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Potassium Transport in the Mammalian Collecting Duct

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Muto, Shigeaki. Potassium Transport in the Mammalian Collecting Duct. *Physiol Rev* 81: 85–116, 2001.—The mammalian collecting duct plays a dominant role in regulating K^+ excretion by the nephron. The collecting duct exhibits axial and intrasegmental cell heterogeneity and is composed of at least two cell types: collecting duct cells (principal cells) and intercalated cells. Under normal circumstances, the collecting duct cell in the cortical collecting duct secretes K^+, whereas under K^+ depletion, the intercalated cell reabsorbs K^+. Assessment of the electrochemical driving forces and of membrane conductances for transcellular and paracellular electrolyte movement, the characterization of several ATPases, patch-clamp investigation, and cloning of the K^+ channel have provided important insights into the role of pumps and channels in those tubule cells that regulate K^+ secretion and reabsorption. This review summarizes K^+ transport properties in the mammalian collecting duct. Special emphasis is given to the mechanisms of how K^+ transport is regulated in the collecting duct.

I. INTRODUCTION

K^+ is the most abundant cation in the intracellular fluid and is required for many normal functions of the cell. The average daily dietary intake of K^+ is ~75–100 meq. Each day 90–95% of dietary K^+ is normally excreted into urine, and the 5–10% is excreted into stools (95, 96, 383). The internal K^+ distribution needs to be tightly regulated, because movement of a range of a mere 1–2% of K^+ from the intracellular to the extracellular fluid compartment can result in a potentially fatal increase in plasma K^+ concentration.

Much of our knowledge of K^+ handling by the mammalian kidney has been based on clearance and in vivo micropuncture studies of the rat kidney, which are necessarily confined to superficial nephrons (78, 96, 173, 185, 383) (Fig. 1). K^+ is freely filtered across the glomerulus. The bulk of the filtered K^+ is reabsorbed in the proximal tubule and the loop of Henle, such that the only 10% is delivered to the distal tubule. In the micropuncture literature, the distal tubule is the nephron segment extending from the macula densa region to the first confluence with another distal tubule. This part of the renal tubule is composed of three ultrastructurally and functionally distinct segments (139, 302): the distal convoluted tubule, the connecting tubule, and the initial collecting tubule. The final urine may contain as little as 5% or as much as 200% of the filtered K^+ load, indicating that the distal nephron, mainly the collecting duct, is capable of either K^+ secretion or reabsorption. Under normal circum-

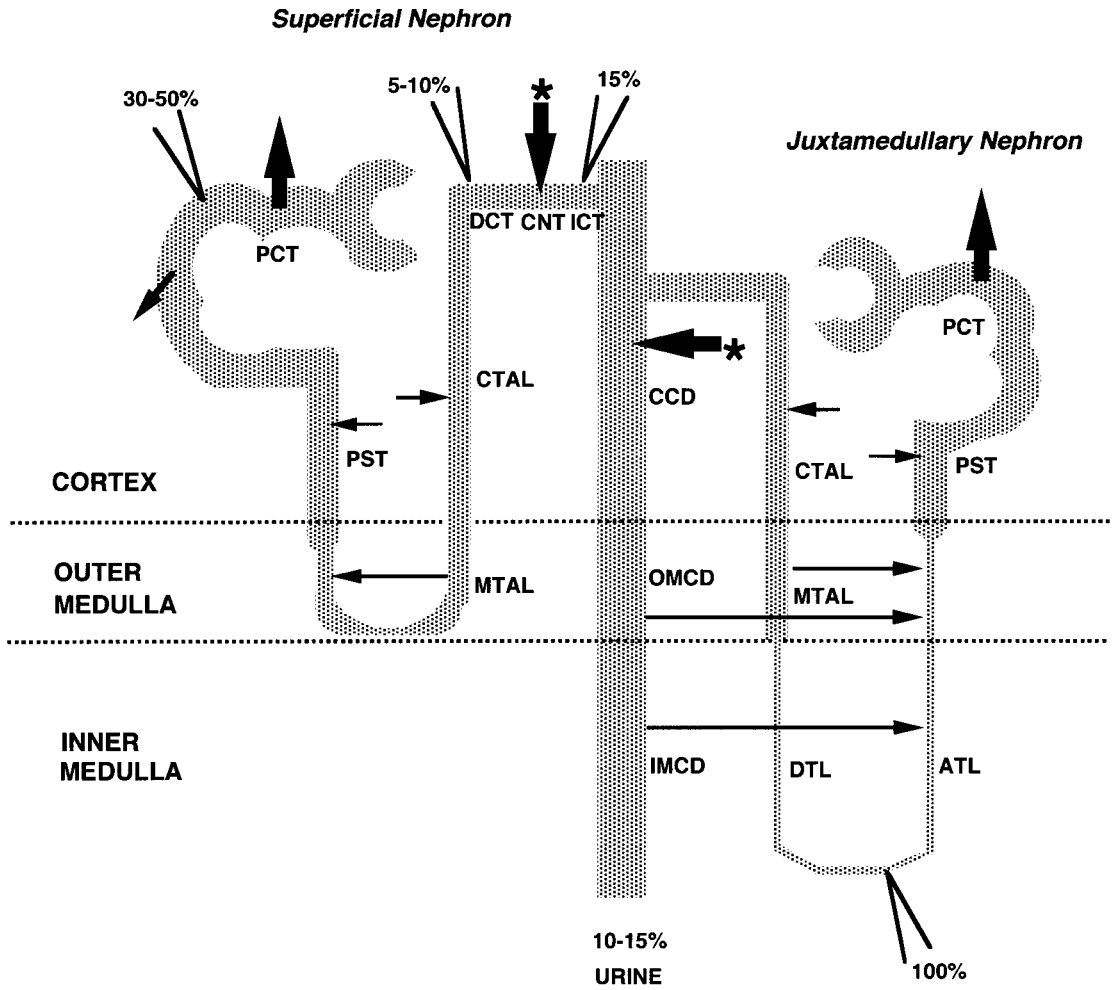

FIG. 1. K^+ transport along the nephron segments (78). Percentage data refer to estimates of the fraction of the filtered K^+ load remaining at the sites shown. Arrows show direction of net K^+ transport (reabsorption or secretion). Asterisk shows major sites of K^+ secretion. PCT, proximal convoluted tubule; PST, proximal straight tubule; DTL, descending thin limb; ATL, ascending thin limb; MTAL, medullary thick ascending limb of Henle's loop; CTAL, cortical thick ascending limb of Henle's loop; DCT, distal convoluted tubule; CNT, connecting tubule; ICT, initial collecting tubule; CCD, cortical collecting duct; OMCD, outer medullary collecting duct; IMCD, inner medullary collecting duct.

stances, K^+ is secreted into the lumen, mainly in the distal tubule and the cortical collecting duct, whereas under K^+ depletion, K^+ is absorbed from the lumen in the outer medullary collecting duct. Therefore, varying the rate of K^+ secretion or reabsorption along the collecting duct determines the final urinary concentration and amount of K^+. On the other hand, K^+ secreted into the distal tubule and the cortical collecting duct is partly reabsorbed in the region of the inner stripe of the outer medulla. K^+ is also absorbed from the thick ascending limb of Henle's loop. The resulting high medullary interstitial concentrations of K^+ provide a gradient favoring passive secretion of K^+ into the proximal straight tubule and the descending thin limb of Henle's loop (K^+ recycling).

Our understanding of the ion transport properties of the mammalian collecting duct, including K^+, relied greatly on the development of the in vitro microperfusion technique of the isolated renal tubule originally described by Burg et al. (37), because the cortical and outer medullary collecting ducts are inaccessible to micropuncture. However, this technique had some limitations because of the presence of different cell types that may vary in their functions. Some of these limitations have been overcome with an application of microelectrode techniques to the isolated perfused collecting duct segments (61, 129, 133, 148–151, 212–224, 235, 238, 239, 267–270, 275, 280, 281, 305, 325, 326). Also, the recent development of the patch clamp and advances in molecular biological techniques provided us further detailed K^+ transport properties of the collecting ducts. Information obtained using the above techniques is reviewed, with emphasis on the cellular and membrane mechanisms. I also consider how K^+ transport in the collecting duct is regulated in response to a number of physiological stimuli.

II. CELLULAR MECHANISMS OF POTASSIUM TRANSPORT IN THE COLLECTING DUCT

The collecting ducts are formed in the renal cortex by the connection of several nephrons. They descend within the medullary rays of the cortex, penetrate the outer medulla, and in the inner medulla they successively fuse together. Based on their location within the kidney, the collecting duct can be subdivided into the cortical collecting duct (CCD), the outer medullary collecting duct (OMCD), and inner medullary collecting duct (IMCD) (138, 182, 331) (see Fig. 1). Furthermore, the OMCD can be subdivided into an outer and inner stripe portion (138, 182, 331). The CCD and OMCD are unbranched along their entire length, whereas the IMCD is a highly branched structure (138, 182).

Studies of the transport properties of various portions of the collecting duct have demonstrated considerable axial heterogeneity. Table 1 summarizes the transepithelial and cellular electrical properties of the various collecting duct segments from rabbit kidneys. In particular, the CCD is a site for K^+ secretion and Na^+ reabsorption. The secretory capacity for K^+ diminishes sharply with the transition to the outer medulla. The transepithelial voltage (V_T) is oriented lumen-negative in the cortex and outer stripe but becomes lumen-positive within the inner stripe. A progressive decline in the magnitude of the basolateral membrane voltage (V_B) along the collecting ducts is also observed. Heterogeneity in the conductive properties of these segments is further apparent from the values of transepithelial resistance (R_T) and fractional apical membrane resistance (fR_A). The R_T increases progressively along the collecting duct, as does the fR_A. This latter parameter is defined as the resistance of the apical membrane divided by the resistances of the apical plus basolateral membranes and indicates a marked reduction of the apical membrane conductance in the medullary segments. Similar findings are also obseved in the rat collecting duct (265, 275, 305).

A. Cortical Collecting Duct

The CCD can be subdivided into the initial collecting tubule (ICT), which together with the connecting tubule (CNT) constitutes the "late distal tubule" in in vivo micropuncture studies, and the portion in the medullary ray that corresponds to the cortical collecting tubule in isolated perfused tubule segments (138, 182, 331). The CCD plays a dominant role in regulating K^+ excretion by the nephron (78, 94, 96, 105, 118, 151, 173, 184–186, 212–224, 237–239, 267–269, 287, 302–309, 316, 318) (Table 1 and Fig. 1).

The cells lining the CCD can be divided into at least two cell types: principal cells and intercalated (IC) cells (76, 125, 138, 166, 182, 216, 224, 235, 256, 272, 302) (Fig. 2). In analogy with the denomination of cell types in the other collecting ducts, which also may have heterogeneous cell populations, in this review I use "collecting duct cell" or "CD cell" instead of "principal cell," according to the recommendation of the Renal Commission of the International Union of Physiological Science (331). The CD cells total ~70–75% of all cells, whereas the IC cells represent the remaining 25–30% of cells (138, 182, 235, 350). The CD cell is mainly involved in the secretion of K^+ and the reabsorption of Na^+ (Fig. 2). Transport involves both passive movement through ionic conductances at both cell borders and active movement through the Na^+-K^+-ATPase pump (Na^+-K^+ pump) at the basolateral border of the cell (61, 115, 151, 213–224, 235, 237–239, 267, 269, 275, 281). K^+ secretion in the CD cell is an active process directly linked to the active Na^+ reabsorption via the basolateral membrane Na^+-K^+ pump. This is followed by the passive diffusion of K^+ from the cell into the lumen, down a favorable electrochemical gradient via an apical membrane K^+ conductance. K^+ also recycles across the basolateral membrane by passive diffusion along a favorable electrochemical gradient via a basolateral membrane K^+ conductance. Both exit steps of K^+ are inhibited by Ba^{2+}. On the other hand, Na^+ is reabsorbed passively from lumen to cell along its electrochemical

TABLE 1. *Electrophysiological and transport heterogeneity of the rabbit collecting duct*

	V_T, mV	R_T, $\Omega \cdot cm^2$	V_B, mV	fR_A	J_{Na}, pmol · $mm^{-1} \cdot min^{-1}$	$-J_K$, pmol · $mm^{-1} \cdot min^{-1}$	Reference No.
CCD	−1.9 to −32.1	81 to 203	−74 to −85	0.31 to 0.54	21.5 to 44.6	7.2 to 28.1	31, 60, 81, 115, 120, 124, 133, 151, 162, 172, 212–218, 220–222, 224, 234, 238, 239, 267, 269, 270, 287, 310, 315, 317, 318, 325, 326, 379
OMCDo	−2 to −10.7	233 to 272	−64 to −67	0.81 to 0.82	7.9	2.5	149, 150, 318
OMCDi	+2 to +47.9	265 to 534	−25 to −32	0.93 to 0.99	1.5	−0.1	116, 133, 148, 164, 172, 219, 224, 317–320, 338

V_T, transepithelial voltage; R_T, transepithelial resistance; V_B, basolateral membrane voltage; fR_A, fractional apical membrane resistance; J_{Na}, net sodium reabsorption rate; $-J_K$, net potassium secretion rate; CCD, cortical collecting duct; OMCDo, outer stripe of the outer medullary collecting duct; OMCDi, inner stripe of the outer medullary collecting duct. V_B and fR_A were taken from collecting duct cells only.

