expressed in *X. laevis* oocytes (a.k.a, BIR9; Ref. 55). Kir5.1 mRNA is present in kidney (55,543), and channel protein is abundantly expressed in PT and in DCT and CCD segments (567) where Kir4.1 is also expressed (234). Recent studies have demonstrated that Kir4.1 or Kir4.2 with Kir5.1 form heteromeric inward-rectifying K⁺ channels with distinct properties in both heterologous expression systems (280,337,543) and native kidney (543). The heteromeric interaction of Kir5.1 with other Kir K⁺ channels is specific for Kir4.x channels and requires a small region in the proximal carboxy terminus of Kir4.1 (280). A recent study showed that the basolateral small-conductance K⁺ channel in distal nephron segments is most similar to heteromeric Kir4.1(Kir4.2)/Kir5.1 channels (337). The most dramatic and specific effect of the Kir4.x-Kir5.1 assembly on K⁺ channel function is the shift in the pK_a for inhibition by internal protons from 6.0 to the physiologically relevant pK_a of 7.4 (435,543,567,625). Internal pH sensitivity of Kir4.1-Kir5.1 is modulated by PIP₂ (636), similarly to Kir1.1 (ROMK; Ref. 315).

3. Kir6.1 channel—Kir6.1 (previously known as uK_{ATP}-1) was originally cloned from a rat pancreatic islet cell cDNA library using Kir3.1 as a probe (232) and belongs to the Kir6.0 (ATP-sensitive; K_{ATP}) subfamily of inwardly rectifying K⁺ channels (Table 1; Refs. 398, 500). Exogenous expression of Kir6.1 channels in *X. laevis* oocytes forms ATP-sensitive channels only when coexpressed with a sulfonylurea receptor protein (SUR; Refs. 69,500). Although this inward rectifier is predominantly found in brain, heart, and vascular tissue, expression in kidney has been documented (133,232). Kir6.1 has been localized to both mitochondria (533) and plasma membranes (65,533). Upregulation of Kir6.1 mRNA has been observed following ischemic injury in rat kidney consistent with the proposed role of K_{ATP} channel activation in protection from ischemic damage (e.g., in the heart; Ref. 9). Recently, Kir6.1 was cloned from rabbit proximal tubule cDNA library, and expression of Kir6.1, SUR2A, and SUR2B in rabbit proximal tubule was confirmed by PCR (65). Functional studies in *X. laevis* oocytes suggested that Kir6.1 may form the basolateral ATP- and taurine-sensitive K⁺ channel involved in the basolateral K⁺ conductance of proximal tubules (Fig. 3; Ref. 65). Adenylate kinase, which promotes phosphoryl transfer between ATP and ADP and associates with K_{ATP} channels (74), has been cloned from the rabbit proximal tubule library (64) and may associate with Kir6.1 in these cells to promote metabolic sensing.

4. Kir7.1 channel—The inward rectifier K⁺ channel Kir7.1 was originally cloned from human brain cDNA libraries after searching the GenBank expressed sequence tag (EST) database using Kir1.1 and Kir6.2 (Table 1; Refs. 283,427). The Kir7.1 K⁺ channel displays unusual K⁺ permeation properties with a low single-channel conductance of 50 fS, low sensitivity to blocking by external Ba²⁺ or Cs⁺, and very low dependence of conductance on external K⁺ (118,283,427). PCR and Western blot analyses have identified Kir7.1 transcripts and protein, respectively, in rat, guinea pig, and human kidney (100,283,413,427). Expression of Kir7.1 along the rat nephron was demonstrated by Western blots of microdissected nephron segments (413) and showed K⁺ channel protein in TAL, DCT, CNT, CCD, OMCD, and IMCD (Fig. 3; Ref. 413). Immunostaining localized Kir7.1 to basolateral membranes of DCT and principal cells (413). In the guinea pig, Kir7.1 protein is expressed in basolateral membranes of proximal tubule and TAL cells (100). In the CCD, Kir7.1 is expressed in principal cells, but not intercalated cells. The unique pore properties of Kir7.1 and its localization close to Na⁺-K⁺-ATPase suggested that this K⁺ channel may be functionally coupled to Na⁺-K⁺-ATPase and involved in K⁺ recycling across basolateral membranes (396,413).

C. 2-Pore K⁺ Channels (K_{2p})

Mammalian K_{2p} channels constitute the largest K⁺ channel family. This family was discovered in 1995 with the first member (TOK1) identified in the sequence database of the yeast *Saccharomyces cerevisiae* (265,453,655). Fourteen mammalian genes have been identified (K_{2p}1.1–7.1, 9.1, 10.1, 12.1, 13.1, 15.1–17.1). Each subunit has four transmembrane segments, containing two pore-forming “P” loops, and functions as a dimer (174, 312; Fig. 4D). These channels are thought to be responsible for background K⁺ leak currents that are expected to play important roles in setting membrane potentials. K_{2p} channels are modulated by mechanical stimuli, cell volume, cytoplasmic and extracellular pH, temperature, lipids, and volatile anesthetics (174,175,408,428).

Eight K_{2p} genes (K_{2p}1.1, 3.1–5.1, 10.1, 12.1, 13.1, and 15.1; Table 1) are expressed in kidney, but their localization and roles largely remain to be elucidated. K_{2p}1.1 and K_{2p}5.1 transcripts have been observed in the proximal tubule (415), and protein for K_{2p}1.1 was immunolocalized to the brush border (90). They may function to stabilize the membrane potential toward the K⁺ equilibrium potential in the face of depolarizing currents associated with electrogenic Na⁺ reabsorption. K_{2p}5.1 may function as a potassium exit mechanism during the RVD response following cell swelling associated with solute transport in the PCT (28,399). Consistent with this view, PCT cells from mice with deletion of the *KCNK5* gene (163) lack cell swelling-induced K⁺ currents (399). If K_{2p}5.1 is also present in apical membranes, the sensitivity of this channel to slight reductions in external pH (28,399) suggests that it may primarily function in the early PCT where luminal pH has not yet been reduced by bicarbonate reabsorption and where solute transport (glucose, amino acids, etc.) is highest.

K_{2p}1.1 and K_{2p}5.1 transcripts and protein are also expressed in distal tubules and collecting duct where they may serve to stabilize the membrane potential during electrogenic Na⁺ absorption through ENaC channels. K_{2p}1.1 immunostaining in the distal tubule and collecting duct is not altered, however, following restriction of dietary Na⁺ or K⁺ (90). The extracellular pH sensitivity of K_{2p}5.1 suggests that it would not be functional in the CNT or CCD when luminal pH is reduced by acid secretion from α -intercalated cells (e.g., during metabolic acidosis). In the future, we expect that mice with deletion of specific K_{2p} channel genes will provide insights into their roles in kidney function.

Although the specific nephron localization of K_{2p}3.1 (TASK1) is not known, this channel, like K_{2p}5.1, is inhibited by reductions in extracellular pH. Interestingly, K_{2p}3.1 channel activity is reversibly inhibited by reduced O₂ levels, suggesting that it may be involved in oxygen sensing in the nephron (249,429).

D. 1-TM (CHIF, Channel Inducing Factor)

CHIF is a single membrane-spanning protein that was originally identified in a rat colonic cDNA library and is most similar to the γ -subunit of Na⁺-K⁺-ATPase (Table 1; Ref. 22). However, a minK (IsK)-like K⁺ channel activity was found when CHIF was expressed in *X. laevis* oocytes (22). Subsequently, CHIF was shown to be expressed at basolateral membranes of the OMCD and IMCD (141,505) where it functions as a regulator of Na⁺-K⁺-ATPase activity, similarly the pump γ -subunit (157). CHIF mRNA is suppressed by a low-K⁺ diet, independently of aldosterone, while a high-K⁺ diet increases CHIF transcripts in an aldosterone-dependent manner (582). In an ischemic reperfusion injury model in rats, both CHIF and ROMK were downregulated and, thereby, could contribute to the hyperkalemia of acute renal failure (170).

V. CONCLUSIONS AND FUTURE DIRECTIONS

While many K^+ channel genes are expressed in the mammalian kidney, there remains limited data on their distribution along the nephron, their localization in specific cell types within these nephron segments, and in which membrane domain (apical or basolateral) they are expressed. In addition, the identification of which gene/protein is responsible for what current identified by patch clamping in specific renal tubule cells remains largely unknown with few exceptions (e.g., ROMK). Moreover, the functional and molecular interactions among K^+ channel genes and other proteins, lipids, and metabolites is still in its infancy. Finally, we are just beginning to elucidate the arrays of regulators (kinases, phosphatases, lipids, metabolites, etc.) that modulate the activities of K^+ channels to changing dietary intakes and other homeostatic demands. We anticipate that deletions of specific K^+ channel genes in mice when coupled to functional studies (metabolic, cell biological, and electrophysiological) will continue to define the specific roles of each of these K^+ channels in renal K^+ handling.

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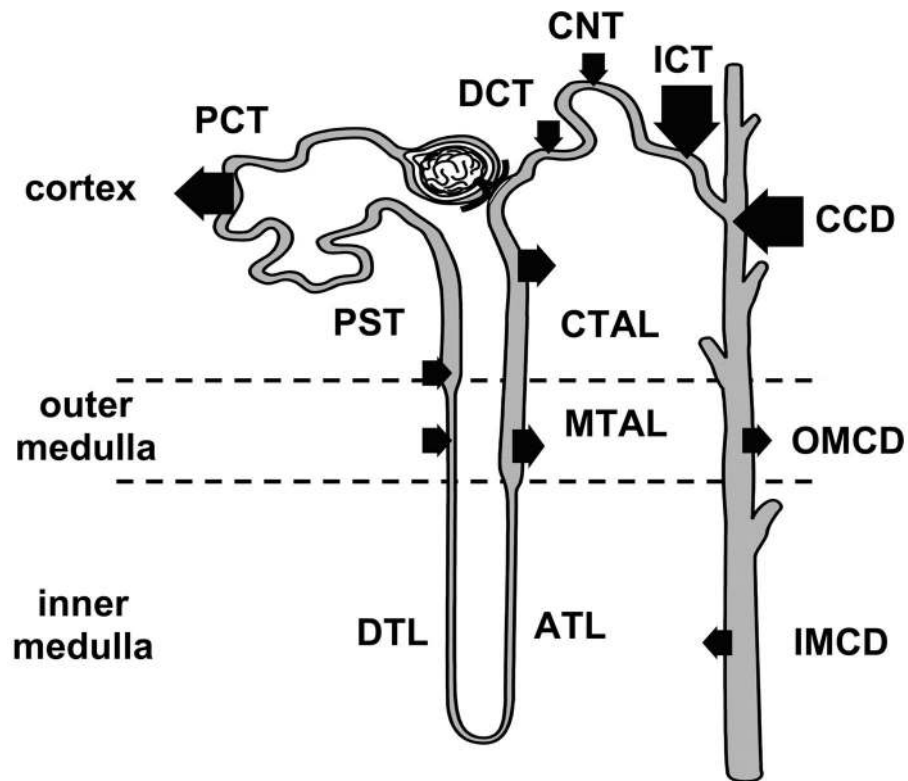


FIG. 1.

