J. Membrane Biol. 184, 225–232 (2001)
DOI: 10.1007/s00232-001-0091-4

The Journal of
Membrane
Biology

Remembrances of Renal Potassium Transport

R.W. Berliner, G. Giebisch
Department of Cellular and Molecular Physiology, Yale University School of Medicine, 333 Cedar St, New Haven, CT 06520, USA

Received: 15 August 2001

Ussing's work with ion transport across frog skin and the concepts he developed from that work have illuminated the way for others in the study and analysis of transport phenomena. The study of renal potassium transport is no exception. The frog skin model of two membranes with basal pump and differentiation permeabilities will be seen to fit well with renal tubule cells. The concept of solvent drag developed by Ussing may well be applicable to movement of ions between tubule cells. And the analysis of electrochemical gradients across renal membranes follows from Ussing's analysis of active and passive movements.

The following outline of the development of our knowledge of renal potassium handling reflects the personal interests of the authors. It should not by any means be interpreted as a comprehensive review, and omits reference to important work of many others. To them our apologies.

The development of the flame photometer in the mid 1940's greatly facilitated measurement of sodium and potassium concentrations and made possible the great expansion of our knowledge about potassium metabolism and excretion that has since occurred. Although there had been occasional earlier observations about potassium using the relatively laborious chemical methods, there were few systematic studies. With the flame photometer, however, the determination became so simple that determination of potassium concentrations could be thrown in with almost no extra effort when the main purpose of an experiment dealt with sodium excretion. It was, in fact, just such an occurrence, an incidental observation about potassium excretion in a study aimed at the effects of diuretics on sodium excretion, that led us to the further study of potassium that we will outline here.

Correspondence to: R.W. Berliner

The striking dissociation of potassium excretion from its rate of glomerular filtration that was often observed when a mercurial diuretic was injected in dogs suggested that potassium might be secreted by the tubules although the amount excreted was only a fraction of the filtered [1]. Secretion would therefore be in violation of one of the tacit but basic assumptions of the clearance approach to the measurement of kidney function—namely, that the difference between the amounts filtered and excreted was the amount reabsorbed or the amount secreted but not some combination of the two.

That there was indeed secretion of potassium by the renal tubules was then conclusively established by demonstrating that excretion could regularly be made to exceed the amount filtered in potassium-tolerant dogs infused with potassium salts [1]. At the same time, excretion of potassium in amounts greater than filtered was discovered by Mudge, Foulks, and Gilman [15]—an incidental finding in a study of osmotic diuresis with urea again intended primarily to explore sodium excretion.

The finding that the rate of potassium excretion was not related to the rate of its filtration after the administration of a mercurial diuretic was the basis for two further interferences: (1) that reabsorption must precede secretion, so that secretion must occur at a site in the nephron more distal than reabsorption, and (2) that, at least under these conditions, the filtered potassium made little or no contribution to the amount excreted. Whether the latter inference extended to more ordinary conditions was a possibility but by no means certain and would eventually depend on micropuncture studies

Not long before the secretion of potassium was observed, Pitts had shown that acidification of the urine was accomplished by secretion of hydrogen ion and proposed that it involved exchange for sodium [16]. It seemed likely that a similar exchange might be involved in potassium secretion. Two series of observations gave support to this hypothesis. The first

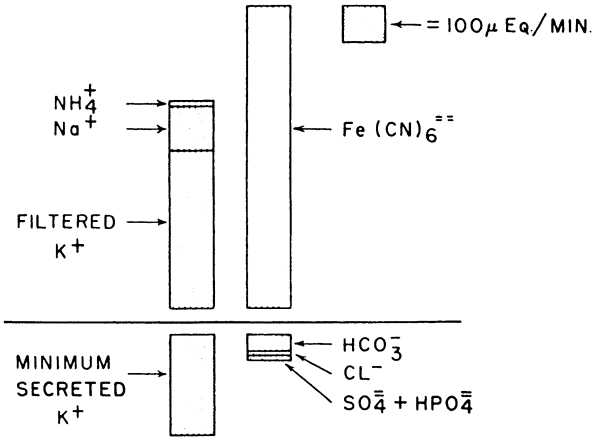

Fig. 1. Electrolyte excretion during infusion of potassium ferrocyanide. (Reproduced with permission from Berliner R.W. "Renal mechanisms for potassium excretion." Harvey Lect. **51:**141–171, 1961)