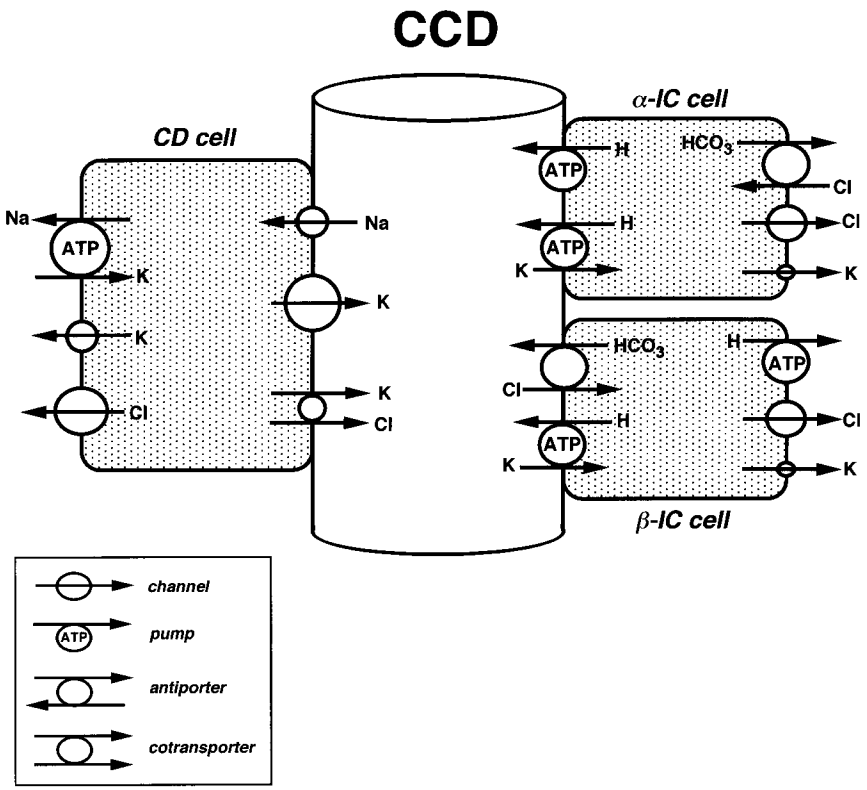

FIG. 2. Major transport systems in the cortical collecting duct (CCD). Models are based on data obtained in the rabbit CCD (61, 115, 151, 206, 213–224, 234–239, 256, 267–270, 283, 298, 315, 317, 318, 325, 326, 369–371, 381). CD cell, collecting duct cell (principal cell); α-IC cell, α-intercalated cell (type A intercalated cell); β-IC cell, β-intercalated cell (type B intercalated cell).

gradient via the apical Na^+ conductance and is transported actively from cell to blood by the basolateral Na^+-K^+ pump. This apical membrane Na^+ conductance is blocked by amiloride. In rat and rabbit CCDs, both Na^+ reabsorption and K^+ secretion are active in nature; however, in the normal rat CCD, transport of Na^+ or K^+ is not detectable (46, 254, 334) and V_T is near 0 mV (46, 254, 334), whereas the normal rabbit CCD has measurable transport rates of Na^+ and K^+ (31, 81, 115, 124, 216, 217, 287, 315, 317, 318) and a lumen-negative V_T (31, 61, 81, 115, 124, 133, 151, 172, 212–222, 224, 234, 238, 239, 267, 269, 270, 287, 310, 315, 317, 318, 325, 326, 379) (see Table 1). In addition, the basolateral membrane of the CD cell has only K^+ conductance in the rat CCD (279); however, in the rabbit CCD, this membrane has an additionally large Cl^- conductance exceeding the K^+ conductance (216, 224, 238, 270, 267) (Fig. 2). Microperfusion studies of superficial distal tubules of rat (67) and of isolated rabbit CCDs (378) have provided evidence for an electroneutral K^+-Cl^- cotransport mechanism in the apical membrane (Fig. 2).

The carbonic anhydrase-rich IC cells consist of at least two cell types with distinct functional polarities: α-IC cells (or type A IC cells) are organized for H^+ secretion and β-IC cells (or type B-IC cells) for HCO_3^- secretion (33, 34, 125, 138, 166, 182, 283, 285, 286, 345, 370, 371). The presence of both types of IC cells in the CCD supports the findings that the CCD can secrete H^+ or HCO_3^- depending on the acid-base status of the whole animal (134, 164, 172, 196–198, 310). Posturated transport pathways in α- and β-IC cells are also illustrated in Figure 2. The V_B in both types of the IC cells is much lower than the surrounding CD cells, averaging -30 to -40 mV, compared with -70 to -80 mV in the CD cells (212, 216, 221, 224, 235). The Na^+-K^+-ATPase in the basolateral membrane of both α- and β-IC cells has a much lower activity than that of the CD cells (74, 219, 272). The apical membrane of both IC cells does not appear to contain appreciable ion conductances (216, 224). Thus there are several important functional differences between IC cells and CD cells. Although both α- and β-IC cells have a large Cl^- conductance (216, 224) and a small K^+ conductance (216, 224) at the basolateral membrane, the distribution of the H^+-ATPase pump (H^+ pump) and the Cl^-/HCO_3^- exchange are opposite (33, 125, 283, 285, 286, 345, 370, 371). The α-IC cell possesses a H^+ pump at the apical membrane and a Cl^-/HCO_3^- exchange at the basolateral membrane, whereas the β-IC cell has a H^+ pump at the basolateral membrane and a Cl^-/HCO_3^- exchange at the apical membrane. The basolateral Cl^-/HCO_3^- exchange is immunologically similar to the Cl^-/HCO_3^- exchange of the mammalian red blood cell, band 3 protein (283, 345) and is sensitive to the disulfonic stilbenes (219, 283), whereas the apical Cl^-/HCO_3^- exchange binds peanut lectin (283, 345) and is resistant to the disulfonic stilbenes (219, 283). Both types of IC cells are not responsible for any direct

transcellular transport of Na^+ or K^+ under normal conditions. In addition, there is axial heterogeneity of both types of IC cells along the collecting ducts; that is, the number of β-IC cells is greater in the cortex, whereas the number of α-IC cells is greater in the outer medulla (224, 283). In contrast to CD cells, an H^+-K^+ exchange pump is identified at the apical membrane of both α- and β-IC cells (206, 298, 369). Under K^+ depletion, the apical H^+-K^+ pump reabsorbs K^+ (393).

B. Outer Medullary Collecting Duct

The outer stripe of the OMCD (OMCDo) in both rats and rabbits is morphologically similar to that of the CCD. The OMCDo is composed of two cell types: CD cells and IC cells (33, 149, 150, 161–163, 182, 256) (Fig. 3). The CD cell reabsorbs Na^+ and secretes K^+, but at rates below those found in the CCD (318) (Table 1). The cellular model of the CD cell in this segment is similar to that described above for the CCD, but some important differences do exist. The apical membrane of the CD cell is dominated by a Na^+ conductance, and only a small K^+ conductance is observed (318). This is in contrast to the apical membrane of the CD cell in the CCD, where the K^+ conductance predominates (see Fig. 2). In addition, the only appreciable conductive pathway in the basolateral membrane of the CD cell in this segment is for K^+ (149). No Cl^- conductance has been demonstrated (149). Because the OMCDo has only been found to secrete H^+, most of the IC cells in this segment are acid-secreting α-IC cells (33, 149, 150, 162–164, 172, 199, 256). An H^+-K^+ exchange pump is also identified at the apical membrane of the IC cell in this segment (38, 40, 161, 381). Therefore, the transport properties of the IC cells in this segment are virtually identical to those described for the α-IC cells of the CCD (see Figs. 2 and 3).

The inner stripe of the OMCD (OMCDi) differs morphologically between rats and rabbits. In the rat, the OMCDi appears to be similar to the OMCDo in that both CD and α-IC cells are present (182). However, in the rabbit, the cells cannot be classified as either IC cells or CD cells based on their ultrastructural features (256), although morphological (255) and immunocytochemical (283) studies suggest that the rabbit OMCDi is heterogeneous with respect to cell composition. Functionally, the rabbit OMCDi specializes in urine acidification (116, 134, 148, 224, 318) and does not participate in either Na^+ or K^+ transport under normal conditions (148, 219, 224, 318) (Table 1). Therefore, this segment is functionally composed of only one cell type: the acid-secreting cell (148, 162, 163, 172, 219, 224, 380) (Fig. 4). The presence of only the acid-secreting cell type in the OMCDi supports the findings that the OMCDi always secretes H^+, irrespective of the acid-base status of the whole animal (134, 164, 172, 319, 320). The apical membrane contains a H^+-ATPase, which behaves as a constant current source extruding positive charges from the cell. No other ion conductances have been identified in this membrane. Cellular HCO_3^- exits across the basolateral membrane in exchange for Cl^- (148, 224). This process is electrically silent and is inhibited by the disulfonic stilbenes (148, 219). The Cl^- that is brought into the cell by the exchanger recycles across the basolateral membrane. This conductive exit step for Cl^- together with the apical membrane H^+-ATPase leads to the bath-to-lumen flow of positive current and results in the generation of a lumen-positive V_T. The lumen-positive V_T in turn provides a driving force for the paracellular movement of ions. Because the paracellular

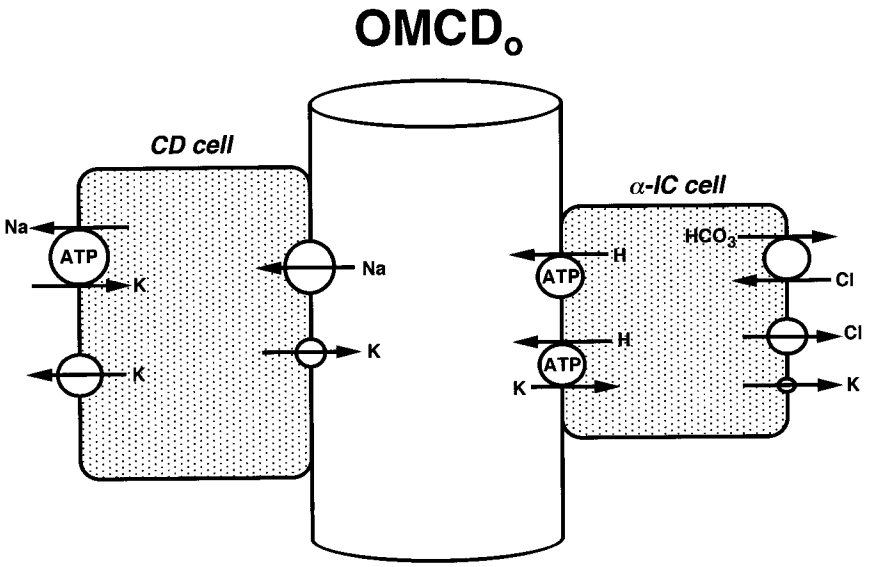

FIG. 3. Major transport systems in the outer stripe of outer medullary collecting duct (OMCDo). Models are based on data obtained in the rabbit OMCDo (149, 150, 161–164, 172, 199, 256). Definitions are as in Figure 2.

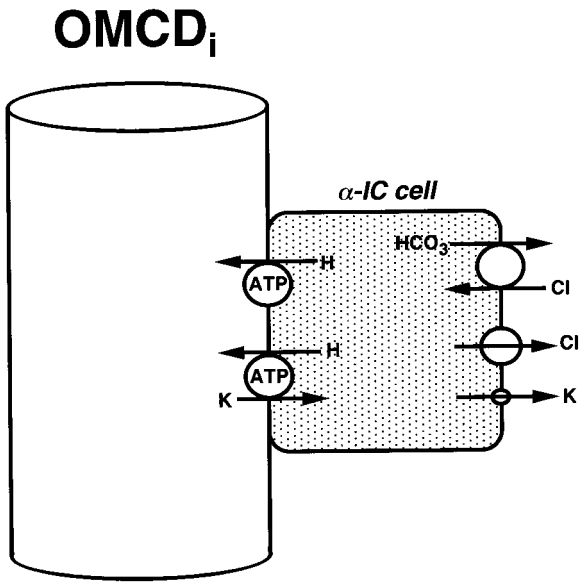

FIG. 4. Major transport systems in the inner stripe of outer medullary collecting duct (OMCDi). Models are based on data obtained in the rabbit OMCDi (9, 148, 161, 163, 219, 224, 256, 286, 315, 376). Definitions are as in Figure 2.

pathway of this segment is relatively nonselective (148), the lumen-positive V_T can drive either cation reabsorption (e.g., K^+) or anion secretion (e.g., Cl^-). An active H^+/K^+ exchange mechanism has been detected in the apical membrane of this segment and has been activated in K^+-deficient rabbits (9, 161, 376, 380) and rats (226). Activation of this transporter contributes to the stimulation of K^+ reabsorption and H^+ secretion that is observed under K^+ depletion. Thus the transport characteristics of the cells in the OMCDi from rabbits are similar to those of the α-IC cells from the CCD (see Figs. 2 and 4).

C. Inner Medullary Collecting Duct

On the basis of morphological and functional data, the IMCD can be subdivided into two regions: the initial IMCD (IMCDi) and the terminal IMCD (IMCDt) (138, 182, 256). The IMCDi comprises the initial one-third to one-half of the IMCD. In the rat, the IMCDi consists of 90% CD cells and 10% acid-secreting α-IC cells (182). In the rabbit, the IMCDi is composed entirely of CD cells (138, 256). This cell has positive staining for carbonic anhydrase and Na^+-K^+-ATPase in the basolateral membrane (256) and therefore appears to be involved in urine acidification. In both species, the IMCDt is also composed of a single cell type (138, 182, 256). Although referred to as CD cells, they do not have the same ultrastructural features of the CD cells of either the CCD or OMCD (182, 256, 308) and therefore are called IMCD cells. The cells possess Na^+-K^+-ATPase in the basolateral membrane (256, 329) but do not stain for carbonic anhydrase (182, 256).

The postulated transport pathways in the IMCD are summarized in Figure 5. When single tubules are perfused in vitro with symmetrical solutions, the V_T of IMCDi is −2 to −3 mV (258, 305), while the V_T of the IMCDt under similar conditions is near 0 mV (129, 158, 259). The V_B in the IMCDi is −50 mV (305), whereas in the IMCDt it is −80 mV (129). The fR_A values in the IMCDi and IMCDt are 0.94 (305) and 0.98 (129), respectively, indicating that the apical membrane conductance in both IMCD subsegments is very low. In the IMCD, Na^+ absorption has been demonstrated but at very low rates compared with the CCD (158, 265). Na^+ enters the cell across the two classes of epithelial Na^+ channels in the apical membrane (168, 229, 241, 349) and exits across the Na^+-K^+ pump in the basolateral membrane (129, 305). One class of the epithelial Na^+ channels is a nonselective cation channel (168, 229, 241). Another class of the Na^+ channels is a highly selective Na^+ channel (240, 349). These two classes of Na^+ channels can be inhibited by amiloride (168, 229, 241, 349). In contrast, net K^+ transport does not occur under normal circumstances. It requires extreme alterations in K^+ intake to affect net K^+ secretion or absorption (57). The H^+-K^+-ATPase is present in the apical membrane of the IMCDt from rat kidneys (222) and in cultured IMCDt cells (352) and appears to be involved in K^+ absorption under K^+ depletion (225). In the basolateral membrane, Ba^{2+}-sensitive K^+ conductance (129, 305), furosemide-sensitive Na^+-K^+-$2Cl^-$ cotransport (108, 258, 390), and DIDS-sensitive HCO_3^- conductance (308) are present. There is no evidence for a Cl^--conductive pathway in the basolateral membrane (308).

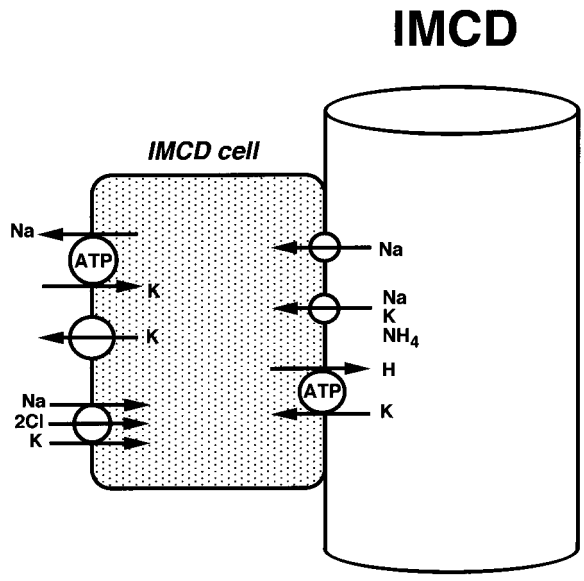

FIG. 5. Major transport systems in the inner medullary collecting duct (IMCD). Models are based on studies done in the rat IMCD (108, 168, 225, 229, 240, 241, 258, 305, 349, 352, 390). Definitions are as in Figure 2.