Potassium transport along a simplified nephron. K^+ is filtered and extensively reabsorbed along the proximal convoluted tubule (PCT). Some K^+ enters the proximal straight tubule (PST) and the thin, descending limb of Henle's loop (DTL). But extensive K^+ reabsorption along the ascending thin limb of Henle (ATL) and along both the medullary (MTAL) and cortical (CTAL) portions of the thick ascending limb sharply reduce the amount of K^+ by the time fluid has reached the beginning of the distal convoluted tubule (DCT). Regulated K^+ secretion takes place in the connecting tubule (CNT), DCT, initial collecting duct (ICT), and cortical collecting duct (CCD), and reabsorption may occur in the terminal nephron segments, the outer (OMCD) and inner (IMCD) medullary collecting duct. The reabsorptive and secretory components of K^+ transport in the loop of Henle and the further distally located nephron segments are subject to regulation, but transport in the proximal tubule does not control urinary K^+ excretion. The arrow size represents relative magnitudes of K^+ secretion and reabsorption.

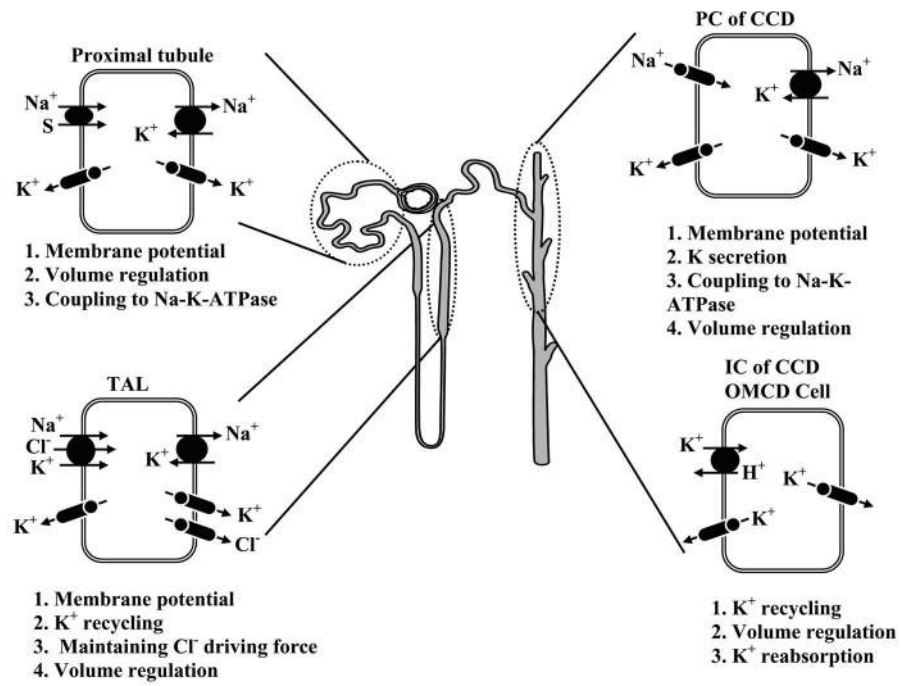


FIG. 2. A model of a single nephron showing the function of renal K^+ channels in proximal tubules, thick ascending limb (TAL), and cortical and outer medullary collecting duct (CCD).

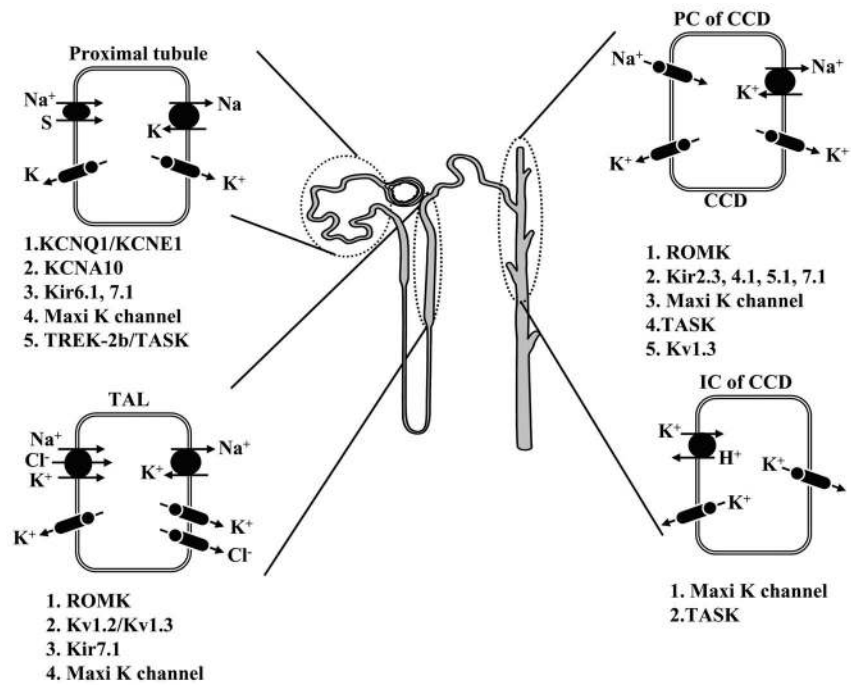
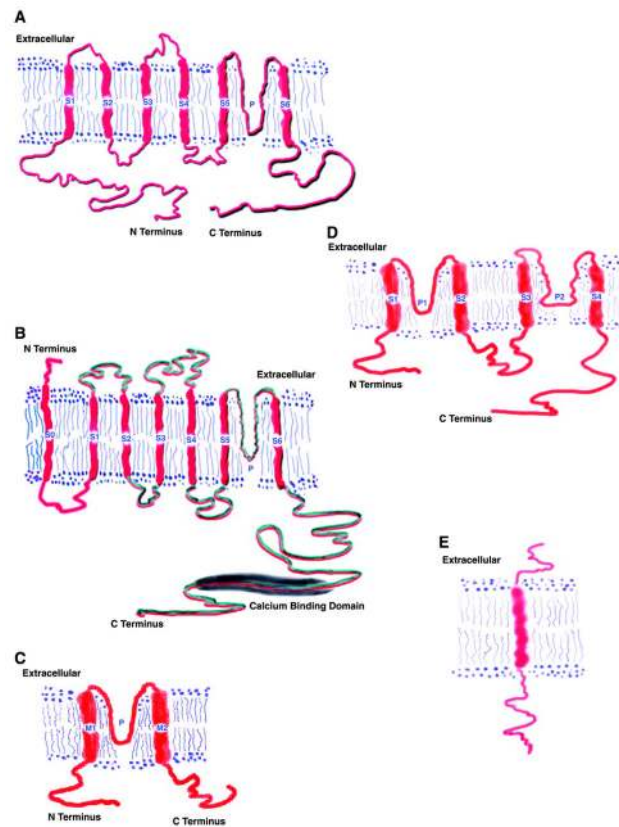


FIG. 3. A model of a single nephron demonstrating the expression of currently known K⁺ channel genes.

**FIG. 4.**

Classification of K⁺ channels and schematic representation of their secondary structure. *A*: the α -subunit of the 6-TM class of K⁺ channels: six transmembrane segments (S1-S6) and one pore (P). S4 represents the voltage sensor of Kv channels. The active channel is a tetramer and can also contain accessory (β) subunits. K⁺ channels belonging to this class include Kv1.1–1.10, IKCa, HERG, and KvLQT. *B*: unlike the other members of the 6-TM class, hSlo appears to have seven transmembrane segments (S0-S6) and the amino terminus is predicted to be located extracellularly. The S4 segment is well conserved, and the cytoplasmic tail contains a calcium-binding domain. The active channel is a heterotetramer and contains accessory (β) subunits. *C*: the α -subunit of the 2-P class of K⁺ channels: 4 transmembrane segments (S1-S4) and 2 pores (P1, P2). These channels do not have an S4 segment. K⁺ channels belonging to this class include TWIK, TRAAK, TASK, and TREK. *D*: MinK and the MinK-related peptides (MiRPs) contain a single transmembrane segment and function as accessory subunits for a variety of 6-TM channels. *E*: the single transmembrane subunit MinK (KCNE1).

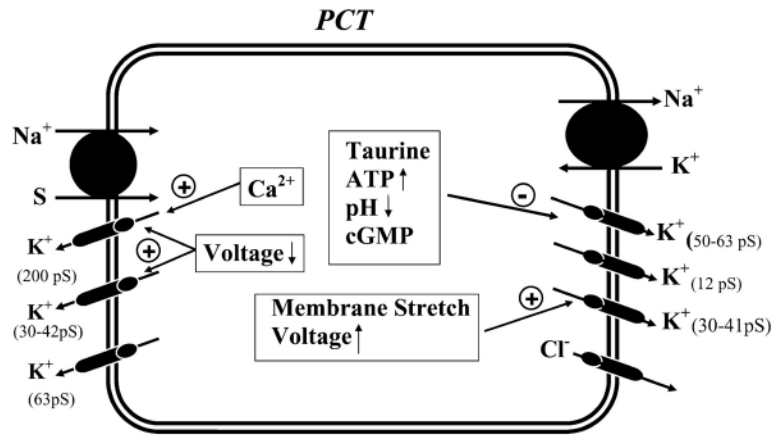


FIG. 5. A model of proximal tubule cell illustrating the location and regulation of K^+ channels. The single-channel conductance of the K^+ channels is indicated. The luminal Na^+ -dependent glucose and other amino acid transporters are indicated by Na/S. The basolateral Na^+ - K^+ -ATPase is also shown.