involved showing that there was no anion that might have been secreted with the potassium. Since potassium secretion occurred late in the tubule system, any anion secreted with it would likely appear in the urine. The ferrocyanide ion, the clearance of which is uniformly equal to the rate of glomerular filtration [2, 18] and thus can be neither reabsorbed nor secreted by the tubules, made possible studies showing that the minimum amount of secreted potassium, the amount in excess of the filtered (assuming excretion of all of the filtered), exceeded several-fold all of the other anions that appeared in the urine [3]. Figure 1 illustrates the data from one such experiment. The cation excretion is divided so that the block below the line represents the excess of some 300 μEq/min of the excretion of potassium over the filtered; this would be the amount secreted even if *all* of the filtered potassium was also excreted. The anions in the urine were almost entirely ferrocyanide, which cannot be secreted. All the other anions in the urine are only a small fraction of the minimum amount of potassium secreted. Thus it could be concluded that no anion was secreted along with the potassium and that the potassium must have been exchanged for another cation, the only cation likely to be available in sufficient quantity being sodium.

If potassium secretion is accomplished at a distal site in exchange for sodium, potassium excretion might depend upon having enough sodium reach the exchange site. Several earlier observations were in accord with that inference. Administration of large amounts of mineralocorticoids were known to produce depletion of potassium when sodium intake was in the usual range, but did not occur if sodium intake was rigidly restricted. And patients in cardiac failure who had very high levels of mineralocorticoids did not lose potassium except when increased sodium became available as a consequence of the administration of diuretics.

It was possible to demonstrate this dependence in dogs in which the urine from each kidney was collected separately while renal blood flow and glomerular filtration were reduced in one kidney [6]. If a high rate of sodium excretion was maintained despite the reduced filtration rate by the administration of diuretics or by the infusion of sodium salts of poorly absorbed anions, the rate of potassium excretion by the experimental kidney remained equal to that of the control kidney when filtration rate was reduced by as much as a third (Fig. 2*a*). If, however, no diuretics were administered, sodium excretion fell off sharply to very low levels when filtration rate was reduced and potassium excretion also dropped rapidly (Fig. 2*b*).

Given that excreted potassium is derived at least in part, and perhaps nearly entirely, from secretion by exchange for sodium at a relatively distal region of the nephron, what determines the rate at which excretion (secretion) occurs?

Excretion is probably not often limited by the delivery of insufficient sodium to the site of exchange except in severely salt-depleted individuals and in conditions characterized by marked salt retention, such as cardiac failure or advanced cirrhosis with ascites formation.

The rate of excretion is often poorly related to the concentration of potassium in the plasma. When potassium salts are infused in dogs, particularly potassium-tolerant animals, the plasma concentration rises to a relatively high level initially while excretion is relatively low; the concentration in plasma then returns to lower levels as excretion increases. This may reflect dependence of secretion on the concentration in cells, which would certainly be appropriate for an almost entirely intracellular ion.

Tolerance to potassium is produced by administering progressively larger amounts of potassium and is characterized by increased rates of excretion at relatively low concentrations in the plasma [1, 17]. The nature of this adaptation is poorly understood. While increased secretion of adrenal steroids is probably part of the phenomenon, tolerance can not be produced by administration of large amounts of steroid. Tolerant dogs do not have elevated concentrations of potassium in their plasma before they receive their daily dosage. It is not clear whether tolerance plays a role in any relatively normal physiologic circumstances or is strictly an experimental phenomenon.

The administration of potassium salts causes the urine to become more alkaline and the administration of bicarbonate causes the excretion of potassium to increase. In fact, the most marked increase in potassium excretion is produced by inhibiting carbonic anhydrase, which severely inhibits the process by which the urine is acidified. These observations led to