III. POTASSIUM CHANNELS IN THE COLLECTING DUCT

A. Apical K^+ Channels

Two types of K^+ channels, low-conductance K^+ channel and maxi K^+ channel, have been found in the apical membrane of the CCD of both rats and rabbits (83, 84, 93, 97, 120, 127, 128, 156, 157, 271, 354–360, 364, 365).

1. Low-conductance K^+ channel

The low-conductance K^+ channel is identified in the apical membrane of the CD cells from both rat (84, 93, 360) and rabbit (271) CCDs. This K^+ channel is inwardly rectifying with an inward slope conductance of 25 pS and an outward slope conductance of 9 pS at room temperature, and the open probability of the channel is near 0.9 over a wide range of membrane potentials (84, 360). The channel is blocked by Ba^{2+} from outside the cell (84) and by reduced intracellular pH (279, 356, 360) and is permeant to Rb^+ (84). Furthermore, it is insensitive to Ca^{2+} in the cytoplasmic side (84) and to tetraethylammonium (TEA) from outside the cell (360). Thus the properties of the channels make them strong candidates responsible for K^+ secretion in the CCD (83, 84). Table 2 summarizes the regulation of the low-conductance K^+ channel.

The number of low-conductance K^+ channel at the apical membrane of the CD cell in the rabbit CCD increases during postnatal life most likely to contribute to the maturational increase in net K^+ secretion (271).

TABLE 2. *Regulation of apical K^+ channels in the cortical collecting duct*

Channel Conductance, pS	Stimulatory Factors	Inhibitory Factors	Reference No.
25–35 (low-conductance K^+ channel)	pH_i ↑ PKA + low ATP Vasopressin High-K^+ diet	Ba^{2+} High ATP PKC CaMKII Arachidonate pH_i ↓ Glyburide Cytochalasin	84, 93, 156, 157, 271, 279, 337, 354–357, 360, 364–366
80–140 (maxi K^+ channel)	pH_i ↑ $[Ca^{2+}]_i$ ↑ Stretch Depolarization	Ba^{2+} TEA Quinine Quinidine Verapamil Diltiazem Charybdotoxin	83, 120, 127, 128, 240, 245, 271, 278

Conductances are single-channel conductances as given by authors. Of course, single-channel conductance varies with potential, K^+ concentration in the pipette, and ambient temperature. Because conditions used were not identical among different studies, the numbers are only in part comparable. CAMKII, Ca^{2+}/calmodulin-dependent protein kinase II; $[Ca^{2+}]_i$, intracellular Ca^{2+}; pH_i, intracellular pH; PKA, protein kinase A; PKC, protein kinase C; TEA, tetraethylammonium.

ATP-sensitive K^+ channels, found in tissues such as heart, pancreatic β-cells, skeletal muscles, smooth muscles, central nervous sytem, and kidney, are a family of K^+ channels defined by their inhibition in response to increased cytosolic ATP concentrations (12, 28, 132, 154, 155, 167). The apical low-conductance K^+ channel of the CCD is also a member of the ATP-sensitive K^+ channels. This is supported by several lines of evidence. Channel activity was inhibited by high concentrations of ATP (1 mM) in inside-out patches (356, 360). The application of an inhibitor of ATP-sensitive K^+ channels, glyburide, inhibited the low-conductance K^+ channel activity (364), whereas an opener of ATP-sensitive K^+ channels, cromakalim, antagonized the inhibitory effect of ATP on low-conductance K^+ channel activity (354). Although millimolar ADP inhibited channel activity, it abolished the inhibitory effect of ATP on channel activity (356, 360). In addition, application of a nonhydrolyzable ATP caused no effect on channel activity (356, 360). Therefore, the cytosolic ATP/ADP ratio rather than the total ATP concentration is the important regulator of the apical low-conductance K^+ channel (356, 360). In the proximal tubule, basolateral ATP-sensitive K^+ channel activity is increased by stimulating transcellular Na^+ transport, which reduces intracellular ATP concentrations (337). If a similar mechanism is present in the CD cell, activation of the basolateral Na^+-K^+ pump could consume more ATP and produce more ADP, and the resulting decline in the ATP/ADP ratio would be expected to release the apical K^+ channel from ATP inhibition. The inhibitory effect of high concentrations of ATP (1 mM) on channel activity in inside-out patches is attenuated by the addition of an exogenous protein kinase A (PKA) catalytic subunit to the bath (356). On the other hand, the channel activity in inside-out patches is restored by low concentrations of ATP (0.05–0.1 mM) in the presence of PKA (356). Thus ATP has dual effects on the channel activity. It has been postulated that ATP at low concentrations is a substrate for PKA that phosphorylates the K^+ channel to maintain normal function, whereas ATP at high concentrations inhibits the channel activity by the inhibition of the PKA-induced channel phosphorylation (356).

The apical low-conductance K^+ channel activity declines progressively upon membrane excision in ATP-free solution (356). This channel rundown can be explained by dephosphorylation induced by membrane-bound protein phosphatases, which are okadaic acid sensitive and Mg^{2+} dependent (156, 356).

As mentioned above, K^+ secretion in the CCD occurs by two separate steps: active uptake of K^+ into the cell via the basolateral Na^+-K^+-ATPase and passive diffusion of K^+ from the cell to lumen via the apical K^+ conductance. The tight coupling between the apical K^+ conductance and the basolateral Na^+-K^+-ATPase turnover may play a crucial role in K^+ secretion. Possible mechanisms that

could account for the coupling between the basolateral and apical transport have been proposed. They include ATP/ADP ratio and intracellular Ca^{2+} concentration (366). In the rat CCD, intracellular Ca^{2+} plays a key role in the coupling between the basolateral and apical transporters (366), as shown in the following observations. Inhibition of the basolateral Na^+-K^+-ATPase by strophanthidin or by removal of bath K^+, a manipulation that raises intracellular Ca^{2+} concentrations through a mechanism involving inhibition of the basolateral Na^+/Ca^{2+} exchange, inhibits apical low-conductance K^+ channel activity, whereas removal of extracellular Ca^{2+} inhibits this effect. The effect of the pump inhibition on channel activity is mimicked by raising intracellular Ca^{2+} with ionomycin, a Ca^{2+} ionophore. Also, the K^+ channel is not sensitive to Ca^{2+} in inside-out patches (84). Therefore, the Ca^{2+}-induced coupling modulation between the basolateral Na^+-K^+-ATPase and the apical low-conductance K^+ channel is indirect (366). At least two Ca^{2+}-dependent signal transduction mechanisms are involved in the inhibitory effect of Ca^{2+} on the channel activity: protein kinase C (PKC) (157, 357, 366) and Ca^{2+}/calmodulin-dependent kinase II (157). In addition to the direct effect of PKC on channel activity, PKC also activates phospholipase A_2, which cleaves phospholipids at the *sn*-2 position to generate lysophospholipids and free fatty acids such as arachidonic acid (13, 98). Arachidonic acid and *cis*-unsaturated fatty acids are also involved in the downregulation of the apical low-conductance K^+ channel activity in the rat CCD (355).

The low-conductance K^+ channel is inactivated by the application of actin filament disruptors cytochalasins B and D (365). The inhibitory effect of cytochalasins on channel activity was blocked by pretreatment with a compound that stabilizes the actin filaments, phalloidin (365). Therefore, the apical low-conductance K^+ channel activity depends on the integrity of the actin cytoskeleton.

A low-Na^+ diet (high plasma aldosterone levels) for rats has no effect on the density of the low-conductance K^+ channel in the rat CCD (84, 246). In contrast to the effects of a low-Na^+ diet, the density of low-conductance K^+ channel at the apical membrane of the CCD is elevated in rats adapted to a high-K^+ diet, which also elevates the endogenous aldosterone levels (360). The reason for the discrepancy in the effects of a low-Na^+ diet and a high-K^+ diet on low-conductance K^+ channel activity is unclear. On the other hand, the mineralocorticoid-induced increase in K^+ secretion in the rat CCD occurs through an increase in the net driving force for K^+ exit across the apical membrane, but not through an increase in the apical membrane K^+ conductance (275). The discrepancy between the two results is unknown.

2. Maxi K^+ channel

The maxi K^+ channels (80–140 pS) are identified at the apical membrane of the CCDs from both rabbits (127, 128, 271) and rats (83, 120, 278). The channels are considerably more abundant on the apical membrane of IC cells than on that of CD cells of both rat and rabbit CCDs (245). They are rarely open at intracellular Ca^{2+} concentration <1 μM and at normal membrane potentials (83, 127, 128). The channels are stimulated by membrane depolarization and by increased cytosolic Ca^{2+} concentrations and are inhibited by Ba^{2+} (83, 127, 128, 278). Channel activity is pH insensitive at high Ca^{2+} concentrations but is decreased by lowering cytosolic pH or by exposure to millimolar concentrations of ATP at more physiologically low Ca^{2+} concentrations (120). Channel activity is also inhibited by quinine, quinidine, and high concentrations of Mg^{2+} (278). The Ca^{2+} channel antagonists verapamil and diltiazem also inhibit this channel activity (278). NH_4^+ is conducted exclusively by this K^+ channel (83). Furthermore, the channel activity is also inhibited by the scorpion venom charybdotoxin, but not by the bee venom apamin (278). The channels are blocked by millimolar TEA from outside the cell (83, 278) and are impermeant to Rb^+ (83). These conductive properties are in sharp contrast to observations from microperfusion studies in which TEA has no effect on either the V_T of the rabbit CCD (83) or the apical membrane voltage of the CD cell in the rat CCD (280), and in which a significant Rb^+ secretion is present (83, 368). These properies of the maxi K^+ channels make it unlikely for them to be major candidates for K^+ secretion in the CCD (83, 84, 245). This channel has also been identified in the amphibian proximal tubule and diluting segments and in many types of excitable cells (359). Table 2 summarizes the regulation of the maxi K^+ channel.

Stretch activation of the maxi K^+ channel in either cell-attached or inside-out patches on the rabbit IC cells occurs through a Ca^{2+}-independent mechanism when pipette suction is applied (245). When the rat CCD is exposed to hypotonic stress, cell swelling causes an increased intracellular Ca^{2+} concentration, which depends on the extracellular Ca^{2+} concentration (120). At this time, cell swelling stimulates the maxi K^+ channel activity and hyperpolarizes the membrane potential of the CCD cell (120). Studies in everted, perfused CCDs of rats also demonstrate the presence of apical maxi K^+ channels whose activity increases with the perfusion of either the lumen with hypotonic saline solutions in the presence of bath vasopressin or the bath with hypotonic solutions (321). Therefore, a possible physiological function of the maxi K^+ channel may be the reduction of the intracellular K^+ concentration after cell swelling. This confirms the findings of activation of apical K^+ conductance of the rabbit CCD during regulatory volume decrease after inhi-

bition of the basolateral Na^+-K^+ pump by ouabain (322). The maxi K^+ channel might also play a role in the flow-dependent K^+ secretion in the late distal tubule and/or the CCD. Increased uptake of Na^+, associated with increased delivery of Na^+, would make the tubule lumen more negative and thereby increase the driving force for K^+ exit into the lumen. Thus the increased flow rate associated with increased luminal pressure could activate the maxi K^+ channels, resulting in an increased K^+ secretion. In fact, in the rabbit CNT apical membrane, the maxi K^+ channel is responsible for the flow-dependent K^+ secretion by coupling with the stretch-activated cation channel (328). However, it is presently unknown whether the maxi K^+ channel in the CCD could also be involved in the flow-dependent K^+ secretion.

B. Basolateral K^+ Channels

The presence of K^+ channels in the basolateral membrane of the CD cell allows part of the K^+ that is taken up into the cell by the Na^+-K^+-ATPase to recycle across this membrane (97, 148, 216, 268, 269, 276, 282, 358, 361). In the rat CCD (276), but not in the rabbit CCD (216), this recycling is necessary for maximal reabsorption of Na^+, because inhibition of the basolateral K^+ conductance by Ba^{2+} reduces the transport rate of the Na^+-K^+-ATPase, and thus Na^+ reabsorption as well as K^+ secretion (274).

Two methods have been used to identify basolateral K^+ channels in the rat CCD. Hirsch and Schlatter (121) have tried to digest the basement membrane of the rat CCD enzymatically by using a combination of in vivo and in vitro enzymatic treatment of the kidney with collagenase and to obtain single kidney tubule cells. They identified two types of basolateral K^+ channels with low and intermediate conductances. The slope conductance of the low-conductance K^+ channel was 67 pS in cell-attached patches and 28 pS in excised patches with asymmetrical KCl solutions, whereas the slope conductance of the intermediate-conductance K^+ channel was 147 pS in cell-attached patches, 85 pS in the excised patches with asymmetrical KCl solutions, and 198 pS in symmetrical high KCl solutions. On the other hand, Wang et al. (367) studied the lateral membrane K^+ channel of the rat CCD by removing single cells mechanically from the split open tubule with a suction pipette and advancing the patch-clamp electrodes to the exposed lateral membrane. They also identified two types of K^+ channels with low and intermediate conductances in the lateral membrane of the rat CCD. In cell-attached patches, the slope conductance of the low-conductance K^+ channel is 27 pS in asymmetrical solutions and 30 pS in symmetrical KCl solutions, whereas the slope conductance of the intermediate-conductance K^+ channel is 85 pS in symmetrical solutions and 45 pS in asymmetrical solutions (363, 367). The 85-pS intermediate-conductance K^+ channel described by Wang and co-workers (363, 367) is activated by hyperpolarization and PKA, whereas the intermediate-conductance K^+ channel described by Hirsch and Schlatter (121, 122) was not affected by either voltage or PKA. Therefore, the two intermediate-conductance K^+ channels may not be the same channel. On the other hand, the slope conductance of the low-conductance K^+ channel in the above two studies is different, but it has been suggested that the channel observed in these two studies may be the same, because both studies have found the same channel conductance in excised patches. In addition, both studies have shown that the low-conductance K^+ channel activity is regulated by cGMP and is not sensitive to either MgATP or PKA (121, 122, 176, 367). The difference between channel conductance in the two studies may be related to the voltage at which it was measured. Table 3 summarizes the regulation of the K^+ channels in the basolateral membrane.

1. *Low-conductance K^+ channel*

The low-conductance K^+ channel described by Wang et al. (367) has a high open probability (~0.8) and is not voltage dependent. The channel activity in excised patches is reduced by the decrease in bath pH from 7.4 to 6.7 (367). With this acidification, a reduction in channel current amplitude is observed (367). The channel activity is also inhibited by bath Ba^{2+} (367) but is not affected by either ATP, TEA, or quinidine (177).

