Recent Advances in the Field of Renal Potassium Excretion: 
What Can We Learn from Potassium Channels?

Gerhard H. Giebisch

Department of Cellular and Molecular Physiology
Yale University School of Medicine, New Haven, Connecticut

(Received May 12, 1997; accepted July 8, 1997)

Potassium channels in the apical and basolateral membranes of tubule cells serve several important functions. They contribute to the generation of the cell-negative potential, mediate volume reductions following cell swelling and play a key role in secretion of potassium in both the thick ascending limb of Henle’s loop and principal tubule cells of the initial and cortical collecting tubules. Secretion of potassium occurs via a well-defined class of potassium channels distinguished by their low single channel conductance, mild inward rectification, high sensitivity to inhibition by low pH, millimolar concentrations of ATP, arachidonic acid and PKC, and stimulation by vasopressin and pretreatment with a high potassium diet. Genes encoding several isoforms of this channel have been cloned and the proteins located to the apical membranes of cells lining the thick ascending limb of Henle’s loop and the collecting tubules, and progress made concerning their structure-function relationship.

INTRODUCTION

Early studies on potassium transport by the kidney

Quantitative information concerning the role of the kidney in potassium (K) homeostasis began to emerge with the introduction of the flame photometer and renal clearance methods. These permitted the comparison of filtered with excreted moieties of potassium and evidence emerged that the renal excretion of K included an important element of secretion by the tubules [1]. Observations that the amount of K in the urine could not be accounted for by filtration alone soon led to the acceptance of a three-component system of renal K excretion, including filtration and extensive proximal reabsorption followed by regulated distal secretion. Clearance methods also provided important information on the tight relationship between sodium and K excretion and the profound effects of acid-base derangements and corticosteroids on K handling by the kidney [1].

Studies of potassium transport at the single nephron level

The application of both free-flow micropuncture and tubule perfusion methods, either in vivo or in vitro, fully supported the early hypothesis of the reabsorptive and secretory components of renal K transport, and they firmly established the key role of K secretion as the determining element of K transport in the kidney [2, 3]. Figure 1 provides a summary of the most salient features of K transport along the nephron. After free filtration, large fractions of K are reabsorbed along the proximal tubule and the loop of Henle, and regulated secretion in the initial and cortical collecting tubule is mainly responsible for K

---

a To whom all correspondence should be addressed: Gerhard H. Giebisch, Department of Cellular and Molecular Physiology, Yale University School of Medicine, New Haven, CT 06520. Tel.: 203-785-4076; Fax: 203-785-4951; E-mail: gerhard.giebisch@yale.edu.

b Abbreviations: PKA, protein kinase A; PKC, protein kinase C; ROMK, renal outer medullary K channel.
excretion [4]. It is at the site of K secretion that such factors as K intake, hormones, tubule flow rate and acid-base-related factors affect K excretion. It should be noted that K secretion can be suppressed in states of prolonged K deprivation so that K reabsorption continues along the whole nephron [3, 4].

An important feature of distal nephron segments involved in the regulation of K excretion is their cell heterogeneity. It has long been known that principal and several sub-populations of intercalated cells line the initial and cortical collecting tubule. They are different from each other with respect to abundance, morphology and function [3]. A combination of morphological techniques, electron probe analysis of single cell ion content, electrophysiological exploration of membrane permeabilities and flux studies have provided strong evidence that principal cells secrete and intercalated cells reabsorb K [3].

**CELL MODELS OF POTASSIUM TRANSPORT ALONG THE NEPHRON**

Extensive exploration of the potassium fluxes and the respective electrochemical driving forces across individual cell membranes of tubule cells has shown that both transcellular and paracellular transport routes must be considered in the analysis of potassium reabsorption and secretion. Figure 2 provides a summary of the present state of our knowledge of K transport along the nephron.