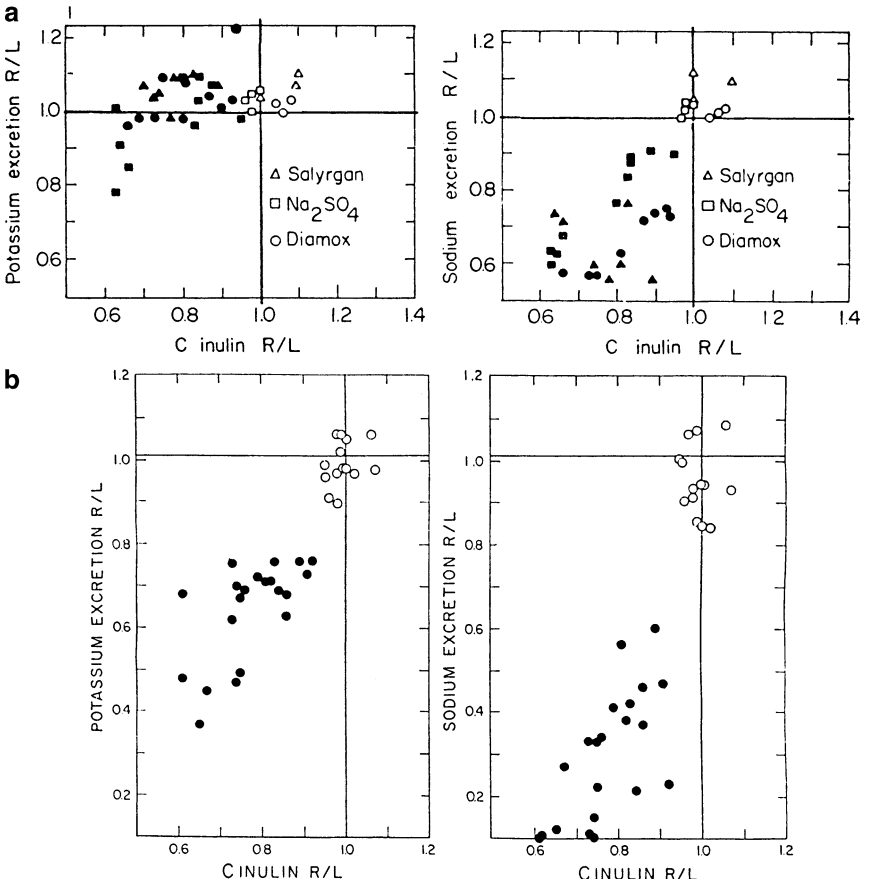

Fig. 2. Effect of reducing glomerular filtration rate on the excretion of potassium and sodium in the dog. Open symbols represent control periods before constriction of the right renal artery, filled symbols during reduction of glomerular filtration rate. (**a**) Sodium excretion maintained by administration of the indicated diuretics. (**b**) With no procedure to maintain sodium excretion. (Reproduced with permission from Berliner RW, "Renal mechanisms for potassium excretion." Harvey Lect. **51:**141–171, 1961.)

the proposal that there is competition for a common exchanger that effects secretion of both potassium and hydrogen ions [4]. More recent observations suggest a different explanation, but the reciprocal relationship is real. It may, at least in part, be explained by the effect on acid-base status of movement of potassium in and out of cells. The extracellular alkalosis associated with potassium depletion is dispelled when potassium salts are administered, not because the urine becomes more alkaline (which it does) but because the shift of potassium into cells is accompanied by a movement of acid from cells to extracellular fluid. The output of alkali in the urine is not nearly sufficient to account for the loss from extracellular fluid. Thus it seems that the intracellular environment is more alkaline when potassium content is high and more acid when potassium content is low. The reciprocal relationship between secretion of hydrogen and potassium ions may reflect the inverse relationship of their concentration in the secreting cells.

The effects of adrenal steroids on potassium excretion have long been well recognized. Adrenal insufficiency is associated with impaired potassium excretion, and administration of large amounts of mineralocorticoids leads to potassium depletion. The dependence of the latter phenomenon on sodium balance has already been mentioned. When mineralocorticoid levels are increased, the increase in sodium reabsorption is usually much greater than any increase in potassium excretion, reflecting the fact that the increase in sodium reabsorption is not limited to the exchange for potassium.

Diuretics that modify potassium excretion have provided important leads to the mechanisms involved. Some of these effects have been described above. Mercurial diuretics increase potassium excretion when it has initially been low and decrease excretion if it has been high. These opposite effects reflect the interplay of two separate effects of the mercurials: 1) inhibition of sodium reabsorption, increasing the delivery of sodium to the exchange site, and 2) a specific inhibitory action on the mechanism of potassium secretion. In bicarbonate-infused animals the administration of mercurials decreases the high level of potassium excretion even though under those conditions there may be no detectable effect on sodium excretion.

The striking increase in potassium excretion produced by inhibitors of carbonic anhydrase have been mentioned above. The fact that the increased potassium excretion can be abolished by adding a mercurial diuretic indicates that it is secretion that accounts for the high rate of excretion. Thiazide diuretics appear to have no specific effects on potassium