Nitric oxide (NO) has a biphasic effect on the channel activity: low concentrations of NO stimulate the channel activity through a cGMP-dependent process (122,

TABLE 3. *Regulation of basolateral K^+ channels in the cortical collecting duct*

Channel Conductance, pS	Stimulatory Factors	Inhibitory Factors	Reference No.
28	pH_i ↑ Low NO cGMP PKC	pH_i ↓ High NO Ba^{2+}	175–178, 367
85	pH_i ↑ PKA Hyperpolarization	pH_i ↓ Ba^{2+} TEA Quinidine	363, 367
147	pH_i ↑ NO cGMP $[Ca^{2+}]_i$ ↓	pH_i ↓ Ba^{2+} TEA Charybdotoxin $[Ca^{2+}]_i$ ↑	120–122, 127, 128, 278, 279

Conductances are single-channel conductances as given by authors. Of course, single-channel conductance varies with potential, K^+ concentration in the pipette, and ambient temperature. Because conditions used were not identical among different studies, the numbers are only in part comparable. $[Ca^{2+}]_i$, intracellular Ca^{2+}; NO, nitric oxide; pH_i, intracellular pH; PKA, protein kinase A; PKC, protein kinase C; TEA, tetraethylammonium.

176), whereas high concentrations of NO inhibit it via a cGMP-independent process. NO reacts with O_2^- to form $OONO^-$, which inhibits channel activity (178). The basolateral low-conductance K^+ channel is coupled with the apical Na^+ channel via Ca^{2+}-dependent NO generation (175). PKC is also involved in the activation of the channel: the stimulatory effect of PKC on the channel activity occurs, at least in part, through phosphorylation of NO synthase (177). Although the low-conductance K^+ channel in the basolateral membrane of the rat CCD has a channel conductance similar to that of the apical low-conductance K^+ channel, the regulation of the basolateral low-conductance K^+ channel is in opposite direction to that of the apical low-conductance K^+ channel: PKC activates the basolateral low-conductance K^+ channel (177), whereas it inhibits the apical low-conductance K^+ channel (156, 357) (see Tables 2 and 3).

2. Intermediate-conductance K^+ channels

The 85-pS intermediate-conductance K^+ channel described by Wang et al. (367) has a low open probability (~0.2) at normal membrane potentials and is voltage dependent so that hyperpolarization activates channel activity. Thus this channel may not be mainly responsible for determining membrane potential under normal conditions, but this hyperpolarization-activated K^+ channel may be important for the rapid response to the stimulation of the Na^+-K^+-ATPase. Ba^{2+} inhibits the channel activity (367). The addition of TEA or quinidine to the bath also inhibits the channel activity in excised patches (363). The channel activity is reduced by decreasing the bath pH from 7.4 to 6.7 (363). With this acidification, this channel showed a reduction in open probability (363). The simultaneous addition of the catalytic subunit of PKA and MgATP to the bath stimulates channel activity in excised patches (363). These characteristics of the channel are similar to those observed in the low-conductance K^+ channel of the apical membrane of the rat CCD (93, 356). Therefore, PKA-mediated phosphorylation plays an important role in the regulation of the intermediate-conductance K^+ channel.

The 147-pS conductance K^+ channel described by Hirsch and Schlatter (121) shows no rectification. This channel is regulated by intracellular pH; reduction in cytosolic pH decreases open probability (121, 279). An inhibition of this channel with Ba^{2+} was observed in excised inside-out and outside-out patches (121). TEA blocked the channel activity in outside-out oriented membranes only (121). Verapamil induced a fast "flicker" block of this channel. This channel was reversibly inhibited by charybdotoxin but not by apamin (120). The channel showed a decrease in open probability with high cytosolic Ca^{2+} concentrations (121). With physiologically low Ca^{2+} concentrations in excised membrane patches, this channel was highly activated (121). This Ca^{2+} dependence is in contrast to the Ca^{2+} dependence of the apical maxi K^+ channel of which it is activated by increasing cytosolic Ca^{2+} concentrations (120, 127, 128, 278). This channel is not sensitive to ATP (121). In excised patches, this channel is activated by cGMP but is inhibited by an inhibitor of cGMP-dependent protein kinase, KT 5823 (122). Furthermore, this channel activity is stimulated by the addition of a NO donor, nitroprusside (122). Inhibitors of protein phosphatases 1 and 2A, calyculin A and okadaic acid, also increased the channel activity in cell-attached patches (122). The low-conductance K^+ channel described by Hirsch and Schlatter (121) is very often colocalized with the intermediate-conductance K^+ channel and have similar properties to those of the intermediate-conductance K^+ channel (121, 122). Thus the basolateral two K^+ channels described by Hirsch and Schlatter (121, 122) appear to be regulated in the same way. The only differences between these channels are their conductance properties and their mean open and closed dwell times (121). Therefore, one cannot exclude the possibility that the two K^+ channels are actually different functional states of one complex transport protein (121, 122).

C. Cloned K^+ Channels

Several groups have reported clones or partial clones for putative K^+ channels in the distal tubule and collecting ducts. They include ATP-sensitive K^+ channels in the distal nephron of rats (ROMK) (27, 123, 392), maxi K^+ channel α-subunit in the rabbit kidney (207), low-conductance K^+ channel of the basolateral membrane in the mouse M1CCD cell (CCD-IRK3) (373), double-pore K^+ channels in the rabbit distal nephron (KCNK1) (242), and *Shaker*-like voltage-gated K^+ channels in primary cultures of the rabbit distal tubule (KC22) (56), in rabbit renal papillary epithelial cell line GRB-PAP1 (348), and in rabbit renal medulla ($rabK_{v1.3}$) (386). Among these cloned K^+ channels, ROMK channels have been extensively characterized.

1. ROMK channels

A cDNA encoding an inwardly rectifying, ATP-regulated K^+ channel (ROMK1) (Kir1.1a) was initially isolated by expression cloning from the outer medulla of a rat kidney (123) (Fig. 6*A*). The ~2-kb cDNA ROMK1 predicts a 45-kDa protein (123). In contrast to channel proteins belonging to the superfamily of voltage-gated and second messenger-gated ion channels, the ROMK1 protein has only two potential membrane-spanning segments (M1 and M1) (123). However, the protein conserves an amino acid segment that is homologous to the pore-forming H5 region of the voltage-gated K^+ channels (123). In addition, a single putative ATP-binding site (P-loop) that is associ-

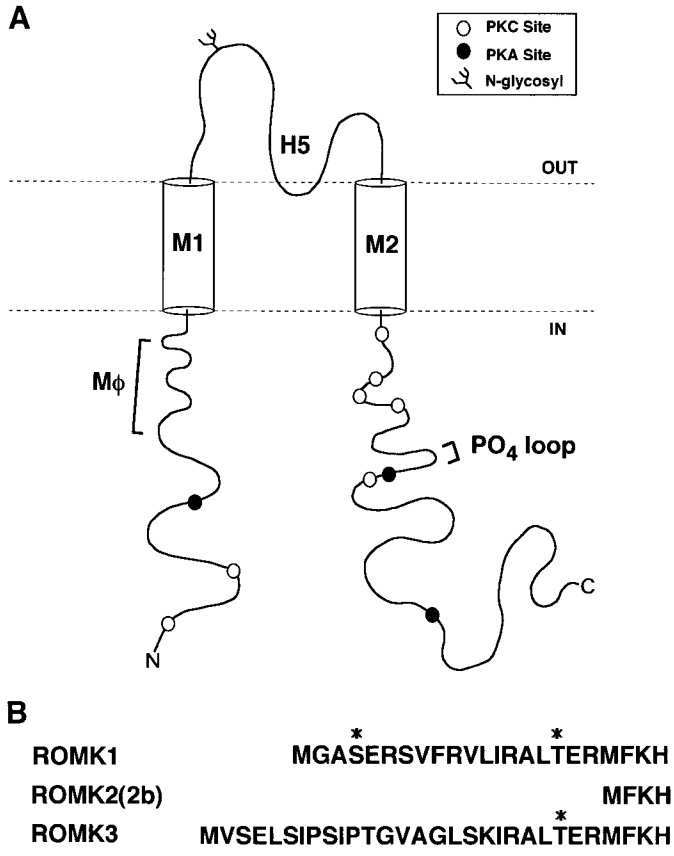

FIG. 6. *A*: schematic representation of the predicted structural model for ROMK channel protein. The nucleotide binding regulatory domain contains a high density of basic residues, a Walker A motif for potential nucleotide binding (PO_4 loop) (123), and several potential protein kinase A (PKA; ●) and protein kinase C (PKC) phosphorylation sites (○) (123). The site for *N*-linked glycosylation (asparagine at position 117) is also shown. *B*: aligned amino-terminal amino acid sequence for splice varients ROMKI, ROMK2, and ROMK3 (23). Note that ROMK2 lacks the first 19 amino acids found in ROMK1 and ROMK3 contains a 7-amino acid extension, but otherwise they are identical. Asterisks show two potential PKC phosphorylation sites (23).

ated with a cluster of potential phosphorylation sites and basic amino acids may form a regulatory domain (123). Other inwardly rectifying K^+ channels with a similar topology have been cloned (12, 28, 132, 154, 155, 167) and together with the ROMK1 channel (123) define a new family of K^+ channels, inwardly rectifying K^+ channel (IRK) family.

Furthermore, splice variants of ROMK1 have been identified (27, 392) (Fig. 6*B*). They display alternative splicing at the 5′-end and give rise to channel proteins differing in their amino-terminal amino acid sequences: ROMK2 (Kir1.1b) lacks the first 19 amino acids of ROMK1, whereas ROMK3 (Kir1.1c) contains a 7-amino acid extension. These alternatively spliced isoforms are differentially expressed along the distal nephron, from the medullary thick ascending limb of Henle's loop (MTAL) to the OMCD (27); ROMK1 transcript is specifically expressed in the CCD and the OMCD (27), and ROMK3 transcript is expressed in the MTAL, macula densa, distal convoluted tubule (DCT), and CNT (27), whereas ROMK2 transcript is widely distributed from the MTAL to the CCD (165). The ROMK protein is also localized at the apical border of the thick ascending limb of Henle's loop (TAL), macula densa, DCT, CNT, CCD, and OMCD (384). Within the CCD and OMCD, this protein is expressed in CD cells, but not in IC cells (384). This localization of ROMK mRNA and protein, together with the observed electrophysiological and regulatory properties of ROMK channels (123, 391, 392), strongly indicates that ROMK forms the low-conductance K^+ channels identified in the apical membrane of the distal nephron segments. A low level of ROMK expression is observed in the IMCD by tissue and isolated tubule in situ hybridization (165).

ROMK channels expressed in *Xenopus* oocytes exhibit biophysical properties comparable to those of the low-conductance K^+ channel identified in the apical membrane of both TAL (25, 361, 362) and CCD (84, 93, 360) of rats. They include a single-channel conductance of 30–40 pS in symmetrical KCl solutions (123, 392), high K^+ selectivity (123, 392), high channel open probability at physiological potentials (123, 392), weak inward rectification from block by intracellular Mg^{2+} and/or polyamines (47, 228, 392), marked sensitivity to external Ba^{2+} but not to TEA (123), marked sensitivity to intracellular pH (73, 340), inhibition by arachidonic acid (188, 189), channel rundown or loss of channel activity in excised patches in the absence of MgATP that involves dephosphorylation by a protein phosphatase (protein phosphatase 2C in *Xenopus* oocytes) (203), reactivation of channels after rundown by reexposure to MgATP and catalytic subunit of PKA (203, 204), and inhibition by glibenclamide (i.e., when ROMK2 is coexpressed with cystic fibrosis transmembrane conductance regulator, CFTR) (200). Therefore, ROMK channels are identical to the low-conductance K^+ channel in the apical membrane of the TAL and CCD. Mutations in the ROMK gene result in one variant of Bartter's syndrome, thus confirming the dependence of NaCl reabsorption in the K^+ flux mediated by these channels (299). However, the mechanisms whereby the mutation in the ROMK gene impairs K^+ channel activity remain unknown.

ROMK channels expressed in *Xenopus* oocytes are regulated by phosphorylation and dephosphorylation processes, with activation of channel activity by PKA (203). The predicted ROMK1 and ROMK2 channel proteins contain only three PKA consensus phosphorylation sites (123) (see Fig. 6*A*). These PKA sites containing serine residues at positions 25, 200, and 294 are demonstrated to be essential for ROMK2 channel activity (385). The phosphorylation sites on the carboxy-terminal serine residues at positions 200 and 294 modulate the open probability of the channel by regulating the stability of the open state,

whereas the phosphorylation site on the amino-terminal serine residue at position 25 determines the number of conducting channels observed at the plasma membrane (181). Also, PKA-induced activation of ROMK1 channel occurs via phosphatidylinositol 4,5-bisphosphate-dependent mechanism (171).

As described above, ROMK channel protein contains a putative ATP-binding site (P-loop) in the carboxy terminus (123) (see Fig. 6*A*). This loop contains a high density of basic residues, a glycine-rich Walker A motif [GXGX2G]. The Walker A mutation of histidine at position 206 to glycine auguments the ATP sensitivity of ROMK2 (204). Thus the Walker A segment in ROMK2 is involved in MgATP binding inhibition interactions (204).

The common functional property shared by the IRKs is their inwardly rectifying current-voltage relationship. Rectification may be weak or strong and is due to a voltage-dependent inhibition of the channel pore by intracellular Mg^{2+} (194) and polyamines (72, 77, 174). Two members of the IRKs, IRK1 and ROMK1, which share 40% amino acid identity, markedly differ in single-channel K^+ conductance and in sensitivity to channel inhibition by intracellular Mg^{2+} (171). In voltage-gated channels (15, 190, 330, 387, 388) and in cyclic nucleotide-gated channels (104), the H5 regions are thought to line the pore. Because of sequence homology, the H5 has been suggested to line the pore of IRKs (123). However, the exchange of the H5 region between IRK1 and ROMK1 had no effect on rectification and little or no effect on K^+ conductance (327). In contrast, the exchange of the amino- and carboxy-terminal regions together transferred Mg^{2+} blockade and K^+ conductance of IRK1 to ROMK1. The exchange of the carboxy terminus but not the amino terminus caused a similar effect. These findings suggest that the carboxy terminus appears to have a major role in specifying the pore properties of IRKs (327). Furthermore, the mutation of aspartate to asparagine at position 172 within the putative transmembrane domain M2 in IRK1 produced ROMK1-like gating, whereas the reverse mutation in ROMK1, the mutation of asparagine to aspartate at position 172, produced IRK1-like gating (374). Therefore, a single negatively charged amino acid residue seems to be a crucial determinant of gating.