*Proximal tubule*

Potassium transport in this nephron segment is tightly coupled to active sodium transport and involves both diffusion and solvent drag [3, 5]. Proximal tubule cells share with
all tubule cells the presence of an active, ATP-ase driven Na-K exchange mechanism in the basolateral cell membrane. This active sodium movement provides the driving force for proximal sodium and fluid absorption, and K ions are entrained in the fluid. A small lumen-positive potential in the early part of the proximal tubule provides an additional force for passive potassium reabsorption. Thus, a large fraction of K ions is reabsorbed rather indiscriminately across the proximal tubule epithelium. Reabsorption of K is inhibited as evidenced by the delivery of larger than normal fractions of filtered K out of the proximal tubule whenever proximal sodium reabsorption declines. Inspection of Figure 2 shows the presence of both basolateral and apical K channels in proximal tubule cells. Basolateral K channels permit not only extensive K recycling but are also responsible for the cell-negative potential which is one of the driving forces for apical transport of charged sodium-dependent cotransport mechanisms [6]. Apical K channels confer a modest K permeability to proximal tubule cells but their functional importance is incompletely defined. They may provide an exit pathway for K during cell swelling and their activation with cell depolarization may be a protective mechanism preventing depolarization of tubule cells during transport of electrically charged solutes across the apical membrane [6, 7, 8]. Most of the K transported into proximal tubule cells recyclies across the basolateral membrane.
Thick ascending limb of Henle

Two transport mechanisms in the apical membrane of this nephron segment are involved in K transport. K reabsorption is mediated by an electroneutral Na-2Cl-K cotransport mechanism which is driven by the low concentration of sodium in the cytoplasm and sensitive to the inhibitory action of loop diuretics [9, 10]. The apical K conductance is due to two distinct K channels and serves as a recycling pathway for K ions [11]. Inhibition of apical K channels lowers the lumen-positive potential and diminishes the delivery of K from the cell to the Na-2Cl-K cotransporter. Additional consequences of altered K channel activity are related to the effects on passive cation movement of the lumen positive potential which depends on K channel activity. As a significant fraction of K is reabsorbed via the paracellular pathway along a favorable electrochemical potential gradient, K (and sodium) reabsorption along both transcellular and paracellular pathways are sharply reduced whenever K channel activity in the apical membrane declines [12].

Initial and cortical collecting tubule

The transport pathways responsible for both K secretion and K reabsorption are also shown in Figure 2. K secretion in principal tubule cells involves two primary and several secondary elements: active uptake across the basolateral membrane by Na-K ATPase and diffusion along a favorable electrochemical potential gradient through K channels across the apical membrane are the two main transports. Secondary elements that modulate K transport in principal tubule cells are the apical sodium permeability, the turnover rate and electronegativity of the basolateral Na-K ATPase, and the activity of basolateral K channels [1, 3, 4]. The latter two components determine the rate of net K uptake from peritubular fluid into the cytoplasm whereas the activity of apical sodium channels modulates K secretion by its ability to depolarize the apical membrane and thus to alter the driving force for passive diffusion. Inspection of Figure 2 also shows that the model of principal tubule cells contains a KCl cotransport mechanism in the apical membrane. This transporter may effect K secretion at low lumen chloride concentration and could mediate KCl loss into the tubule fluid during cell swelling.

Active K reabsorption has been localized to a subpopulation of intercalated cells and recent studies have identified the underlying transport mechanism [13]. Detailed studies of ATPase activity in isolated cortical collecting tubules from control and K-depleted animals have led to the discovery of a K-activated ATPase which is significantly upregulated in K depletion. Its mode of action involves electroneutral exchange of K for hydrogen ions. A similar mechanism has also been shown to be present in medullary collecting ducts [14].

Table 1. Function of renal potassium channels.

|   |   |
|---|---|
| 1 | Maintenance of negative potential of tubule cells (basolateral). |
| 2 | Regulation of cell volume of tubules (VRD) (apical and basolateral, direct or Ca-mediated) |
| 3 | A: Recycling across apical cell membrane of thick ascending limb of Henle's loop: to supply potassium to Na-2Cl-K cotransporter and to generate membrane potential |
|   | B: Recycling across basolateral cell membrane to supply potassium to Na-K-ATP-ase |
| 4 | Secretion of potassium in initial and cortical collecting tubule |
Figure 3. Location of ATP-regulated potassium channels along the nephron. Note the presence of such K channels in the basolateral membrane of proximal tubule cells, and in the apical membrane of cells in the thick ascending limb and the cortical collecting tubule. Not shown are stretch-sensitive "maxi" K channels and other stretch-activated K channels that are found both in the apical and basolateral membranes of tubule cells (from Ref. 16).