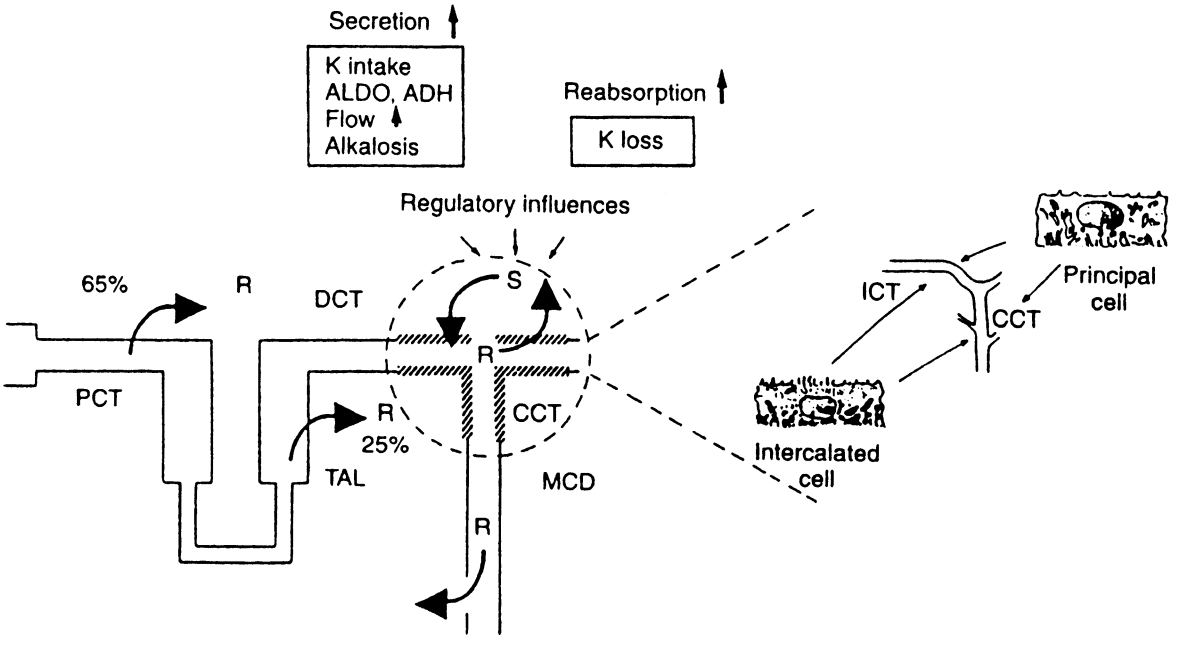

Fig. 3. Summary of potassium transport along the nephron. Following filtration, potassium is extensively reabsorbed along the proximal tubule and the loop of Henle. Potassium is secreted along the initial and cortical collecting tubule. Net secretion can be replaced by net reabsorption in states of potassium depletion. Also shown are the two cell types lining the distal tubule and cortical collecting duct. *PCT*, proximal tubule; *TAL*, thick ascending limb; *CCT,* cortical collecting tubule; *DCT,* distal convoluted tubule; *S*, secretion; *R*, reabsorption; *ALDO*, aldosterone; *ADH*, antidiuretic harmone; *MCD*, medullary collecting duct, *ICT*, initial connecting tubule (Reproduced with permission from Giebisch and Wang [9].)

transport and changes that occur when they are administered probably reflect their effects on sodium excretion. So-called loop diuretics are known to inhibit a transport process that involves potassium as well as sodium and the marked increase that occurs when they are administered probably reflects at least one situation in which depressed potassium reabsorption contributes to the increased excretion.

Our understanding of renal potassium transport was significantly enhanced by the resurgence of micropuncture studies in the 1950s. Micropuncture of single mammalian nephrons had been introduced by Walker, Bott, Oliver and MacDowell, and their landmark paper on the collection and analysis of fluid from nephrons of the mammalian kidney had appeared in 1941 [20]. More than ten years had elapsed before micropuncture re-emerged as a powerful tool for the direct exploration of nephron function. Micropuncture of single tubules not only permitted the systematic exploration of the sites where potassium was reabsorbed and secreted but also provided new information concerning the transport mechanisms. The introduction of methods of isolating and perfusing single renal tubules in vitro permitted the study of potassium transport in subcortical tubule segments, such as the loop of Henle and cortical and medullary collecting ducts not accessible to micropuncture. The development of appropriate methods for measuring accurately the concentrations of both potassium and sodium in nanoliter samples of collected tubule fluid further facilitated these investigations.

An extensive series of micropuncture studies fully supported the major role of potassium secretion along distal tubules as an essential and variable element of potassium excretion [7, 9, 14]. Figure 3 summarizes the result of in vivo micropuncture studies, which showed that most of filtered potassium is reabsorbed along the proximal tubule and elements of the loop of Henle, whereas the initial and collecting ducts are the major sites of potassium secretion. The conclusion that potassium secretion is the major source of potassium excretion and that changes in secretion modulate potassium excretion was thus confirmed. Potassium excretion drops sharply when dietary input of potassium is reduced and it has been observed that reabsorption of potassium may replace secretion along distal tubules. This raises the possibility that net transport of potassium results from opposing secretory and reabsorbtive components, a feature that may account for the great flexibility of transepithelial potassium transport. The major factors that regulate potassium secretion and reabsorption are included in Fig. 3: factors, such as potassium intake, aldosterone and antidiuretic hormone, diuretics (flow rate and sodium delivery) and systemic acid-base changes, alter potassium excretion by

modulating the rate at which potassium is secreted by the initial and cortical collecting duct.