As mentioned above, ROMK1 and ROMK2 channels, when expressed in *Xenopus* oocytes, have a high sensitivity to internal but not to external pH within the physiological pH range (73, 201, 340). This pH sensitivity of the ROMK1 and ROMK2 channel is similar to that reported for low-conductance K^+ channels in the apical membrane of the rat CCD (279, 356, 360). When the cytosolic pH is decreased from 7.4 to 7.0, the reduction in channel activity is due primarily to reduction in the number of active channels (i.e., complete channel closure) (201). At cytosolic pH levels below 7.0, the decreased channel activity appears to be a combination of both reduction in the number of open channels together with a modest effect on open probability (201). It has been speculated that any of the nine histidine residues in the ROMK1 sequence may be involved in the pH regulation of the ROMK1 channel (340). When the histidine residue (position 206 in the Walker site) in the carboxy terminus of ROMK (which is involved in MgATP binding inhibition of ROMK channel activity) is mutated to glycine, the curve of pH sensitivity is shifted to the right (201). Furthermore, changing lysine at position 80 to methionine altered the sensitivity of ROMK1 channels to intracellular pH (73). Therefore, the pH-dependent modulation of ROMK may not be entirely attributable to a single amino acid residue (73, 201, 340).

The single *N*-glycosylation consensus sequence of ROMK1 is located at amino acids 117–119 and has been assigned to the first extracellular loop between the M1 and H5 segments (123) (See Fig. 6*A*). When glycosylation is inhibited by changing the posision of 117 asparagine to glutamine, or by an inhibition of *N*-glycosylation with tunicamycin, both whole cell currents and single-channel currents are greatly reduced (284). Thus the *N*-linked oligosaccharide is involved in the stabilization of the open channel state.

When ROMK1, ROMK2, and ROMK3 channels are expressed in *Xenopus* oocytes, the ROMK1 channel alone is completely inhibited by arachidonic acid in a manner similar to that of the native channel (188), but not ROMK2 or ROMK3 channels, that lack the serine residue at position 4. ROMK1 variant, in which the amino-terminal animo acids 2–37 were deleted, and a mutant ROMK1, in which the serine residue at position 4 was mutated to alanine, are not sensitive to arachidonic acid (189). Therefore, the phosphorylation of serine residue at position 4 is involved in mediating the effect of arachidonic acid.

Recent evidence suggests that ATP-sensitive K^+ channels are formed by multimeric subunit interactions. In pancreatic β-cells (132, 264), smooth muscle cells (135), cardiac cells (131, 264), and skeletal muscle cells (131, 264), as well as renal distal tubule cells (200), ATP-sensitive K^+ channels are complexes composed of at least two subunits: the inward-rectifying K^+ channel subunit and the channel regulator/drug binding subunit. The channel regulator/drug binding subunit belongs to a member of the ATP-binding cassette transporter superfamily with multiple transmembrane-spanning domains and two potential nucleotide-binding folds. This family includes sulfonylurea receptors (SUR1 and SUR2) (2, 8, 131) and CFTR (200). Both types of subunits are necessary for channel functions and sulfonylurea sensitivity (131, 132, 135, 200, 264). For example, in pancreatic β-cells, when both subunits (Kir6.2 and SUR) are coexpressed, inwardly rectifying K^+ channels inhibited by ATP and by sulfonylurea compounds are identified, although neither subunit, when expressed alone, exhibits channel activity (131). Similarly, patch-clamp studies of ROMK2 expressed into

Xenopus oocytes demonstrate that coexpression of ROMK2 with CFTR enhances the sensitivity of ROMK2 to the sulfonylurea compound (glibenclamide), although, when expressed alone, ROMK2 is relatively insensitive to glibenclamide (200). Therefore, CFTR not only enhances sulfonylurea sensitivity of ROMK2 but also modulates the outwardly rectifying Cl^- channel in cultured airway cells (289). The first nucleotide binding fold of the CFTR protein is necessary for the CFTR-ROMK2 interaction that confers sulfonylurea sensitivity (202).

IV. CONTROL OF POTASSIUM TRANSPORT IN THE COLLECTING DUCT

The ICT and CCD are the main sites of control of renal K^+ excretion. Both nephron segments are distinguished by marked cell heterogeneity, and the net transport of K^+, either in the secretory or reabsorptive direction, results from varying rates of K^+ secretion through CD cells and K^+ reabsorption through IC cells.

Luminal factors include the rate of distal fluid and Na^+ delivery and the composition of fluid entering the distal tubule or CCD (luminal Na^+ and Cl^- concentrations) (383). Peritubular factors include changes in ion concentrations (K^+, H^+, and HCO_3^-) and hormones (aldosterone and vasopressin) (383). Systemic changes that affect these factors include adrenal steroids, K^+ intake, acid-base balance, and vasopressin (383).

A. Rate of Distal Fluid and Na^+ Delivery

Enhanced delivery of fluid and Na^+ to the distal tubule is one of the most powerful and frequently activated mechanisms of distal tubule K^+ secretion. Several manipulations increase distal fluid delivery, including osmotic diuresis by mannitol, diuretic therapy, including furosemide and thiazide diuretics, metabolic alkalosis, prolonged diabetes insipidus, postobstructive diuresis, and contralateral nephrectomy. It is important to recognize that sustained diuresis often leads to severe K^+ depletion. K^+ adaptation by a high-K^+ diet (143, 184, 308) or after a mineralocorticoid administration (300, 303, 306) magnifies the response to increases in fluid delivery, whereas K^+ depletion by a low-K^+ diet blunts the kaliuretic response to diuresis (143, 184).

Microperfusion studies of the isolated CCD from rabbit kidneys have shown that no relationship exists between K^+ secretion and perfusion rates in the range of 4–16 nl/min (315). On the other hand, K^+ secretion is a flow-dependent process below 5–6 nl/min but is saturated at flows of >5–6 nl/min (70). In contrast, flow-dependent K^+ secretion in the rat distal tubule shows no such saturation even at flows of 30 nl/min (99–101, 143, 159). This discrepancy may reflect a higher maximal capacity for K^+ secretion in the rat distal tubule than the rabbit CCD (99–101, 143, 159).

Two separate factors contribute to the markedly enhanced rate of K^+ secretion following enhanced delivery of fluid and Na^+ into the distal tubule. First, when flow increases in the distal tubule, the luminal K^+ concentration decreases moderately (100, 159). However, the reduction of luminal K^+ concentration is proportionally much smaller than the increase in flow rate, thereby K^+ secretion increases. The decline in the luminal K^+ concentration may steepen the chemical concentration gradient of K^+ across the apical membrane and facilitate K^+ secretion into the lumen (100). Basolateral K^+ uptake must increase sharply to maintain cell K^+ concentration. This idea is based on the data from the rat DCT (100, 159). In contrast, microperfusion studies of the isolated rabbit CCD have shown that there is no significant effect of flow rate on K^+ secretion when tubules were perfused with a 10-fold increase in the luminal K^+ concentration (70). The second factor responsible for increased K^+ secretion, associated with enhanced flow rates, may be the elevation of luminal Na^+ concentrations following NaCl loading and administration of loop or thiazide diuretics. During NaCl diuresis, Na^+ delivery into the distal nephron enhances and increases Na^+ entry into cells across the apical membrane, facilitates the basolateral Na^+-K^+ exchange, and thereby increased Na^+ reabsorption occurs (143, 159). As a result, cell K^+ concentration would be expected to increase, stimulating the movement of K^+ from cell to lumen. Also, increased Na^+ entry into the cell across the apical membrane could cause the apical membrane to depolarize, resulting in an enhanced K^+ secretion across this membrane. During saline diuresis, luminal K^+ concentrations undergo only small changes (143), and electron-probe studies have confirmed that K^+ gradient across the apical membrane of the CD cell remains unaltered (20). Thus the K^+ gradient across the apical membrane would not be changed. The inhibition of Na^+ entry into the cell with luminal amiloride inhibited flow-dependent K^+ secretions in the distal tubule (184). In the isolated perfused rabbit CCD, the rate of Na^+ reabsorption is also dependent on flow rates and is closely related to that of K^+ secretion (70).

Malnic et al. (184) distinguished the relevant processes at low and high flow rates. At low flow rates, K^+ secretion causes significant increase in luminal K^+ concentrations, which decreases the driving force for K^+ secretion across the apical membrane. As a consequence, the net flow of K^+ into the lumen is limited and is far removed from the maximal capacity of the Na^+-K^+ transport system. At high flow rates, luminal K^+ concentration decreases, causing an increased K^+ chemical gradient. Additionally, the gradual saturation of Na^+ reabsorption with increased Na^+ delivery causes an increase in luminal Na^+ concentrations, with consequent depolarization of

the apical membrane also favoring K^+ secretion. However, the ultimate limit in Na^+ reabsorption will eventually cause saturation of K^+ secretion. The continued increase in Na^+ transport in free-flow experiments may explain the lack of saturation in K^+ secretion.

Chronic administration of furosemide to rats in vivo caused an increased K^+ excretion. Under these conditions, K^+ secretion and Na^+ reabsorption in the distal tubule were enhanced (309). At the same time, Na^+-K^+-ATPase activity in the CCD (69, 277) and DCT (277) was increased. The increased Na^+-K^+-ATPase activity is accompanied by amplification of basolateral membrane areas of the DCT cells, CNT cells, and CD cells of the CCD (137, 140). These functional, enzymatic, and morphological alterations by furosemide administration occur independent of plasma aldosterone (69, 140, 309). The increased Na^+ delivery to the distal nephrons contributes to these changes by furosemide (137, 140, 277).

Several animal models of reduced renal mass demonstrate that K^+ balance can be maintained effectively, even when the number of nephrons is reduced drastically, due to increased excretions of K^+ by the remaining nephrons (117, 160, 282, 294). This adaptive response can be attributed largely to enhanced secretions of K^+ by the ICT and CCD (21, 81, 160, 294). The CCDs from remnant kidneys after a reduction of the renal mass exhibit an adaptive increase in Na^+ reabsorption (342) and K^+ secretion (81). These changes are accompanied by an increase in Na^+-K^+-ATPase activity (210, 276) and an amplification of the basolateral membrane area of the CD cell (389). The CCDs from remnant kidneys in rabbits, 14 days after uninephrectomy, showed structural hypertrophy and increases in apical Na^+ and K^+ conductances, as well as in basolateral Na^+-K^+ pump activity and K^+ conductance, independently of plasma aldosterone (61). Because the initial effect of the nephrectomy on the CD cell is an increase in the apical Na^+ conductance and the secondary effects are increases in the apical K^+ conductance and the basolateral Na^+-K^+ pump activity and K^+ conductance (215), increased Na^+ delivery into the CD cell through increased glomerular filtration rate can stimulate K^+ secretion. Similar electrical changes have been observed in the CCDs from untouched contralateral kidneys 24 h after unilateral ureteral obstruction (222). The mechanisms for the tight coupling between the basolateral Na^+-K^+ pump activity and the apical cation conductances are still unclear at present.

Ureteral obstruction causes abnormalities in Na^+ (39, 144, 262) and water (39) conservation and in H^+ (255, 262, 332) and K^+ (144, 262) secretion in the distal nephron segments, including the CCD. The in vitro microperfusion studies of the rabbit CCD have demonstrated that ureteral obstruction leads to decreases in the lumen-negative V_T (39, 109) and in Na^+ reabsorption (39). Decreased Na^+-K^+-ATPase activity (262) and Na^+-K^+ pump in situ turnover (144) are observed in the CCDs from obstructed rat kidneys. Microelectrode studies of the isolated perfused CCD from obstructed kidneys 24 h after ureteral obstruction show that apical membrane Na^+ and K^+ conductances as well as basolateral Na^+-K^+ pump activity and K^+ conductance are decreased (222). One of the factors suggested to be responsible for the decreased Na^+ and K^+ transports in the CCD after ureteral obstruction is increased intraluminal pressure, since the decreased Na^+ and K^+ transport properties of the CD cell in the CCD after ureteral obstruction is partially restored by renal decapsulation (213), a maneuver that partially blocks the increase in renal pressure (111, 142). In addition, other factors that may affect Na^+ and K^+ transport in the CCD of obstructed kidneys are a decreased flow rate (70), an increased prostaglandin production (63), and/or a resistance to aldosterone and vasopressin (147).

B. Composition of Luminal Fluid

1. Luminal Na^+ concentration

Luminal Na^+ concentrations influence K^+ secretion in the distal tubule (99) and the CCD (315). In vivo microperfusion studies of the rat distal tubule have shown that net K^+ secretion and V_T can be affected by luminal Na^+ concentrations: when the luminal concentrations of Na^+ in the distal tubule are reduced below 30 mM, the net K^+ secretion by this nephron and the V_T across its wall are both decreased (99). Likewise, in the isolated perfused rabbit CCD, both K^+ secretion and lumen-negative V_T are decreased by reducing luminal Na^+ concentrations to <8 mM and are unaffected by varying luminal Na^+ concentrations from 30 to 145 mM (315). Thus the luminal Na^+-dependent K^+ secretion could be caused by the changes in V_T. Measurements of cell Na^+ concentration will be required to further clarify the underlying cellular mechanisms.

2. Luminal Cl^- concentration

Luminal Cl^- concentrations are also one of the factors that influence K^+ secretion in the distal tubule. When luminal Cl^- concentrations are reduced to levels below 10 mM, net K^+ secretion in the rat distal tubule is increased independent of changes in V_T (66, 99, 344). The Cl^--dependent fraction of K^+ secretion is unaffected when the conductive pathway for K^+ in the apical membrane is blocked by Ba^{2+} (66, 344). Thus the Cl^--dependent K^+ secretion is thought to occur through electroneutral K^+-Cl^- cotransport. In vivo microperfusion studies of subsegments of the rat superficial distal tubule demonstrated that the ICT apical membrane appears to be the primary site of the K^+-Cl^- cotransport (343).