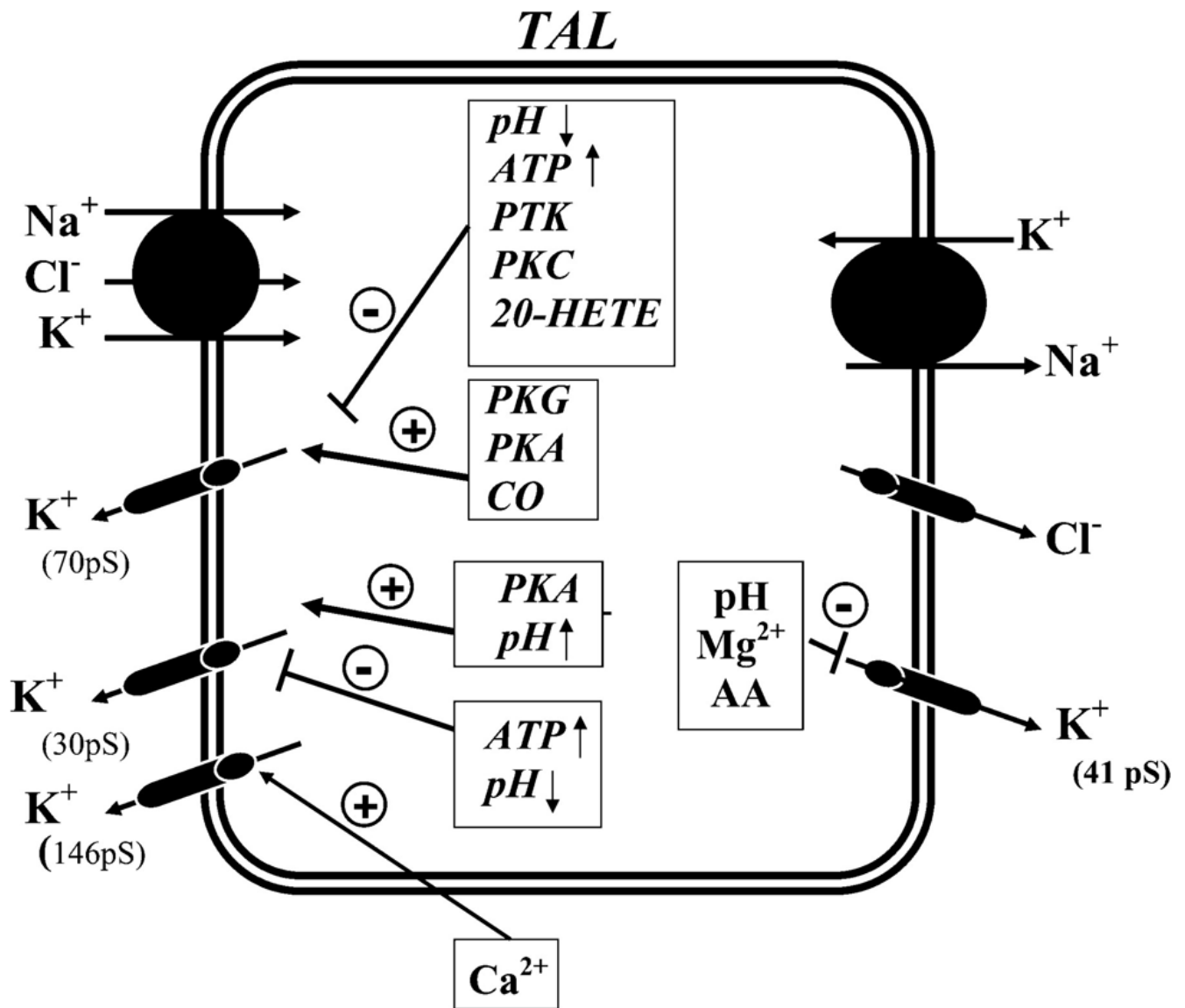
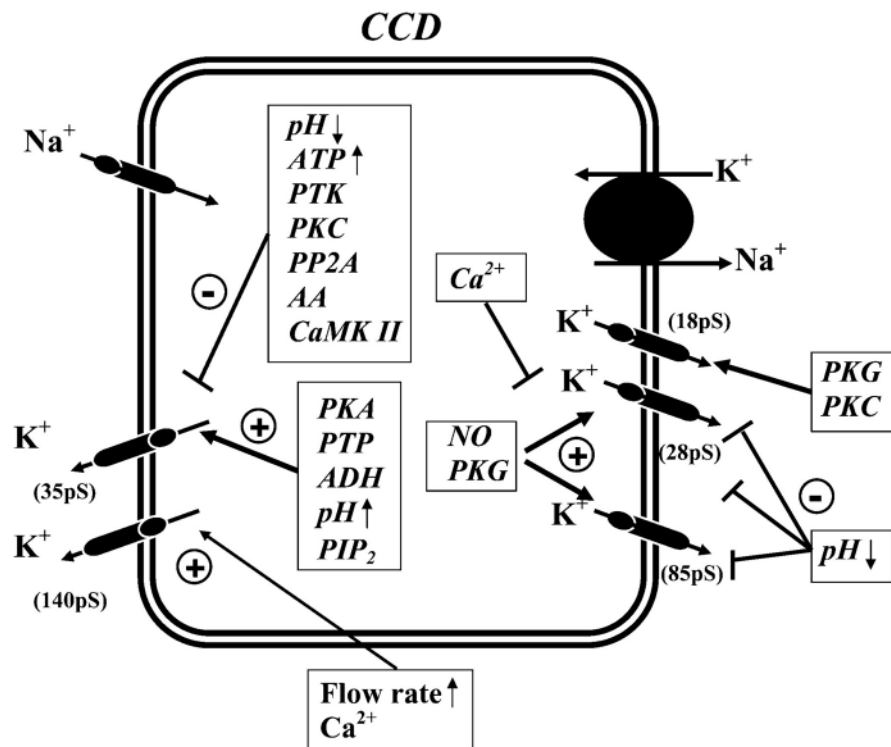


FIG. 6. A model of TAL cell showing K^+ channels and their regulation. The single-channel conductance of the K^+ channels is indicated. The luminal $Na^+-K^+-Cl^-$ cotransporter and the basolateral $Na^+-K^+-ATPase$ are shown. 20-HETE, 20-hydroxyeicosatetraenoic acid; PKC, protein kinase C; PKA, protein kinase A; PKG, cGMP-dependent protein kinase; PTK, protein tyrosine kinase; CO, carbon monoxide; AA, arachidonic acid.

**FIG. 7.**

A model illustrating the K^+ channels and their regulation in principal cells from the CCD. The luminal epithelial Na^+ channel (ENaC) and the basolateral Na^+ - K^+ -ATPase are shown. PKC, protein kinase C; PKA, protein kinase A; PKG, cGMP-dependent protein kinase; PTK, protein tyrosine kinase; PTP, protein tyrosine phosphatase; CaMK II, calcium and calmodulin-dependent kinase II; CO, carbon monoxide; NO, nitric oxide; AA, arachidonic acid; PP2A, protein phosphatase 2A; ADH, antidiuretic hormone.

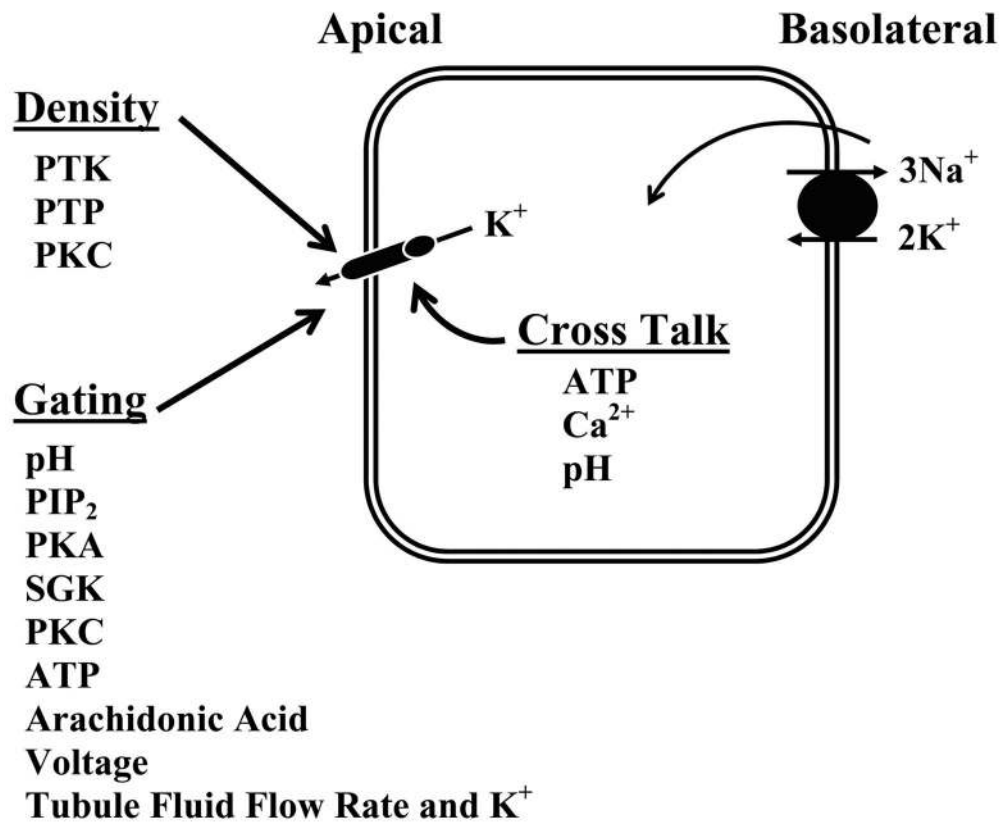
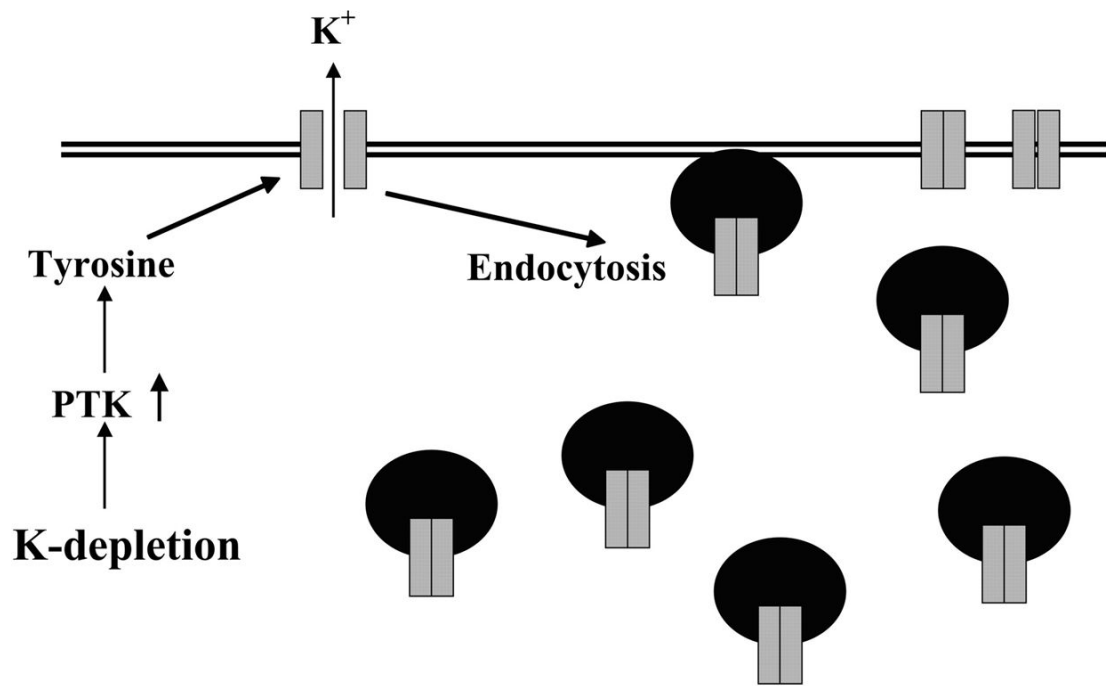


FIG. 8. A cell model showing the mechanisms regulating the activity of apical K⁺ channels in the kidney. Possible mechanisms for interaction between basolateral Na⁺-K⁺-ATPase and apical K⁺ channels are illustrated (cross talk).