Figure 3 also shows that the nephron segment responsible for regulated potassium transport is made up of two types of cells, principal and intercalated cells, which differ with respect to their morphology and abundance. It is generally accepted that principal cells secrete potassium and intercalated cells reabsorb potassium.

The exploration of the mechanisms of potassium transport by the kidney has been further advanced by the application of electrophysiological techniques. Measurements of transepithelial and transmembrane potential differences, combined with measurements of intracellular potassium activities by ion-selective microelectrode, have identified the nature and location of active and passive potassium transport in apical and basolateral membranes. These biophysical approaches defined the transport processes governing potassium secretion and reabsorption, and have provided evidence that potassium transport may also involve paracellular movement between cells. Models of the cellular mechanisms of potassium transport in proximal tubule, thick ascending limb of Henle's loop, and in principal and intercalated cells of cortical collecting tubules are summarized in Fig. 4.

As can be seen in Fig. 4, the transepithelial voltage is lumen-negative in the early proximal tubule and positive in the more downstream convolutions. Proximal tubule cells have a large *basolateral* potassium conductance, a property shared by all tubule cells [10]. Basolateral potassium channels are important for the generation of the cell-negative potential, which is a major driving force for apical electrogenic transport, such as sodium-dependent organic solute reabsorption. Potassium channels normally confer only a small potassium conductance to the *apical* membrane: they are stimulated only under conditions of cell swelling and membrane depolarization. Thus, despite a favorable electrochemical gradient for secretion across the luminal membrane, potassium is effectively reabsorbed along the proximal tubule.

Potassium retrieval from the proximal tubule fluid has been shown to be coupled to and dependent on proximal water and sodium transport, and is not dependent upon a specific transport mechanism [7]. Two mechanisms have been suggested: solvent drag and diffusion [24]. Solvent drag is produced by active sodium reabsorption coupled to osmotically driven water movement, potassium being entrained in the reabsorbate. The low reflection coefficient of potassium in proximal tubules fits the possibility that solvent drag may be responsible [23]. Potassium diffusion would be driven by the favorable electrochemical gradient established by the lumen-positive transepithelial potential across the second half of the proximal tubule and a potassium concentration in the

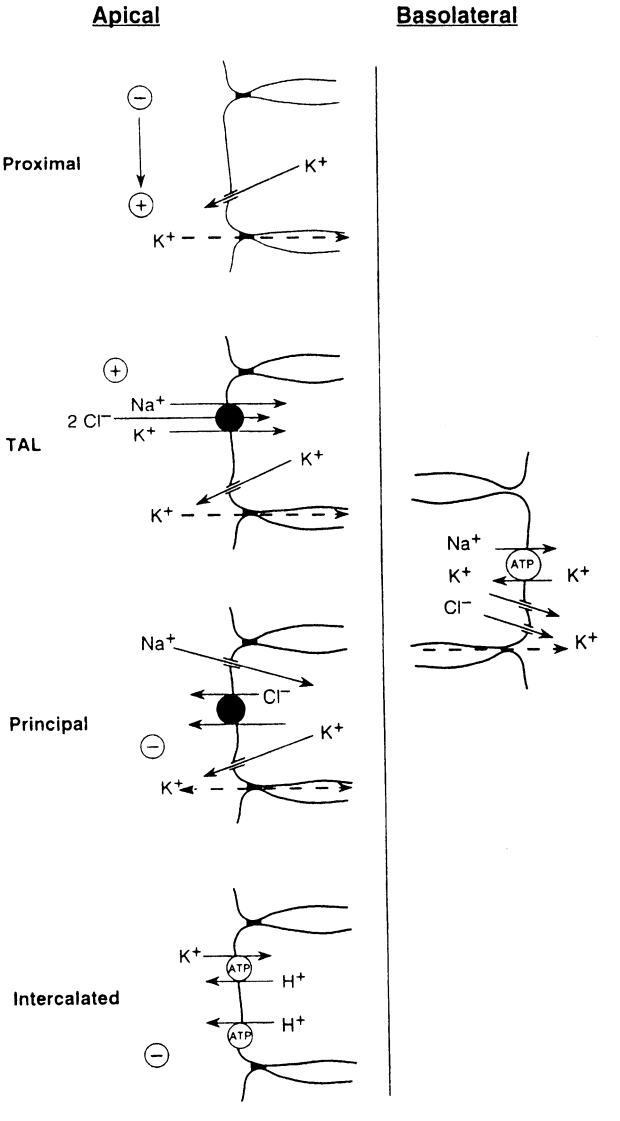

Fig. 4. Cell models of potassium transport along the nephron. Note similarity of transporters in the basolateral membrane and different transporters in the apical membrane. (Reprinted with permission from Giebisch and Wang [9].)

lumen that slightly exceeds that in the peritubular fluid. Although the issue has not been extensively investigated it appears that potassium reabsorption is not specifically regulated in the proximal tubule.