C. Adrenal Steroids (Mineralo- and Glucocorticoids)

1. Mineralocorticoids

As mentioned above, in the normal rat CCD, transport of Na^+ or K^+ is not detectable (46, 254, 334) and V_T is near 0 mV (46, 254, 334), whereas the normal rabbit CCD has measurable transport rates of Na^+ and K^+ (31, 81, 115, 124, 216, 217, 287, 315, 317, 318) and a lumen-negative V_T (31, 61, 81, 115, 124, 133, 151, 172, 212–222, 224, 234, 238, 239, 267, 269, 270, 287, 310, 315, 317, 318, 379). On the other hand, in the CCDs from both rabbits and rats with chronic exposure to deoxycorticosterone acetate (DOCA) in vivo, the Na^+ reabsorption (46, 217, 237, 287, 300, 303, 334) and K^+ secretion (217, 237, 275, 287, 300, 303, 334), as well as the lumen-negative V_T (46, 151, 214, 217, 237, 269, 270, 275, 277, 318, 334), are increased. After chronic exposure to DOCA, the apical membrane conductance of the rabbit CD cell is elevated (151, 214, 269, 270). Conversely, a deficiency of mineralocorticoids by adrenalectomy (ADX) causes decreased apical membrane conductance (216). Microelectrode studies of the rat CD cell also demonstrate that the apical membrane Na^+ conductance is closely modulated by aldosterone (275). Similarly, the apical membrane K^+ conductance in the rabbit CD cell also appears to be closely controlled by aldosterone (151, 214, 269, 270). Apical membrane K^+ conductance is respectively increased or decreased according to the excess levels of mineralocorticoid (151, 214, 269, 270) or their depletion (216). Chronic DOCA treatment stimulates Na^+ entry into the cell via apical Na^+ conductance, resulting in increased lumen-negative V_T and depolarization of the apical membrane (151, 269) (Fig. 7). Alternatively, this depolarization of the apical membrane increases the electrical driving force for K^+ exit across this membrane (151, 269) (Fig. 7). Therefore, in the rabbit CD cell, the exit of K^+ from the cell into the lumen can be explained by increases in both apical membrane K^+ conductance and net driving force for K^+ exit across the apical membrane (269). On the other hand, the K^+ transport properties of the apical membrane in the rat CD cell after chronic exposure to DOCA are different

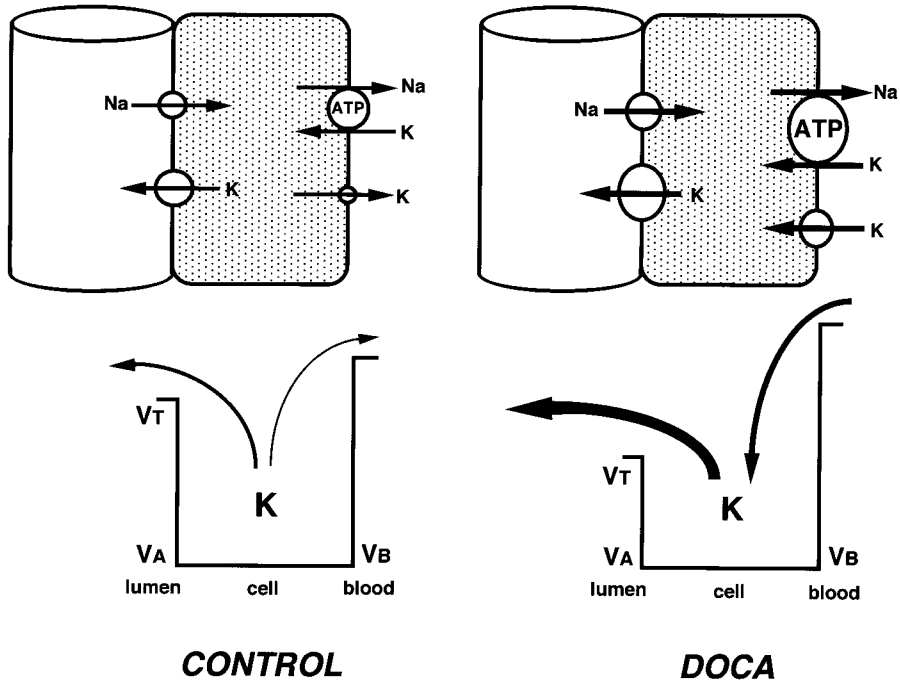

FIG. 7. Electrical potential profile of the rabbit collecting duct (CD) cells and model for regulation of Na^+ and K^+ transport by deoxycorticosterone acetate (DOCA) (151, 214, 217, 267, 269, 270). Under control conditions, an entry of Na^+ into cell through apical Na^+ conductance causes an electrical asymmetry that results in a lumen-negative transepithelial voltage (V_T) that favors the movement of K^+ from the cell toward the lumen. Chronic DOCA treatment raises the apical membrane Na^+ conductance, resulting in an increase of the lumen-negative V_T and depolarization of the apical membrane. This depolarization of the apical membrane increases the electrical driving force for K^+ exit across this membrane, causing an increased K^+ secretion into the lumen. In the CD cell from control rabbits, the basolateral membrane voltage appears to be near the equilibrium potential for K^+ across the basolateral membrane. In contrast, in the CD cell from DOCA-treated rabbits, the basolateral membrane is hyperpolarized by ~20 mV due to mineralocorticoid-induced upregulation of the Na^+-K^+ pump activity and the associated Na^+-K^+ pump current. This hyperpolarization can exceed the outward-directed K^+ equilibrium potential, thereby producing a net driving force for K^+ uptake into the cell. V_A, apical membrane voltage; V_B, basolateral membrane voltage.

from those of the rabbit CD cell. In the rat CD cell, chronic treatment with mineralocorticoids in vivo results in an increase in the net driving force for K^+ exit across the apical membrane without causing an increase in apical membrane K^+ conductance (275).

Chronic DOCA treatment of rabbits in vivo hyperpolarizes the basolateral membrane of the CD cell by ~20 mV and increases the basolateral membrane conductance as well (151, 214, 267, 269, 270). Conversely, in ADX animals, the basolateral membrane is depolarized by 10–20 mV, although the basolateral membrane conductance is not affected (216). Therefore, the V_B appears to be influenced by plasma aldosterone levels (151, 214, 216, 269, 270). After chronic mineralocorticoid treatment, increases in basolateral K^+/Cl^- permeability ratio (267) as well as in the relative basolateral K^+ conductance (151, 214, 267, 270) are observed, although the absolute magnitude of the basolateral Cl^- conductance is also elevated in the CD cell (270). Therefore, after chronic DOCA treatment, the basolateral membrane of the rabbit CD cell is predominantly selective to K^+.

In the CD cell from control rabbits, the V_B appears to be near the equilibrium potential for K^+ across the basolateral membrane, because addition of Ba^{2+} to the bath has no effect on V_B (151, 214, 270). In sharp contrast, in the CD cell from DOCA-treated rabbits, the basolateral membrane is hyperpolarized by ~20 mV due to mineralocorticoid-induced upregulation of the Na^+-K^+ pump activity and the associated Na^+-K^+ pump current (270) (Fig. 7). This hyperpolarization can exceed the outwardly directed K^+ equilibrium potential, thereby producing a net driving force for K^+ uptake into the CD cell (270) (Fig. 7). This notion is supported by the following evidence. First, addition of Ba^{2+} to the bath causes the basolateral membrane to hyperpolarize in the CD cell from chronically DOCA-treated rabbits (214, 270). This is best explained by the elimination of inwardly directed K^+ flux. Second, in the CCD from DOCA-treated rabbits, addition of Ba^{2+} to the bath reduces net K^+ secretion, although it has no effect in the CCD from normal rabbits (217). Therefore, in addition to an increase in Na^+-K^+ pump activity, elevations in both K^+ conductance and driving force for K^+ uptake across the basolateral membrane further stimulate an increased K^+ uptake across the basolateral membrane (270) (Fig. 7). Alternatively, this can result in increased K^+ secretion from the cell into the lumen via the apical membrane K^+ conductance. On the other hand, increased Na^+ reabsorption results from increases in apical Na^+ conductance and basolateral Na^+-K^+ pump activity (Fig. 7). Thus the amount of increase in K^+ secretion is relatively greater than that of increase in Na^+ reabsorption (217, 237).

Na^+-K^+-ATPase, which is mainly localized in the basolateral membrane of the CD cell (141), is the active, ouabain-sensitive, and energy-consuming process that actively extrudes Na^+ from the cell and actively takes up K^+ into the cell. Chronic exposure to mineralocorticoids stimulates Na^+-K^+ pump activity in the CD cell (151, 214, 270) as well as Na^+-K^+-ATPase activity (68, 236, 248) in the CCD from rabbits and rats. Also, the amplification of only the basolateral membrane area of just the CD cell from rabbits and rats is observed (350, 351). Conversely, ADX leads to a reduction in basolateral Na^+-K^+ pump activity (216), basolateral Na^+-K^+-ATPase activity (68, 208, 209, 248), and basolateral membrane area (350). Specific [^{3}H]ouabain binding studies of the CCDs from rats and rabbits have shown that chronic mineralocorticoid treatment increases the number of Na^+-K^+-ATPase units without affecting the turnover rate of each catalytic unit (17).

Na^+-K^+-ATPase is composed of at least two subunits, α and β (170, 324). The α-subunit is the catalytic unit, involved in ion transport, and β-subunit is implicated in the functional maturation and membrane insertion of the synthesized pump. Three α-subunit isoforms (α_1, α_2, and α_3) have been reported to differ markedly with respect to ouabain sensitivity (24, 324), Na^+ affinity (179), and tissue distribution (244). The α_1-isoform is expressed in virtually all cells and most likely represents the "housekeeping" enzyme responsible for maintaining the electrochemical gradients of Na^+ and K^+ across the plasma membrane (324). In contrast, α_2 and α_3 are expressed in tissues with greater Na^+ affinity and ouabain sensitivity, including brain, axolemma, skeletal muscle, heart, and pineal gland (170, 244, 324). On the other hand, at least two isoforms (β_1 and β_2) exist for the β-subunit in mammalian cells, with β_1 being found in all tissues, while β_2 is predominantly in the nervous system (97, 192). In the kidney, at the level of the whole organ, it has been repeatedly shown that the α_1- and β_1-isoforms are exclusively or essentially expressed (170, 192, 324). Because of the cellular heterogeneity of the kidney, it is of interest to know which cell type expresses which isoform in various nephron segments, including the CCD. The predominant isoforms in the CCD from rat kidneys are α_1- and β_1-isoforms (74, 339), but it is possible that other isoforms, including α_3- and β_2-isoforms, exist in this segment (75, 339). In the rat CCD, ADX causes a decrease in α_1-mRNA expression without causing any changes in α_2- or α_3-mRNA expression (16). Likewise, in the rabbit CCD, aldosterone selectively increases α_1-subunit protein levels (372). Furthermore, the effects of ADX on α_1- and β_1-mRNA levels in the rat CCD appear to be dissociated; α_1-mRNA levels decreased without changing levels of β_1-mRNA (74, 336). Aldosterone replacement restored α_1-mRNA levels toward control levels (336). In contrast, at the protein level, aldosterone increases the α_1-subunit protein levels in parallel with an increase in β_1-subunit protein levels in the rabbit CCD (372). Further studies will be required to resolve this discrepancy.

The aldosterone action on Na^+ transport in the toad urinary bladder can generally be divided into two phases (92): *1*) an early or rapid phase (2–3 h) in which a large increase in Na^+ transport and a parallel decrease in R_T occur by activation of apical membrane Na^+ conductance and *2*) a late or slow phase in which Na^+ transport continues to increase for 6–12 h while the R_T is stable. This phase can be followed for ~24 h in amphibian epithelia in vitro, but morphological and functional changes described above continue to occur over a much longer period when experimental animals are chronically exposed to mineralocorticoids (269, 270, 350, 351). In this late phase, the transcription rate of the gene expression of Na^+-K^+-ATPase is stimulated, and then insertion of functioning Na^+-K^+-ATPase molecules into the basolateral membrane occurs.

The early phase of aldosterone actions results in a relatively rapid increase in the number of Na^+ channels located at the apical membrane of the toad urinary bladder (92). This increase in the number of Na^+ channels appears to be due to activation of preexisting Na^+ channels at the apical surface, but not due to increased synthesis of new channels (10, 145, 146). In contrast to the early effects, late or chronic effects of aldosterone on apical Na^+ channels in A6 cells stimulate de novo channel synthesis (10). Also, aldosterone administration or a low-Na^+ diet causes upregulation of the epithelial Na^+ channel α-subunit mRNA (11, 193, 240, 349) and protein (193) in the rat kidney. Conversely, ADX reduces the epithelial Na^+ channel α-subunit mRNA levels in the rat kidney (71).

Time course studies of mineralocorticoid treatment have also extended in mammalian CCDs. The microelectrode studies showed that a primary effect of DOCA treatment of rabbits with intact adrenal glands was an increase in the apical membrane Na^+ conductance of the CD cell within 24 h (269). A secondary, delayed effect, occurring after 24 h, was an increase in the apical membrane K^+ conductance and hyperpolarization of the basolateral membrane (269). In addition, Na^+-K^+-ATPase activity in the CCD from rabbits with intact adrenal glands was also increased by chronic DOCA treatment, but again with a delay of at least 24 h (236). In contrast, in studies employing ADX rabbits, the DOCA treatment caused rapid increases in apical membrane Na^+ and K^+ conductances as well as basolateral membrane Na^+-K^+ pump activity after 3 h (268). After 18 h of DOCA treatment in vivo, further increases in both apical membrane K^+ conductance and basolateral membrane Na^+-K^+ pump activity were observed without causing further increases in apical membrane Na^+ conductance (268). Thus mineralocorticoids in ADX rabbits act much faster to induce increases in Na^+ and K^+ transport as compared with their effects on the adrenal-intact rabbits. In ADX animals, the number of Na^+-K^+-ATPase units is relatively low (68, 208, 209, 248), and hence, the rates of Na^+ and K^+ transport are relatively low. An increase in the apical membrane Na^+ conductance after DOCA treatment could immediately stimulate Na^+ uptake into the cell, resulting in a rapid rise in intracellular Na^+ concentrations. This rise in cell Na^+ concentration could cause a rapid upregulation of the apical K^+ conductance and the basolateral Na^+-K^+ pump activity during the late phase. In comparison, in adrenal-intact animals, in which the number of Na^+-K^+-ATPase units is greater than in ADX animals (208, 248), an increase in the apical membrane Na^+ conductance after DOCA treatment may result in a relatively smaller rise in cell Na^+ concentration and thereby a slower upregulation of the apical and basolateral transporters during the late phase.

In the CCD from ADX (248) and adrenal-intact (236) rabbits, a reduction in Na^+ entry into the cell by infusing amiloride into the animals inhibits the aldosterone-induced increases of Na^+-K^+-ATPase activity. In addition, in the CCD from ADX rabbits (268), preventing the apical Na^+ entry into the cell with amiloride in vivo simultaneously inhibits aldosterone-induced increases in the apical membrane K^+ conductance as well as the basolateral membrane Na^+-K^+ pump activity, but not the apical membrane Na^+ conductance. Similarly, patch-clamp studies of the CCD from rats on a low-Na^+ diet demonstrated that the primary effect of aldosterone is to increase the apical membrane Na^+ permeability, and the basolateral membrane Na^+-K^+ pump activity is then regulated mainly by the intracellular Na^+ concentration (247). Moreover, in Madin-Darby canine kidney (MDCK) cells, the acute or early effect was an increase in the number of Na^+-K^+-ATPase units owing to insertion of presynthesized units to Na^+ entry through an amiloride-sensitive apical pathway, and the delayed effect was an increase in the number of Na^+-K^+-ATPase units by de novo synthesis (293). Therefore, Na^+ entry may, at least in part, modulate the secondary or delayed effects of aldosterone on the basolateral membrane Na^+-K^+ pump activity and the apical membrane K^+ conductance.