**FIG. 9.**

A scheme illustrating the mechanism by which a low-K⁺ diet decreases the surface expression of ROMK channels in principal cells from the CCD. With adaptation to a low K⁺ intake, protein tyrosine kinase (PTK) activity increases. The augmented PTK increases the rate of endocytosis, thereby reducing the number of K⁺ channels in the apical membrane.

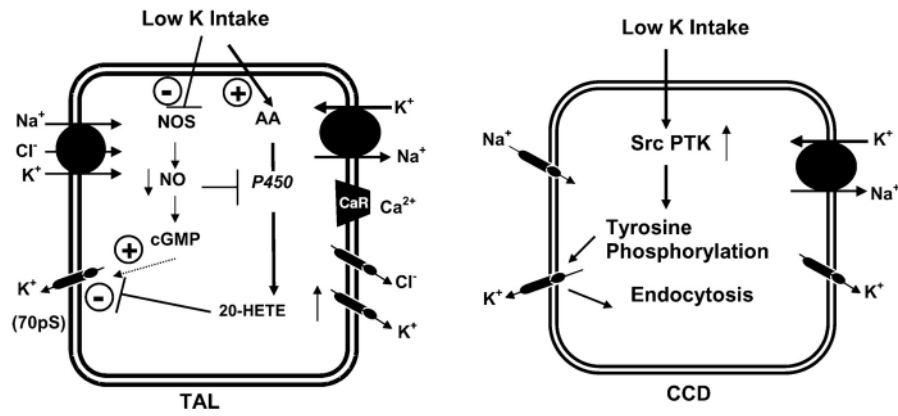


FIG. 10. Cell models showing the signaling pathways involved in modulation of apical K⁺ channels in principal cells by low K⁺ intake. See text for discussion.

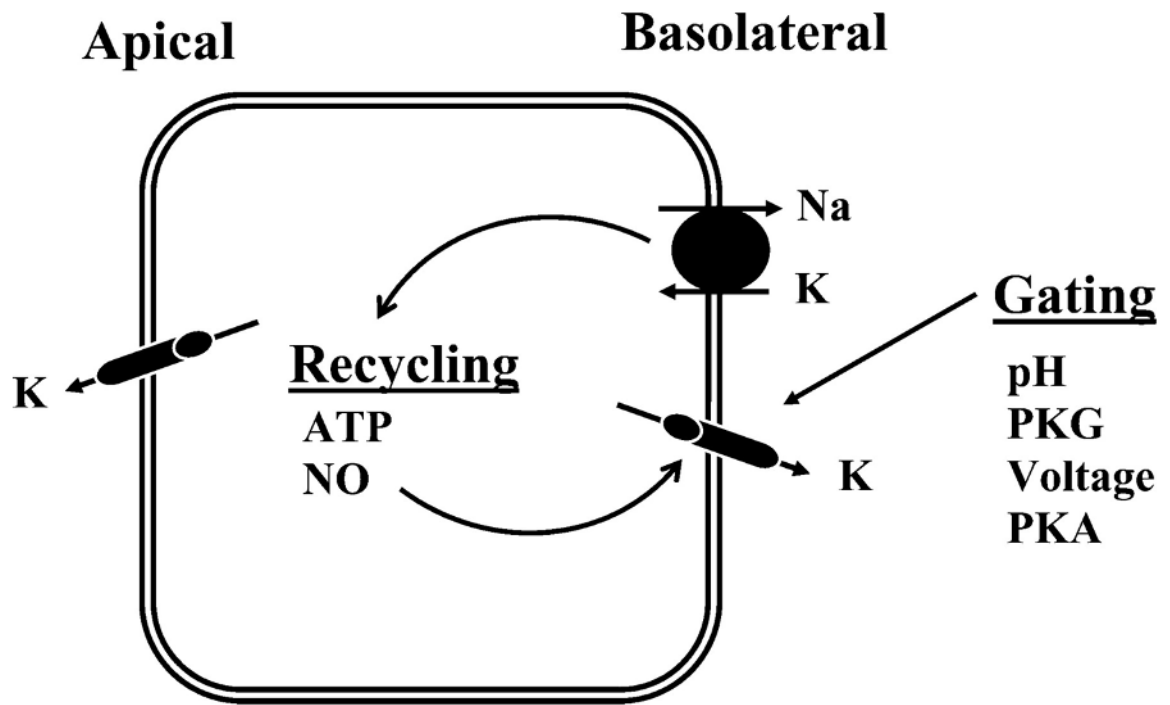


FIG. 11. A cell model showing the signaling pathways involved in modulation of basolateral K⁺ channels in principal cells.

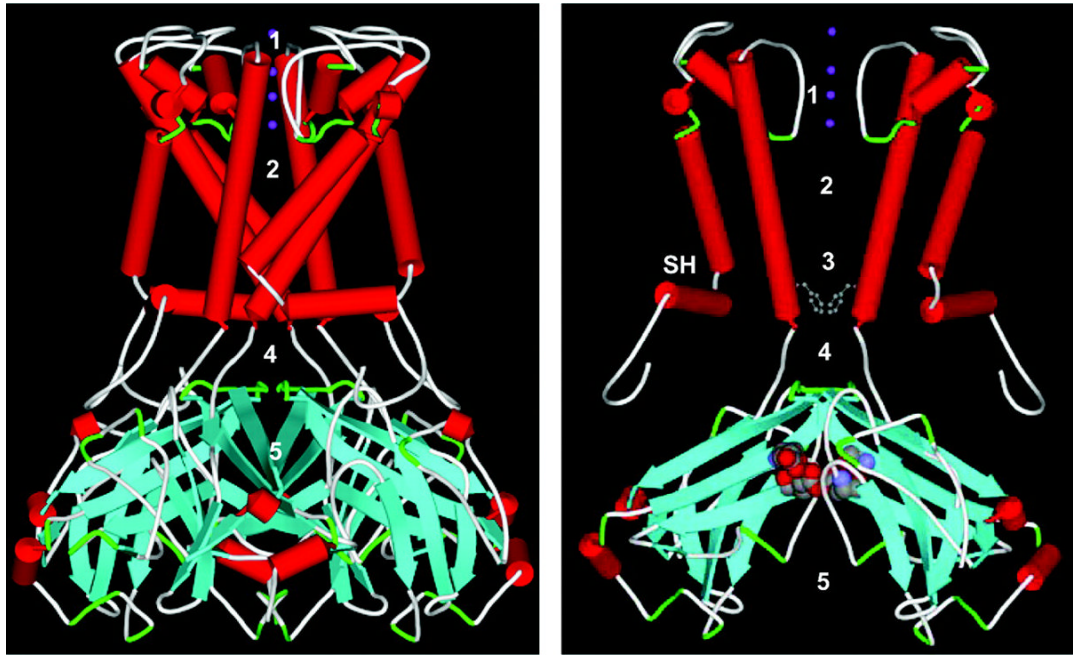


FIG. 12. Structure of the bacterial inward rectifier K⁺ channel KirBac1.1, illustrating the five structural regions of the pore. Mammalian inwardly rectifying K⁺ channels like ROMK are believed to be structurally similar.

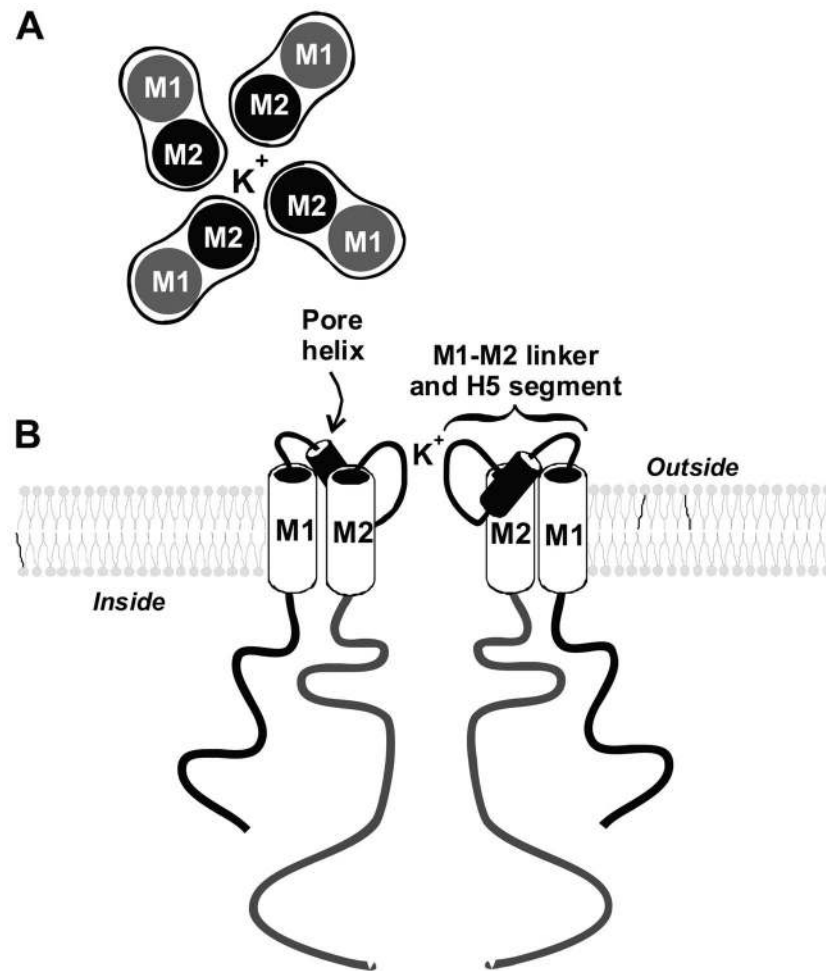


FIG. 13. A schematic model of ROMK. *A*: the proposed subunit structure with the 2nd transmembrane helices, M2, lining the pore. *B*: two of the four subunits forming the channel illustrating the pore helix in the M1-M2 linker.