Potassium reabsorption in the *thick ascending limb of Henle* (TAL) occurs both via transcellular and paracellular pathways [7, 11, 12]. Potassium reabsorption depends on Na-2Cl-K cotransport (the mechanism sensitive to inhibition by loop diuretics such as furosemide and bumetamide). Apical potassium channels permit recycling of potassium, essential for maintaining the supply to the Na-2Cl-K cotransporter, and they are also responsible, in part, for the lumen-positive electrical potential, which is a significant driving force for passive paracellular

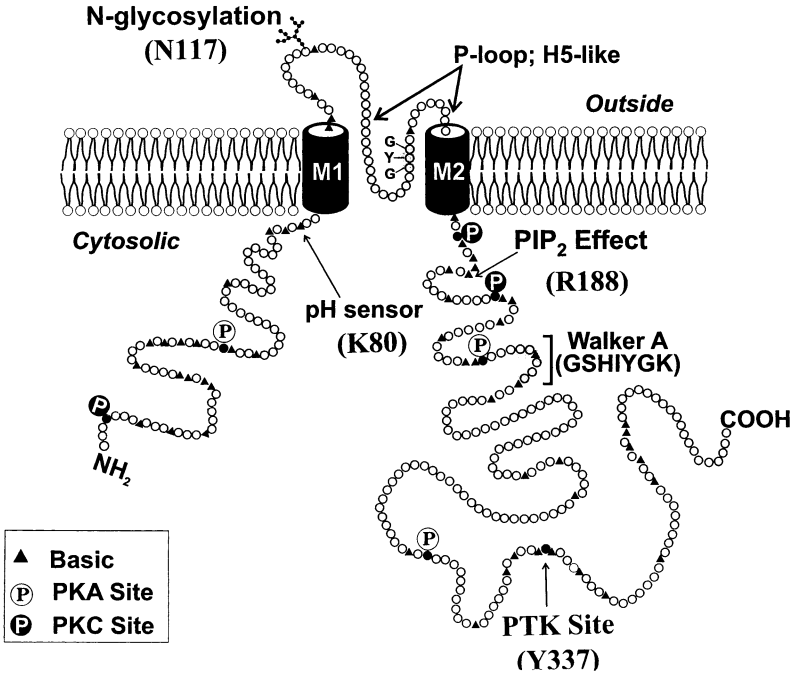

Fig. 5. Topology of ROMK (K_{ir} 1.1) K^+ channel. M1 and M2 represent the two membrane-spanning domains characterizing the inward-rectifier family of potassium channel. Some important functional sites are indicated. A short amphipathic segment in the M1-M2 linking segment in ROMK is homologous to the pore-forming (*P*-loop) or H5 region of classic voltage-gated *Shaker* K^+ channels cloned from the fruit fly. The canonical G-Y-G amino-acid sequence found in all K^+ channels is shown in the H5 segment. *PKA*: protein kinase A; *PKC:* protein kinase *C*; *PTK*: protein tyrosine kinase; *PIP_2*: phosphoinositolphosphate (Reproduced with permission from Giebisch and Wang [10]).

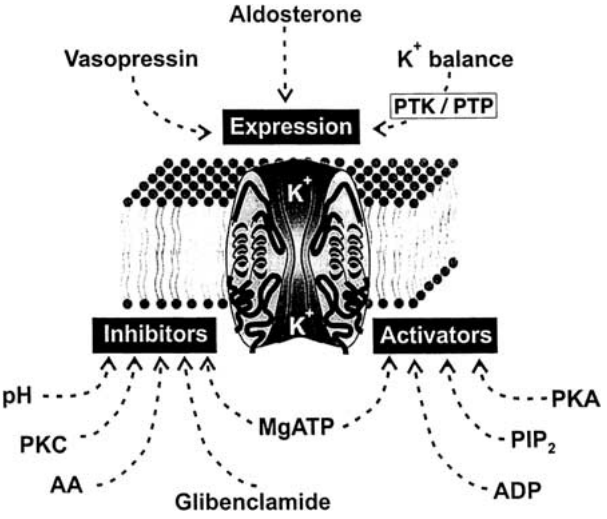

Fig. 6. Summary of factors modulating the function of the low-conductance secretory K channel in principal tubule cells. *AA*: arachidonic acid; *PTP*: protein tyrosine phosphate; *PTK*: protein tyrosine kinase (Reproduced with permission from Wang and Hebert [21]).

potassium reabsorption. Except for the action of diuretics, modulation of potassium transport in the TAL does not alter potassium excretion in a major way.