The Na^+-K^+-ATPase activity in the CCD decreases to relatively low levels over several days after ADX (68, 208, 209, 248). When aldosterone is replaced in ADX animals, the Na^+-K^+-ATPase activity in the CCD is rapidly restored to near control values within 1–3 h (68, 248). Such a rapid recovery is in marked contrast to the slow rate of stimulation of Na^+-K^+-ATPase activity observed in adrenal-intact animals as mentioned above. It has been demonstrated that, in the presence of aldosterone, a rise in intracellular Na^+ concentrations induces the recruitment and/or activation of latent pumps at the basolateral membrane of the rabbit and rat CCDs (18, 26). Because the Na^+-induced recruitment and/or activation of the latent pumps occurs over a very short period of time (within 1–2 min) in the rabbit CCD (53), it may constitute a rapid

adaptive response to increased cell Na^+ concentration. This pump recruitment is not affected by inhibitors of the cytoskeleton, stimulation of PKC, or an increase in cell Ca^{2+} concentration (53). In frog skin (112), amphibian kidney cells (231), and MDCK cells (230, 347), aldosterone activates Na^+/H^+ exchange, leading to both cytoplasmic alkalinization and increased cell Na^+ concentration, and eventually to stimulation of preexisting Na^+-K^+-ATPase. In contrast, Na^+-independent rapid adaptation of Na^+-K^+-ATPase induced by aldosterone has been reported (17, 85). Fujii et al. (85) have provided evidence that the rapid effects of aldosterone on the Na^+-K^+ pump activity (stimulation of Rb^+ uptake) in the rat CCD can proceed independently of changes in Na^+ entry, since they are unchanged by incubation in a Na^+-free medium or in the presence of amiloride or nystatin. Barlet-Bas et al. (17) also reported that the effect of aldosterone plus 3,3′,5-triiodothyronine on Na^+-K^+-ATPase activity in the rat CCDs from ADX rats in vitro is independent of Na^+. Thus there are Na^+-dependent and Na^+-independent mechanisms for the aldosterone-induced Na^+-K^+-ATPase stimulation.

2. Glucocorticoids

It has been recognized for several decades that infusion of glucocorticoids can increase renal K^+ excretion (19, 23, 41). However, these effects of glucocorticoids can be attributed to nonspecific or indirect effects of the steroids by the following evidence. In the CCD, pharmacological doses of glucocorticoids increase both Na^+-K^+-ATPase activity (251, 252) and basolateral membrane area of CD cells (350), whereas low doses of these steroids have no effect on K^+ transport (80, 287, 303), Na^+-K^+-ATPase activity (90, 209, 236, 248), or basolateral membrane area of CD cells (308). It has usually been observed that, coincident with stimulation of urinary K^+ excretion, glucocorticoids produce increases in glomerular filtration rate, frequently also in Na^+ excretion, and in the urinary flow rate, whereas these changes are rarely observed after the administration of mineralocorticoids at physiological doses (23, 91, 341). Glucocorticoid-induced kaliuresis usually ensues more rapidly and is of shorter duration than that following mineralocorticoids (19). Although the kaliuretic response to aldosterone is blunted in animals on a low-Na^+ (126) or normal-K^+ (375) diet, these dietary factors are without effect on the response to glucocorticoids (19, 41). The plasma K^+ concentration is usually normal or elevated during glucocorticoid treatment but is often decreased with mineralocorticoids (19). Furthermore, the increase in K^+ excretion after mineralocorticoids is inhibited by the mineralocorticoid receptor antagonist (spironolactone), which does not affect the response to glucocorticoids at all (41, 341). When the distal tubules of ADX rats were perfused in vivo at a constant flow rate, acute intravenous infusion of dexamethasone had no effect on the rate of net K^+ excretion in the perfused tubule, whereas final urinary K^+ excretion after dexamethasone was enhanced, along with the increased excretion of Na^+ and fluid (80). Therefore, increased K^+ excretion by glucocorticoids can be a result of increased fluid delivery rates into the distal tubule and collecting ducts, secondary to increased glomerular filtration rate, rather than being a direct effect on the distal tubule and collecting ducts.

Here, the questions arise as to why glucocorticoids do not directly act on the collecting ducts, despite the presence of glucocorticoid receptors in the collecting ducts (75). In general, mineralo- and glucocorticoids bind to cytosolic receptors. The mineralo- and glucocorticoid receptors are coexpressed in the collecting ducts (75) and act as transcription factors to modulate gene expression (346). It has been shown that mineralo- and glucocorticoid hormones display the same affinity for the mineralocorticoid receptors (86). In mineralocorticoid-target tissues, including the collecting ducts, mineralocorticoid selectivity is ensured by the presence of the enzyme 11β-hydroxysteroid dehydrogenase (11β-OHSD) (29, 30, 62, 86, 227, 261, 292). This enzyme transforms native glucocorticoids, corticosterone (rats) or cortisol (humans) (which circulate at plasma concentrations much higher than that of aldosterone), into 11-dehydro derivatives (11-dehydrocorticosterone or cortisone, respectively) with very low affinity for the mineralocorticoid receptors, thus protecting mineralocorticoid receptors against illicit occupancy by glucocorticoids (29, 62, 86, 292). This transformation maintains the mineralocorticoid receptor free for aldosterone binding and action. On the other hand, since the affinity of 11-dehydrocorticosterone and cortisone for the glucocorticoid receptor is also very low (86), 11β-OHSD is likely to affect binding and action of glucocorticoids via its own receptor as well. A deficiency of this enzyme, either congenital (syndrome of apparent mineralocorticoid excess type I) (211, 312) or when the enzyme is inhibited by licorice (or its derivative carbenoxolone) (313, 314), glucocorticoids illicitly occupy the mineralocorticoid receptor in the CCD, causing Na^+ retention and kaliuresis.

Two isoforms of 11β-OHSD have been cloned: 11β-OHSD1 (1) and 11β-OHSD2 (6). 11β-OHSD2 appears as the actual mineralocorticoid receptor-protecting enzyme, with high affinity for glucocorticoids, an exclusive dehydrogenase activity, and selective localization in aldosterone-sensitive cells (6, 7, 261, 292). In contrast, the ubiquitous 11β-OHSD1 has low affinity for glucocorticoids and bidirectional (dehydrogenase and reductase) activity (1, 292). 11β-OHSD1 depends on the cofactor NADP, while 11β-OHSD2 depends on NAD. Both isoforms are expressed in the kidney. It has been reported that the collecting duct expresses an enzyme form that has all the

properties of 11β-OHSD2 (7, 261, 292), while the properties of the proximal tubule enzyme are similar to those of 11β-OHSD1 (7, 261, 292). Mutations of the 11β-OHSD2 gene cause the syndrome of apparent mineralocorticoid excess type I (211).

D. K^+ Intake

Increased dietary intake of K^+ (143, 159, 184, 308) or an acute intravenous K^+ loading (143, 159, 302, 308) stimulates urinary K^+ excretion. In contrast, removal of K^+ from the diet leads to a prompt and dramatic decrease in urinary K^+ excretion (143, 184, 186, 306). Renal enhanced excretion or conservation of K^+ is mediated by the distal tubule and the collecting ducts.

1. K^+ loading

During the first several hours after an increase in K^+ intake, K^+ secretion by the distal tubule and the CCD is stimulated by direct and indirect effects of hyperkalemia. An increase in plasma K^+ concentration directly stimulates K^+ secretion by the CD cell (80, 191). K^+ excretion also rises, because hyperkalemia causes a diuresis and natriuresis by inhibiting Na^+ and water absorption by the proximal tubule (32). An increase in tubular flow rate is one of the most potent stimuli of K^+ secretion by the distal tubule and the CCD. Hyperkalemia also stimulates K^+ excretion indirectly by elevating plasma aldosteorne levels, which enhance K^+ secretion by the ICT and CCD (80).

In vivo micropuncture and microperfusion studies at a constant flow rate have shown that an elevation in plasma K^+ concentration induces a saturable increase in K^+ secretion in the rat distal tubule; a maximal rate of K^+ secretion occurs at a plasma K^+ concentration of ~6 meq/l (308). The high K^+-induced K^+ secretion is due to elevated aldosterone levels (308). The hyperkalemia also directly stimulates K^+ secretion (217). Studies of isolated perfused CCD from normal rabbits have shown that acute elevation of peritubular K^+ from 2.5 to 8.5 mM greatly enhanced transcellular K^+ secretion and Na^+ reabsorption (217). Such increases in K^+ and Na^+ transport after physiological elevation of bath K^+ concentration are sharply enhanced in the CCDs of DOCA-treated rabbits (217). Thus the high K^+-induced K^+ secretion occurs through aldosterone-dependent and aldosterone-independent (K^+-dependent) mechanisms. Microelectrode studies of the CD cell in the rabbit CCD demonstrated that acute elevation of bath K^+ from 2.5 to 8.5 mM initially activates the basolateral Na^+-K^+ pump, which secondarily elevates the apical Na^+ and K^+ conductances, and that DOCA pretreatment in vivo increases the basolateral K^+ conductance and augments the response to the rise of both the basolateral Na^+-K^+ pump activity and the apical cation conductances (214). The intracellular signaling mechanisms for the tight coupling between the basolateral Na^+-K^+ pump and the apical cation conductances remain to be elucidated.

Chronic exposure to a high-K^+ diet causes a dramatic functional and structural adaptation. The ability of the distal tubule and the CCD to secrete K^+ and to reabsorb Na^+ increases sharply compared with the rate of transport during acute phase of K^+ adaptation. The accelerated rate of urinary K^+ excretion in K^+-adapted animals can be attributed to an increase in K^+ secretion by the distal tubule (119, 301, 303, 308) and the CCD (81). When the tubular flow rate and the composition of the fluid entering the distal tubule were controlled by continuous microperfusion, K^+ secretion was significantly greater in tubules from rats given a high-K^+ diet for a long period compared with animals on a normal-K^+ diet (308). Furthemore, Na^+-K^+-ATPase activity in the CCD from K^+-adapted animals is increased (58). Chronic exposure to a high-K^+ diet also caused basolateral membrane amplification of the CD cell in both rat (119, 250, 302) and rabbit (139) CCDs. These functional and structural changes are due to elevated plasma aldosterone levels. On the other hand, several reports provide evidence that K^+ secretion across the ICT and the CCD can be modulated by a high-K^+ diet independently of aldosterone. For instance, imposition of chronic high K^+ load in ADX animals, in which steroid levels were "clamped" to low levels, still induced significant K^+ secretion in the CCD (382). Such K^+ loads also elevated Na^+-K^+-ATPase activity in the CCD (88) and caused basolateral membrane amplification of the CD cell (302). Electrophysiological studies in the CD cell of the CCD from ADX rabbits have shown that a high-K^+ diet directly increased the apical Na^+ and K^+ conductances, as well as the basolateral Na^+-K^+ pump activity (223). Therefore, long-term administration of a high-K^+ diet stimulates K^+ secretion in the ICT and the CCD through aldosterone-dependent and aldosterone-independent (K^+-dependent) processes. Future studies will be required to clarify the mechanisms whereby high-K^+ diet directly modulates activity of the apical and basolateral transporters in the CD cell.

2. K^+ depletion

When K^+ is eliminated from the diet, the urinary excretion of K^+ declines sharply (169, 257). After 1 day on a low-K^+ diet, urinary K^+ excretion in rats is only 1–3% of the amount filtered by the glomeruli (14, 169, 257). This decline in urinary K^+ excretion is due to a reduction in plasma aldosterone levels, since DOCA treatment coincident with the low-K^+ diet inhibits the reduction in K^+ excretion (169). After 72 h of K^+ depletion, urinary K^+ excretion occurred independent of mineralocorticoids and was accompanied by a reduction in the permeability

of the distal nephron to K^+ and a decrease in cell K^+ content (169). Decreased urinary K^+ excretion by K^+ depletion occurs through both decreased K^+ secretion and increased K^+ absorption. In the CCD from rat kidneys (64, 87, 130), K^+ depletion decreases Na^+-K^+-ATPase activity, probably in relation to the decreased K^+ secretion in this segment. However, the cellular mechanisms for the decreased K^+ secretion in the CD cell after K^+ depletion remain unknown. Only in the OMCD from K^+-depleted rats Na^+-K^+-ATPase activity is increased (64, 113, 130). This is accompanied by increased levels of Na^+-K^+-ATPase α_1- and β_1-subunit protein (195). After K^+ repletion, the stimulatory effects of K^+ depletion on Na^+-K^+-ATPase activity in the OMCD were restored to control levels (113). When ouabain was added to the perfusate in isolated perfused kidneys from normal or K^+-depleted rats, it stimulated K^+ excretion in the K^+-depleted kidneys, whereas it caused no effect on K^+ excretion in the normal kidneys (114). The binding of [^{3}H]ouabain to intact OMCD, which reflects the number of enzyme units in the basolateral membrane, was similar in K^+-depleted and in normal rats. However, when the tubules were permealized by hypotonic lysis and freeze-thawing, there was a significant increase in [^{3}H]ouabain binding in K^+-depleted tubules compared with that of the control tubules (113). These findings suggest that the Na^+-K^+-ATPase induced by K^+ depletion may be located either at intracellular space or at the apical membrane and may be involved in active K^+ reabsorption. However, it is presently unknown whether the increased Na^+-K^+-ATPase activity in the OMCD facilitates K^+ reabsorption during hypokalemia. On the other hand, K^+ reabsorption occurs mainly in the OMCD via two different processes, paracellular passive K^+ absorption (377) and transcellular active K^+ absorption (9, 161, 376, 380).

Paracellular passive K^+ absorption has been demonstrated in the rabbit OMCDi perfused in vitro (377). Because the V_T is oriented lumen positive, and this segment is permeable to K^+, imposition of a K^+ concentration gradient directed from the lumen to bath stimulates net K^+ absorption (148, 377). Because the apical membrane of the OMCDi has no appreciable conductance to K^+ (148, 219, 224) and the electrochemical gradient of K^+ across the tubule in vivo is directed from the lumen into the blood, it is possible that a small amount of K^+ is absorbed in situ when the K^+ concentration in tubular fluid is sufficiently high. Conditions that stimulate the paracellular K^+ permeability, such as dietary K^+ depletion, would enhance K^+ absorption (377).

Chronic K^+ depletion is associated with a remarkable hypertrophy of the rat kidney (65, 113, 233, 333). However, renal growth is not uniform and hypertrophy of the OMCD is most prominent (65, 113, 130, 311). Some investigators (233, 333) reported that the number of IC cells increased after K^+ depletion, whereas others (110, 311) did not. Elger et al. (65) demonstrated an increased number of both IC cells and CD cells without changing the relative number of these cells. However, all investigators have noted increased luminal membrane area of IC cells in the OMCD after K^+ depletion (65, 233, 311, 333). Elger et al. (65) also reported increased basolateral membrane area of the IC cell. The IC cell in this segment exhibits an increased number of rod-shaped particles at the apical membrane and a decreased number of subapical cytoplasmic vesicles lying below the apical membrane (311). These morphological observations suggest that the increased apical membrane area of the IC cell in the OMCD from K^+-depleted rats apparently reflects an increased capacity to reabsorb K^+.