STUDIES OF RENAL POTASSIUM CHANNELS

The introduction of patch-clamp techniques has provided a unique tool to advance our understanding of the function and molecular structure of potassium channels in the kidney. It has also allowed useful comparisons to be made between native and cloned channels; identification on the channel protein of specific sites for modulation by a variety of enzymes, hormones and metabolic alterations has begun to emerge.

Table 1 and Figure 3 provide a summary of the functions and the intrarenal localization of renal K channels. Basolateral K channels in all tubule cells allow extensive recycling of K across the basolateral membrane of tubule cells and they provide a key element for the generation of the cell-negative electrical potential, the main driving forces across the apical cell membrane for passive entry of positively charged molecules. A special group of K channels has also been identified to mediate volume regulatory decrease, the loss of solutes from tubule cells following cell swelling. Such stretch-activated K channels occur in both apical and basolateral membranes. In the thick ascending limb of Henle's loop, apical K channels are essential for K recycling across the apical membrane: their inhibition blocks the activity of the electroneutral Na-2Cl-K cotransporter. Finally, K channels in the apical membrane of principal tubule cells provide the transport pathway for diffusion of K from cell to lumen and thus play a key role in potassium secretion [4, 6, 7, 15, 16]. In the following, emphasis will be placed on the function and structure of K channels in the apical and basolateral membrane of principal tubule cells.
Apical K channels

The K channel that mediates K secretion across the apical membrane of principal tubule cells is a small-conductance K channel distinguished by high open probability, modest magnesium-dependent inward rectification, relatively modest selectivity of K over rubidium and high selective for K over sodium. In view of the high open probability of this channel under physiological conditions, activation of K conductance takes place largely by recruitment of additional channels from a pool of dormant channels in the apical membrane. Whether additional channels from the cytoplasm are targeted to and inserted into the apical membrane during adaptation to a high K diet is presently not known [6, 15, 16].

The application of patch-clamp techniques has permitted the exploration of many factors that regulate the activity of the low-conductance K channel. The most important of these are summarized in the upper panel of Figure 4 [16]. Of particular physiological importance are the stimulating effects of a high K diet and aldosterone, of cyclic AMP and protein kinase A (PKA)β-dependent stimulation by vasopressin. The channel is also exquisitely sensitive to the inhibitory effects of cytosolic acidification (see Figure 5). Low

![Figure 4. Cell model of principal tubule cell of cortical collecting tubule. The upper panel shown summarizes factors regulating the apical low-conductance potassium channel; the lower panel shows the presence of three distinct potassium channels and their regulation in the basolateral membrane. Not shown are stretch-and depolarization-activated potassium channels in the apical membrane (from Ref. 16).](image-url)
Figure 5. Potassium channel recording from an inside-out patch of a principal tubule cell. Shown are the effects of changes in cytosolic pH. C: baseline. $P_o$: open probability. Note that two channels are initially active. Channel activity is sharply diminished by lowering pH but can be promptly restored when pH returns to the control value of 7.4 (modified from Ref. 37).

Figure 6. The effects of mM concentrations of MgATP on potassium channel activity recorded from an inside-out patch from the apical membrane of a principal tubule cell. C: baseline. Note that channel activity disappears when the membrane patch is exposed to 3 mM ATP, and that ADP relieves the ATP-induced inhibition of channel activity (from Ref. 38).
concentrations of ATP are necessary for channel phosphorylation but higher concentrations of ATP inhibit activity (see Figure 6). Moreover, PKA-induced phosphorylation and Mg-dependent dephosphorylation processes have been shown to affect channel activity. This explains the fact that the channel’s activity can be prevented from “run-down” (the gradual disappearance of channel activity after membrane excision) by low concentrations of Mg-ATP and PKA.