Figure 4 illustrates two apical mechanisms that mediate potassium secretion across the apical membrane of *principal tubule cells* [7, 9]. Passive diffusion and potassium-chloride cotransport are both driven by the favorable electrochemical gradient. Apical sodium channels play an important role in the process of potassium secretion: diffusion of sodium ions from the lumen into the cytosol depolarizes the apical membrane, thus minimizing the hyperpolarizing effect of the diffusion of potassium into the lumen, the latter tending to impede potassium secretion. Thus, optimal conditions for potassium secretion require that *both* potassium and sodium conductances be activated in parallel, as indeed has been found to occur with administration of a high-potassium diet, hyperaldosteronism, metabolic alkalosis and hyperkalemia [7].

The secretion of potassium across the apical membrane depends on its active uptake by Na-K ATPase across the basolateral membrane. Potassium recycling across the basolateral membrane is normally low because the membrane potential is close to the potassium equilibrium potential but can compromise secretion should the membrane be depolarized. In contrast, stimulation of basolateral Na-K ATPase has been shown to hyperpolarize the membrane to such high levels that potassium ions move passively from the peritubular fluid into the cytoplasm [7, 9]. It has been a consistent observation that changes in net secretion of potassium occur by coordinated changes in apical and basolateral transport mechanisms. Such transport adjustments minimize changes in cytosolic concentrations of potassium and sodium and they also prevent volume changes during widely varying rates of potassium secretion and sodium reabsorption [8].

A mechanism for potassium-chloride cotransport has been suggested by the observation of chloride-dependent potassium secretion when apical potassium channels are inhibited [19]. The possible physiological

role of such cotransport is, however, uncertain. Activation of cotransport-dependent potassium secretion may be involved in enhanced potassium secretion that occurs when principal cells are exposed to high luminal bicarbonate, and accordingly low chloride, concentrations.

There is also a mechanism for active reabsorbtion of potassium, in exchange for hydrogen ions. As shown in Fig. 4, this process is confined to intercalated cells and is activated by potassium depletion [5]. The importance of this exchange in physiological conditions is not clear. The observation that steady-state potassium concentrations in the lumen at the secretory site are always much lower than expected form the transepithelial electrical potential with passive diffusion is consistent with active reabsorption of potassium. However, specific inhibitors of potassium-hydrogen exchange affect hydrogen secretion (measured by bicarbonate transport) only during potassium depletion, implying that activation of potassium-hydrogen exchange is limited to conditions of potassium depletion.

The application of patch-clamp techniques to the membranes of tubule cells and the cloning of renal potassium channels has provided new insights into molecular aspects of potassium transport. The analysis of single-channel activity in the membranes of tubule cells has demonstrated the wide-spread presence of potassium channels in renal tissue, provided information on the structure and biophysical properties of these channels and permitted comparison of native with cloned renal potassium channels.

There is a low-conductance, slightly inwardly-rectifying potassium channel with a very high open-probability in the apical membrane that mediates potassium recycling in the thick ascending limb and potassium secretion in principal cells of the cortical collecting duct [10]. A large-conductance, calcium-activated potassium channel is also found in the apical membrane of the thick ascending limb and in both principal and intercalated cells of the cortical collecting duct. This channel under physiological conditions has a very low open-probability and is thought to be involved in cell volume control and in the flow-dependent increase in potassium secretion [10]. Additional potassium channels have been detected in renal tubule cells and we are beginning to learn more about their physiological function.

The cloning of a renal potassium channel (ROMK KIR 1.1) that shares many properties with the native, low-conductance potassium channel in the apical membranes of the thick ascending limb and cortical collecting duct has provided considerable insight into the molecular mechanisms that control renal potassium transport [13, 21]. The topology of ROMK, as depicted in Fig. 5, includes two membrane-spanning segments and several regulatory domains located on the amino and caboxy termini. The channel has a very high open-probability and most changes in function are the result of recruitment of additional channel units. Structure-function studies have identified the sites at which specific amino acids interact with protons, nucleotides, arachidonic acid and phosphoinositides (PIP2), and the sites for phosphorylation by protein kinases A and C, calcium calmodulin kinase, protein tyrosine kinase and several protein phosphatases. Figure 6 illustrates the factors that modulate channel activity.

ROMK has a tetrameric structure and several isoforms that are differentially expressed along the nephron. Changes in potassium intake result in changes in the number of potassium channels in the apical membranes of principal cells, an effect that is mediated by tyrosine kinase activity and alterations in the balance between channel insertion and endocytosis [22]. There are interactions of ROMK with membrane proteins such as the cystic fibrosis transmembrane conductance regulator and the sulphonylurea receptor, but the physiological role of these interactions is uncertain, as are interactions of the channel with the cytoskeleton and the A kinase anchoring protein.