The H^+-K^+-ATPase is localized to the apical membrane of the rabbit OMCDi (161, 376, 380). Also, it is present in the apical membrane of both α- and β-IC cells in the rabbit CCD (206, 298, 369) and of α-IC cells in the rabbit OMCDo (161) but is absent in the CD cell of the rabbit OMCDo (161). Under K^+ depletion, K^+ is actively absorbed through H^+-K^+-ATPase located at the apical membrane of the OMCD. This is based on enzymatic (48, 59, 64, 89), immunocytochemical (381), fluorescence (161), flux (9, 376, 380), and molecular biological (3–5, 38, 40, 60, 136, 153) studies. The H^+-K^+-ATPase, like Na^+-K^+-ATPase, belongs to a member of the P-type ATPase (since it is inhibited by vanadate) and is composed of two subunits, α and β (249). The α-subunit is the site of ATP hydrolysis and ion translocation. At least two α-subunit isoforms have been reported: cDNAs encoding highly homologous H^+-K^+-ATPase α-subunits have been cloned from mammalian stomach (296) and distal colon (54). Gastric isoform of the α-subunit is sensitive to Sch28080 and omeparazole and insensitive to ouabain (263, 291), whereas the colonic isoform of the α-subunit is resistant to Sch28080 and omeprazole, but relatively sensitive to ouabain (51, 55, 323). At least two β-subunit isoforms from stomach (38, 42, 43, 180, 183, 295) and colon (266) have been reported. The β-subunit protein has a single transmembrane domain with an extracellular carboxy-terminal region that is extensively glycosylated and is regulated for efficient cell-surface targeting and assembly of the enzyme (103). Both α- and β-subunits are required for the physiological function of the enzyme (49), since both isoforms of the H^+-K^+-ATPase α-subunit can assemble productively with the gastric H^+-K^+-ATPase β-subunit when these proteins are coproduced in heterologous expression systems (51, 103, 107). Although which isoforms of the H^+-K^+-ATPase α-subunit are expressed in the kidney from normal and K^+-deprived animals still remains controversial, at least gastric and colonic isoforms of the H^+-K^+-ATPase appear to be expressed in different cell types of the collecting duct from rats and rabbits, and to be differentially regulated under normal and K^+-depleted conditions (3–5, 35, 38, 40, 50, 59, 60, 136, 152, 161, 206,

225, 226, 232, 297, 298, 309, 369, 376, 380, 381, 391, 394). The gastric H^+-K^+-ATPase β-subunit is expressed in the entire collecting duct of the rat and rabbit kidneys (38, 40). The colonic H^+-K^+-ATPase β-subunit is also expressed in the rat kidney (266). However, it is not known whether the expression of both β-subunits mRNA is enhanced in the collecting duct after chronic K^+ depletion. The cytoplasmic tail of the gastric H^+-K^+-ATPase β-subunit includes a four-amino acid motif that is highly homologous to tyrosine-based endocytosis signals (52, 102). Mice expressing the β-subunit of the gastric H^+-K^+-ATPase in which the tyrosine residue in this sequence was mutated to alanine exhibited higher concentrations of plasma K^+ and lower excretions of urinary K^+ compared with the wild-type mice (353). These data suggest that the tyrosine-based signal in the cytoplasmic tail of the gastric H^+-K^+-ATPase β-subunit functions in the kidney. However, the underlying cellular and molecular mechanisms are not clear. Under K^+ depletion, upregulation of the colonic isoform (α-subunit) has been reported in the rat kidney (35, 50, 60, 152, 225, 226). However, when mice carrying a disruption of the colonic isoform of the H^+-K^+-ATPase α-subunit gene were maintained on a K^+-deficient diet, urinary K^+ excretion was decreased to similar levels in both wild-type and knockout mice, whereas fecal K^+ excretion was greater in the knockout mice (205). These findings suggest that the colonic isoform is a major mechanism for K^+ conservation in the colon, but not in the kidney, during K^+ depletion. Future studies will be required to clarify the precise role of the gastric and colonic isoforms of the H^+-K^+-ATPase α- and β-subunits in K^+ transport of the mammalian collecting duct.

Under normal (K^+ replete) conditions, the rabbit CCD (393) and OMCDi (9, 380) possess an apical H^+-K^+-ATPase capable of significant HCO_3^- absorption, yet absorptive K^+ flux was inhibited in the CCD (394) or was not detected in the OMCDi (14, 318). The H^+-K^+-ATPase-dependent HCO_3^- absorption in these segments was inhibited by the luminal addition of Ba^{2+} (9, 394). Thus it has been proposed that luminal K^+ transported by the H^+-K^+-ATPase would recycle back into the lumen via a Ba^{2+}-sensitive mechanism (9, 394). However, the exact pathway for the Ba^{2+}-sensitive mechanism remains unclear. In contrast, under K^+ depletion, an apical H^+-K^+-ATPase in series with a basolateral Ba^{2+}-sensitive exit mechanism, presumably a K^+ channel, apparently permits substantial net K^+ absorption in the CCD (393). In the OMCDi, K^+ depletion also stimulates active net K^+ absorption (376). Thus, of critical importance in predicting the magnitude of the H^+-K^+-ATPase-mediated K^+ absorptive flux in the CCD and OMCDi is the characterization of the basolateral K^+ conductance in the unique cell types.

E. Acid-Base Balance

Derangements of acid-base balance exert a powerful effect on renal K^+ excretion. In general, acidosis inhibits and alkalosis stimulates renal K^+ excretion (94, 187, 288, 307, 335). An extensive micropuncture study of the rat superficial distal tubule demonstrated that acid-base imbalance modifies distal and collecting duct K^+ transport (187).

1. Metabolic acidosis

Several studies have reported that an acute metabolic acidosis inhibits renal K^+ excretion (187, 335). When urine flow rate is kept constant, acidosis inhibits K^+ excretion into urine (243, 335). In vivo microperfusion studies of the rat superficial distal tubule also reported that distal tubule K^+ secretion decreased during metabolic acidosis, when the flow rate and Na^+ delivery were held constant (307). In sharp contrast, in other studies both metabolic acidosis (260, 290) and isohydric reduction of plasma HCO_3^- (22) increase rather than decrease renal K^+ excretion. In these studies, however, the enhanced K^+ excretion during acidosis is associated with an increase in renal excretion of Na^+ and fluid. Free-flow micropuncture studies of the rat kidney (307) also demonstrated enhanced K^+ secretion in the distal tubule during metabolic acidosis. At the same time, an increase in the rate of fluid and Na^+ delivery to the distal tubule was observed (307). Reductions in plasma HCO_3^- concentrations inhibited Na^+ and fluid reabsorption in the proximal tubule (36, 106, 243), and thereby increased the urine flow rate and Na^+ excretion occurred. Therefore, during acute metabolic acidosis, an enhanced delivery of fluid and Na^+ to the distal tubule causes an increase in K^+ secretion in the distal tubule. Accordingly, the inhibitory effect of metabolic acidosis on distal K^+ secretion may be masked by secondary flow-dependent alterations of K^+ transport.

In vitro microperfusion studies of the rabbit CCD show that decreased bath pH from 7.4 to 6.8 by reduction in HCO_3^- concentrations or by HEPES buffer in the absence of HCO_3^- caused decreases in lumen-negative V_T and net K^+ secretion to the same magnitude (326). These results indicate that the decreased bath pH, but not the decreased HCO_3^- concentration, contributes to the decreased K^+ secretion during metabolic acidosis. Furthermore, the in vitro metabolic acidosis in the isolated perfused CCD depolarized the basolateral membrane of the CD cell with increases in both R_T and fR_A, although it caused no effect on the lumen-to-bath Na^+ flux (326). Luminal Ba^{2+} partially attenuated the inhibitory effect of the acidosis on net K^+ secretion (326). Thus the basolateral acidosis partly inhibits Ba^{2+}-sensitive apical K^+ conductance of the CD cell, and thereby decreased K^+ secretion occurs. This is also supported by the patch-clamp

studies of the rat CCD in which low-conductance K^+ channel in the apical membrane of the CD cell is exquisitely pH sensitive, with reduction of the bath pH from 7.4 to 6.9 completely blocking channel activity in excised patches (279, 356, 360). Because the basolateral membrane of the CD cell possesses Na^+/H^+ exchange that regulates intracellular pH (45), changes in blood pH are likely to affect CD cell K^+ transport possibly via changes in the activity of the basolateral Na^+/H^+ exchange. On the other hand, there has been some controversy regarding the effect of luminal pH on K^+ secretion in the distal tubule and the CCD. Decreased luminal pH has been reported to inhibit K^+ secretion in the rabbit CCD (31). In support of this, O'Neil and Sansom (239) found a decrease in apical membrane K^+ conductance of the CD cell with luminal acidification, albeit with a reduction in apical pH from 7.4 to 4.0. In contrast to these findings, an in vivo micropuncture study of the rat distal tubule showed no effect of luminal pH on K^+ secretion (307).

2. Metabolic alkalosis

Metabolic alkalosis is a potent stimulus of renal K^+ excretion (94, 187, 307, 335). Alkalosis has been reported to increase distal tubule K^+ secretion (187, 288, 307, 335). Several factors, including increased delivery of fluid and HCO_3^- as well as increased peritubular pH, are responsible for enhanced distal K^+ secretion during alkalosis. First, metabolic alkalosis increases distal delivery of HCO_3^-. In vivo microperfusion studies of the rat distal tubule demonstrated that luminal HCO_3^- substitution for Cl^- enhances significantly K^+ secretion through electroneutral K^+-Cl^- cotransport across the apical membrane in the distal tubule (343). Furthermore, metabolic alkalosis leads to increased distal delivery of Na^+ and intracellular Na^+ concentrations of the DCT cells, CNT cells, and CD cells, causing an increased Na^+ reabsorption (20). The increased Na^+ reabsorption could secondarily stimulate K^+ secretion through activation of the basolateral Na^+-K^+ pump in the distal tubule. Second, Stanton and Giebisch (307) found in the late distal tubule of the rat that metabolic alkalosis following systemic HCO_3^- infusion stimulates K^+ secretion when changes in luminal flow rate, pH, and HCO_3^- delivery are minimized by microperfusion. These findings indicate that elevated plasma pH or HCO_3^- have a direct stimulatory effect on K^+ secretion in the distal tubule. In vitro microperfusion studies of the rabbit CCD (325) show that intracellular alkalosis following elimination of HCO_3^- and CO_2 from the bathing solution (bath pH is kept constant) increased K^+ secretion with increases in lumen-negative V_T and V_B of CD cells and decreases in R_T and fR_A. Thus changes in intracellular pH are important modulators of K^+ secretion in the distal tubule and the CCD during metabolic alkalosis.

F. Vasopressin

In the rabbit CCD, vasopressin in the bath produced only a transient stimulation of Na^+ absorption and hyperpolarization of the V_T (82, 124) without any appreciable K^+ transport (82). Within 15 min of the hormone addition, these parameters fell to control levels (82). These earlier studies were conducted only in the rabbit CCD because of the greater ease of dissection in this species. Thereafter, it has been possible to study the rat CCD (253, 254, 273–275, 281, 334) by using pathogen-free rats. In the distal tubule (79) and the CCD (253, 254, 273, 274, 334) from this species, vasopressin in the peritubular fluid produced an increase in Na^+ reabsorption and K^+ secretion. The physiological significance of the stimulation of K^+ secretion by vasopressin in the distal tubule and CCD may lie in the need to maintain K^+ excretion during antidiuresis when slower volume flow rates would tend to limit the rate of K^+ secretion (79). The increased Na^+ reabsorption induced by vasopressin can be accounted for by increased apical membrane Na^+ conductance in the CD cell (281). Alternatively, this increased apical membrane Na^+ conductance caused depolarization of the apical membrane, and thereby increased driving force for K^+ across the apical membrane, and consequently an increased K^+ secretion occurs (275). In sharp contrast, vasopressin has been reported to directly increase the density of low-conductance K^+ channels in the apical membrane of the CD cell of the rat CCD (44). The increased K^+ secretion induced by vasopressin may also be explained by the activation of low-conductance K^+ channels in the apical membrane. The reasons for this discrepancy between the mechanisms of the vasopressin-induced K^+ secretion are unclear at present.

V. CONCLUSIONS

The mammalian collecting duct has morphological and functional cell heterogeneity along the axis and is composed of at least two cell types: CD cells and IC cells. In the CD cell of the CCD, K^+ secretion occurs, whereas under K^+ depletion, K^+ reabsorption occurs in the IC cell. The K^+ secretion in the CD cell is mediated by active uptake of K^+ by the basolateral Na^+-K^+-ATPase pump and passive diffusion by the apical K^+ conductance. An additional transport pathway in the CCD is an apical membrane K^+-Cl^- cotransporter. Under K^+ depletion, K^+ absorption occurs via the apical membrane H^+-K^+-ATPase pump, but the basolateral K^+ exit mechanisms remain unresolved. Regulation of K^+ transport along the collecting duct is mediated by activation of specific renal and extrarenal stimuli acting on both basolateral and apical K^+ transport mechanisms. These synchronized mechanisms, also referred to as "cross-talk," between the

active pump and passive ion conductances could prevent rapid and possibly deleterious disturbances of cell volume, cell ion concentrations, and cell potential with changes of vectorial Na^+ or K^+ transport. This could occur also in pathophysiological conditions in which ion transport and metabolism are seriously compromised. Possible mechanisms that could account for coupling between the basolateral and apical transport include modulation of intracellular pH, intracellular Ca^{2+}, intracellular Na^+, cell ATP, NO, and membrane polarization; however, they have not fully been demonstrated. By using the patch-clamp technique, properties of K^+ channels in the apical and basolateral membranes of the collecting ducts have been well characterized. However, it has not been fully investigated whether most properties of the K^+ channels in the collecting ducts actually explain well the behavior of macroscopic K^+ conductance. The cloning of the ROMK channels provided several major developments in the field. This channel is identical to the low-conductance K^+ channel in the apical membrane of the CCD and TAL and is thought to be a secretory K^+ channel in the apical membrane of those tubules. Several factors affect K^+ transport by the distal tubule and the collecting ducts. Luminal factors include the rate of distal fluid and Na^+ delivery and the composition of the luminal Na^+ concentration, whereas peritubular factors include changes in aldosterone, plasma K^+ concentration, acid-base status, and vasopressin. However, it is still unclear how the ROMK channels, as well as other K^+ channels, are involved in the K^+ secretion induced by the luminal and peritubular factors. Although the collecting duct is composed of heterogeneous cells with different functions along the axis, it is not known whether there is mutual interaction of these cells with regard to K^+ transport, and if so, the underlying mechanisms are unknown. Analyses of the above questions will provide novel insights into the mechanisms underlying genesis and therapy of inherited and acquired disorders of K^+ balance.

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