The low-conductance K channel in the apical membrane of principal tubule cells is not directly sensitive to changes in cytosolic calcium concentrations [Ca], but several maneuvers that raise cell Ca have been demonstrated to decrease channel activity [4, 17]. This inhibitory effect is mediated by the activation of both protein kinase C (PKC) and calcium calmodulin-dependent kinases [16, 18, 19]. Thus, maneuvers that increase cell Ca, for instance blocking basolateral Na-K ATPase activity [17] or cyclosporin administration [20], have been shown to down-regulate apical K channels. A representative example is shown in Figure 7 where the sequence of Ca-dependent events following inhibition of basolateral Na-K ATPase activity is summarized. Taken together, these effects of PKA and PKC are consistent with at least two functionally separate phosphorylation processes, either stimulating or inhibitory, affecting channel activity. The presence of several distinct membrane-bound Mg-sensitive and Mg-insensitive phosphatases [21] underscores the importance of such phosphorylation–dephosphorylation processes.

**Basolateral K channels.**

The exposure of basolateral membranes of single principal tubule cells poses considerable technical problems but has been overcome by two approaches: selective removal of
intercalated cells surrounding principal tubule cells in the split-open preparation of the cortical collecting tubule followed by recording of channel activity from the exposed lateral membrane [22], or gentle collagenase treatment of isolated collecting ducts, a procedure that permits access to the basal membrane of principal tubule cells [23]. Several K channels of differing single channel conductance have been identified. The lower panel of Figure 4 summarizes factors that alter their activity [16]. It is of interest that basolateral K channels are stimulated by cGMP, PKC and membrane hyperpolarization [25], effects that distinguish these K channels from their apical analogs (see upper panel of Figure 4).

The voltage dependence of the 85 ps K channel confirms previous studies in which measurements of macroscopic ion currents in amphibian principal tubule cells had strongly suggested a similar relationship between membrane polarization and K conductance [24]. Since the electrogenicity of the basolateral Na-K ATP-ase leads to hyperpolarization, an increase in sodium reabsorption and subsequent stimulation of basolateral active Na extrusion would lead to an increase in the basolateral K conductance and thus tightly couple basolateral Na-K ATPase with K channel activity. This effect would be further enhanced by PKA and vasopressin-related activation of Na transport [26].

A striking feature of some basolateral K channels is their sensitivity to nitric oxide and cGMP (see lower panel of Figure 4) [16, 27]. Several patch-clamp studies of the low-conductance basolateral K channel suggest that NO stimulates these K channels. Available evidence also suggests that the effects of NO are mediated through a cGMP-dependent pathway, although the mechanism underlying such activation needs further exploration. The potential physiological importance of cGMP-dependent regulation is suggested by observations that addition of cGMP hyperpolarizes the cell potential of principal tubule cells. In view of the strong voltage-dependence of apical Na channels, Na reabsorption could increase as a consequence of the expected rise of the apical membrane potential and the increase of the driving force for passive sodium entry [28]. Since the activity of the NO synthase is Ca-dependent, changes in cell Ca levels are indirectly involved in the regulation of basolateral K channels and have been shown to participate in their complex regulation in several experimental settings [16].

A relevant example of the calcium-triggered modulation of basolateral K channels is their downregulation that follows inhibition of apical sodium entry by Na channel blockers: with the reduction of cell Na, calcium extrusion across the basolateral membrane increases and the measured concentration of calcium in the cytoplasm falls. As the formation of NO declines, the activity of basolateral K channels decreases [29].

**MOLECULAR STRUCTURE OF RENAL K CHANNELS**

The genes for several K channels of renal origin have been cloned, including isoforms of voltage-sensitive and cGMP-gated Shaker-like channels [16, 30, 31]. Information on the precise localization within different tubule cell populations, the role in K transport and/or cell volume regulation of these channels is incomplete, but it is possible that some of the cloned cGMP-sensitive K channels are similar to those in the basolateral membrane of principal tubule cells.