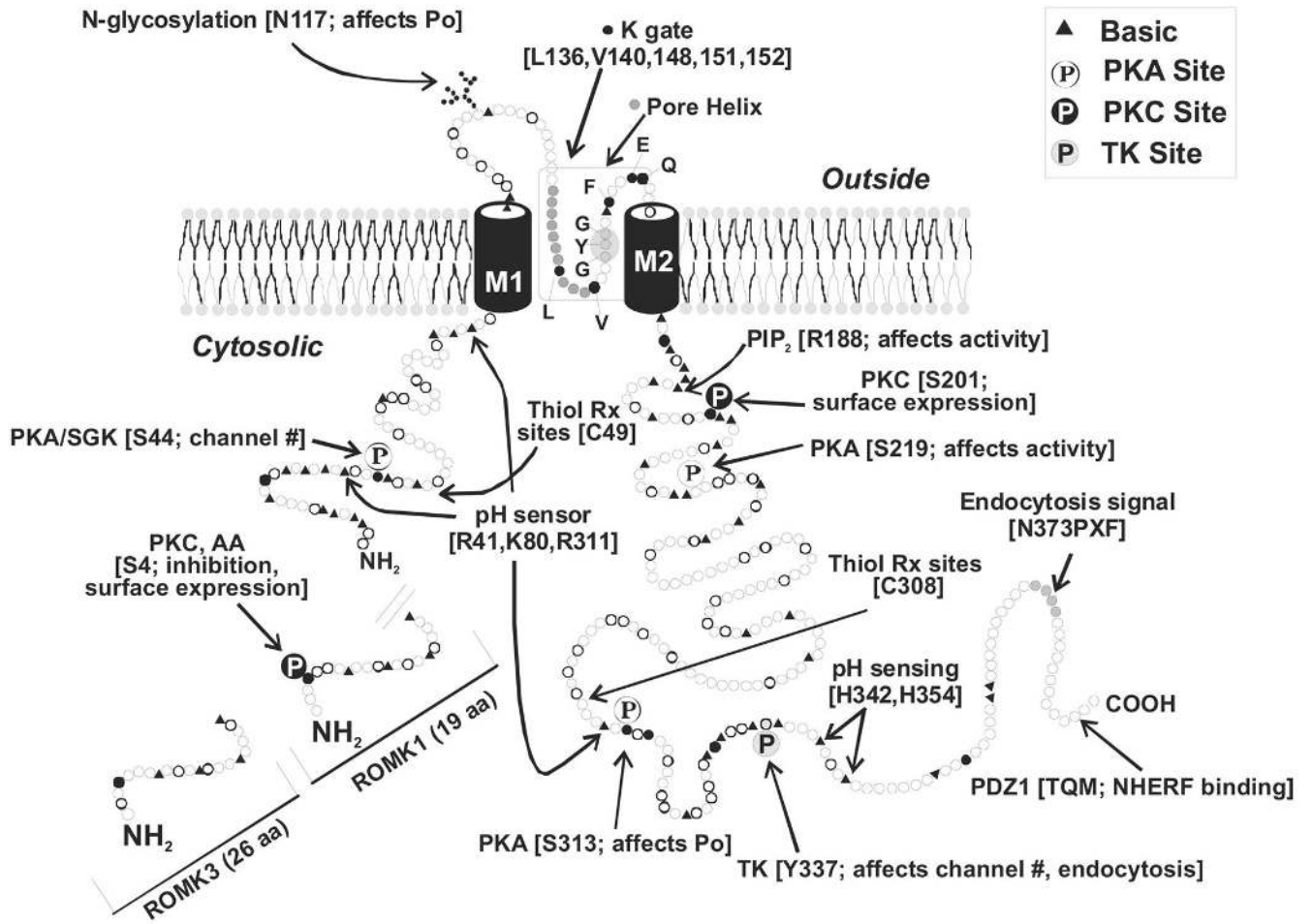


FIG. 14. A schematic model of a single ROMK subunit in the channel tetramer showing the amino-terminal extensions forming ROMK1 and ROMK3, as well as the amino acids that mediate regulation of this channel.

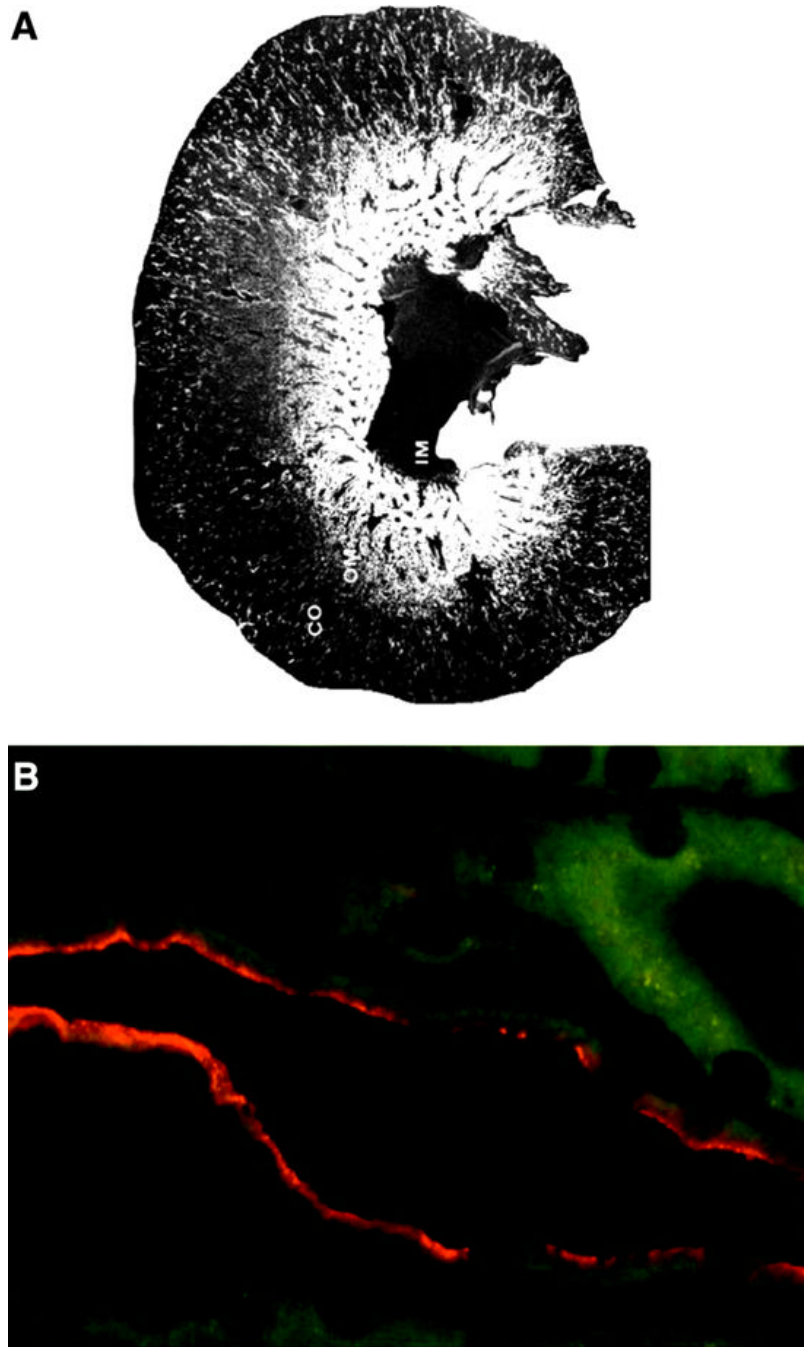


FIG. 15. Expression of ROMK in the rat kidney. *A*: in situ hybridization showing the wide expression of ROMK in cortex, mainly in medullary rays, and in outer medulla. *B*: Western blot showing the apical expression of ROMK in the medullary thick ascending limb (MTAL).

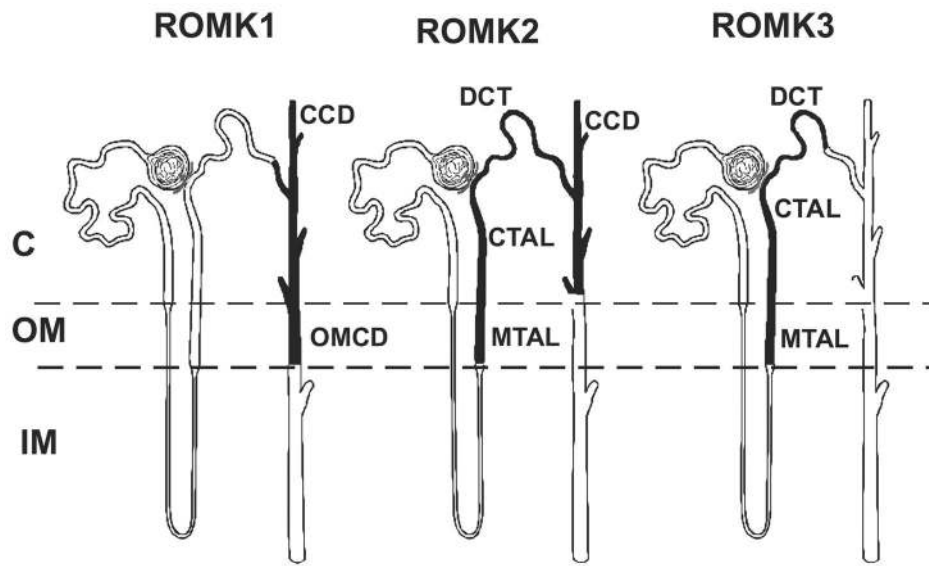


FIG. 16.
Distribution of ROMK isoforms along the nephron.