References

1. Berliner, R.W., Kennedy, T.J. Jr. 1948. Renal tubular secretion of potassium in the dog. *Proc. Soc. Exptl. Biol. Med.* **67:**542–545
2. Berliner, R.W., Kennedy, T.J. Jr, Hilton, J.G. 1950. Renal mechanisms for excretion of potassium. *Am. J. Physiol.* **162:** 348–367
3. Berliner, R.W., Kennedy, T.J. Jr, Hilton, J.G. 1950. Renal clearance of ferranocyanide in the dog. *Am. J. Physiol.* **160:**325–329
4. Berliner, R.W., Kennedy, T.J. Jr. Orloff J. 1951. Relationship between acidfication of the urine and potassium metabolism. *Am. J. Med.* **11:**274–282
5. Buffin-Meyer, B., Deschenes, G., Doucet A, 1999. Renal K-ATPases: structure, function and dysfunction. *Nephrologie* **20:** 319–327
6. Davidson, D.G, Levinsky, N.G., Berliner, R.W. 1958. Maintenance of potassium excretion despite reduction of glomerular filtration during sodium diuresis. *J. Clin. Invest.* **37:**548–555.
7. Giebisch, G. 1998, Renal potassium transport: mechanisms and regulation. *Am. J. Physiol.* **274:**F817–F833
8. Giebisch, G. 1999. Physiological roles of renal potassium channels. *Semin. In Nephrol*, **19:**458–471
9. Giebisch, G. Wang, W. 1996. Potassium transport: From clearance to channels and pumps. *Kidney Int.* **49:**1624–1631.
10. Giebisch, G, Wang, W. 2000. Renal tubule potassium channels: function, regulation and structure. *Acta Physiol. Scand.* **170:** 153–173.
11. Greger, R. 1985. Ion transport mechanisms in thick ascending limb of Henle's loop of mammalian nephron. *Physiol. Rev.* **65:** 760–797.
12. Hebert, SC., Andreoli, T.E. 1984. Control of NaCl transport in the thick ascending limb. *Am. J. Physiol.* **246:**F745–F756.
13. Ho, K., Nichols C.G., Lederer, W.J., Lytton, J., Vassilev, P.M., Kanazirska, M.V., Hebert, S.C. 1993. Cloning and expression of an inwardly rectifying ATP-regulated potassium channel. *Nature* **362:**31–38.

14. Malnic, G, Klose, R., Giebisch, G. 1964. Micropuncture study of renal potassium excretion in the rat. *Am. J. Physiol.* **206:** 674–686.
15. Mudge, G.H., Ames, A., Foulks, K., Gillian, A. 1950. Effects of drugs on renal secretion of potassium in the dog. *Am. J. Physiol.* **161:**151–158.
16. Pitts, R.F., Alexander, R.S. 1945. The nature of the renal tubular mechanism for acidifying the urine. *Am. J. Physiol.* **144:**239.
17. Thatcher, J.S., Radike, A.W., 1947. Tolerance to potassium intoxication in the albino rat. *Am. J. Physiol.* **151:**138–146.
18. Van Slyke, D.D., Hiller, A., Miller, B.F. 1935. The clearance, extraction percentage and estimated filtration of sodium ferrocyanide in the mammalian Kidney. Comparison with inulin, creatinine and urea. *Am. J. Physiol.* **113:**611–628.
19. Velázquez, H., Ellison, D.H., Wright, F.S. 1987. Chloride-dependent potassium secretion in early and late renal distal tubules. *Am. J. Physiol.* **253:**F555–F562.
20. Walker, A.M., Bout, P.A., Oliver, J., MacDowell. M.C. 1941. The collection and analysis of fluid from single nephrons of the mammalian Kidney. *Am. J. Physiol.* **134:** 580
21. Wang, W., Hebert, S.C. 2000. The molecular biology of renal K Channels. *In: The Kidney, Physiology and pathophysiology,* 3rd ed., D.W. Seldin, G., Giebisch, editors. pp 243–270. Lippincott Raven Press, Philadelphia.
22. Wang, W., Lerea, K.M., Chan, M., et al. 2000. Protein tyrosine kinase regulates the number of renal secretory K channels. *Am. J. Physiol.* **278:**F165–F171.
23. Wareing, M., Winson, R.W., Kibble, J.D., Green, R. 1995. Estimated potassium reflection coefficient in perfused proximal convoluted tubules of the anaesthetized rat in vivo. *J. Physiol.* **488:**153–161
24. Weinstein, A.M.,1988. Modeling the proximal tubule: Complications of the paracellular pathway. *Am. J. Physiol.* **254:**F297–F305