A considerable body of information is available on inwardly-rectifying ATP-regulated K channels that share striking similarity with the native low-conductance K channel in the apical membrane of principal tubule cells [16, 30]. Genes for several isoforms of such a K channel (ROMK) have been cloned from the cRNA of outer medulla of the renal cortex and their protein structure is depicted in Figure 8. The channel protein has two membrane-spanning helices that flank a pore region similar to that found in voltage-gated K channels [32]. The expression of this channel transcript in the collecting duct suggests its
involvement in K secretion [16, 30]. Table 2 provides data concerning the similarity between ROMK(1) and the low-conductance secretory K channel in the apical membrane of principal tubule cells [16].

The pH sensitivity of the native low-conductance K channel is also present in the ROMK channels [16]. A decrease in pH from 7.4 to 6.8 lowers channel activity dramatically without altering channel conductance whereas other inwardly rectifying K channels lack pH sensitivity. The cloned channel shares with its native analog rapid run-down following membrane excision, and it has been shown that removal of Mg from the bath solution, a maneuver known to depress Mg-dependent phosphatases, or addition of PKA prevents the decline of channel activity [33]. This observation demonstrated significant PKA sensitivity of ROMK channels, and in vitro phosphorylation studies have extended such studies by showing that three serine residues in ROMK1 can be phosphorylated. Their

Table 2. Comparison of ROMK with native low-conductance apical potassium channel in principal tubule cells (from Ref. 16).

| Property                        | ROMK              | Principal Cell in CCD |
|---------------------------------|-------------------|-----------------------|
| Channel Conductance (ps)        | 35-45             | 25-35                 |
| Selectivity                     | K⁺>>Na⁺           | K⁺>Rb⁺>>Na⁺           |
| Inward rectification            | Yes               | Yes                   |
| Open probability (Pₒ)           | High (0.8-0.9 for > -40 mV) | High (> 0.9)         |
| ATP Inhibits (mM)               | Yes (MgATP > Na₂ATP) | Yes (MgATP > Na₂ATP) |
| Run-down by phosphatase         | Yes               | Yes                   |
| Reactivation by MgATP + PKA     | Yes               | Yes                   |
| pH dependence (inhibited by ↓pH)| Yes               | Yes                   |
| Arachidonate                    | Yes (ROMK1)       | Yes                   |
| PKC                             | Yes               | Yes                   |
| Glibenclamide                   | Yes (with CFTR)   | Yes                   |

Figure 8. Topology model of ROMK1 channel. Note presence of a phosphate-binding loop and potential protein kinase A and protein kinase C phosphorylation sites (from Refs. 30 and 32).
inactivation by mutagenesis completely suppressed K currents although these ROMK mutants were expressed in the plasma membrane of human embryonic kidney (HEK293) cells [34].

The sensitivity of the native low-conductance K channel to arachidonic acid is also maintained in ROMK channels and a specific serine residue, suggested to be a tentative PKC phosphorylation site, appears to be essential for PKC and arachidonic acid to express their inhibitory action [16, 35].

The inhibitory action of 1 mM ATP on cloned ROMK channels has already been mentioned. The finding that a nucleotide binding site has been identified in ROMK channels (see Figure 8) raises the possibility that this segment, a Walker A site motif within the phosphate-binding loop may be involved in channel regulation by ATP. Indeed, experiments in which the structure of the Walker A segment was altered by mutagenesis have confirmed that this segment of the channel’s carboxy terminus is a major role in inhibition of K channel activity by Mg-ATP [16, 33]. Similar to the native channel, cytosolic acidification confers upon ROMK channels increased sensitivity to inhibition by ATP. That ROMK channels can form association with other proteins is strongly suggested by the finding that sensitivity to inhibition by glibenclamide, a sulfonylurea compound, can be restored in ROMK channels by coexpression with CFTR [36].

CONCLUSION

The exploration of the function and structure of cloned renal K channels and their careful comparison with native K channels is an excellent example of the progress made possible by combining functional and molecular biological techniques. It is also an example of how synthesis of very reductionist methods with “classical” techniques such as tubule perfusion, ion transport measurements and cell electrophysiology deepens our understanding of the cellular and molecular events that control K secretion in principal tubule cells.