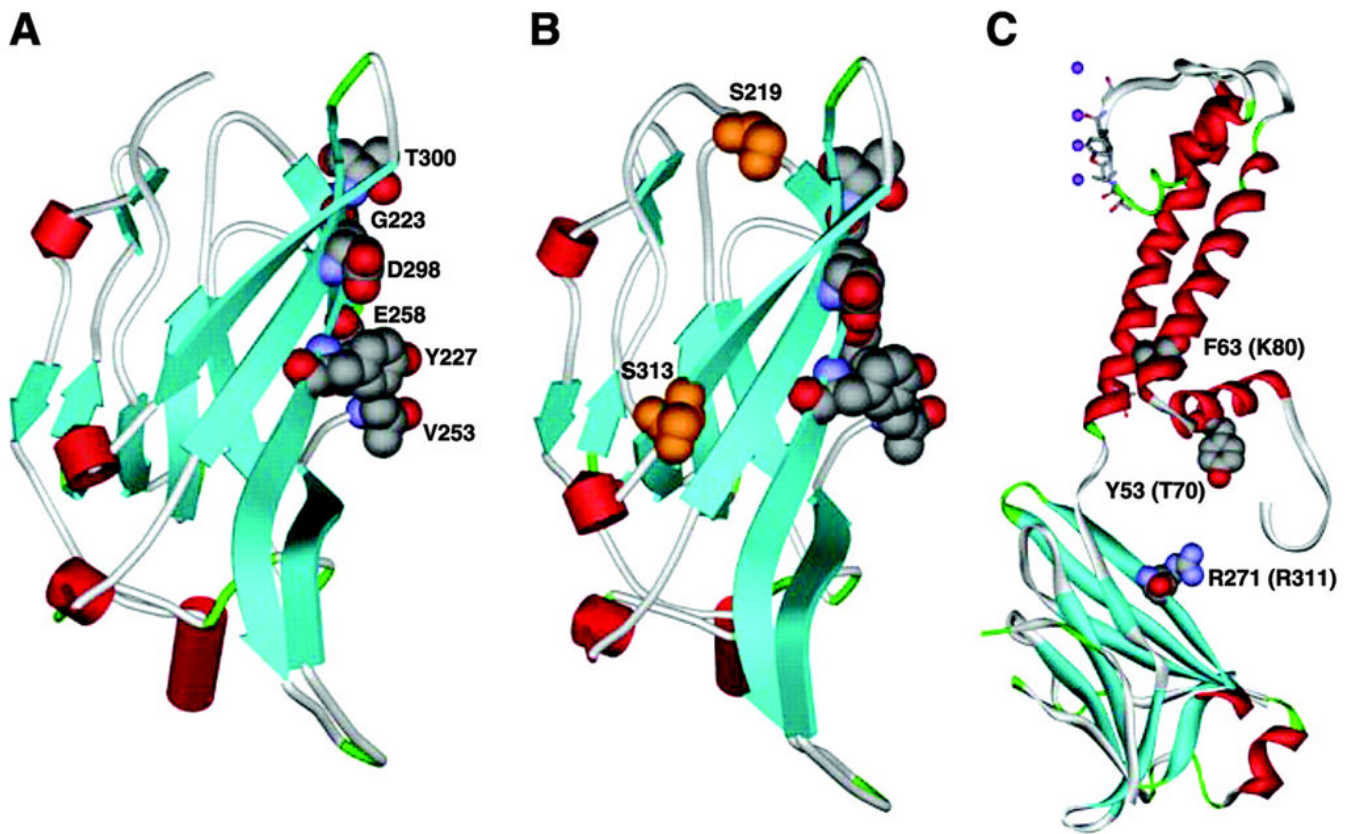


FIG. 17.
A and *B* are computer-generated models of the structure of the cytoplasmic carboxy terminus of ROMK produced by threading ROMK using Kir-Bac1.1 as a template (Swiss-Model). *A*: the residues that have been identified to line the cytoplasmic pore and involved in interaction with cations mediating inward rectification. *B*: the carboxy-terminal serine residues that are phosphorylated by protein kinase A. *C*: localization of the equivalent residues on KirBac1.1 that form the pH sensor on ROMK.

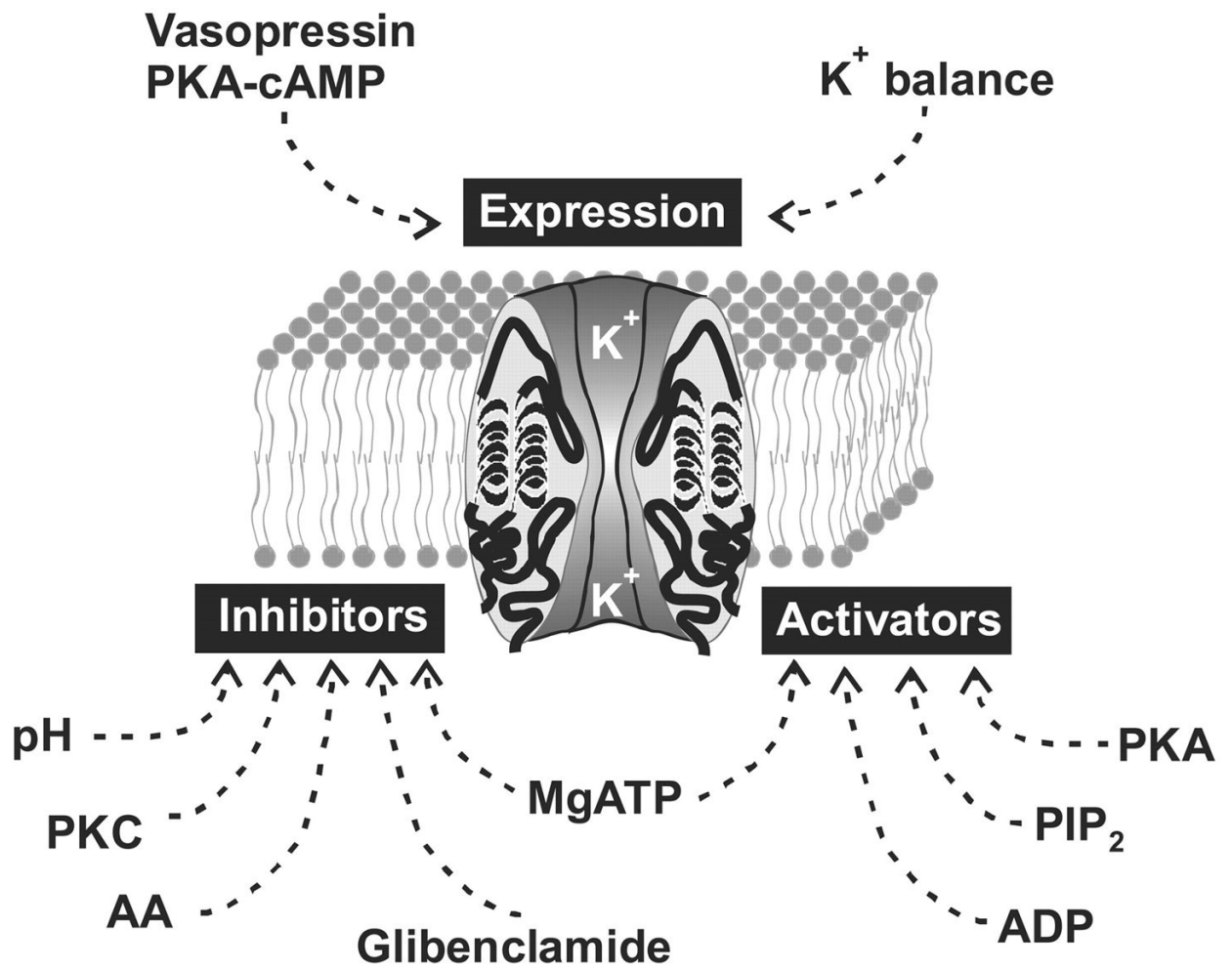


FIG. 18.
Overview of the factors and mechanisms of regulation of ROMK.

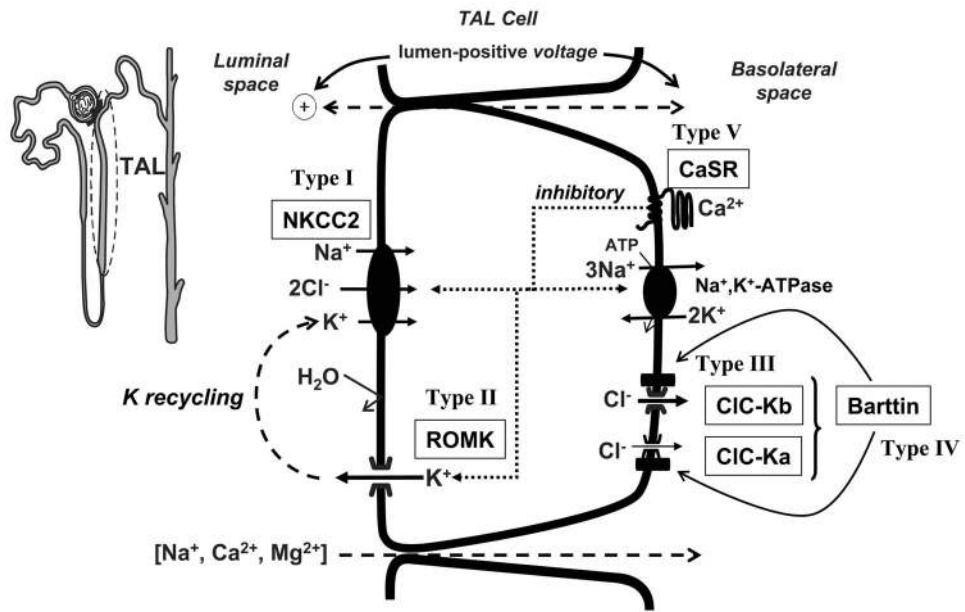


FIG. 19. Schematic model of the TAL illustrating the transporters that cause Bartter's syndrome.

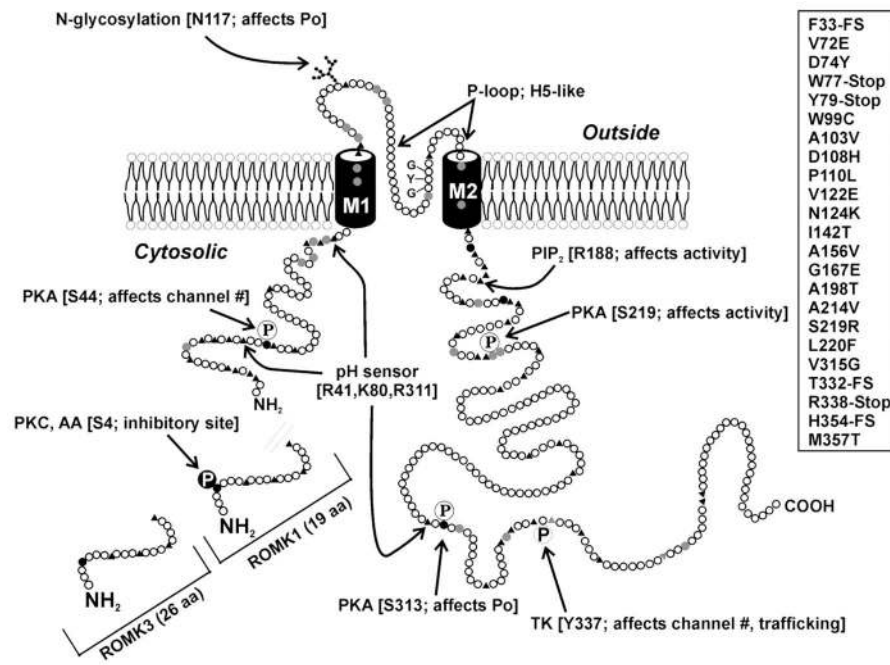


FIG 20.
Mutations in ROMK that are associated with Bartter's syndrome.