ACKNOWLEDGEMENTS: Work in the author’s laboratory was supported by NIH grant DK17433.

REFERENCES

1. Berliner, R.W. Renal mechanisms for potassium excretion. Harvey Lect. 55:141-171, 1961.
2. Malnic, G., Klose, R.M., and Giebisch, G. Micropuncture study of renal potassium excretion in the rat. Am. J. Physiol. 106:674-686, 1964.
3. Stanton, B.A. and Giebisch, G.H. Renal potassium transport. In: Windhager, E., ed. Handbook of Physiology - Renal Physiology. Oxford Univ. Press, NY, 1992. pp. 813-874.
4. Giebisch, G. and Wang, W. Potassium transport: From clearance to channels and pumps. Kid. Int. 49:1624-1631, 1996.
5. Weinstein, A.M. Modeling the proximal tubule: complications of the paracellular pathway. Am. J. Physiol. 154:F297-F305, 1988.
6. Giebisch, G. Renal potassium channels: An overview. Kid. Int. 48:1004-1009, 1995.
7. Sackin, H. Mechanosensitive channels. Ann. Rev. Physiol. 57:333-353, 1995.
8. Wang, W., Sackin, H., and Giebisch, G. Renal potassium channels and their regulation. Ann. Rev. Physiol. 54:81-96, 1992.
9. Gregor, R. Ion transport mechanisms in thick ascending limb of Henle’s loop of mammalian nephron. Physiol. Rev. 65:760, 1985.
10. Hebert, S.C. and Andreoli, T.E. Control of NaCl transport in the thick ascending limb. Am. J. Physiol. 146:F745-F756, 1984.
11. Wang, W.H. Two types of K channels in TAL of rat kidney. Am. J. Physiol. 167:F599-F605, 1994.
12. Hebert, S.C. and Andreoli, T.E. Effects of antidiuretic hormone on cellular conductive pathways in mouse medullary thick ascending limbs of Henle: II. Determinants of the ADH-mediated increases in transepithelial voltage and in net Cl⁻ absorption. J. Membr. Biol. 80:221-233, 1984.
13. Doucet, A. and Marisy, S. Characterization of K-ATPase activity in distal nephron: Stimulation by potassium depletion. Am. J. Physiol. 253:F418-F423, 1987.
14. Wingo, C.S. and Straub, S.S. Active proton secretion and potassium absorption in the rabbit outer medullary collecting duct. Functional evidence for proton-potassium-activated adenosine triphosphatase. J. Clin. Invest. 84:361-365, 1989.
15. Wang, W.H. View of K⁺ secretion through the apical K⁺ channel of cortical collecting duct. Kid. Int. 48:1024-1030, 1995.
16. Wang, W., Hebert, S.C., and Giebisch, G. Renal K⁺ channels: Structure and function. Ann. Rev. Physiol. 59:413-436, 1997.
17. Wang, W., Geibel, J., and Giebisch, G. Mechanism of apical K⁺ channel modulation in principal renal tubule cells: effect of inhibition of basolateral Na-K-ATPase. J. Gen. Physiol. 101:673-694, 1993.
18. Wang, W. and Giebisch, G. Dual modulation of renal ATP-sensitive K-channel by protein kinase A and C. Proc. Natl. Acad. Sci. U.S.A. 88:9722-9725, 1991.
19. Kubokawa M., Wang, W., McNicholas C.M., and Giebisch, G. Role of Ca²⁺/CaMK II in Ca²⁺-induced K⁺ channel inhibition in rat CCD principal cell. Am. J. Physiol. 268:F211-F219, 1995.
20. Ling, B.N. and Eaton, D.C. Cyclosporin A inhibits apical secretory K⁺ channels in rabbit cortical collecting tubule principal Cells. Kid. Int. 44:974-984, 1993.
21. Kubokawa, M., McNicholas, C.M., Higgins, M.A., Wang, W. and Giebisch, G. Regulation of ATP-sensitive K⁺ channel by membrane-bound protein phosphatases in rat principal tubule cell. Am. J. Physiol. 269:F355-F362, 1995.
22. Wang, W.H., McNicholas, C.M., Segal, A.S., and Giebisch, G. A novel approach allows identification of K⁺ channels in the lateral membrane of rat CCD. Am. J. Physiol. 266:F813-F822, 1994.
23. Hirsch, J. and Schlatter, E. K⁺ channels in the basolateral membrane of rat cortical collecting duct. Pflügers Arch. 424:470-477, 1993.
24. Horisberger, J.-D. and Giebisch, G. Voltage dependence of the basolateral membrane conductance in the *Amphiuma* collecting tubule. J. Membr. Biol. 105:257-263, 1988.
25. Wang, W.H. Regulation of the hyperpolarization-activated K⁺ channel in the lateral membrane of the CCD. J. Gen. Physiol. 106:25-43, 1995.
26. Schlatter, E. and Schafer, J.A. Electrophysiological studies in principal cells of rat cortical collecting tubules. ADH increases the apical membrane Na⁺-conductance. Pflügers Arch. 409:81-92, 1987.
27. Lu, M. and Wang, W.H. Nitric oxide regulates the low-conductance K⁺ channel in the basolateral membrane of the cortical collecting duct. Am. J. Physiol. 270:C1336-C1342, 1996.
28. Lu, M., Giebisch, G., and Wang, W. Nitric oxide-induced hyperpolarization stimulates low-conductance Na⁺ channel of rat CCD. Am. J. Physiol. 272:F498-F504, 1997.
29. Lu, M., Giebisch, G., and Wang, W.H. Nitric oxide links the apical Na⁺ transport to the basolateral K⁺ conductance in the rat CCD. J. Gen. Physiol. 110:717-726, 1997.
30. Hebert, S.C. An ATP-regulated, inwardly rectifying potassium channel from rat kidney (ROMK). Kid. Int. 48:1010-1016, 1995.
31. Desir, G.V. Molecular characterization of voltage and cyclic nucleotide-gated potassium channels in kidney. Kidney Int. 48:1031-1035, 1995.
32. Ho, K., Nichols, C.G., Lederer, W.J., Lytton, J., Vassilev, P.M., Kanazirska, M.V., and Hebert, S.C. Cloning and expression of an inwardly rectifying ATP-regulated potassium channel. Nature 362:31-38, 1993.
33. McNicholas, C.M., Yang, Y.H. Giebisch, G. and Hebert, W.C. Molecular site for nucleotide binding on an ATP-sensitive renal K⁺ channel (ROMK2). Am. J. Physiol. 271:F275-F285, 1996.
34. Xu, Z-C., Yang, Y. and Hebert, S.C. Phosphorylation of the ATP-sensitive, inwardly-rectifying K⁺ channel, ROMK, by cyclic AMP-dependent protein kinase. J. Biol. Chem. 271:9313-9319, 1996.
35. Wang, W., Cassola, A.C. and Giebisch, G. Arachidonic acid inhibits the secretory K⁺ channel of cortical collecting duct of rat kidney. Am. J. Physiol. 264:F554-F559, 1992.
36. McNicholas, C.M., Guggino, W.B., Schwibert, E.M., Hebert, S.C., Giebisch, G. and Egan, M.E. Sensitivity of a renal K⁺ channel (ROMK2) to the inhibitory sulfonamide compound, glibenclamide, is enhanced by co-expression with the ATP-binding cassette transporter CFTR. Proc. Natl. Acad. Sci. U.S.A. 93:8083-8088, 1996.
37. Wang, W., Schwab, A., and Giebisch, G. Regulation of small-conductance K⁺ channel in apical membrane of rat cortical collecting tubule. Am. J. Physiol. 259:F494-F502, 1990.
38. Wang, W., and Giebisch, G. Dual effect of adenosine triphosphate on the apical small conductance K⁺ channel of the rat cortical collecting duct. J. Gen. Physiol. 98:35-61, 1991.