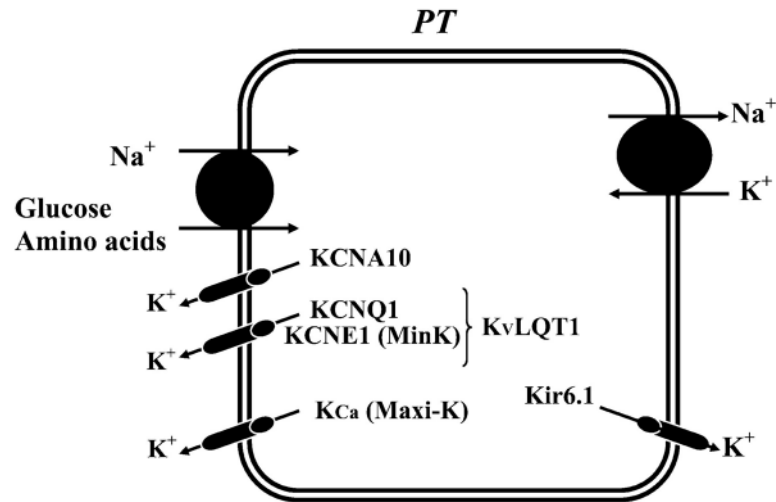


FIG. 21. Localization of 6-TM channels in the apical membrane of the proximal tubule. Also shown is the single TM subunit KCNE1 (MinK) that forms the KvLQT1 channel with the 6-TM subunit KCNQ1. These K^+ channels are thought to stabilize the apical membrane potential that supports entry of amino acids and glucose via their respective Na^+ -coupled electrogenic transporters.

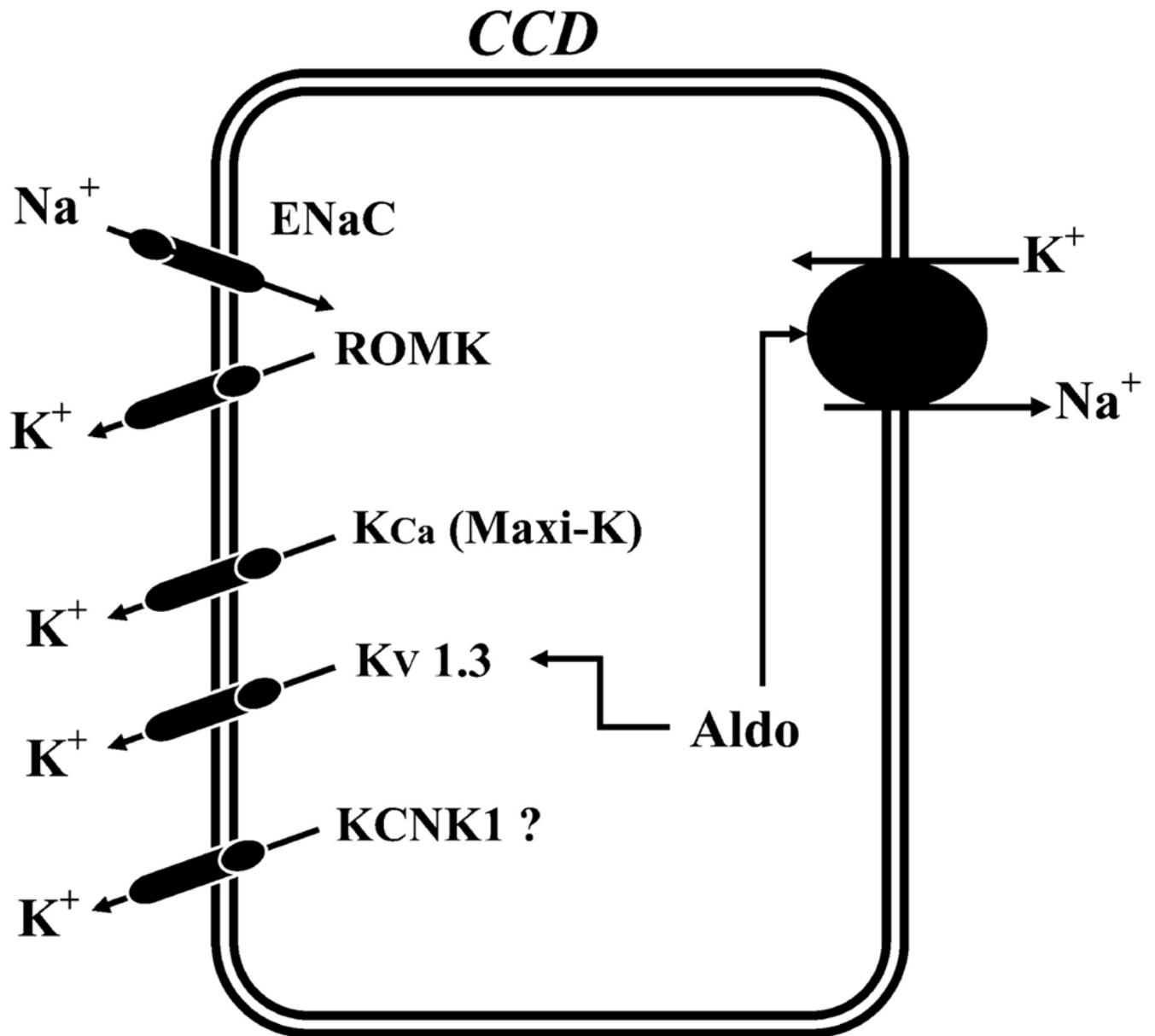


FIG. 22. Localization of 6-TM channels in the apical and basolateral membranes of distal tubular cells. These channels may help stabilize the apical membrane potential when Na⁺ entry (via the epithelial channel, ENaC) activity is increased by aldosterone (Aldo).

TABLE 1

K⁺ channel genes identified in the kidney

Channel Type	Common Name: Gene Name	Chromosome	Disease	Transcript	Protein	Properties	Modulators	Accessory Subunits	Accession Nos.	Reference Nos.	
Voltage-gated (Kv) α -subunits	Kv1.1: KCNA1	12p13.3	Episodic ataxia, myokymia	RPA PCR		$V_{1/2} = -30$ mV, $\gamma \approx 9-14$ pS, no inactivation	Blockers: 4-AP (290 μ M), TEA (0.3 mM), KTX (40 nM), DTX (20 nM), nifedipine (90 μ M)	Kvb1, Kvb2	NM_000217 XM_006987	67,104,106, 182,624	
	Kv1.2: KCNA2	1p13		RPA PCR		$V_{1/2} = -27$ mV, $\gamma \approx 18$ pS, no inactivation	Blockers: 4-AP (590 μ M), TEA (560 mM), MgTX (30 nM), DTX (17 nM), ChTX (14 nM), nifedipine (20 μ M)	Kvb1 (confers rapid inactivation), Kvb2	AC025151 AC011184 NM_004974	104,106,516	
	Kv1.3: KCNA3	1p21-13.3		RPA PCR	Immuno: CCD, (AP) principal cells	$V_{1/2} = -20$ to -35 mV, $\gamma \approx 10-14$ pS, C-type inactivation	Blockers: 4-AP (195 μ M), TEA (10 mM), MgTX (150 μ M), KTX (650 pM), ChTX (3 nM), ShK-Dap22 (50 pM), correolide (300 nM), nifedipine (5 μ M), verapamil (6 μ M)	KChAP, Kvb1, Kvb2	M55515 XM_052282 AA811374	151,361,638, 639	
	Kv1.5: KCNA5	12p13		Northern		$V_{1/2} = -3$ mV, $\gamma \approx 8$ pS, no inactivation	Blockers: 4-AP (270 μ M), TEA (330 mM), nifedipine (80 μ M), flecainide (101 μ M)	Kvb3 induces inactivation, Kvb1, Kvb2	AC005906 H19662 AA220960	23,316,416, 539	
	Kv1.10: KCNA10	1p13.1		RPA PCR	Immuno: PT, (AP)	$V_{1/2} = 0$ mV, $\gamma \approx 12$ pS, no inactivation	Blockers: 4-AP (1.5 mM), TEA (50 mM), ChTX (100 nM), verapamil (45 μ M), pimoziide (300 nM) Opener: cAMP	KCNA4B increases current expression and sensitivity to cAMP	AL358215 NM_005549	300,414,552, 640,641	
	Kv2.1: KCNB1	20q13.2		Northern		$V_{1/2} = -10$ mV, slow inactivation	Blocker: TEA, hamatoxin (42 nM)	Kvb induces inactivation, KChAP increases current expression, Kv9.3	L02840 X68302	91,297,517, 615	
	Kv4.1: KCND1	Xp11.23-11.3		Northern		$V_{1/2} = -10$ mV, A-type fast inactivation	Blocker: 4-AP (9 mM), arachidonic acid ($IC_{50} \approx 25$ μ M)		M64226 S64320	59,530	
	Kv9.3: KCNS3	2p24		Northern		No expressed current			XM_141545	530	
	Voltage-gated (Kv) β -subunits	Kv1.3: KCNA3	7q35-q36	Long QT syndrome (LQT2)	PCR		$V_{1/2} = 0$ mV, $\gamma \approx 2-10$ pS, rapid voltage-dependent inactivation	Blockers: 4-AP (100 mM), TEA (33 mM), terfenadine (350 nM), ketoconazole, flecainide (20 μ M), dofetilide (12 nM) Opener: cAMP	MinK	U04246 U04270	257,461,472, 560,583
		KvLQT1: KCNQ1	11p15.5	Long QT syndrome (LQT1)	Northern, PCR	Immuno: PT, (AP)	$V_{1/2} = -40$ mV, $\gamma \approx 5$ pS, no inactivation	Blocker: chromanol-292B, Opener: stilbenes, L-364, 373, fenamates	MinK increases current and alters activation kinetics	AF000571 U89364 U40990 U71077	27,50,60,293, 471,501,554
Kv4.1: KCNA4B		13		Northern PCR	Immuno: cytoplasmic	Increases expression level of Kv1.3, Kv2.1, Kv4.3			AF029056 XM_002207	57,264,430, 504,523	

Channel Type	Common Name: Gene Name	Chromosome	Disease	Transcript	Protein	Properties	Modulators	Accessory Subunits	Accession Nos.	Reference Nos.
	MinK: KCNE1	21q22.1-22.2	Long QT syndrome (LQT5)	Northern PCR	protein Glomerulus, PT Immuno: PT, (AP)	Associates with KVLQT1			M22412 X60457	3, 27, 584
	MiRP2: KCNE3	11q13-14	Periodic paralysis	Northern		Associates with Kv3.4			AF07653 AF076532 AF302494	1, 50
Large- conductance Ca ²⁺ - activated	Maxi-K: KCNMA1	10q23.1		Northern PCR	Western	$\gamma \approx 150$ – 250 pS, activated by calcium (K_d 0.1–10 μ M) and voltage	Blockers: TEA (160 μ M), iberiotoxin (10 nM), KTX (20 nM), ChTX (3 nM)	Associates with KCMB1 or KCMB2	AF118141 U13913 U11717	124, 368, 562
β -Subunits of maxi-K	BKcab2-subunit: KCNMB2			Northern		Associates with KCMA1			NM_005832 AY062429	44, 110, 123, 376, 571
	BKcab4-subunit: KCNMB4	12q14.1-q15		Northern		Associates with KCMA1			XM_113249 AB050637	40, 377
Small- conductance Ca ²⁺ - activated	SK2: KCNN2	5q21.2-q22.1		Northern		$\gamma \approx 5$ pS, calcium activation: K_d 0.7 μ M	Apamin, scyllatoxin, D-tubocurarine		XM_011226	270, 456, 524
Inward rectifiers (Kir)	Kir1.1: KCNJ1	11q24-25	Bartter's	Northern PCR	Immuno: TAL, DCT, CD (AP)	$\gamma = 28$ pS	Blockers: δ -dendrotoxin, tetiapin Ba^{2+} , regulators: ATP, K^+ diet	Possibly CFTR or SUR2B	O547736 Q456388	53, 213, 228, 247, 259, 284, 305, 379, 513, 579, 629, 637, 652
	Kir2.3 (a.k.a. CCD-IRK ₃)			Northern PCR		$\gamma = 14.5$ pS	Inhibitors: Ba^{2+} , quinine Insensitive to: olfendamide TEA		G1708551 G1708552	306, 307, 308, 387, 412, 614
	Kir4.1 (a.k.a., Kir1.2, BIRK1, K _{AB} -2, BIR10, KCNJ10)	1			Co-IPs with Kir5.1 in rat immuno: DCT, CNT and CCD (BL)		pH	Forms heteromer with Kir5.1	G1352478 G2274795 G1518530	234, 507, 543, 567
	Kir4.2 (a.k.a. Kir1.3, KCNJ15)	21q22.2	Down's region	Northern					Y10745	179
	Kir5.1 (a.k.a. BIR9)				Co-IPs with Kir4.1 in rat	Nonfunctional when expressed alone		Forms heteromer with Kir4.1	G13878925	55, 543, 567
	Kir6.1 (a.k.a., uKATP1)				PT	$\gamma = 35$ – 70 pS	Inhibitors: glibenclamide when expressed with SUR Regulators: ATP	SUR2A SUR2B	Q2493602 AF417509	14, 39, 65, 232, 544
	Kir7.1			PCR	Western: TAL, DCT, CNT, CCD, OMCD, IMCD Immuno: PT, TAL (BL)	$\gamma = 50$ fS– 12.7 pS	External blockers: low sensitivity to Ba^{2+} , Cs^+ Regulators: K^+ diet, reduced mRNA and protein with low- K^+ diet, reversed by high- K^+ diet	AB013889 AB013890	100, 118, 283, 413, 427	

Channel Type	Common Name: Gene Name	Chromosome	Disease	Transcript	Protein	Properties	Modulators	Accessory Subunits	Accession Nos.	Reference Nos.
2-Pore channels	K _{2p} 1.1 (a.k.a., KCNK1, TWIK-1, hOHO)	1q42-43	Unknown	Northern PCR: CTAL, CNT, CCD	PCT(AP), CTAL, MTAL, CD(IC)	$\gamma = 30-40$ pS $Rb > K > Cs > NH4 >> Na > Li$	Blocker: Ba ²⁺ , quinidine but not TEA	Not established	NM_002245	16 90 174 309 311 312 375 415 607
	K _{2p} 3.1 (a.k.a., KCNK3, TASK-1, TBAK-1, OAT-1)	2p24.1-23.3	Unknown	Northern	Unknown	$\gamma = 10$ pS	O ₂ sensing inhibitors: Ba ²⁺ low pH _i , AA Activators: halothane, isoflurane	Not established	NM_002246	122 174 312 429
	K _{2p} 4.1 (a.k.a., KCNK4, TRAAK)	11q13	Unknown	Northern	Unknown	$\gamma = 46$ pS	Blocker: Gd ³⁺ Activator: AA, unsaturated FA, mechanical stress	Not established	NM_016611	313 357 375 417
	K _{2p} 5.1 (a.k.a., KCNK5, TASK-2)	6p21	Unknown	PT, distal tubules and CCD	Unknown	$\gamma = 15$ pS	Cell volume; Blockers: quinidine, low pH _i , lidocaine, bupivacaine	Not established	NM_003740	28 389 399 455
	K _{2p} 10.1 (a.k.a., KCNK10, TREK-2)	14q31	Unknown	PCR	Unknown	$\gamma = 100$ pS	Blocker: quinidine Activators: AA, low pH _i , volatile anesthetics, mechanical stress	Not established	NM_138317	25 186 269 375
	K _{2p} 12.1 (a.k.a., KCNK12, THIK-2)	2p22-p21	Unknown	PCR	Unknown	Not established	Not established	Not established	NM_022055	449
	K _{2p} 13.1 (a.k.a., KCNK13, THIK-1)	14q24.1-24.3	Unknown	PCR	Unknown	Not established	Not established	Not established	NM_022054	449
	K _{2p} 15.1 (a.k.a., KCNK125, TASK-5, KT3.3)	20q12	Unknown	In kidney by PCR but not by Northern	Unknown	Not established	Not established	Not established	NM_022358	20 268

RPA, RNase protection assay; PCR, polymerase chain reaction; V_{1/2}, voltage for half-maximal activation; γ , single-channel conductance; 4-AP, 4-aminopyridine; TEA, tetraethylammonium; KTX, kaliotoxin; DTX, dendrotoxin; MgTX, margatoxin; ChTX, charybdotoxin; AA, arachidonic acid; FA, fatty acids; CCD, cortical collecting duct; DT, distal tubule; PT, proximal tubule; AP, apical; BL, basolateral.

TABLE 2

Properties of K⁺ channels in the kidney

Tubule/Species	Location	γ	P_o	Voltage	Regulation	Reference Nos.
Proximal/rabbit	BL	54/10 pS* (127/127K)	0.06	Depolarization	Unknown	426
	BL	41/11 pS [†] (145/4.7K)	0.3–0.4	Unknown	Not sensitive to Ca ²⁺	260
	BL	50–61/17 pS [†] (150/5K)	0.15–0.20	Depolarization	pH, taurine, ATP	35, 260, 405, 563
	BL	12/? pS [†] (150/140K)	0.67	Unknown	Unknown	405
	AP	33/10 pS [†] (145/4.7K)	Unknown	Unknown	Unknown	171
	AP	200/200 pS* (140/140K)	<0.01	Depolarization	pH, Ca ²⁺	380
	AP	42/42 pS* (140/140K)	0.5	Unknown	Unknown	380
	Unknown	138/225 pS [†] (150/4.7K)	<0.01	Unknown	Stretch, Ca ²⁺	262
Proximal/mouse	AP	63/63 pS [†] (145/4.7K)	Unknown	Unknown	Unknown	171
Proximal/ <i>Necturus</i>	BL	31/? pS [†] (100/2.5K)	0.01	Hyperpolarization	Unknown	261
	BL	36/36 pS* (70/70K)	0.02	Hyperpolarization	Stretch	468
	BL	24.5/3.7 pS [†] (95/2.5K)	0.4	Unknown	PKA, PKC, pH, ATP	367
	AP	30/? pS [†] (100/2.5K)	0.01	Depolarization	Unknown	261
Proximal/frog	BL	30/6 pS* (100/100K)	0.2	Depolarization	Unknown	218
	BL	30/29 pS [†] (100/100K)	0.03	Hyperpolarization	Stretch	260
Macula densa/rabbit	AP	41/? pS [†] (140/5K)	0.8	Unknown	pH, Ca ²⁺ (inhibition)	221
TAL/rabbit (culture)	BL	35/7 pS [†] (140/5K)	0.2	Unknown	pH	222
	AP	146/146 pS* (140/140K)	0.01	Depolarization	AA, Ca ²⁺	172
TAL/rat and mouse	BL	41/10 pS	0.5	Depolarization	20-HETE, low pH _i	183, 431
TAL/rat and rabbit	AP	30–35/10 pS [†] (140/5K)	0.9	Voltage independent	PKA, ATP	504, 599
TAL/rat	AP	70–75/19 pS* (145/4.2K)	0.4	Depolarization	PKA, PKC, pH, AA, cGMP, CO, ATP	49, 589
Diluting tubule/frog	AP	26/10 pS* (100/100K)	0.6	Depolarization	pH	222
DCT/rabbit	BL	48–60/? pS [†] (130/5K)	Unknown	Unknown	pH	545
CCD (principal cell)/rat	AP	35–40/12 pS* (140/140K)	0.9	Slightly activated by depolarization	PKA, PKC, AA, ATP, Mg ²⁺	153, 324, 478, 598

Tubule/Species	Location	γ	P_o	Voltage	Regulation	Reference Nos.
	AP	>?/110 pS [†] (5/5K)	0.01	Depolarization	pH, Ca ²⁺	152, 207, 220, 525
	BL	18/5 pS* (140/140K)	0.5	NO	PKG, pH	605
	BL	85/? pS* (140K/140K)	0.05	Hyperpolarization	PKA, pH	605
	BL	148/? pS* (145/3.6K)	0.6	Unknown	PKG, NO, pH	208, 209
	BL	67/? pS [†] (145/3.6K)	Unknown	Unknown	PKG, NO, pH	208, 209

The channel conductance (γ) is denoted as inward/outward. The K⁺ concentrations (mM) are shown as pipette/bath solution. The patch-clamp configurations are indicated as for inside-out patch (*) or as for cell-attached patches ([†]). BL and AP are basolateral membrane and apical membrane, respectively. See text for other definitions.